Single Technology Appraisal

Belzutifan for treating tumours associated with von Hippel-Lindau disease [ID3932]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Belzutifan for treating tumours associated with von Hippel-Lindau disease [ID3932]

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from** Merck Sharp & Dohme

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. Action Kidney Cancer
   b. VHL UK Ireland

3. **Comments on the Draft Guidance from experts:**
   a. Professor William Drake – Clinical expert, nominated by Merck Sharp & Dohme
   b. Professor Patrick Maxwell – Clinical Expert, nominated by UK Kidney Association

4. **Comments on the Draft Guidance received through the NICE website**

5. **External Assessment Group critique of company comments on the Draft Guidance**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Merck Sharp & Dohme (UK) Limited

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A (we are the company bringing the treatment to NICE for evaluation)
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Younan Zhang

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	MSD is grateful for the opportunity to respond to the draft guidance for belzutifan for treating tumours associated with von Hippel-Lindau disease (VHL). The belzutifan pivotal trial MK-6482-004 demonstrates the profound clinical efficacy for patients with the three VHL associated tumours specified in the GB marketing authorisation (renal cell carcinoma [RCC], central nervous system haemangioblastomas [CNS Hb] and pancreatic neuroendocrine tumour [pNET]), see Figure 1 below.

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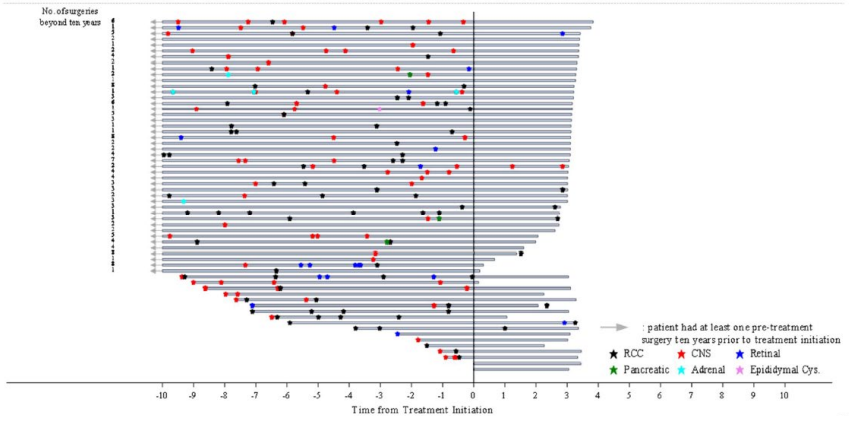
Figure 1 Distribution of all surgeries pre- and post-treatment initiation over time for individual patients - safety analysis set



Horizontal bars represent each patient.
Only pre-treatment surgeries less than 10 years prior to treatment initiation are presented.
Length of the bars on the right side of the y-axis represents duration of treatment at time of data cut-off.
Surgery is defined as a tumour reduction procedure excluding radiation.
Date of Data Cut-off: 01-APR-2022

As part of this response to the draft guidance, MSD has revised its patient access scheme (PAS). [redacted]. With the revised PAS and adjustments to the economic base-case detailed below, the company base-case ICER is below the 1.2 severity modifier threshold of £36,000 per quality adjust life year (QALY) gained. MSD asserts that the correct threshold for this technology appraisal is £51,000 per QALY gained in line with the 1.7 severity modifier. As such, belzutifan offers both profound clinical and economic value to patients in England and Wales and to the NHS in these nations.

In this response document we address the key issues raised in the draft guidance, specifically the generalisability of the trial data to the GB indication wording. We also reflect expected use in the UK and address technical points raised regarding the indirect treatment comparison (ITC) and the economic model. We consulted clinical experts, using as formal methods as possible in the timeframe available, to address specific points as required.

Trial population

It has become clear that trial summary statistics have not well conveyed the severity of disease experienced by the patient population in the MK-6482-004 trial. We apologise for not addressing this earlier. We have now provided comprehensive baseline disease characteristics for the patients in the MK-6482-004 study, see Appendix 3. We believe this could reassure the committee that the trial population is generalisable to the GB indicated population and any

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	residual uncertainty regarding the efficacy of the product in the target English and Welsh patient population can be disregarded. UK clinicians told us they want belzutifan only for a very small number of patients, approximately 3% of their VHL caseload (Appendix 1). These are patients for whom localised procedures are not an option. When describing the characteristics of these patients, clinicians focus on multisystem and CNS Hb involvement and / or patients on the precipice of organ failure. These patients, i.e. patients with complex multi-system involvement and significant CNS Hb presentation, are well-represented in MK-6482-004 and the clinical efficacy of belzutifan has been demonstrated in this population with an Objective Response Rate (ORR) for CNS Hbs of 44.0%. Stable Disease was 46%, with 6% progressing and 4% not evaluable, at the 1st April 2022 data cut. Clinicians tell us this level of response is unheard of in haemangioblastomas. **Indirect Treatment Comparison (ITC)** The draft guidance document flagged some concerns with the suitability of the ITC to estimate relative treatment efficacy. The company has accepted these concerns and so has replaced the ITC data estimating treatment efficacy with respect to surgery rates with the data from the MK-6482-004 pre-belzutifan-treatment period. **Economic model adjustments** Addressing points raised in the draft guidance document, we have adjusted the economic model as follows: • The immediate surgery assumption has been removed. A 4-month delay to surgery has been implemented as recommended. • Time to Surgery (TTS) for the RCC cohort in the Standard of Care (SoC) arm now uses data from the pre-belzutifan-treatment period rather than the Natural History Study, Matching Adjusted Indirect Comparison (MAIC). • We have revised the disutility value for End Stage Renal Failure (and erythroderma). • We have used a multiplicative approach for calculating disutilities. • The three cohorts have been re-weighted based on UK clinical expert feedback. Following all of these adjustments, plus the PAS revision, the company base-case ICER is below the £36,000 threshold and is below this threshold across a range of plausible scenarios using both deterministic and probabilistic ICERs estimates. **Access** MSD acknowledges that the ultra-rare, highly heterogeneous nature of this disease means there is some uncertainty in the evidence package. We consider that the ICERs presented herein, against a decision making of

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	£51,000 aligned with the 1.7 severity modifier, represents value to the NHS in the UK. The company's priority is patient access to this treatment option. As such we would consider either a positive recommendation to routine commissioning or into the Cancer Drugs Fund (CDF). If a CDF recommendation were made, we would need an extended duration in the scheme, for example five years, due to the small number of patients and the rarity of events. We have discussed this with the head of the CDF and believe this could be acceptable. Similarly, we recognise that gaps in evidence in the SoC arm will not be addressed through data collection in SACT. Therefore, we also commit to undertaking the necessary real world evidence studies to address any remaining gaps in the SoC arm. **Conclusion** Unmet need for treatment in the VHL population covered by the GB label is substantial. MSD kindly requests the committee reconsiders its draft decision and applies the flexibility available due to the innovative nature of this technology and the rarity of this disease if there are any residual concerns about uncertainty in this submission. We request the committee revises its position to ensure all UK patients have access to this transformative treatment.

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2	**CLINICAL** Comments under this subsection address section 3.1 to 3.9 of the draft guidance. **Summary of key points** • Extensive analyses on the detailed baseline characteristics of patients in the MK-6482-004 study has been conducted which has conclusively found that that the study population is demonstrably representative of that of the GB marketing authorisation. • MSD has conducted further expert input elicitation to better characterise the patients UK clinicians would want to treat using belzutifan and how they are managed: ○ The number of patients is very small, approximately ≈3% of patients currently managed at VHL-disease centres, representing a very small decision-risk for the NHS if belzutifan is recommended for use, even with data uncertainty due to the rarity and heterogeneity of the disease ○ Treatment decision-making in this population is dominated by consideration of how best to manage multi-system disease and CNS Hb, with CNS Hb usually the priority concern in patients with multi-system disease. ○ The maximum time interval between a decision to treat being made and the surgery would be 4 months. • Relative treatment effect of belzutifan versus standard of care with respect to the outcome of surgery in the revised cost-effectiveness analyses base-case is now informed by direct comparison between the pre-treatment versus post-belzutifan-treatment-initiation periods of the MK-6482-004 study instead of the indirect treatment comparison (ITC) that uses data from the VHL natural history. This ameliorates concerns the NICE committee had about the VHL natural history study and the ITC.
2a	**<u>Relevant population</u>** A recurrent point raised in the draft guidance document is that the pivotal trial, MK-6482-004, is not generalisable to the GB indication wording. We address this below in detail to demonstrate that the trial *is* suitable to support decision making for the GB indicated population. We also provide clinician feedback regarding the numbers, characteristics and distribution of VHL patients in whom clinicians would like to use belzutifan. MSD consulted a number of clinicians on the population they would like to treat using belzutifan (with additional follow up with clarification questions as needed, details provided in Appendix 1) and considered information received from two specialist centres that have sufficient patient numbers and cover more than one specialism to support this response.

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	1. Number of patients with VHL disease-associated tumours managed under specialist services who clinicians want to treat with belzutifan UK clinical experts who manage VHL specialist services in England and Wales communicated that belzutifan would be the appropriate treatments for only 2-3 patients in each specialist clinic (i.e. ~3% of patients with VHL disease; described in Appendix 1). This therefore means that only an extremely small number of patients in England and Wales are expected to receive treatment with belzutifan and consequently the decision-risk associated with this appraisal is very low. **2. Characteristics and distribution of the belzutifan target patient population** Clinicians also described the characteristics and distribution of the patients in whom they would like the option to use belzutifan. This indicated that, of the patients that they would like to treat using belzutifan, what would drive treatment decision making is the presence of multi-system disease (multiple VHL disease-associated tumours across different locations/organs) in 40%-50%, CNS Hbs in 40%-50%, and RCC in 10%-15%, of these patients. On clarification clinicians confirmed that they expected very few patients would have pNET as the tumour driving treatment decision-making. Acknowledging that we do not have a 'multi-system cohort' in the economic model, we reviewed in detail the MK-6482-004 patients and again discussed with clinicians (Appendix 1). Examination of the MK-6482-004 study patient baseline characteristics data indicated that over 80% of patients have both RCC and CNS Hb (see Figure 2 below). Of the 61 patients in the study (who all had to have RCC), 34 (55.7%) had >2 CNS tumours and 17 (27.9%) had 1-2 CNS tumours. Clinical experts highlighted that multisystem disease is dominated by CNS Hb involvement. This confirms that the MK-6482-004 study is representative of the patient population UK clinicians want to treat with belzutifan and the company's cost-effectiveness analyses. Accordingly, we have redistributed patients in the economic model across the CNS Hb, RCC and pNET cohorts resulting in distributions as follows: 80% are in the CNS Hb cohort, 15% in the RCC patients, and 5% in the pNET cohort. **3. Alignment between the MK-6482-004 study population and the belzutifan marketing authorisation population.** Section 3.5 of the draft guidance document notes the concern that "there could be clinical differences between the trial, marketing authorisation and comparator populations" and that "the committee noted that MK-6482-004 represented a population with different needs than the population in the marketing authorisation" which "severely limited the generalisability and applicability of the clinical-effectiveness evidence". Section 3.9 also stated that the committee considered that for the belzutifan arm "a less severe population was implicitly assumed". Firstly, it is important to highlight that the marketing authorisation for belzutifan was derived from the MK-6482-004 study. To suggest that the MK-6482-004 study

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	population is not generalisable to the marketing authorisation population, implies that the marketing authorisation itself is not based on the study. It appears the committee may think the MK-6482-004 population does not have "severe" disease. We acknowledge that summary statistics obscure essential detail about the severity of the patients in MK-6482-004. For example: • One patient did not require immediate surgery and only had one RCC tumour at baseline and may appear to have non-severe disease. However, this patient had had a prior left total nephrectomy, right partial nephrectomy, and distal pancreatectomy indicating both severe disease and eligibility for treatment with belzutifan under the GB marketing authorisation. • Another patient had multi-system disease; two RCC tumours and eight CNS Hbs, one of which was located in the brain stem, making local procedures undesirable, again they would be eligible for treatment with belzutifan under GB marketing authorisation. • A third patient had multi-system disease with two RCC tumours on their right kidney and six CNS Hb who does not have pNETs anymore as they have already undergone a Whipple's procedure, had also previously undergone a partial nephrectomy in their right kidney as well as two craniectomies and a spinal resection for haemangioblastomas, is an example of someone who has indisputably severe disease and eligibility for treatment with belzutifan under the GB marketing authorisation. We have presented baseline characteristic data for MK-6482-004 trial participants to provide a better picture of the extent of their disease. Examining in particular their baseline characteristics and prior treatment history to assess to what extent the population of the MK-6482-004 study aligns with the patient characteristics as specified in the marketing authorisation. The data show that: In terms of the number of VHL-disease associated tumours at baseline: • Of the 61 patients with RCC, 42 (69%) had 1-2 RCC tumours, 15 (25%) had 3-4 RCC tumours, and 4 (7%) had ≥5 RCC tumours. • Of the 22 patients with pNETs, 20 (90%) had 1-2 pNETs and 2 (9%) had 3-4 pNETs (none had ≥5 pNETs). • Of the 50 patients with CNS Hb, 17 (34%) has 1-2 CNS Hbs, 15 (30%) had 2-3 CNS Hbs, and 18 (36%) had ≥5 CNS Hbs. • Of the 50 patients with CNS Hbs, 3 (6%) had them in the brainstem, 42 (84%) had them in the cerebellum, 27 (54%) had them in the spine/spinal cord, and 11 (22%) had them in other locations (a patient may have a CNS Hb in more than one location, these percentages are provided out of the population of 50 patients CNS Hb in each instance). In terms of patients with tumours in different locations, all patients in the MK-6482-004 study had RCC, and the majority also had multi-system disease with CNS Hb and/or pNET, as shown in Figure 2.

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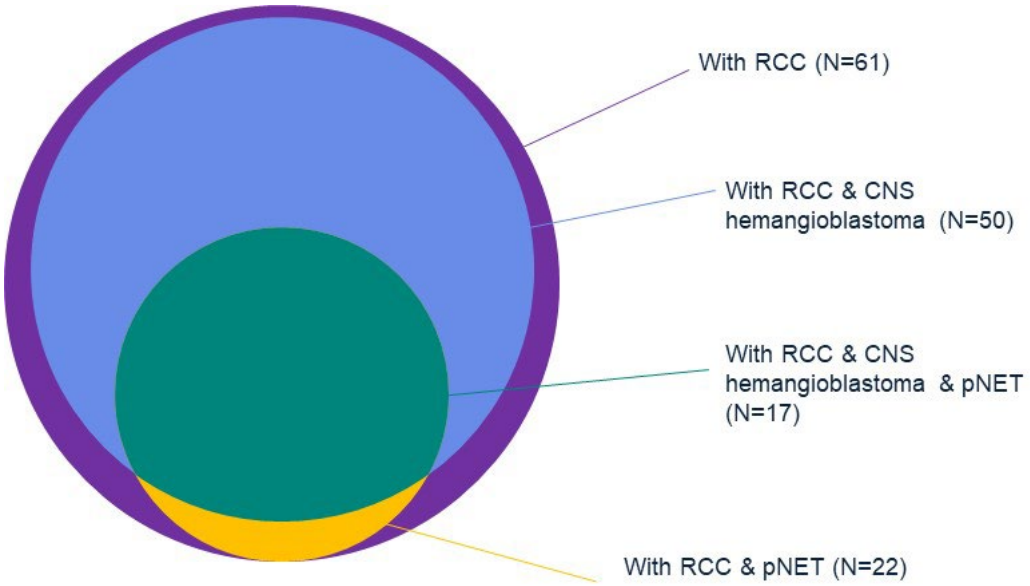
Figure 2 Summary of subgroups based on tumour locations in the MK-6482-004 study (to scale)



In terms of prior localised procedures related to VHL-disease associated tumours:

- Of the 61 patients in the study, 14 (23%) had not undergone any surgery for RCC, 23 (38%) had undergone procedures in only one kidney, and 24 (39%) had undergone procedures in both kidneys.
- Of the 61 patients in the study, 52 (85%) had not undergone any surgery for pNET, 6 (10%) had undergone distal or partial pancreatectomy, and 3 (5%) had undergone a Whipple's procedure of pancreaticduodenectomy.
- The average number of CNS Hb procedures undergone in the 61 patients was 2.72.

These are also illustrated in the summary figures below and are also provided in tabular format in Appendix 2. These data indicate a trial population who had a number of concurrent tumours and were not naïve to an extensive history of prior procedures.

Figure 3 MK-6482-004 study baseline population number RCC tumours in patients with RCC (N=61)

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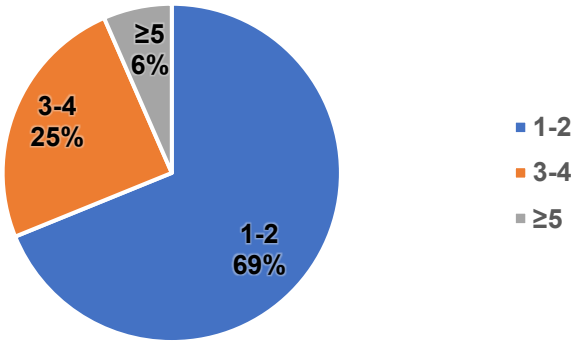

Figure 4 MK-6482-004 study baseline population number pNET tumours in patients with pNET (N=22)

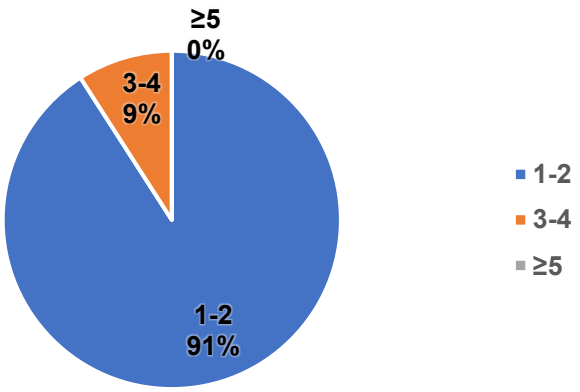

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Figure 5 MK-6482-004 study baseline population number CNS Hb tumours in patients with CNS Hb (N=50)

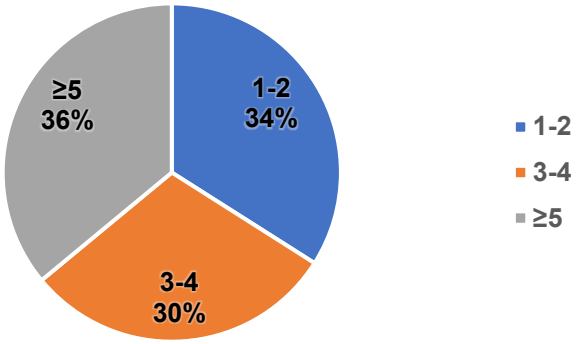

Figure 6 MK-6482-004 study baseline population number of patients with prior RCC procedures (N=61)

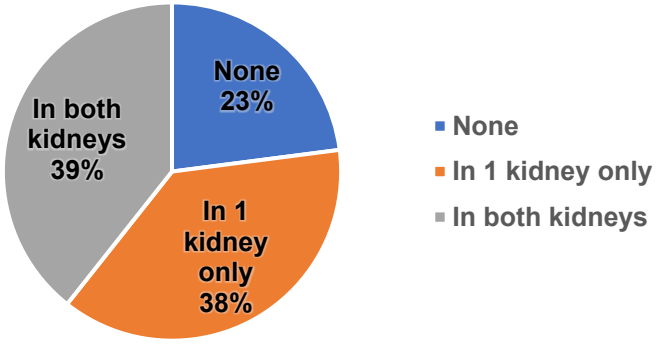

Figure 7 MK-6482-004 study baseline population number of patients with prior pNET procedures (N=61)

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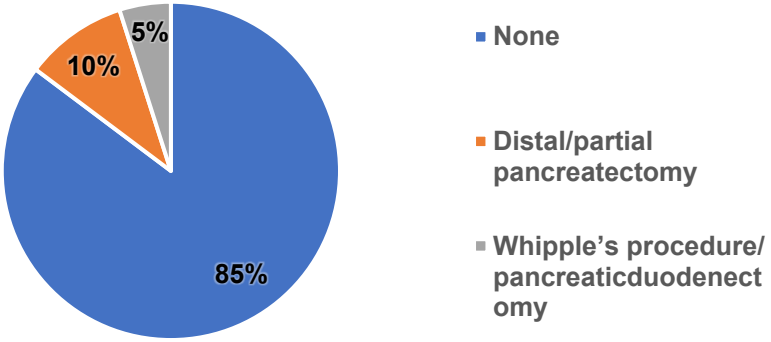

These summary statistics and looking wholistically at each patient indicate that the MK-6482-004 study population fall within the characteristics specified in the marketing authorisation for belzutifan (the positioning/relevant population for this appraisal), and accordingly that the effects of belzutifan treatment observed in the MK-6482-004 study are generalisable to that which would be seen in the population as defined in the indicated population for this appraisal.

To further highlight the severity of the patients in MK-6482-004, the baseline characteristics, medical history, tumours present at baseline, and prior therapies for VHL disease of four hypothetical patients (created via a composite of characteristics from the patients in the study to preserve anonymity) are presented in Table 5 of Appendix 2. It can be seen from these how devastating VHL disease and heavily treated these patients can be. These hypothetical patient data have been presented due to the highly confidential nature of the individual patient baseline characteristics and these are provided in Table 6 of Appendix 3 (strictly confidential).

4. Other points of clarification in the draft guidance

- It is stated in section 3.5 that "the company's main clinical trial (MK-6482-004) included people who:
  - had at least 1 more measurable VHL-associated RCC only (could have other tumours), and
  - did not need imminent surgery and may have had pNETs or CNS Hbs."

  It would be clearer to bear in mind the relevant inclusion criteria of the MK-6482-004 study as provided in section B.2.3 of the company submission i.e. that:
  - Patients were included if they:
    - Had a diagnosis of VHL disease based on a germline VHL alteration.
    - Had at least 1 measurable solid RCC tumour and no RCC tumour greater than 3.0 cm that requires immediate surgical intervention.
    - Participants could have VHL disease-associated tumours in other organ systems.

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	○ Patients were excluded if they had an immediate need for surgical intervention for tumour treatment. • It is also stated in this section that "It also noted that MK-6482-004 was originally designed only to include people with VHL-associated RCC tumours. The occurrence of CNS Hbs and pNETs within the trial population was coincidental, but was granted marketing authorisation for RCC, CNS Hbs and pNETs." It would be wrong to describe the presence of other tumours (CNS Hbs and/or pNETs) in patients with VHL disease-associated RCC as "coincidental". VHL is a genetic disease that affects all the cells in a patient's body, and is therefore usual (rather than coincidental) for there to be the occurrence of multiple tumours at multiple sites of the body.
2b	**Comparator data** **Data now used to inform the comparator in the cost-effectiveness analyses** In order to address the NICE committee's concerns about the use of the VHL natural history-based indirect treatment comparison (ITC), the updated company cost-effectiveness analyses now use a base-case where the surgery rates in the comparator (SoC) arm are informed by data from the pre-treatment period of the MK-6482-004 study instead of the VHL natural history study and the MAIC conducted using it. Consequently, the VHL natural history study and any potential issues relating to the treatment effect for time to surgery estimated no longer have a meaningful impact on the cost-effectiveness analyses. Further details on how this relates to establishing relative treatment effect in the updated cost-effectiveness analyses are discussed in section 2d later in this table.
2c	**Outcomes** Section 3.8 of the draft guidance contains text that we think reflects some misunderstanding about the disease. These are clarified below, and it can be seen that the outcomes in the cost-effectiveness analyses are appropriate: • It is stated in section 3.8 of the draft guidance, with regard to outcomes measured in the studies and considered in the cost-effectiveness analyses/model, that "The committee noted that these outcomes are not the same as those used in standard NICE cancer topic evaluations". We would not expect outcomes in this unique ultra rare disease to have all the same outcomes used in a "standard NICE cancer topic evaluations". • It is stated in section 3.8 "Outcomes" of the draft guidance that the time to surgery outcome represented a highly heterogenous on "that is closely related to loss of organ or neurological function, which were not well characterised in the VHL natural history study. The committee concluded that there was

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	considerable uncertainty in eligibility criteria for MK-6482-004 and the VHL natural history study compared with the population of interest and more information may be required on outcomes that more closely match loss of organ or neurological function". The VHL natural history study is no longer used to inform this outcome in the revised cost-effectiveness analyses base case and so alignment of the populations/participant eligibility criteria between the MK-6482-004 study and the VHL natural history study is no longer a relevant issue. As this outcome data informing both the belzutifan and standard of care arms in the cost-effectiveness analysis now come from the same study, there is now also no issue with regard to alignment of population or outcome definitions (including e.g. with regard to whether they closely match loss of organ or neurological function) between these two arms. As detailed in previous sections, the population of the MK-6482-004 study (for which we have detailed as can be seen in Appendix 3) can also be considered to be appropriately representative of the population in the decision problem of this appraisal (i.e. the population as defined in the GB marketing authorisation for belzutifan), and so the outcomes sourced from that study and incorporated into the cost-effectiveness analyses are appropriate. **Profound benefit of treatment with belzutifan** It should be stressed that treatment with belzutifan has a profound impact on patients, as described in section B.2.6 of the company evidence submission. A comparison of the VHL disease-associated tumour-related surgeries patients in the MK-6482-004 study underwent before and after initiation of treatment with belzutifan showed that the frequency of VHL disease-associated surgeries in the time period after initiation of treatment with belzutifan radically lower than observed in the time period before, indicative of the transformational effect of belzutifan treatment on subsequent rate of VHL disease-associated surgeries (shown in Figure 12 in Appendix 8).
2d	**Establishing relative treatment effect** **Alternative methods of indirect treatment comparison between belzutifan and standard of care.** The base-case of the cost-effectiveness analyses has been updated such that it now uses data from the MK-6482-004 within-study comparison (i.e. the comparison of data from the pre-treatment period versus the study period) to inform the relative effectiveness of belzutifan versus standard of care (specifically in terms of the time-to-surgery in the RCC population) instead of the ITC, and so is no longer sensitive to the results of the ITC, regardless of what methodology is used for the ITC. Section 3.15 of the draft guidance document lists further analyses and exploration by the company on "the ITC approach and using the propensity-score weighting

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	method, which were highly uncertain, with alternative methods explored" as one of the things the committee would like to see. In particular, it is noted in section 3.9 of the draft guidance document that the committee "would also like to have seen alternative methods explored such as a simulated treatment comparison in line with NICE DSU Technical Support document 18". No additional ITC analyses using the simulated treatment comparison (STC) method have been conducted as these would be unlikely to be address the committee's uncertainties. As the underlying data to inform an STC-based ITC would be the same as that of the MAIC-based ITC, the results obtained would not be more robust. More importantly, such a STC-based ITC would, similar to the existing ITC, output results for a comparison of belzutifan versus standard of care in only the population of patients with characteristics analogous to that of the MK-6482-004 study, without providing any additional information on what would happen specifically in patients with characteristics matching those specified in belzutifan's marketing authorisation, which is the fundamental uncertainty in the clinical-effectiveness data noted by the committee. **Immediate surgery assumption** Section 3.9 notes that "the committee also considered this immediate surgery assumption too simplistic and not evidence based" and earlier in section 3.4 "noted that there may be intervals of 4 months between a tumour reaching the treatment threshold and the decision to proceed with surgery". The model has now been revised to remove the immediate surgery assumption and implement surgery at 4 months for the SoC arm; in consultation with clinicians, this was the longest possible interval for a patient who requires therapy to receive surgery (Appendix 1). This now means the model begins at the treatment decision point rather than the treatment initiation point. By label definition, patients "require therapy" and clinical expert opinion has informed that in the absence of belzutifan, these patients would undergo surgery which can result in life-changing consequences. We have accepted the committee's critique of the immediate surgery assumption and assumed the 4-month interval between reaching treatment threshold and the decision to proceed with surgery. Unfortunately, due to time constraints, we are unable to test alternative time periods as this interval is computationally incorporated as a binary option (immediate surgery vs. 4-month delay to surgery). This also addresses the committee's concern that MK-6482-004 trial excluded patients who required immediate surgery as such patients are no longer included in the economic model. **Points of clarification** Section 3.9 of the draft guidance contains some unclear/ambiguous language when describing the issues, for facilitate a clearer and more appropriate understanding of these issues, these are described and clarified below:

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	• It is stated with reference to the MAIC, that "After matching, this made it easy to compare outcomes because the populations were likely to be more balanced". It would be more correctly understood that this should mean that "After matching it is easier to compare outcomes between treatment with belzutifan and standard of care because the populations from which the adjusted outcomes data are now derived are now similar". • It is also stated that "The company compared the results of MK-6482-004 and collected data for the SoC arm of the cost-effectiveness model." It would be more correctly understood that this should mean that "In the company's cost-effectiveness model, the treatment effects of belzutifan were compared to that of standard of care using data from the MK-6482-004 study and re-weighted VHL Natural History Study data, respectively".
3	**ECONOMIC MODEL** Comments under this subsection address sections 3.10 to 3.14 of the draft guidance. **Summary of key points** • The heterogenous nature of disease and scarcity of data makes it difficult to build a comprehensive model; however, the key and relevant outcomes of VHL disease are captured: surgery, its sequelae, disease progression and risk of metastases and how these impact quality of life. • Surgery rates for SoC no longer rely on the ITC for the RCC cohort which was a source of uncertainty; it is now estimated from the pre-treatment period of the MK-6482-004 trial. • As requested by the committee, further exploratory analyses have been conducted for time on treatment and treatment effect waning with results presented in Appendix 7C. • The committee recommendation to use the multiplicative approach to applying disutility and revising the disutility estimate for dialysis has been accepted and the company base-case has been revised accordingly. • We have included our Manage Access Agreement Proposal in Appendix 4, should we be recommended into the Cancer Drugs Fund (CDF), in which we are committed to a number of data collection efforts. We have assumed we would need a data collection period of 5-years in line with preparatory discussions where this time period is expected to be required. • We recognise the uncertainty and have provided an updated PAS discount. Based on committee recommendations, the revised base-case ICER for the VHL-GB MA population is [redacted] with the updated PAS. A 1.7 severity modifier should apply for this indication indicating a threshold of £51,000 per QALY. Nevertheless, the revised company base-case and a under a range of relevant scenario analyses, ICERs remain robustly below a 1.2 severity modifier threshold of £36,000 per QALY.
3a	**Model structure and outputs** (Section 3.10)

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	In section 3.10 of the draft guidance document, it is stated that "The committee questioned the company for using a starting age of 41 years. This was because the marketing authorisation population was likely to have had many more surgeries and was much later in the treatment pathway." The starting age in the model uses the mean age from the MK-6482-004 trial which is appropriate for the marketing authorisation as evidenced by the detailed analyses of the patient baseline characteristics as explained in comment 2a. Section 3.10 also stated that "The EAG considered the company's model structure was appropriate for only the RCC cohort". We would like to distinguish here model structure issues from data issues. The model structure is appropriate for all cohorts, the data come from the MK-6482-004 study population who all had RCC. Some of the same population also concurrently had CNS Hbs and pNETs which are represented by the additional cohorts. The EAG also noted a high level of uncertainty, specifically "The rate of surgeries (moving from pre-surgery to surgery) was based on surgeries for the primary tumour. But it was not clear from the trial and the VHL natural history study whether the data used to specify these rates related to the treatment of primary tumour." To clarify, the rate of surgeries is specific to the relevant primary tumour for the respective cohort with these rates determined based on the efficacy of belzutifan on the primary tumour. Section 3.10 noted some committee considerations on the model structure that we will address in turn. The proportions receiving surgery were noted by the committee "the company assumed 90% of people with RCC in the standard care arm had immediate surgery. It also assumed that, in 80% of these people, the surgery would lead to end-stage renal disease or dialysis." Whilst these percentages may appear extreme, it is important to remember the population considered in this appraisal. Clinical experts have highlighted that belzutifan is reserved for patients "on the precipice of organ failure" and the very few patients they expect to be eligible for treatment. They acknowledge that when looking at the indication wording, it is helpful to invert it i.e., if a patient can have a localised procedure, they should. They confirmed that given the positioning and low patient numbers, high proportions receiving surgery and its sequelae are expected (Appendix 1). It is stated that "the committee considered the company's model was too complex to include all VHL cohorts". The company consider the model structure to be simple: – it is a Markov cohort model with death as the absorbing state and four alive health states: pre-surgery, surgery, event-free after surgery and metastatic disease. The event-free health state would be better named a non-metastatic health state. We accept that how the various transition probabilities are estimated and included is complex and would like to take the opportunity to provide a simple description (reflecting the updated base case). A tabulated summary of the transition probability approach is provided in Appendix 5. Figure 8 illustrates the model schematic. • Patients begin in the pre-surgery health state. Transition to surgery is estimated by time-to-surgery (TTS) applying an exponential distribution. For the belzutifan arm, the source is the MK-6482-004 study. For the SoC arm, the source for the first 4 months is the pre-treatment period. The marketing authorisation reflects

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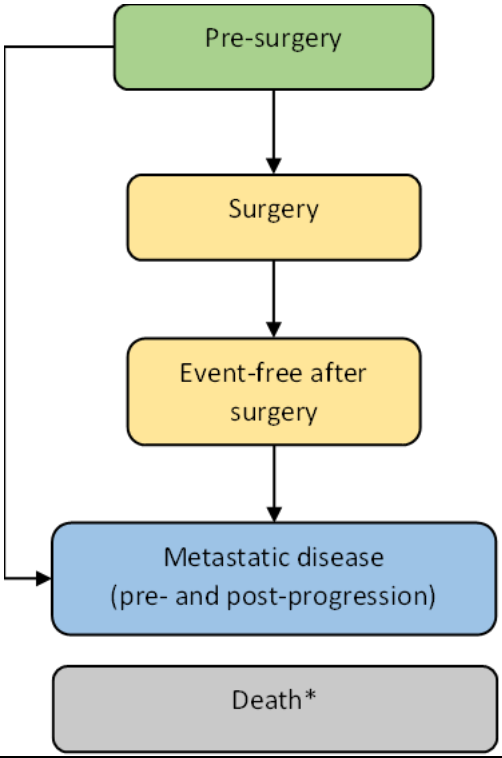
a population "who require therapy"; therefore, an assumption is made in the SoC arm at 4 months majority of patients move into the surgery state (see comment 2d).

- Transition from pre-surgery to metastatic disease for the SoC arm is estimated by time-to-metastases (TTM) applying an exponential distribution with the VHL Natural History Study as the source. Due to few events in MK-6482-004, the belzutifan arm is estimated using a hazard ratio approach assuming an equivalent treatment effect to surgery rates.
- Transition from pre-surgery to death for the SoC arm is estimated as the maximum of background mortality and VHL Natural History Study mortality. For the belzutifan arm, it uses the same method as the SoC arm; however, accounts for a CNS Hb mortality benefit using a hazard ratio approach assuming an equivalent treatment effect to surgery rates.
- Following surgery, patients enter the event-free after surgery state. Transition to metastatic disease and death are assumed equivalent to the respective pre-surgery transitions. There is an exception for the RCC cohort where the VHL Natural History study has data available, so time-to-event (TTE) data are used for the SoC arm for these event-free after surgery transitions. For the belzutifan arm, therefore, a hazard ratio approach is applied for the transition to metastatic disease in a similar method to the respective transition from the pre-surgery health state.

Figure 8 Model schematic for the economic evaluation of belzutifan in VHL-associated RCC, pNET or CNS Hb



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	*Transitions to death are possible from all health states. Arrows to the death state are omitted from the diagram for simplicity. Note: Analogous Markov cohort structures are used for each of the three tumour-specific populations (VHL-associated RCC, CNS Hb and pNET). In each of these populations, subsets of patients also have one or both of the other two tumour types. In the Markov model, the surgery states refer specifically to surgeries corresponding to the primary tumour type for each population. Costs and QALY decrements due other tumour types are modelled separately for each population and layered onto the costs and QALYs that are modelled accordingly to patients' Markov state residency over time. CNS Hb: central nervous system haemangioblastoma; pNET: pancreatic neuroendocrine tumour; RCC: renal cell carcinoma; QALY: quality adjusted life year; VHL: Von Hippel Lindau It is also stated that "The committee considered that the model included 3 cohorts with overlapping evidence and that the assumptions used in the model were not based on firm evidence". Evidence gaps are expected in an ultra-rare highly heterogenous disease. Throughout the process, we have continuously engaged with clinical experts to elicit evidence to aid modelling. It has been consistently difficult for them to make generalisations in such a heterogenous population in which they only care for a handful of these patients in their career. The overlapping evidence reflects the nature of VHL disease as patients have multiple tumours in different organs and are therefore rarely only in a single cohort. However, treatment decisions are usually driven by a dominant "primary" tumour; therefore, the 3 cohorts capture the differences in sequelae from a dominant "primary" tumour. We see this reflected in the trial evidence; for example, a patient with 5 prior partial nephrectomies and a brain stem located CNS Hb would mean they are in both the RCC and the CNS Hb cohorts despite being the same patient, but usually one of these would be driving the treatment decision. To reiterate, the cohorts represent the tumour types eligible for belzutifan treatment as indicated by the marketing authorisation. It is a limitation in the model that we cannot fully value multi-system disease over time. VHL disease is an ultra-rare genetic disorder with limited evidence and therefore requires assumptions to be made. This is somewhat complicated by the MHRA's marketing authorisation in comparison to the MK-6482-004 study population. Below we have categorised these assumptions into three groups: due to limited data, due to the marketing authorisation and due to model structure with the justifications and sources for each. *Assumptions due to limited data* • Treatment effect waning: As MK-6482-004 trial does not provide conclusive evidence of treatment effect waning and as belzutifan is a new first-in-class treatment, an assumption is made allowing treatment effect waning to occur from the end of the follow-up period using assuming growth rate for RCC tumours reverts to pre-treatment levels. This growth rate is estimated among patients in the MK-6482-004 trial. A similar assumption was made for CNS Hb & pNET cohorts due to the small sample size of discontinued patients in the CNS Hb and pNET subgroups who had an available CNS Hb and pNET measurement near to the time of treatment discontinuation (see comment 3c below). • Real-world SoC adjustment: Both the MK-482-004 trial and the VHL Natural History Study (which is now only used as a source of metastases rates in the revised base case assumptions) reflect an elevated SoC compared to normal UK practice as informed by clinical expert opinion (Reference 3 of

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	Document B). In these settings surgery rates were considered to be higher and hence metastases rates lower than would be expected in UK centres. Adjustments were made to metastases rates in both arms to reflect this. *Assumptions due to the marketing authorisation* • Positioning: Surgery for primary tumour is 'last resort' resulting in loss of organ function and/or problematic sequelae per the marketing authorisation "localised procedures are unsuitable or undesirable". This is supported by clinical experts as noted in section 3.3 of the draft guidance. • SoC arm receiving surgery: The label wording specifies patients "who require therapy"; clinical experts note that in the absence of belzutifan, this therapy is surgery. By definition, all patients in the comparator arm should receive surgery. Clinical experts note the high proportion who receive surgery but stated it is reasonable given the positioning and the very low numbers expected to be eligible for treatment (Appendix 1). • Treatment decision to treatment initiation interval for SoC: As stated in comment 2d, based on committee recommendations and clinical expert elicitation (Appendix 1) an interval maximum of 4 months has been implemented into the revised base-case. • Risk of complications: Risk of perioperative mortality, surgical complications and metabolic consequences have been validated by clinical experts in prior engagements (see *ID3932 Stakeholder engagement response form - MSD v1.0 (CIC)*) and was discussed again at recent engagements with clinical experts (Appendix 1). In the context of the positioning of the patient population, these were deemed appropriate. *Assumptions due to the model structure* • Use of three cohorts: Our response to technical engagement (*ID3932 Stakeholder engagement response form - MSD v1.0 (CIC)*) details how the final marketing authorisation was reached and how the model was subsequently adapted. Three cohorts are used to represent the three tumour types in the marketing authorisation and reflect the relevant outcomes and unique characteristics of sequelae for the different types of tumour manifestation. This assumption means that the full nature of multi-system disease is not captured and therefore value of belzutifan is underestimated. It is also stated that the committee "would have preferred to see a model structure based on the natural history of VHL disease rather than individual tumours and the surgery associated with them." As stated above, the model distinguishes between tumour types to reflect the relevant sequelae associated with the different types of tumour manifestation defined in the marketing authorisation. Based on the available data, modelling separate overlapping cohorts of patients required fewer assumptions and adjustments to estimate parameter inputs than modelling a combined cohort, allowing for a more transparent and data-driven model. The expansion of the indication wording that specifies VHL-associated CNS Hb and pNET posed challenges for creating a combined cohort as there were no patient-level datasets or literature sources available to directly estimate clinical inputs for a combined cohort of patients with only VHL-related RCC, CNS Hb or pNET, particularly for the belzutifan arm. Given the data constraints, modelling three

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	separate overlapping cohorts had the following key advantages over a single combined cohort: 1. Modelling three separate cohorts allows the model to account for the expectation of the distribution of the tumour driving treatment decisions across the three tumour types in the UK. Clinical expert elicitation has informed the weighting of the cohorts based on the tumour burden/driver in the target population they intend to treat. Modelling a single combined cohort would not account for this distribution nor the expectation that one tumour type, that is not suitable for surgery, is the one driving the treatment decision. 2. It is important to consider belzutifan's mechanism of action in the model design. Belzutifan targets the HIF-2α protein in which levels are raised in patients with VHL disease leading to tumour growth; however, it does not treat the underlying cause of VHL disease. Therefore, it is more appropriate to model belzutifan's outcomes based on the VHL-associated tumours rather than VHL disease itself. The critique on the model structure made us reflect on the original model concept and the relevant outcomes for VHL disease which are: surgery, its sequelae, disease progression and risk of metastases, and how these impact quality of life. The key benefits of belzutifan are these outcomes: avoid or delay surgery and therefore the consequences of surgery, delay growth of tumours and progression to metastases, and improve quality of life. Acknowledging the model structure is not based on the natural history of VHL disease, it is important to recognise that all the relevant and most impactful outcomes are captured in the economic model and therefore the model remains appropriate for decision-making. Finally, it is stated that the committee "noted that the relative efficacy derived from the ITC introduced additional uncertainty…". As mentioned above, we have taken a more simplistic approach and restricted use of the MAIC to post-surgery transitions only. The relative efficacy on surgery rates is now based on the pre-treatment period for all three cohorts.
3b	**Time on treatment** (Section 3.11) In section 3.11, it is stated that "the committee concluded it would have preferred to see the modelling using belzutifan continued until progression or until side effects because this would more closely match the target population". We would like to reiterate that VHL-disease is not a typical cancer where treatment and progression are inherently linked. In VHL-disease, progression is non-linear, and the disease is characterised and impacted more so by surgical outcomes than metastases. Therefore, modelling time on treatment for belzutifan until progression is not appropriate for this genetic disorder. Nevertheless, modelled time on treatment (ToT) based on progression-free survival (PFS) has now been included in the model. A full description of its implementation in the economic model is provided in Appendix 7A. This scenario results in an ICER estimate of [redacted] per QALY which is below the appropriate £51,000 per QALY threshold and marginally above a £36,000 per QALY threshold. Modelling time on treatment until side effects was not

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	feasible in the timeframe to provide these responses as it was not a pre-specified analysis in the trial.
3c	**Treatment waning** (Section 3.12) In section 3.12, it is noted that "the EAG explained that the duration of assumed residual benefit over a period of 2.71 years might be appropriate for RCC but could be different for CNS Hbs and pNETs" and the committee "reiterated that there were concerns around the generalisability of the data for the population of interest". The treatment effect waning period for the CNS Hb and pNET cohorts were assumed to be equivalent to the RCC cohort due to the small sample size of discontinued patients in the CNS Hb and pNET subgroups in the MK-6482-004 study who had an available CNS Hb and pNET measurement near to the time of treatment discontinuation. Critically, clinicians found the CNS Hb response particularly compelling and found significant value in that. They agree that the approach to treatment effect waning is plausible for CNS Hb and pNET. We have conducted further sensitivity analyses and testing alternative assumptions of the treatment effect waning period in the CNS Hb and pNET cohorts. This is reported in Appendix 7C and ICER estimates range from [redacted] to [redacted]. These estimates are well below the appropriate £51,000 per QALY threshold and the maximum ICER is just above the £36,000 per QALY threshold. To reiterate, treatment effect waning cannot begin earlier than the trial follow-up period as this already accounts for discontinuation and potential loss of treatment effect that occurs during the trial period.
3d	**Health-related quality of life** (Section 3.13) In section 3.13, it is noted that the committee prefers the multiplicative method for combining disutilities in line with the NICE manual. We acknowledge this preference and have applied this approach. A full description of its application in the economic model is provided in Appendix 7A. It is also noted that the committee agreed that the approach to deduct the disutility value for end-stage renal disease (ESRD)/dialysis from a quality of life from 1 was not appropriate and suggested a more appropriate approach would be to compare an absolute estimate of utility on dialysis with an age- and sex-matched expectation from the general population. We acknowledge this and apologise for this error. We have corrected the approach and deducted from an age- and sex-matched general population disutility as recommended. This results in a utility ratio of 0.44 using the multiplicative approach (ratio of utility with dialysis versus without dialysis) which is consistent with the UK estimate reported in Cooper et al. (2020), an SLR of HRQoL utility weights for economic evaluation through different stages of chronic kidney disease (1). (Note: this approach was also implemented to correct the disutility associated with short-term erythroderma, no other disutilities were deducted from 1). The multiplicative approach to combining disutilities and the corrected calculated disutilities have been implemented in the revised company base-case ICER of [redacted]

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	[redacted] which is below the threshold even where a 1.2 severity modifier (£36,000 per QALY threshold) is assumed. Section 3.13 of the draft guidance points to disutility estimates for dialysis in NICE's guidelines on renal replacement therapy and conservative management and chronic kidney disease. We could not find a utility/disutility estimate reported in the guidelines for chronic kidney disease; however, we found a utility estimate in the guidelines for renal replacement therapy and conservative management (2). This reports a utility value whilst alive on haemodialysis (HD) or haemodiafiltration (HDF) of 0.56. Based on clinical expert elicitation (Appendix 1), this estimate is higher than what is expected as it does not account for VHL disease. Nevertheless, use of this estimate was tested in scenario analysis producing an ICER of [redacted] which is below a threshold of £36,000 per QALY where a 1.2 severity modifier is assumed.
3e	**Severity** (Section 3.14) It is stated that the committee may apply a greater weight to QALYs if technologies are indicated for conditions with a high degree of severity. Following changes to the company base-case, the absolute and proportional QALY shortfall estimates have been recalculated and are reported in Appendix 6. The company position remains that a severity weight of 1.7 should apply to the population eligible for treatment in GB under the MHRA indication. Section 3.2 of the draft guidance notes the outcomes faced by patients with VHL disease; for example, the need for lifelong medical intervention such as dialysis or paralysis following brain or spine surgery. With the high likelihood of such outcomes in the target population, it is inconceivable that a disease this debilitating should qualify for anything other than the 1.7 severity modifier. It is noted that "The committee concluded it was unable to apply an appropriate severity weight based on the calculations presented by the company because of uncertainty in its underlying assumptions". Any uncertainty in the data to determine this absolutely does not equate to evidence that the disease and specifically the indicated population have less severe disease. Application of anything other than the 1.7 modifier should be considered unreasonable and unfair in the light of the patients' lived experiences. The NICE methods guide states that modifiers that cannot be included in the estimated QALYs "*can be taken into account **qualitatively through committee discussion** or quantitatively through QALY weighting*" (paragraph 6.2.11). We ask that the committee view this technology through a rare disease lens. Although calculations may appear to produce a lower QALY weight, evidence around the severity of disease in the patient population clearly demonstrates that it would meet the highest severity modifier. We ask that the committee take particular consideration to the rarity and heterogeneity of this disease and the challenges in

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	capturing its full impact on patients, noting this is also a highly innovative technology. Lastly, we note that this appraisal has been through the process to be routed via HST on multiple occasions. The final criteria checklist undoubtedly confirms the rarity and severity of this disease as defined by the TSOP with the following criteria met: • Normally no more than 300 people in England are eligible for the technology in its licensed indication and no more than 500 across all its indications. • The very rare disease for which the technology is indicated significant shortens life or severely impairs quality of life. Against a decision-making threshold of £51,000 per QALY (reflecting a 1.7 severity modifier), with this technology appraisal reporting an ICER of [redacted] below a threshold of £36,000 per QALY (reflecting a 1.2 severity modifier), MSD considers it offers profound value for the NHS and that the uncertainty has been addressed in the value proposition. [redacted]
4	**COST-EFFECTIVENESS ESTIMATES** Comments under this subsection address sections 3.15 and 3.16 of the draft guidance.
4a	**Uncertainties in the evidence and company's modelling assumptions** (Section 3.15) Section 3.15 of the draft guidance document lists the further analyses and exploration by the company that the committee would like to see. These are reproduced below and direct to the relevant comments above. • *the evidence for the generalisability of the MK-6482-004 population to the marketing authorisation population (see section 3.5)* As outlined in comment 2a above, individual patient data analyses on patient's baseline characteristics and prior procedural history were conducted to indicate generalisability of the MK-6482-004 population to the marketing authorisation population. This is further corroborated by clinical expert opinion (Appendix 1). • *the ITC approach and using the propensity-score weighting method, which were highly uncertain, with alternative methods explored (see section 3.9)* Please see comment 2d above for justification of the ITC approach. The base-case model assumption for surgery risk in the RCC cohort under SoC has now been revised from the MAIC to the pre-treatment period of the MK-6284-004 trial to address the committee's concerns around the uncertainty of the MAIC. We acknowledge that establishing relative efficacy for a highly heterogenous and imperfect data set using a MAIC introduces additional uncertainty, and a more

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	simplistic approach of a within-trial comparison can produce more reliable results for decision making. • *the uncertainty in the model input parameters and assumptions and uncertainties in the model outputs (see section 3.10)* Please see comment 3a which addresses uncertainty in model input parameters and assumptions. As previously outlined, further clinical expert elicitation was conducted which corroborated these assumptions and validated model outputs (Appendix 1). • *modelled time on treatment for belzutifan until progression or until side effects (see section 3.11)* Please see comment 3b for further discussion on the modelled time on treatment and Appendix 7C for the explored modelling based on PFS. • *extensive sensitivity analyses and testing alternative assumptions on the treatment waning effect across the tumour types (see section 3.12)* Please see comment 3c for further discussion on treatment effect waning and Appendix 7C for further sensitivity analyses. • *the uncertainty in the company's approach to surgery-associated disutility values, with an exploration of the multiplicative approach and use of validated disutility values against literature for similar outcomes (see section 3.13).* Please see comment 3d for further discussion around health-related quality of life estimates and description of the revised approach.
4b	**Summary of updated company cost-effectiveness analysis base-case.** A full description of updates to the economic model is provided in Appendix 7A. In summary, the company base-case has been revised with the following: • Immediate surgery removed; surgery now occurs at 4 months in the SoC arm • TTS for RCC cohort in SoC arm now based on pre-treatment period rather than VHL Natural History Study (MAIC) • Revised disutility for ESRD/dialysis (and erythroderma) • Disutilities applied using a multiplicative approach. • Cohort weighting based on clinical expert elicitation. These revisions produce a revised base-case ICER of [redacted] (not adjusted for severity weighting). Scenario analyses ICER results range from [redacted] to [redacted] (not adjusted for severity weighting). The revised base-case ICER is well below the appropriate £51,000 per QALY threshold (reflecting a 1.7 severity modifier) and also below a £36,000 per QALY threshold (where a 1.2 severity modifier is

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	assumed). The ICER remains robustly below a £36,000 per QALY threshold across a range of scenarios. 6 out of 20 scenarios have an ICER above this threshold but these are considered more extreme scenarios and still remain under the appropriate £51,000 per QALY threshold. Full results are reported in Appendix 7 alongside sensitivity and scenario analyses. **Social care costs** During our consultation with clinical experts (Appendix 1), the dominance of VHL CNS Hb in the label population has become more apparent. Additionally, the risk of paralysis either from surgery or from tumour burden has also been highlighted. Therefore, we have identified the social care cost associated with neurological complications akin to paralysis may not have been fully captured. Using estimates of home care hours and costs from McDaid et al. (2019), an economic analysis of spinal cord injuries in the UK (3), we have incorporated these costs in scenario analysis. The ICERs when assuming social care costs of neurological complications akin to tetraplegia or paraplegia show dominance (costs of belzutifan are fewer and QALYs greater when compared with SoC). We acknowledge not every CNS Hb patient suffers such extreme consequences, but for the few that are likely to, belzutifan offers significant value. When considering spinal cord D injuries, a scenario more representative of the average CNS Hb population, the ICER is [redacted]. (Note: An ASIA impairment scale score of D describes incomplete injury with partial motor function. Those with AIS D have full range of motion against gravity for at least half of the key muscle functions below level of injury). **Validation of model outcomes** After implementing the changes recommended by clinical experts into the revised company base-case, namely the 4-month time interval delay to surgery on SoC and the distribution of weighting across the 3 cohorts with CNS Hb as the majority, outcomes were validated on a subsequent call (see Appendix 1). The expert aligned with the positioning reiterating the small patient numbers. He also agreed with the proportions who receive surgery at 4 months in SoC and the risks of the metabolic consequences of surgery. He stated that whilst these proportions and risks may appear high, they are reasonable in the context of the very small number of patients included in the label. When presenting the life years gained as an output from the model, the expert highlighted that particularly for the CNS Hb cohort in SoC these are likely at the upper end of survival expectations. A limitation of the model is that OS cannot be directly adjusted as it is an output rather than an input of the model; due to time constraints we were not able to make this amendment to the model. However, we expect the impact of lower survival for the CNS Hb cohort in SoC to provide increased value to belzutifan and produce a lower ICER estimate. Average utility values were also presented to the expert; the expert highlighted that utility is expected to be very low in SoC particularly with CNS Hb. This is expected to decline over time as life expectancy shortens. He also highlighted that utility for the RCC cohort should account for ESRD/dialysis and additional considerations of VHL disease.

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4c	**Cancer Drugs Fund** (Section 3.16) In order to address the concerns raised by the committee (as described in section 3.16 of the draft guidance) with regard to their uncertainty on whether the Cancer Drugs fund may provide the opportunity to collect additional data to address the issues of belzutifan's comparative effectiveness with standard of care, a revised Cancer Drugs Fund (CDF) Managed Access Agreement (MAA) proposal has now been submitted (shown in Appendix 4, comments have been left in as this version of the MAA proposal has not been finalised between MSD and NHSE). In line with preparatory discussions that have occurred with the NHS England Managed Access team, a 5-year managed access period is expected to be required in this case to address the relevant uncertainties. Information on patients treated with belzutifan and the outcomes of such treatment will be collected: • As part of Systemic Anti-Cancer Therapy (SACT) data collection during the CDF period. • In the prospective patient registry non-intervention post-authorisation study to be set up as a condition of marketing authorisation (4). The two activities described above focus on collection of data on patients treated with belzutifan, without necessary providing any additional information on patients managed with current SoC (i.e. the comparator for CDF exit technology assessment). For any remaining data required on current SoC that are not collected in the two activities described above, MSD commits to: • Conducting a thorough retrospective case note review of all patients who start treatment with belzutifan during the CDF period to ascertain the nature and outcomes of disease management prior to the introduction of belzutifan. • Working with UK centres specialising in the management of patients of VHL disease to conduct a comprehensive retrospective analysis of UK VHL disease patients to ascertain their natural history. The outputs of the ongoing MK-6482-004 study, NHS Digital routine population-wide cancer data collection (including SACT data collection), the prospective patient registry non-intervention post-authorisation study, as well as the additional data collection efforts committed to, will provide robust information for future cost-effectiveness analyses (when belzutifan would exit the CDF) to address the uncertainties that have been identified during this appraisal including: • The baseline characteristics of patients eligible for belzutifan treatment in England in the MHRA licensed population, including distribution of patients across those with RCC/pNET/CNS Hb.

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	• Duration of belzutifan treatment in the MHRA licensed population. • Longer-term effectiveness and safety of belzutifan in the MHRA licensed population. • The outcomes (i.e. rate of surgery, rate of metastasis, etc.) associated with UK standard of care in the MHRA licensed population.
5	**OTHER FACTORS** Comments under this subsection address sections 3.17 to 3.19 of the draft guidance.
5a	**Rarity of disease and applying greater flexibility** (Section 3.17) MSD believes belzutifan should have been assessed against the Highly Specialised Technology (HST) incremental cost-effectiveness ratio threshold of £100,000. Despite the NICE Topic Selection Oversight Panel (TSOP) determining in 2022 that belzutifan in this indication did not meet the criteria for routing into the HST programme MSD disagrees with the conclusion on the basis that the published description of the rationale for NICE TSOP's decision making (https://www.nice.org.uk/guidance/gid-ta10817/documents/supporting-documentation), shows that the determination was made erroneously based on misunderstanding of the epidemiology, burden, and nature of the current treatment pathway of VHL disease and the specific indication relevant to belzutifan. The HST threshold is higher than the Single Technology Appraisal (STA) threshold; the HST committee is more experienced in handling small datasets, gaps in data, and integration of patient evidence into decision making. Given this is being reviewed as STA, uncertainty flexibility should be applied, as stated in the NICE manual regarding structured decision making (paragraph 6.2.34): "*The committee will be mindful that there are certain technologies or populations for which evidence generation is particularly difficult because they are:* ***rare disease****, for use in a population that is predominantly children (under 18 years old),* ***innovative*** *and complex technologies. In these specific circumstances, the committee may be able to make recommendations accepting a higher degree of uncertainty. The committee will consider how the nature of the condition or technology(s) affects the ability to generate high-quality evidence before applying greater flexibility.*" The significance of this product being assessed in the wrong process for patients should not be underestimated.

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5b	**Equalities** (Section 3.18) It should be noted that belzutifan for this indication is already available to patients living in Scotland after it was accepted for use within NHS Scotland following assessment by the Scottish Medicines Consortium (SMC) in October 2023 (5). That patients in England and Wales do not have access to this treatment while patients in Scotland do constitute a source of inequality.
5c	**Innovation** (Section 3.19) It should also be noted that belzutifan is a first-in-class treatment that works via a novel mechanism of action (inhibition of hypoxia-inducible factor alpha [HIF-2α]) that was elucidated via Nobel Prize-winning scientific research (6). As this is an entirely new mode of treatment, there may be as yet unknown additional benefits to treatment with belzutifan which are yet to become apparent that have not been considered.

Insert extra rows as needed

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Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is [redacted] and information that is [redacted]. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

References

1. Cooper JT, Lloyd A, Sanchez JJG, Sorstadius E, Briggs A, McFarlane P. Health related quality of life utility weights for economic evaluation through different stages of chronic kidney disease: a systematic literature review. Health Qual Life Outcomes. 2020;18(1):310.
2. NICE. RRT and conservative management - Cost-effectiveness analysis: HDF versus high flux HD - NICE Guideline NG107. Economic analysis report [Internet]. 2018. Available from: https://www.nice.org.uk/guidance/ng107/evidence/costeffectiveness-analysis-hdf-versus-highflux-hd-report-pdf-6543882397.
3. McDaid D, Park AL, Gall A, Purcell M, Bacon M. Understanding and modelling the economic impact of spinal cord injuries in the United Kingdom. Spinal Cord. 2019;57(9):778-88.

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4. MHRA. Welireg 40 mg film-coated tablets (belzutifan) - Public Assessment Report2022. Available from: https://products.mhra.gov.uk/product/?product=WELIREG.
5. SMC. belzutifan (Welireg) - SMC25872023. Available from: https://www.scottishmedicines.org.uk/medicines-advice/belzutifan-welireg-full-smc2587/.
6. Nobel Foundation. 2019 Nobel Prize in Physiology or Medicine2019. Available from: https://www.nobelprize.org/uploads/2019/10/press-medicine2019.pdf.

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Appendix 1: Additional clinical expert input elicitation

Background

To address some of the gaps highlighted in the appraisal committee document it was deemed necessary to carry out an informal clinical elicitation exercise to seek expert input and advice to address some of the key issues raised after the first Appraisal Committee Meeting and validate some of the assumptions and outputs documented so far in the process.

Given the short timeframe and imminent deadline a full Structured Expert Elicitation Resource (STEER) /Sheffield Elicitation Framework (SHELF) was not feasible. To meet the needs of the NICE appraisal process, MSD utilised a structured survey method. The structured survey asked clinicians three key questions (**Table 1**). Given the highly heterogenous nature of the disease and the multi-disciplinary nature of its management, MSD reached out to wide range of clinical experts as part of the survey via email. Out of 15 clinical experts asked, 9 responded to the survey. The breakdown of clinical expert specialties is presented in **Table 2**. These responses were then validated via a virtual teleconference call with two clinical experts who are the service leads for the largest VHL clinics in the UK. Following this validation call, MSD implemented the validated clinical expert input into the model with the intent of validating the new model outcomes with a clinical expert. MSD validated these updated outcomes in a subsequent virtual teleconference with one of the VHL clinical experts on the previous call.

Table 1 Questions asked to clinical experts in structured survey.

No.	Question
1	Please describe the patients who you would like to treat with belzutifan. Why do you want to treat these specific patients?
2	Of the patients that you would like to treat with belzutifan, which is the tumour driving this decision? CNS Hb, pNET or RCC? Why is this tumour driving a preference to treat with belzutifan? (In your practice what is the % split of VHL patients by these three 'primary' tumour types. Note, we use primary tumour here to mean tumour driving treatment decision making)
3	If these patients do not receive treatment with belzutifan, what is the likely course of their disease? Please reference any similar patients you may have treated in the past.

Table 2 Breakdown of clinical expert specialties

Specialty/Position	No. of respondents
Endocrinologists/ Professors of endocrinology	2
Neurosurgeon/Neuro-oncologist	2
Urologist/ Oncologists	1
Consultant Geneticists/ Genetic counsellors	4

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Specialty/Position	No. of respondents
VHL service leads (overlap with the above specialties)	4

The aforementioned clinicians granted permission for their insights to be shared with NICE as part of the ongoing process. The raw written responses to the survey are presented in Appendix 1A below. Following the validation call, a summary of meeting minutes was shared with the two clinical experts. The summary shared with the experts are presented in Appendix 1B. The summary of the final validation call, in which updated model outcomes were validated with a clinical expert can be seen in Appendix 1C.

Summary of Survey Outputs

Question 1: Please describe the patients who you would like to treat with belzutifan. Why do you want to treat these specific patients?

In response to the first question most respondents agreed that they would want to treat patients who were on the cusp of organ failure or loss and that this would be in a very small group of their VHL patients. The clinicians strongly felt that surgery and localised treatment would remain the main option for the vast majority of VHL patients requiring therapy. This was consistent amongst the different tumour types. Patients who could no longer undergo further surgical or local interventions including radiotherapy and ablation were described as the patients' clinicians would want to treat with belzutifan.

The justification for this in the survey was consistently due to organ failure/loss or further surgical intervention being associated with significant morbidity and mortality both during and following the procedures. For example, from a CNS Haemangioblastoma (CNS Hb) perspective, clinicians will always look to and do treat patients through multiple rounds of neurosurgery and stereotactic radiosurgery. However, for a proportion of patients there comes a time where both these modalities are no longer an option due to the declining risk/benefit ratio, multiple small tumours in a single organ that require multiple procedures, increased risk of surgery or radiation related brain injury, neurological deficit, and premature death. In such patients there isn't a therapeutic option and both neurosurgeons, and neuro-oncologists highlighted that these would be the patients they would want to treat with belzutifan.

Another cohort of patients highlighted by the clinicians were those with multi-systemic VHL disease (i.e., with ≥2 organs affected with VHL related tumours e.g., a patient with both a pNET and CNS Hb). Respondents highlighted the fact that this cohort of patients would require multiple interventions over multiple NHS departments, an action that would leave them with a much poorer quality of life, inability to care for family members with VHL and an inability to contribute to the work economy.

Belzutifan use in the multi-systemic disease patients was desired for these patients due to its potential to prevent deterioration across multiple organ systems whilst simultaneously greatly reducing the burden on the NHS of their care.

Question 2: **Of the patients that you would like to treat with belzutifan, which is the tumour driving this decision? CNS Hb, pNET or RCC? Why is this tumour driving a preference to treat with belzutifan? (In your practice what is the % split of VHL patients by these three 'primary'**

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tumour types. Note, we use primary tumour here to mean tumour driving treatment decision making)

Multiple clinicians highlighted the multi-systemic disease VHL patient in response to this question, they considered this a 4th group, in addition to CNS Hb, pNET and RCC driven disease. Some clinicians felt that multi-systemic disease rather than a "primary" tumour drove this decision due to impact on disability and multi-departmental procedures. Many clinicians did respond stating that CNS Hb tumours tended to be the 'primary' tumour due to it tending to lead to the greatest disability in terms of interventions required and impact on quality of life and ability to work. Respondents reported looking through the patient data within their own service before answering this question. Some responses went into more specificity and stated the most common indication was multiple CNS Hbs that had required multiple surgeries in the past but the patients still had multiple brain lesions which, if they progressed, further surgical intervention was likely to be hazardous. Spinal and brainstem CNS Hbs were specifically called out as the biggest driver for treatment decisions in practice in multiple responses.

It also became apparent from the responses that most of the multi-systemic disease VHL patients were afflicted with a CNS tumour as part of their multi-systemic disease presentation.

The VHL service leads involved also shared a breakdown of their patient populations across the 3 'primary' tumours included in belzutifan's license. On average, the % split across the respondents was:

Multi-systemic/multi-site disease: 40-50%

CNS Haemangioblastoma: 40-50%

Renal Cell Carcinoma: 10-15%

Pancreatic Neuroendocrine Tumours: 5%

Retinal Haemangioblastoma (note clinicians are aware this is not within scope of belzutifan's license): 5%

Note the above does not round up to 100% and is a rough estimate from the clinicians due to the difficulty in being precise about which tumours would be a major driver. These numbers were further validated with 2 service leads of the largest VHL services in the UK and their response can be seen below.

Question 3: If these patients do not receive treatment with belzutifan, what is the likely course of their disease? Please reference any similar patients you may have treated in the past.

Responses to this question were also consistent. Clinicians highlighted a lack of therapeutic options for the patients they would treat with belzutifan. They detailed the progression of the disease in this specific scenario, the depreciating quality of life and the need to undergo increasingly 'risky' surgery. It was clear from the responses that treatment decisions were made via shared decision making processes between treating clinician and patient, with a clinician responding that despite the great risk associated with surgical intervention for this specific cohort (e.g. excessively likely they will not survive the procedure, significant morbidity), that they still often recommend intervention over surveillance and patients typically agree.

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The clinical experts also emphasised that the outcome for these patients is usually progressive motor decline resulting in the need for care with all activities of daily living and eventually death from hydrocephalus, other manifestations of VHL or infectious consequences of immobility. A clinician highlighted that the goal of treatment would not only be to prolong life but also to prolong independence and delay need for costly care and social care. Respondents believed that the speed of decline may vary but that it is often inevitable for the specific patients the clinicians would like to treat with belzutifan. A significant decline in mental health and uptake of risky health behaviour was also cited.

For pNET driven disease, patients would likely develop brittle or Type 3c diabetes, be at greater risk of infection, develop severe gastrointestinal complications, require long inpatient stays and intense diabetes follow up. From an RCC perspective, clinicians felt without treatment there was a high likelihood of metastatic disease or dialysis/renal replacement therapy, linked by the respondents to a higher likelihood of death within 5 years.

Another response explained how these patients will often go on to develop multi-system disease involving the CNS, eyes, pancreas, and kidneys. They would then require multiple procedures across neurosurgeons, urologists, interventional radiology, ophthalmology which significantly impacts on the patients ability to work and contributes to great disability in the long term due to the progressive nature of the disease and its management.

The clinicians shared some short anonymous vignettes on patients in their practice they thought were relevant to the discussion. These can be seen in the appendices.

Summary of Validation meeting

On 15th December 2024, MSD engaged with two VHL clinical experts to validate the outcomes and findings from the clinician 'survey' carried out in the weeks prior. This was to gauge how representative these survey findings were and to validate the quantification and assumptions inferred from the responses. The VHL experts lead the two largest VHL clinics in the UK with approximately 100 and 60 patients respectively. A full summary of the meeting can be seen in Appendix 1B. Some key points raised in the meeting.

- A 4-month time interval is reasonable but would generally be considered the maximum waiting time between decision to operate and surgery in current practice.
- Describing the patients they would like to treat with belzutifan: Patients with a local problem should have a local solution. Belzutifan reserved for those on the precipice of organ failure.
    - From their own practice they would use belzutifan in approximately 3% of patients (Of 60 patients in practice, would use belzutifan for maybe 2-3 patients and of 100 patients in practice, would use belzutifan for maybe 3 patients)
- Perspective on what would happen to the ~3% of patient in whom they would consider belzutifan, their perspective was in keeping with the clinical experts involved in the survey. Highlighted catastrophic metabolic syndromes, patients becoming paraplegic and premature death.
- Agreed with survey responses that CNS Hb is highly influential in treatment decision making in practice and that majority of multi-system disease includes CNS Hb presentation.
- Described the expected distribution of those prescribed belzutifan due to RCC, CNS Hb or pNET being 80% multi-system disease driven by CNS Hb, 15% RCC and 5% pNET as reasonable.

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Summary of Updated Model Outcome Validation meeting

On 8th January 2024, MSD engaged a clinical expert from the previous teleconference call to validate the updated model outcomes. Following the meeting on the 15th December 2024, MSD implemented the validated survey responses and suggestions from the 2 clinical experts on the teleconference call into the health economic model. The new model outcomes following this implementation were discussed in this meeting, some key points:

- Clinical expert was in alignment with belzutifan positioning stressing that they would only consider belzutifan in a small specific minority of patients. The agreed with the shorthand for the label indication: if a patient can have a local procedure they should, belzutifan is reserved for those who cannot.
- Clinical expert was in agreement with model transitions to surgery on SoC and its complications. He highlighted that whilst proportions receiving surgery and therefore metabolic complications seem high, they are reasonable in the context of the label population.
- Expert queried whether gastrointestinal complications such as malnutrition and 'dumping syndrome' had been considered following a Whipple's procedure in the pNET cohort
- On model outcomes, life years expectancy for the SoC CNS Hb patient seemed higher than expected given the specific patients in whom the expert would consider belzutifan. Clinician explained that model estimates are likely at the upper-end of survival
- When discussing quality of life, the clinician highlighted that he would expect this to be better with belzutifan than on SoC
- He also highlighted the variability/heterogeneity inherent in VHL disease and how it is challenging to model an "average" patient, particularly given the very small number of patients.

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Appendix 1A: Raw Survey responses

Respondent: Consultant Geneticist/supra-regional service lead

1) Please describe the patients who you would like to treat with belzutifan. Why do you want to treat these specific patients?
So whilst the LIFESPARK-004 trial focused on VHGL patients with RCC, I think that in the vast majority of VHL patients with a RCC surgery would remain the main option. However, [the] situation in which you would like to have belzutifan as an option would be:

1. Patients requiring partial nephrectomy or ablative therapy with renal impairment and who would require renal replacement therapy post treatment – especially if there are other health issues that mean anticoagulation for haemodialysis is contraindicated or there are contraindications to peritoneal dialysis (previous abdominal surgery etc)
2. Patients with pancreatic NETs who would require major surgery (Whipple procedure) whose general health is poor and would tolerate surgery or post-operative complications (diabetes, malabsorption) poorly – again particularly if there are other VHL-related tumours that also needed treatment
3. Brain stem and spinal haemangioblastomas – these are often very hazardous to treat by surgery and if multiple the results of surgery are often poor.
4. Recurrent cerebellar haemangioblastomas – isolated cerebellar lesions are generally amenable to treatment but many patients go on to have recurrent tumours and require multiple cranial surgeries. This makes surgery more hazardous and increases the risk of neurological deficit. As with brain stem and spinal haemangioblastomas, patients who are left with neurological disability have a impaired quality of life/premature death but also can require care packages that are a major financial burden
5. Whilst most retinal angiomas will be treated by laser, if optic disc lesion(s) are difficult to treat because of treatment induced optic nerve damage causing vision loss (I was contacted about a case like this a couple of months ago)
6. VHL with metastatic RCC or PNET – particularly if they have other tumours – it can be argued that the clinical trial evidence for this use isn't yet available the scientific rationale for having it as a treatment option is strong

2) Of the patients that you would like to treat with belzutifan, which is the tumour driving this decision? CNS Hb, pNET or RCC? Why is this tumour driving a preference to treat with belzutifan. (In your practice what is the % split of VHL patients by these three 'primary' tumour types. Note, we use primary tumour here to mean *tumour driving treatment decision making)*
It is difficult to be precise about which tumours would be the major indication but perhaps multisite 40-50%; CNS haemangioblastomas 40-50%; renal 10-15%, retinal 5%

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3) If these patients do not receive treatment with belzutifan, what is the likely course of their disease? Please reference any similar patients you may have treated in the past.

I'm planning to go through the VHL patients in Birmingham (largest VHL clinic) to see if we can be more precise.

4) (Additional follow up question) **What is the rough size of your current VHL patient population in your practice and roughly how many of these patients would you want to treat with/ do you think would be eligible for belzutifan?**

Number of patients in VHL service - ~100 patients in total

"Review of patients attending a large VHL clinic revealed that ~2% of clinic attendees would be strong candidates for belzutifan if it were to be available in 2024. In both cases the major indication would be multiple central nervous system haemangioblastomas that were not considered to be amenable to surgical intervention. A further 3% of patients were considered to be potential candidates in the future, depending on disease progression, Again the most common indication was that multiple CNS haemangioblastomas that had required multiple surgeries in the past but the patients still had multiple brain lesions which, if they progressed, further surgical intervention was likely to be hazardous."

5) (Additional follow up question) **In the insight you shared below, there wasn't an estimate PNET % of your patient population, could I double check whether you see any patients with PNET 'driven' disease in your clinics/practice? Appreciate this would be an estimate.**

There weren't currently any patients with PNETs that are a concern at present. In the past there have been but as rough estimate it would likely be around 5-10% of patients who were strong candidates for belzutifan in which a PNET would be the primary concern. Of course with increasing experience of belzutifan his might increase.

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Respondent: Response received from Consultant Geneticist/VHL service lead who had discussed with and copied in Urologist

1) Please describe the patients who you would like to treat with belzutifan. Why do you want to treat these specific patients?

I would ideally like to treat patients with multi-system disease with ≥2 organs affected with VHL related tumours. These patients cumulatively end up with needing multiple treatments across multiple NHS departments, with multiple interventions across neurosurgeons, urologists, interventional radiology, ophthalmology etc. Their quality of life and ability to contribute to the working economy is severely impacted by the multiple different organs affected, impacting on outpatient appointment numbers, procedures, and time off work. Intervention when multi-system disease is identified would likely prevent deterioration across multiple organ systems, thus cumulatively greatly reducing the burden on the NHS of their care.

2) Of the patients that you would like to treat with belzutifan, which is the tumour driving this decision? CNS Hb, pNET or RCC? Why is this tumour driving a preference to treat with belzutifan. (In your practice what is the % split of VHL patients by these three 'primary' tumour types. Note, we use primary tumour here to mean tumour driving treatment decision making)

As above, I consider that multi-organ disease rather than a “primary” tumour should drive this decision due to the impact on reduction of disability and procedures across different departments. If I had to pick 1, I would say the CNS tumours as this tends to lead to the greatest disability in terms of interventions required and impact on quality of life and ability to work. I note retinal angiomas are not included here but the benefit on the eyes and reduction in progression to loss of sight and blindness is significant as well.

Note the consultant geneticist also shared their patient numbers from a VHL service confidentially

3) If these patients do not receive treatment with belzutifan, what is the likely course of their disease? Please reference any similar patients you may have treated in the past.

They develop multi-system disease involving the CNS, eyes, pancreas and kidneys. They then require multiple procedures across neurosurgeons, urologists, interventional radiology, ophthalmology which significantly impacts on their ability to work and contributes to great disability in the long term due to the progressive nature of the disease and progressive procedural interventions across multiple organ types.

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Respondent: Professor of Endocrinology

1) Please describe the patients who you would like to treat with belzutifan. Why do you want to treat these specific patients?

The specific patients I would wish to consider for belzutifan would be younger patients with VHL and growing pancreatic tumours. We know that such pancreatic neuroendocrine tumours (NETs) occur in at least 10% of patients with VHL, but the true prevalence is probably higher. At present, as for sporadic pancreatic NETs, we would consider a size of >2cm to be an indication for surgery. Our initial treatment for those 1-2cm and showing growth would be a somatostatin analogue, but most will eventually escape from this treatment. However, the surgery is pretty major in most cases. For a distal lesion one might be able to consider a distal pancreatectomy, but for the more common proximal lesions the patients would require either a total or partial pancreatectomy, Whipple's procedure. Even in expert hands such pancreatic surgery is challenging, has a high morbidity and occasional mortality, and there is high risk of permanent insulin-dependent diabetes.

2) Of the patients that you would like to treat with belzutifan, which is the tumour driving this decision? CNS Hb, pNET or RCC? Why is this tumour driving a preference to treat with belzutifan. (In your practice what is the % split of VHL patients by these three 'primary' tumour types. Note, we use primary tumour here to mean *tumour driving treatment decision making)*

Note, Not answered, clinical expert only sees/treats VHL patients with pNETs

3) If these patients do not receive treatment with belzutifan, what is the likely course of their disease? Please reference any similar patients you may have treated in the past.

As these tend to be young patients, often in their 20s and 30s (unlike those with sporadic NETs), we have at present the difficult decision whether to submit such a young patient to partial or complete pancreatectomy, with possible life-long insulin therapy, as opposed to simple surveillance with the risk of metastatic spared which increases with the size of the tumour. Thus, the availability of belzutifan for this group of patients with pancreatic NETs escaping somatostatin analogue therapy could be life-changing for such patients.

I have many patients with pancreatic NETs who have undergone the Whipple's procedure, with often prolonged hospital stays and the need for intense follow-up for their diabetes.

4) (Additional follow up question) What estimated proportion of your patients are in the 'young somatostatin escapee group' and currently, do the majority of these patients opt for surgical intervention over potentially developing metastatic disease?

I think my numbers are too small to provide any useful data from that point of view. Regarding surveillance versus surgery, most patients accept our advice, which is to go for surgery.

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Respondent: Consultant Neuro-oncologist

1) Please describe the patients who you would like to treat with belzutifan. Why do you want to treat these specific patients?

From a neuro-oncology perspective we would look to treat patients with multiple unresectable haemangioblastomas. Many of these patients undergo multiple rounds of neurosurgery and stereotactic radiosurgery, however we reach a point where we can longer undertake surgery as the risk of surgery increases with each operation and the benefits decline particularly when there are multiple tumours requiring multiple different surgical approaches.

Stereotactic radiosurgery is a useful adjunctive treatment to open surgery and can be used to target multiple small tumours however we are limited to a small volume of tumour/brain that we can treat with this modality without causing unacceptable levels of radiation related brain injury. In such patients there is no other therapeutic option.

As a result, we have a small number of patients that have already had multiple open surgeries and are no longer candidates for further open surgery in whom the volume of residual disease is too great for stereotactic radiotherapy. These patients are often young to middle aged and in some cases still working.

2) Of the patients that you would like to treat with belzutifan, which is the tumour driving this decision? CNS Hb, pNET or RCC? Why is this tumour driving a preference to treat with belzutifan. (In your practice what is the % split of VHL patients by these three 'primary' tumour types. Note, we use primary tumour here to mean tumour driving treatment decision making)

CNS- Hb, particularly spinal

3) If these patients do not receive treatment with belzutifan, what is the likely course of their disease? Please reference any similar patients you may have treated in the past.

The clinical outcome for these patients is usually progressive motor decline resulting in the need for care with all activities of daily living and eventually death from hydrocephalus / or some other manifestation of VHL/ infectious consequences of immobility. The hydrocephalus obviously can be treated with shunting if the patient wishes at a cost of prolonging life with a poor quality. The goal of treatment therefore would not only be to prolong life but also to prolong independence and delay need for costly care.

The speed of decline is variable as the growth rate for haemangioblastomas is variable, even within the same patient, but this process typically occurs over a small number of years.

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Respondent: Consultant neurosurgeon

1) Please describe the patients who you would like to treat with belzutifan. Why do you want to treat these specific patients?

I would identify two groups in my particular area of practice:

I occasionally see patients with an unusually heavy load of CNS tumours in particular ***solid*** juxta-brainstem tumours that are very high surgical risk particularly when accounting for other systemic consequences of their disease. Radiosurgical treatment of such lesions in our experience has been of limited value and carried a significant risk of swelling in the tumour producing brainstem symptoms.

The second subset are patients with multiple small lesions in the posterior fossa where it is not possible to be certain which nodule is driving cyst formation. Surgery cannot hope to resect every tumour and thus they are exposed to the risk of requiring multiple procedures.

Over the past 12 months colleagues in the US have reported the susscessful use of Belzutifan to treat such patients:
Zamarud A, Marianayagam NJ, Park DJ, Yener U, Yoo KH, Meola A, Chang SD. The outcome of central nervous system hemangioblastomas in Von Hippel-Lindau (VHL) disease treated with belzutifan: a single-institution retrospective experience. J Neurooncol. 2023 Nov;165(2):373-379. doi: 10.1007/s11060-023-04496-z. Epub 2023 Nov 13. PMID: 37955759.

Belzutifan treatment for von Hippel-Lindau (VHL) disease–associated central nervous system (CNS) hemangioblastomas (HBs) in the phase 2 LITESPARK-004 study.
Othon Iliopoulos, Ane Bundsbæk Bøndergaard Iversen, Katy Beckermann, Vivek Narayan, Benjamin L. Maughan, Stephane Oudard, Tobias Else, Jodi K. Maranchie, Wei Fu, Rodolfo F. Perini, Yanfang Liu, W. Marston Linehan, Ramaprasad Srinivasan, and Eric Jonasch

Journal of Clinical Oncology 2023 41:16_suppl, 2008

2) Of the patients that you would like to treat with belzutifan, which is the tumour driving this decision? CNS Hb, pNET or RCC? Why is this tumour driving a preference to treat with belzutifan. (In your practice what is the % split of VHL patients by these three 'primary' tumour types. Note, we use primary tumour here to mean *tumour driving treatment decision making)*

Not answered, clinical expert only sees/treats VHL patients with CNS tumours

3) If these patients do not receive treatment with belzutifan, what is the likely course of their disease? Please reference any similar patients you may have treated in the past.

I have one patient currently who is no longer a candidate for surgical decompression of the brainstem having declined surgery up to a point where I now judge it excessively likely that [they] will not survive the procedure. In the face of advancing brainstem compression only palliative measures will remain open to [them] as radiosurgery already failed to arrest the growth of this large solid haemangioblastoma.

I recently re-operated on a [patient] with multiple juxtamedullary solid haemangioblastoma where I could only offer partial debulking of the tumour as its manipulation at the brainstem in significant

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neurophysiological deterioration. [They] too has already received radiosurgery which has not helped and although the latest surgery has achieved short term goals, [they] faces multiple further such debulking each individually high-risk if [their] tumours continue to progress at the rate they have been.

edit in square brackets by company to protect anonymity

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Respondents: Response received from Oncologist who had discussed with and copied in Consultant Geneticist

1) Please describe the patients who you would like to treat with belzutifan. Why do you want to treat these specific patients?

Patients who have already lost function in one organ e.g. eye or kidney despite multiple interventions. Without treatment, patient's organ function will continue to deteriorate and they will almost certainly lose function. This will have a huge impact on their quality of life.

2) Of the patients that you would like to treat with belzutifan, which is the tumour driving this decision? CNS Hb, pNET or RCC? Why is this tumour driving a preference to treat with belzutifan. (In your practice what is the % split of VHL patients by these three 'primary' tumour types? Note, we use primary tumour here to mean *tumour driving treatment decision making)*

Although not my area of expertise, brainstem lesions in particular are often inoperable and cause significant morbidity. These trigger treatment due to the levity of the side effects patients experience.

Clinician references patient with a high C-spine lesion, paraesthesia, right arm numbness and mobility issues

3) If these patients do not receive treatment with belzutifan, what is the likely course of their disease? Please reference any similar patients you may have treated in the past.

With retinal disease, vision will deteriorate inexorably, and ultimately patients will go blind (this could happen suddenly, if for example they were to suffer retinal detachment). If a patient loses their vision, they will be unable to work or act as carer for family (which is often the case with this disease). It is anticipated that patients could experience a significant deterioration in mental health (which could already be suffering as a result of the disease and the anticipation of sight loss) and their ability to lead an independent life.

Clinician references a patient at risk of sudden blindness after rapid progression over a few months, and loss of vision in one eye already- clinician aware retinal tumours are not within scope of belzutifan's license

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Respondent: Consultant Geneticist/VHL service lead

1) Please describe the patients who you would like to treat with belzutifan. Why do you want to treat these specific patients?
Neuroendocrine
Renal if had multiple tumours removed and risk of needing transplant
High spinal lesions

2) Of the patients that you would like to treat with belzutifan, which is the tumour driving this decision? CNS Hb, pNET or RCC? Why is this tumour driving a preference to treat with belzutifan. (In your practice what is the % split of VHL patients by these three 'primary' tumour types. Note, we use primary tumour here to mean *tumour driving treatment decision making)*
40 High spinal
20 Neuroendocrine
40 RCC

2b) (Additional follow up question at a later date) **I realise that I hadn't offered multisystemic disease as an option for driving treatment decisions in the previously asked question. From speaking to other VHL specialists we've got the below estimates and I wanted to validate them with you. Of the patients you would treat with belzutifan, would the following be similar or different in your clinics:**

40-50% treatment decisions would be driven by multisystemic disease
40-50% driven by primarily CNS/Spinal disease,
10-15% driven by primarily renal disease,
5-10% driven by primarily retinal disease
5-10 % are driven by primarily PNETs

Yes, this would be a very good estimate

3) If these patients do not receive treatment with belzutifan, what is the likely course of their disease? Please reference any similar patients you may have treated in the past.

High spinal tumours that struggle with treatment options—increased pain and cord compression related abnormalities

Malignant renal tumours-metastatic disease and high likelihood of death in under five years

Neurological compromise-general deterioration and risk of urinary tract infection and chest infections

Mental health and risky health behaviour (smoking, alcohol, and missing screening) due to a lack of hope-the largest issue and had the largest impact to date in terms of quality of life and years lost.

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Respondent: Consultant endocrinologist – VHL service lead

1) Please describe the patients who you would like to treat with belzutifan. Why do you want to treat these specific patients?

- For myself at present based on the available evidence, it would be for patients with ccRCC in whom further structural intervention (surgery/RFA etc) would lead to an unacceptable loss of renal function meaning dialysis became inevitable/rapidly advanced.
- I am genuinely uncertain at present about my thoughts on its use in other tumour types in similar situations (i.e. unacceptable/irreversible loss of normal function – e.g. a pNET requiring Whipples/total pancreatectomy or a very high risk brainstem haemangioblastoma)

2) Of the patients that you would like to treat with belzutifan, which is the tumour driving this decision? CNS Hb, pNET or RCC? Why is this tumour driving a preference to treat with belzutifan. (In your practice what is the % split of VHL patients by these three 'primary' tumour types. Note, we use primary tumour here to mean *tumour driving treatment decision making)*

- As above, for me at present (although this will change as more is published), this would almost always by ccRCC, but acknowledging (as above) that there might be cases of pNET/HB when it could be considered as an option

3) If these patients do not receive treatment with belzutifan, what is the likely course of their disease? Please reference any similar patients you may have treated in the past.

- Expectation of increased treatment related morbidity – e.g. requirement for dialysis in RCC, loss of neurological function in HB, development of brittle diabetes in pNET
- An example - a current patient of mine has a large RCC in [their] single remaining kidney (previous nephrectomy for VHL-associated RCC). [they] wanted to avoid dialysis, so is currently having treatment with pazopanib (initial treatment stability to date), but my firm preference would be for belzutifan in this situation.

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Appendix 1B: MSD – Clinical expert Validation call – 15th December 2023

Summary of main discussion points

Clinical Experts: Professor of Endocrinology and VHL service lead, [redacted]

Consultant clinical geneticist and VHL service lead, [redacted]

Time between decision to operate and surgery in current practice

- 4-month time interval is reasonable but would generally be considered the maximum waiting time. This depends on the tumour type – an RCC tumour would have been watched for years, a symptomatic CNS spinal Hb may be operated on sooner
- Timing can depend on several factors e.g. preparations for dialysis

Eligibility for belzutifan

- Patients with a local problem should have a local solution. Belzutifan reserved for those on the precipice of organ failure.
- Propose a national/supra-regional MDT for patients who should be prescribed belzutifan
- [redacted]*:* Of 60 patients in practice, would use belzutifan for maybe 2-3 patients
    - In describing what would happen to these patients without belzutifan:
        - A patient with both adrenal glands removed, presence of many pNETs and mother died from metastatic pNET. Would have very poor QoL, catastrophic metabolic syndromes and need lifelong pancreatic enzyme replacement therapy.
        - A patient with multisystem disease – 21 years of age, one kidney, blind in one eye, several lesions in other kidney which will be lost quite soon, CNS Hb - would slowly become paraplegic. With nothing will have a paraplegic, dialysis for life from age 21
- [redacted]*:* Of 100 patients in practice, would use belzutifan for maybe 3 patients
    - In describing what would happen to these patients without belzutifan:
        - Patients with an inoperable CNS Hb who is symptomatic. They would continue to progress, would become progressively incapacitated and need lifelong care
        - Example of two other patients with multiple CNS Hb who died as a result, both were aged under 40. One had multiple surgeries, ICU for months, went home but died within 1 year of going home. Other had been in wheelchair for 10-15 years, was in early 20s when becoming paraplegic.
        - Tumour can progressively squash the medulla and slowly compress the spine which can lead to decreased mobility after surgery, neurologic deficits and breathing difficulties.

Expected distribution of those prescribed belzutifan due to RCC, CNS Hb or pNET

- Assuming 80% multisystem driven by CNS Hb, 15% RCC and 5% pNET would be reasonable
- Would be a small number of pNET as pNET behaviour is quite unpredictable.
- CNS Hb is highly influential, and presentation is in around 70-80% of VHL patients

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Presentation of a complex multisystem patient with extensive prior interventions (example of type of patient seen in the trial)

32 year old White male.

Medical history: Nervous system - seizures, parasthesia; GI disorders; psychiatric disorders; Reproductive - low testosterone, testicular atrophy; Endocrine - thyroid mass; Anaemia; Hypertension

Tumours present: RCC in left kidney, Two CNS haemangioblastomas each in the left cerebellum and right cerebellum as well as one in the spinal cord.

Prior VHL-related treatments: Surgery - Left cerebellar haemangioblastoma resection, Right partial adrenalectomy x2, right partial nephrectomy x3, spinal laminectomy x2.

- Difficult to say exactly what would happen to such patients. Worst outcome would be the spinal Hb is operated on, left paraplegic and require life-long care with a life expectancy of <10-15 years.

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Appendix 1C: MSD – Model Outcomes Clinical expert Validation call – 8th January 2024

Model transitions & positioning

- Aligns with positioning and expects to use this in a small minority of patients.
- Proportions receiving surgery at 4 months in standard of care (SoC) and risk of surgical complications/consequences are reasonable. Whilst they may appear high, they are reasonable in the context very small numbers of patients included in the label.
- Following a Whipple's procedure for a pNET, would also consider malnutrition and 'dumping syndrome' in addition to diabetes.

Model outcomes

- Life years expectancy for the CNS Hb cohort are at the upper end of survival. On average, with SoC, would expect to see 5-6 additional years. With belzutifan this is harder to predict but would be more since belzutifan is expected to delay/prevent progression but long-term efficacy is unknown.
- Utility is expected to be very low in SoC particularly with CNS Hb. This is expected to decline over time as life expectancy shortens. Noted some example patients:
    - Patient wheelchair bound in 20s and lived for a further 10-15 years.
    - Patient in 40s with inoperable brain stem tumour lived for ~2 years with symptoms equivalent to severe stroke.
- Utility in RCC cohort for SoC would take into account ESRD/dialysis and other considerations/complications of VHL disease.
- Challenging to model the target patients given the highly heterogenous and variable nature of the disease

Additional topics

- Discussion around patients with retinal lesions being treated with belzutifan in the UK, particularly for those who have been treated for RCC, CNS Hb or pNET independently.
- Discussion on patients in the MK-6482-004 trial, highlighted that when looking for those to include in the trial, particular consideration was made for the more severe patients i.e. those with multiple tumours, multi-system involvement and prior surgical history. These were patients who would be motivated to be in the trial, they have had surgical history and would need surgery in the future.

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Appendix 2: MK-6482-004 study participant tumour burden and prior treatment history at baseline

Table 3: MK-6482-004 number of VHL-disease associated tumours eligible for treatment with belzutifan at study baseline

	RCC (N=61)			pNET (N=22)			CNS Hb (N=50)			CNS Hb location*			
	1-2	3-4	≥5	1-2	3-4	≥5	1-2	3-4	≥5	Brain stem	Cerebellum	Spine/spinal cord	Other
Number (%) of patients	42 (69%)	15 (25%)	4 (7%)	20 (90%)	2 (9%)	0 (0%)	17 (34%)	15 (30%)	18 (36%)	3 (6%)	42 (84%)	27 (54%)	11 (22%)

CNS Hb: central nervous system haemangioblastoma; pNET: pancreatic neuroendocrine tumour; RCC: renal cell carcinoma;
*A patient may have a CNS Hb in more than one location, percentages are provided out of the population of 50 patients CNS Hb.

Table 4: MK-6482-004 prior-procedures related to VHL-disease associated tumours eligible for treatment with belzutifan at study baseline

	RCC (N=61)			pNET (N=61)			CNS Hb (N=61)
	None	In 1 kidney only	In both kidneys	None	Distal/partial pancreatectomy	Whipple's procedure/ pancreaticduodenectomy	Average number of procedures
Number (%) of patients*	14 (23%)	23 (38%)	24 (39%)	52 (85%)	6 (10%)	3 (5%)	2.72

CNS Hb: central nervous system haemangioblastoma; pNET: pancreatic neuroendocrine tumour; RCC: renal cell carcinoma;
*Percentages are provided out of the whole MK-6482-004 population of 61 patients.

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Table 5: Hypothetical patients created via a composite of baseline characteristics from the MK-6482-004 study [this is illustrative only]

Age, sex, race	Medical history	Tumours present at study initiation	Prior therapy for VHL disease
42/F, Unknown	Retinal haemangiobastomas; Cataract; Eye allergy; Eye pruritis; ; Skin pain; Diabetes mellitus; Gastrooesophageal reflux disease; Hyperlipidaemia; Mouth sore; General pain; Hypertension; Allergic rhinitis	RCC - T1 left kidney, T2 left kidney, T3 right kidney, T4 right kidney, NT1 kidney bilateral. pNET - PT1. CNS Hb - CNST1 leptomeningeal bilateral, CNST2 temporal lobe left, CNSNT1 cerebellum left	Left partial nephrectomy, Left partial nephrectomy, Left renal cryotherapy, Resection hemangioblastoma lumbar spine, Resection hemangioblastoma thoracic spine, Resection haemangioblastoma C6-7, Resection of Right Optic Nerve tumour with loss of vision in the right eye, Right Partial Nephrectomy, Right Partial Nephrectomy, Right adrenalectomy, Right partial nephrectomy, Suprapubic catheter placed under cystoscopic guidance,
62/F, Black or African American	Temporomandibular joint dysfunction; Headache; Anxiety, retinal haemangioblastoma	RCC - T1 right kidney pNET - PT1, PT2 pancreas CNS Hb - CNST1 brain stem right, CNSNT1 left cerebellum, CNSNT2 right cerebellum	Brain HB: R cerebellar HB surgery, s/p VP shunt placement, Intradural resection of intramedullary hemangioblastoma, kidney surgery, Laminectomy T2-T3, RETINAL CRYOABLATION- Right Eye, hemangioblastoma resected
26/M, White	Eye disorders; Nervous system - neuropathy, parasthesia; GI disorders; Anxiety	RCC - T1 right kidney, NT1 kidney bilateral. pNET - PT1, PT2, PT3. CNS Hb - CNST1 spine, CNST2 spine, CNST3 spine, CNST4 spine	Resection of cerebellar hemangioblastomas, Resection of pancreatic neuroendocrine tumour, Right enucleation for retinal hemangioblastomas, right placement of prosthetic eye for retinal haemangioblastomas
64/M, Asian	Vision loss; Congenital Hamartoses; Abnormality of gait; Memory Loss; Lack of Coordination; Paralysis; Benign neoplasm of the cranial nerve; Constipation; Renal Cancer; Spinal	RCC - T1 left kidney. pNET - PT2. CNS Hb - CNSNT1 cerebellum right	Surgery - Kidney ablation, Retinal laser coagulation x2, Left partial nephrectomy, Lumbar haemangioma resection, Nervous

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Age, sex, race	Medical history	Tumours present at study initiation	Prior therapy for VHL disease
	Hemangioblastoma; Deep Venous Thrombosis; Hearing loss; pancreatic mass; Diabetes type 2, controlled; Incomplete paraplegia; Neurogenic bladder; Retinal angioma; Blepharitis of both eyes; Dry Eye Syndrome; Optic disc pallor; Cervical spinal cord injury; Hemangioblastoma of the brain; Pheochromocytoma; Skin Rash		system neoplasm surgery x2 - resection of C4-5 & L3 hemangioblastoma

CNS Hb: central nervous system haemangioblastoma; pNET: pancreatic neuroendocrine tumour; RCC: renal cell carcinoma;
NOTE: these are example patients created via a composite of patient baseline characteristics from the patients of the MK-6482-004 study and are not specific real patients from the study.

Appendix 3: MK-6482-004 study baseline individual patient data (confidential)

Table 6: MK-6482-004 study baseline individual patient data on medical history, tumours present, and prior treatments (confidential)

#	Baseline characteristics	Medical history	Tumours present at study initiation	Prior VHL therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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#	Baseline characteristics	Medical history	Tumours present at study initiation	Prior VHL therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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#	Baseline characteristics	Medical history	Tumours present at study initiation	Prior VHL therapy
[redacted]				

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#	Baseline characteristics	Medical history	Tumours present at study initiation	Prior VHL therapy
[redacted]				

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#	Baseline characteristics	Medical history	Tumours present at study initiation	Prior VHL therapy
[redacted]				

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#	Baseline characteristics	Medical history	Tumours present at study initiation	Prior VHL therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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#	Baseline characteristics	Medical history	Tumours present at study initiation	Prior VHL therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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#	Baseline characteristics	Medical history	Tumours present at study initiation	Prior VHL therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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#	Baseline characteristics	Medical history	Tumours present at study initiation	Prior VHL therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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#	Baseline characteristics	Medical history	Tumours present at study initiation	Prior VHL therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Appendix 4: Updated Cancer Drugs Fund Managed Access Agreement proposal

[The finalised Managed Access Agreement for this indication has now been published separately on the NICE webpage for this appraisal. Please refer to that document for the finalised details.]

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Appendix 5: Summary of transition probability estimation approach from pre-surgery and event-free after surgery health states

Table 7: Summary of transition probability estimation approaches from pre-surgery and event-free after surgery health states

Transition probability	VHL-RCC	VHL-CNS Hb	VHL-pNET
Pre-surgery → surgery	*Belzutifan:* TTS is estimated from MK-6482-004 trial applying exponential distribution	*Belzutifan:* TTS is estimated from MK-6482-004 trial applying exponential distribution	*Belzutifan:* % reduction in the hazard rate of this TP (for belzutifan vs. SOC) for VHL-pNET cohort is assumed equal to the % reduction in the hazard rate of this TP for VHL-RCC cohort multiplied by the complement ORR ratio
	SOC: 90% receive immediate surgery. For the remaining 10%, TTS is estimated from re-weighted VHL Natural History Study applying exponential distribution	*SOC:* 100% receive the outcomes associated with immediate surgery.	*SOC:* 90% receive immediate surgery. For the remaining 10%, TTS is estimated from the pre-treatment (looking backwards) applying exponential distribution
Pre-surgery → metastatic disease	*Belzutifan:* Hazard ratio of pre-surgery → surgery (for belzutifan vs. VHL Natural History Study) is applied to the hazard rate of pre-surgery → metastatic disease from the SOC arm	*Belzutifan:* % reduction in the hazard rate of pre-surgery → surgery (for belzutifan vs. VHL Natural History Study) is assumed equal to the % reduction in the hazard rate of pre-surgery → metastatic disease which is applied to the SOC hazard rate*	*Belzutifan:* Hazard ratio of pre-surgery → surgery (for belzutifan vs. VHL Natural History Study) is applied to the hazard of pre-surgery → metastatic disease from the SOC arm
	SOC: TTM from the re-weighted VHL Natural History Study applying exponential distribution	*SOC:* TTM from the re-weighted VHL Natural History Study applying exponential distribution*	*SOC:* TTM from the re-weighted VHL Natural History Study applying exponential distribution

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Transition probability	VHL-RCC	VHL-CNS Hb	VHL-pNET
Pre-surgery → death	*Belzutifan:* Maximum of background mortality and VHL Natural History Study mortality and accounting for CNS Hb mortality benefit of belzutifan.	*Belzutifan:* % reduction in the hazard rate of pre-surgery → surgery (for belzutifan vs. VHL Natural History Study) is assumed equal to the % reduction in the hazard rate of pre-surgery → death which is applied to the SOC hazard rate	*Belzutifan:* Maximum of background mortality and VHL Natural History Study mortality and accounting for CNS Hb mortality benefit of belzutifan.
	SOC: Maximum of background mortality and VHL Natural History Study mortality	*SOC:* Maximum of background mortality and VHL Natural History Study mortality	*SOC:* Maximum of background mortality and VHL Natural History Study mortality
Event-free after surgery → event	*Belzutifan:* Hazard ratio of pre-surgery → metastatic disease (for belzutifan vs. VHL Natural History Study) is multiplied to the hazard rate of event-free after surgery → metastatic disease respectively in the SOC arm. For event-free after surgery → death: Maximum of background mortality and VHL Natural History Study mortality (for patients with ≥ 1 renal surgery) and accounting for CNS Hb mortality benefit of belzutifan.	*Belzutifan:* Event-free after surgery → event assumed equal to pre-surgery → event	*Belzutifan:* Event-free after surgery → event assumed equal to pre-surgery → event
	SOC: TTE from the re-weighted VHL Natural History for patients with ≥ 1 renal surgery applying exponential distribution. For event-free after surgery → death: Maximum of background mortality and VHL Natural History Study mortality (for patients with ≥ 1 renal surgery).	*SOC:* Event-free after surgery → event assumed equal to pre-surgery → event	*SOC:* Event-free after surgery → event assumed equal to pre-surgery → event

*Assumes metastatic disease from non-primary tumour sites.

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Appendix 6: Updated QALY shortfall analysis

The QALY shortfall analysis has been updated under the revised base-case assumptions. To reiterate, heterogeneity and rarity of disease means that data are scarce and imperfect. Hence, the QALY weight estimate of 1.2 is not representative of the UK target population and a 1.7 modifier should apply.

Table 8: Summary of transition probability estimation approaches from pre-surgery and event-free after surgery health states

Cohort	Expected total QALYs for the general population	Total expected QALYs for people with VHL on current SOC	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
VHL-associated RCC	18.15	[redacted]	[redacted]	[redacted]	1.2
VHL-associated CNS Hb	18.15	[redacted]	[redacted]	[redacted]	1.2
VHL-associated pNET	18.15	[redacted]	[redacted]	[redacted]	1.2
VHL- GB marketing authorisation population (weighted cohort)	18.15	[redacted]	[redacted]	[redacted]	1.2

Appendix 7: Updated cost-effectiveness estimates

Appendix 7A: Summary of updates to economic model (NICE ID3932 STA Submission CEA v6.0 (CIC))

Updates to the disutilities associated with two RCC-related surgical complications (end stage renal disease and/or dialysis and erythroderma):
In the original model, two disutilities of the following RCC surgery complications were calculated using a utility of 1 to approximate the utility of individuals in the general population without the complication. As per the committee recommendations, these disutilities have been recalculated by instead using the utility equation from Ara et al. (2010) to estimate the age- and sex-matched general population utility without the complication. The original and revised disutility inputs are summarized below, the revised inputs are implemented in the company base-case.

Complication	Original values		Revised values	
	Disutility	*Source*	*Disutility*	*Source*
End stage renal disease and/or dialysis *(a long-term complication of RCC surgery)*	-0.527	Lee et al. (2005) (weighted average of hemodialysis and peritoneal dialysis utilities) minus 1	-0.422	Lee et al. (2005) (weighted average of hemodialysis and peritoneal dialysis utilities) minus general population utility (calculated based on Ara et al.

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				2010 and the age and gender distribution from MK-6482-004)
Erythroderma *(a short-term complication of RCC surgery)*	-0.335	Poole et al. (2010) (severe atopic dermatitis) minus 1	-0.231	Poole et al. (2010) (severe atopic dermatitis) minus general population utility (calculated based on Ara et al. 2010 and the age and gender distribution from MK-6482-004)

The draft guidance provides a source for a utility estimate whilst on dialysis which reports a value of 0.56 (2). This was tested in scenario analysis by editing the numerator (i.e., $U_{VHL, \text{ with comp } i}$) of the ratio of utility for VHL patient with vs. without complication in the *"Surgery"* tab in cell K54. The full multiplicative approach is described below.

Option to assume additive or multiplicative disutility from concurrent surgical complications:
The originally submitted model presented an additive approach to estimate the total disutility impact of various VHL-related surgical complications that patients may experience concurrently. In line with the NICE manual and committee preference for a multiplicative approach to estimate disutility from concurrent conditions, the model has been updated with the flexibility to assume either additive or multiplicative disutility from concurrent surgical complications. The multiplicative approach is now applied in the revised company base-case.

Dropdown menu *(added to the "Specifications" and "Surgery" tabs)*	**Options**
Select approach to estimate disutility from concurrent surgical complications:	1. Assume additive disutility from concurrent complications 2. Assume multiplicative disutility from concurrent complications

Both approaches use the same set of additive disutilities to represent the disutilities associated with individual surgical complications. However, the approaches differ with respect to how the disutilities from multiple complication types are combined.

The table below summarizes the key assumptions underlying the multiplicative approach and how these assumptions are reflected in the model calculations.

Key assumptions under the multiplicative approach:	**Implementation within the model:**

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Patients are at risk of experiencing concurrent short-term complications from the same surgery event.	1. For each short-term complication i, the ratio of utility for a VHL patient with vs. without the complication (i.e., $U_{VHL, with\ comp\ i}$ / $U_{VHL, without\ comp\ i}$) was approximated as ($U_{SD}$ + D_i)/U_{SD} , where U_{SD} represents the utility associated with having stable disease in a non-metastatic health state (i.e., 0.754, as estimated in the VHL RW QoL Disease Burden Study) and D_i represents the additive disutility from complication i. These calculations are shown in column K of the short-term complication tables in the "Surgery" tab. 2. Using the ratio calculated above ($U_{VHL, with\ comp\ i}$ / $U_{VHL, without\ comp\ i}$) and the per-surgery risk of each short-term complication i, the ratio of ($U_{VHL, with\ or\ without\ comp\ i}$ / $U_{VHL, without\ comp\ i}$) was computed, where $U_{VHL, with\ or\ without\ comp\ i}$ represents the mix of patients with and without complication i. These calculations are shown in columns V:Y of the "Surgery" tab. 3. The ratios calculated in step #2 are multiplied together for all short-term complications associated with a given surgery type. The resulting product is converted to a lump-sum per-surgery QALY decrement for that surgery type, with the assumption that all short-term complications have disutility impact lasting 4 weeks. This step is shown in the "Surgery" tab (rows labeled with "Using multiplicative approach to estimate disutility from concurrent complications").
Patients are at risk of experiencing concurrent long-term complications from all types of surgeries.	1. For each long-term complication i, the ratio of utility for a VHL patient with vs. without the complication (i.e., $U_{VHL, with\ comp\ i}$ / $U_{VHL, without\ comp\ i}$) was approximated in the same way as described above for short-term complications. 2. In each weekly cycle, the ratio calculated above ($U_{VHL, with\ comp\ i}$ / $U_{VHL, without\ comp\ i}$) and the cumulative risk of each long-term complication i was used to compute the ratio of ($U_{VHL, with\ or\ without\ comp\ i}$ / $U_{VHL, without\ comp\ i}$). These calculations are shown in columns EG:FC of each "Trace_..." tab. 3. In each weekly cycle, the ratios calculated in step #2 are multiplied together for all long-term complications across all surgery types (see column FE of each "Trace_..."), and this product is converted into a QALY loss for that cycle (see column FF of each "Trace_...").

Of note, the multiplicative approach (as described above) assumes that short-term complications from *different* surgery events will not co-occur, as the patient would have to undergo both surgeries within 4 weeks to experience any overlapping short-term complications from these different events. QALY decrements from short-term complications for different surgeries were therefore still treated additively under this approach. In addition, for simplicity, short-term complications were modeled as being non-concurrent with long-term complications.

<u>Option to assume delayed surgery for primary VHL-related tumors under SOC</u>:
The following new dropdown menu has been added to the "Specifications" tab:

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Dropdown menu *(added to the "Specifications" tab)*	**Options**
Select weekly cycle in which patients undergo immediate surgery for primary VHL-related tumors under SOC:	1. Cycle 1 2. Cycle 17 (i.e., 4-month delay)

When the newly added second option is selected is selected, the timepoint for upfront surgery in the SOC arm is postponed from cycle 1 to cycle 17. Under this scenario, the proportions of patients undergoing upfront surgery in the SOC arm (as specified elsewhere on the "Specifications" tab) are applied only to the subset of patients who remain in the pre-surgery state at cycle 16.

Update to the weighted distribution across cohorts for the overall VHL-GB MA population:
Following clinical expert elicitation, the model proportion split across the three cohorts was updated and implemented in the revised base-case. This has been implemented in the results tabs namely, "Disaggregated Base-Case Results", "Summary Base-Case Results" and "Base-Case QALY Shortfall". As discussed in the relevant comments above, the proportion split across cohorts is now:

Cohort	**Proportion/weighting**
VHL-RCC	15%
VHL-CNS Hb	80%
VHL-pNET	5%

Scenario analysis to approximate belzutifan time on treatment (ToT) using progression-free survival (PFS):
In the base case, belzutifan ToT is modeled using a parametric distribution (i.e., exponential, Weibull, Gompertz, log-logistic, log-normal, gamma, or generalized gamma) fitted directly to patient-level time on treatment data in MK-6482-004. As requested by the committee, a newly added scenario analysis has been added where belzutifan ToT is instead modeled using a parametric distribution fitted to patient-level data on PFS in MK-6482-004. This scenario analysis can be run by selecting the second option from the following new dropdown menu:

Dropdown menu *(added to the "Tx Duration" tab)*	**Options**
Select approach used to model ToT for belzutifan:	1. Parametric distributions fitted to observed time on treatment (ToT) 2. Parametric distributions fitted to progression-free survival (PFS) as a proxy

The best-fitting distribution under both options is the Gompertz distribution. The validation figure and fit statistics on the "ToT" tab has been updated to display the distributions fitted to either ToT or PFS, depending on which option is selected from the above dropdown menu.

Scenario analysis of social care costs among patients with neurological complications from CNS Hb surgery:

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In the base case, the costs of social care associated with neurological complications is estimated from Fineberg et al. (2013). Following clinical expert elicitation, additional scenarios of social care costs have been added to explore the impact of paralysis and symptoms akin to spinal cord injury following surgery. This scenario analysis can be run by selecting options 2-4 from the following new dropdown menu:

Dropdown menu *(added to the "Specifications" and "Surgery" tabs)*	**Options**
Select source for social care costs among patients with neurological complications from CNS Hb surgery	1. Feinberg et al. (2013), based on the social care cost of brain disorders. 2. McDaid et al. (2019), based on professional home care for paraplegia AIS-ABC grade spinal cord injuries 3. McDaid et al. (2019), based on professional home care for tetraplegia AIS-ABC grade spinal cord injuries 4. McDaid et al. (2019), based on professional home care for AIS-D grade spinal cord injuries

McDaid et al. (2019) is an economic modelling analysis to understand the economic impact of spinal cord injuries in the UK. Social care costs are estimated using the mean hours of professional home care per week multiplied by the home care rate per hour. Feinberg et al. (2013) estimate still remains for the company base case. McDaid et al. (2019) estimates are explored in scenario analyses. The annual costs and estimation method for each source are reported below.

Scenario	**Annual Cost**	**Estimation method**
Feinberg et al. (2013), based on the social care cost of brain disorders	£849.11	The social care cost of brain disorders based on direct non-medical cost per subject in the UK (26.8% of €3,126, converted to 2013 GBP and inflated).
McDaid et al. (2019), based on professional home care for paraplegia AIS-ABC grade spinal cord injuries	£55,351.65	The professional home care cost for paraplegia AIS-ABC grade spinal cord injuries from McDaid et al. (2019) (30.9 hours per week × £30.75/hour, inflated from 2016 GBP)
McDaid et al. (2019), based on professional home care for tetraplegia AIS-ABC grade spinal cord injuries	£104,075.42	The professional home care cost for tetraplegia AIS-ABC grade spinal cord injuries from McDaid et al. (2019) (58.1 hours per week × £30.75/hour, inflated from 2016 GBP)
McDaid et al. (2019), based on professional home care for AIS-D grade spinal cord injuries	£8,956.58	The professional home care cost for AIS-D grade spinal cord injuries from 'McDaid et al. (2019) (5 hours per week × £30.75/hour, inflated from 2016 GBP)

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Appendix 7B: Deterministic results with revised base-case (with PAS)

The following changes/selections were made to the economic model to produce a revised company base-case:

- Immediate surgery removed; surgery now occurs at 4 months in the SoC arm
- TTS for RCC cohort in SoC arm now based on pre-treatment period rather than VHL Natural History Study (MAIC)
- Revised disutility for ESRD/dialysis and erythroderma
- Application of multiplicative approach to disutilities
- Cohort weighting based on clinical expert elicitation
- Updated PAS

Table 9 Deterministic results with revised company base-case (with PAS)

Technologies	Total costs (£)	Total QALYs	Total LYs	Incremental costs (£)	Incremental QALYs	Incremental LYs	ICER vs. comparator (£/QALY)
VHL-RCC cohort *(weighting 15%)*							
Belzutifan	[redacted]	[redacted]	[redacted]	-	-	-	-
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VHL-CNS Hb cohort *(weighting 80%)*							
Belzutifan	[redacted]	[redacted]	[redacted]	-	-	-	-
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VHL-pNET cohort *(weighting 5%)*							
Belzutifan	[redacted]	[redacted]	[redacted]	-	-	-	-
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VHL- GB marketing authorisation population (weighted cohort)							
Belzutifan	[redacted]	[redacted]	[redacted]	-	-	-	-
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: ICERs are not severity-modifier adjusted.

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Appendix 7C: Key scenario analyses around revised base-case (with PAS)

Table 10 Key scenario analyses around revised company base-case (with PAS)

#	Scenario	VHL-GB MA population ICER
-	Base case (revised)	[redacted]
1	Assume PFS as a proxy for belzutifan ToT	[redacted]
2	Assume 4-year duration of treatment effect waning for CNS Hb & pNET cohorts	[redacted]
3	Assume 3.5-year duration of treatment effect waning for CNS Hb & pNET cohorts	[redacted]
4	Assume 3-year duration of treatment effect waning for CNS Hb & pNET cohorts	[redacted]
5	Assume 2.5-year duration of treatment effect waning for CNS Hb & pNET cohorts	[redacted]
6	Assume 2-year duration of treatment effect waning for CNS Hb & pNET cohorts	[redacted]
7	Assume 1-year duration of treatment effect waning for CNS Hb & pNET cohorts	[redacted]
8	ESRD/dialysis utility value of 0.56 as per NICE Guideline NG107	[redacted]
9	Assume immediate surgery for SoC	[redacted]
10	Source for surgery risks under SoC in the VHL-RCC cohort as VHL Natural History Study (MAIC)	[redacted]
11	Assume additive disutility from concurrent complications	[redacted]
12	Assume caregiver disutility	[redacted]
13	Social care costs as per McDaid et al. (2019), based on professional home care for paraplegia AIS-ABC grade spinal cord injuries	[redacted]
14	Social care costs as per McDaid et al. (2019), based on professional home care for tetraplegia AIS-ABC grade spinal cord injuries	[redacted]
15	Social care costs as per McDaid et al. (2019), based on professional home care for AIS-D grade spinal cord injuries	[redacted]

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#	Scenario	VHL-GB MA population ICER
16	Proportion receiving immediate surgery in SoC arm reduced to 80% in RCC & pNET cohorts and to 40% (with additional 40% receiving equivalent sequelae) in CNS Hb cohort	[redacted]
17	Reduce metabolic consequences risk: ESRD/dialysis for RCC surgery to 60% (consequently CKD increased to 40%), stroke for CNS Hb surgery to 65%, diabetes and immunocompromisation for pNET surgery to 80%.	[redacted]
18	Omit the adjustment to risk metastases based on the Optum Clinformatics Data Mart data.	[redacted]
19	Omit relative risk adjustment of non-metabolic surgical complications and perioperative mortality risk	[redacted]
20	Distribution for ToT: Weibull	[redacted]

Note: ICERs are not severity-modifier adjusted.

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Appendix 7D: Deterministic sensitivity analyses (DSA) around revised base-case (with PAS)

Figure 9 DSA Tornado diagram for belzutifan vs. SoC with revised company base-case in the VHL-GB MA population (PAS price – ICERs unadjusted)

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Appendix 7E: Probabilistic sensitivity analyses around revised base-case (with PAS)

Table 11 Probabilistic results with revised company base-case (with PAS)

Technologies	Total costs (£)	Total QALYs	Total LYs	Incremental costs (£)	Incremental QALYs	Incremental LYs	ICER vs. comparator (£/QALY)
VHL-RCC cohort *(weighting 15%)*							
Belzutifan	[redacted]	[redacted]	[redacted]	-	-	-	-
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VHL-CNS Hb cohort *(weighting 80%)*							
Belzutifan	[redacted]	[redacted]	[redacted]	-	-	-	-
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VHL-pNET cohort *(weighting 5%)*							
Belzutifan	[redacted]	[redacted]	[redacted]	-	-	-	-
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VHL- GB marketing authorisation population (weighted cohort)							
Belzutifan	503,089	6.26	14.39	-	-	-	-
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: ICERs are not severity-modifier adjusted.

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Figure 10 PSA Cost-effectiveness plane with revised company base-case in the VHL-GB MA population (PAS price – ICERs unadjusted)

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Figure 11 Cost-effectiveness acceptability curve (CEAC) with revised company base-case in the VHL-GB MA population (PAS price – ICERs unadjusted)

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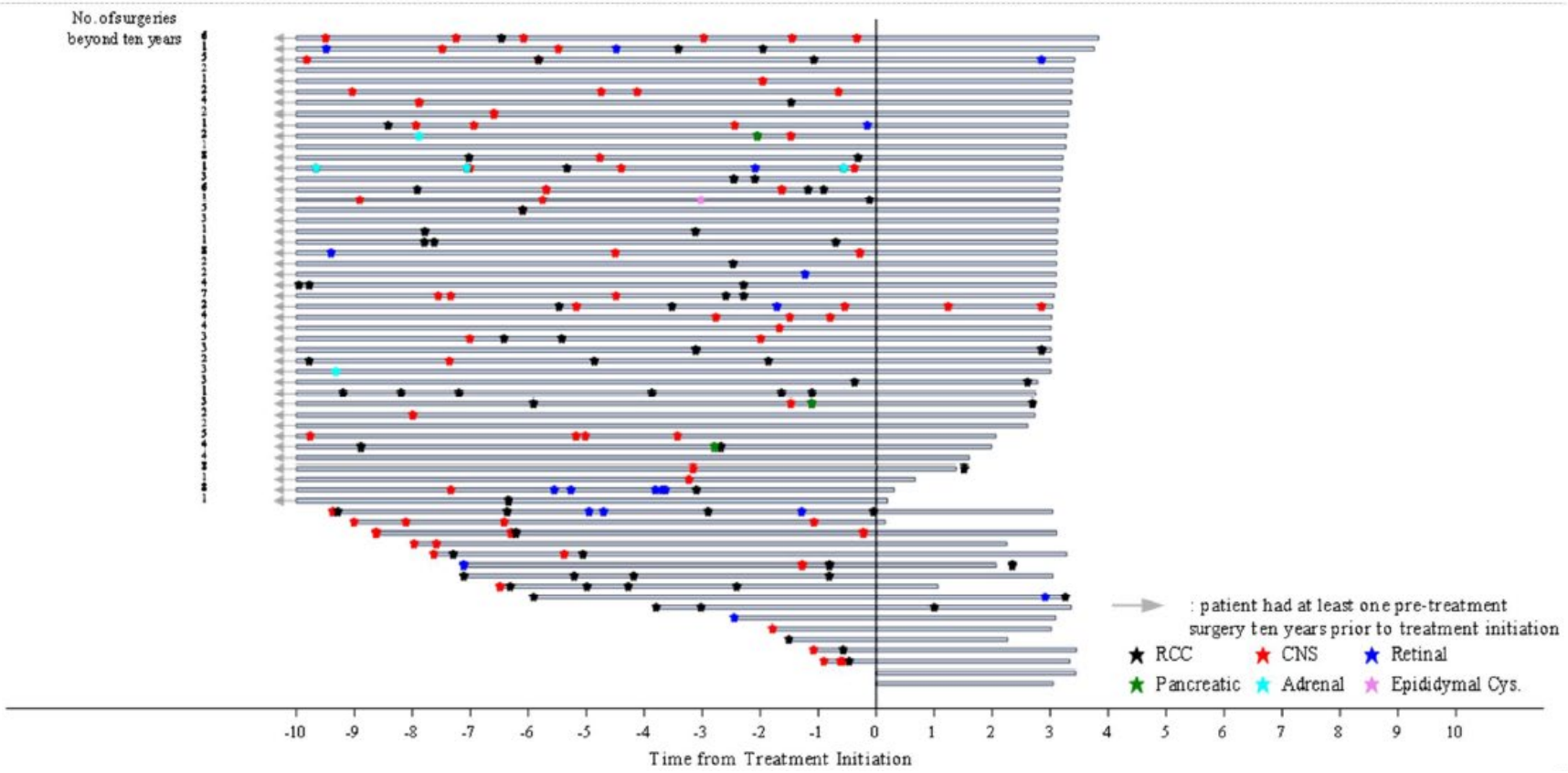
Appendix 8: Treatment effect of belzutifan on key surgical rate outcomes

Figure 12 Distribution of all surgeries pre- and post-treatment initiation over time for individual patients - safety analysis set



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Horizontal bars represent each patient.
Only pre-treatment surgeries less than 10 years prior to treatment initiation are presented.
Length of the bars on the right side of the y-axis represents duration of treatment at time of data cut-off.
Surgery is defined as a tumour reduction procedure excluding radiation.
Date of Data Cut-off: 01-APR-2022.

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Action Kidney Cancer

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	MSD £15,000 Ask the Expert video project Ongoing
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Von Hippel Lindau disease (VHL) is a rare genetic, multi-system disorder caused by a mutation in the VHL gene. This mutation causes cells to grow abnormally, resulting in the development of cysts or tumours, primarily in the kidneys, brain, and pancreas. This can lead to renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, and pancreatic neuroendocrine tumours (NET). Patients can have multiple tumours in different organs. The committee have accepted that VHL is a rare condition, affecting only 842 people in the UK (a prevalence between 1 in 68,000 to 1 in 91,000). It is estimated that no more than 300 people in England

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	are eligible for belzutifan treatment in its licensed indication. Because VHL is a genetic condition, patients are often very young, with a mean age of 26 years at diagnosis. Nearly all people with VHL have symptoms by the age of 65. VHL is a lifelong condition. People live with constant pain, loss of balance and motor skills, loss of vision, breathlessness, coughing, headaches, confusion, severe nausea, and fatigue. People also live with the constant worry of the development of new tumours and the disability caused by surgery. These symptoms severely impact the quality of life of the patient and their family and carers who are supporting them. Because people are young when they are diagnosed with VHL, they can live for many years with these symptoms. They live with the constant fear of surgery and its risks, especially CNS surgery that can have catastrophic outcomes resulting in severe neurological deficit, loss of eyesight or death. This severely impacts the mental health and wellbeing of the patients, their family, and carers. The psychological and physical burden of multiple complex surgeries needs to be considered. Currently, the only treatment for VHL tumours is surgery and other localised procedures, such as ablation. People often have multiple surgeries throughout their lives to remove tumours. This can lead to the loss of eyesight, chronic kidney disease, or diabetes, leaving patients needing lifelong medical intervention, such as dialysis and insulin replacement. There are no other treatment options for these patients. Any systemic anti-cancer treatments that are given are widely accepted by physicians as ineffective and are used as a last resort because there are no other options. There is a significant unmet need for an effective systemic anti-cancer treatment for this condition, to reduce the need for surgery and subsequent medical intervention. We do not understand why belzutifan for VHL was not appraised as a highly specialised technology because of the small target patient population (well within NICE's definition of a rare disease prevalence of 1 in 50,000), the distinct nature of this population, the chronic and severely disabling nature of the disease, the high unmet need for a systemic treatment, and the potential for prolonged use, especially in patients who are diagnosed when young. The decision to disregard the highly specialised technology route for appraisal shows a complete lack of understanding of the complexity and uniqueness of VHL disease and its impact on patients, their families, and carers.
2	The committee is not willing to consider belzutifan for inclusion in the Cancer Drugs Fund (CDF) due to uncertainty about the clinical evidence and the economic modelling of cost-effectiveness. Because of the small patient population, the appraisal is based on data from an open-label phase II study (LITESPARK-004) for patients with VHL-associated RCC (although patients could have other tumours), which is currently ongoing. A total of 61 patients with VHL-associated RCC were enrolled in the trial. Of these patients, 22 also had pancreatic neuroendocrine tumours, 50 had CNS hemangioblastomas and 12 had retinal hemangioblastomas. Inclusion of belzutifan in the CDF for up to 3 years would enable collection of further clinical evidence from this rare group of patients, both from the LITESPARK-004 trial and real-world data from the clinic. This would help to resolve the uncertainty regarding clinical evidence and cost effectiveness for this complex disease involving multiple tumour types. It would also enable the collection of further data to confirm the clinical effectiveness of belzutifan for the treatment of pancreatic and CNS lesions, data that is deficient from the LITESPARK-004 trial. At the same time, the CDF would allow access to belzutifan for patients looking for an effective, tolerable, and easily administered systemic treatment offering a potential long-term response, the avoidance of multiple complex and sometimes dangerous surgeries, and less medical intervention for chronic kidney disease, diabetes, neurological deficit or paralysis, and loss of eyesight.
3	The committee accepts that the only treatment for VHL patients is regular surveillance and surgery to remove tumours once they meet certain size criteria or become symptomatic. There is no treatment that addresses the underlying cause of VHL. Surgery can be complex and dangerous, especially for CNS and retinal hemangioblastomas, and tries to preserve organ function. However, multiple surgeries can

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	result in bilateral nephrectomy or chronic kidney disease and the need for dialysis, pancreatectomy and long-term diabetes, neurological deficit or paralysis, or loss of eyesight. The development of multiple tumours and the need for multiple surgeries and the subsequent potential complications is emotionally challenging for both the patient and their families and carers. This can lead to psychosocial issues, such as anxiety, depression, low self-esteem, and relationship problems. Patients also worry about passing the VHL gene onto their children and grandchildren. Patients experience difficulties with daily living and often need support from their family and friends. Multiple surgeries and the subsequent complications and morbidities come at a high cost to patients in terms of their effect on quality of life, and a high financial cost to the NHS due to the number and complexity of surgeries, the longevity of the morbidities and the medical interventions needed. Belzutifan has proven to be effective and well tolerated in the LITESPARK-004 study, where disease control rates were more than 90% for all VHL-associated tumour types. Because belzutifan was effective at reducing the size of VHL tumours, there was a dramatic reduction in the number of tumour-reduction procedures after the start of belzutifan treatment in the LITESPARK-004 study. In the 10 years before treatment began, 327 procedures were performed in the 61 patients in the study. In the 2.5 years after treatment with belzutifan started, there were only 3 procedures. This is shown in Figure 1 in the publication in the NEJM: Belzutifan for renal cell carcinoma in von-Hippel-Lindau disease. In another publication in the Journal of Clinical Oncology belzutifan was estimated to decrease annual surgery and complication costs by 96% in a trial-based cost-consequence analysis. This was based on observed reductions in VHL-related surgeries: Burden of surgeries and surgical complications in patients with Von Hippel Lindau (VHL) disease before and after treatment with belzutifan. These publications show that not only can the use of belzutifan for the treatment of VHL disease reduce the number of surgeries, but this also results in a cost-benefit for NHS England. The reduction in the burden of multiple surgeries for patients is priceless in terms of the improvement to quality of life for VHL patients and their families and friends. Patients may be hospitalised for many days or weeks following surgery, during which time they start rehabilitation. This requires physiotherapy to encourage the patient to walk and pain relief with opiates while they recover from surgery. Recovery and rehabilitation can take at least 6 weeks, sometimes many months before patients get back to daily activities, such as shopping, driving, exercise, gardening, housework and returning to work. This has a major impact on their lives and reduces their quality of life while they are in recovery. It also has a financial implication to both the patient and the family or carers if the patient is not able to work during recovery from surgery, especially if complications arise and recovery takes longer than expected. Some patients and/or family members or carers are required to give up work altogether and are not able to work due to the consequences of surgery. This obviously has major implications on the quality of life for both the patient and their family or carers and a huge financial impact for the family if one or more family members do not have an income. The most important outcomes of treatment for both the patient, family members and carers are living for as long as possible with a good quality of life. Being able to go back to doing the things that they could do before their diagnosis, such as working, enjoying holidays, and socialising with family and friends, without the constant worry of multiple surgeries.
4	Belzutifan has proven to be effective and well tolerated and was granted priority review status by the FDA. Having priority review status, belzutifan was fast tracked for approval in the USA, where it has been available since August 2021. It also became available in Canada, Australia, and Scotland in 2023, based on the phase II LITESPARK-004 trial data. We already know that some VHL patients and their families are seriously considering relocating to one of these countries to access belzutifan.

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5	Belzutifan is an innovative new treatment for VHL-associated RCC, with a new mode of action. There is no recognition in the draft ACD of the fact that this drug is a well-tolerated, innovative, multisystemic treatment that is transforming the lives of VHL patients in the real world. Currently, patients with VHL-associated RCC are treated with immune checkpoint inhibitors in the first line. This requires regular and frequent clinic visits (every 2-3 weeks) for immunotherapy infusions. Clinic visits for immunotherapy infusions often take place in regional cancer centres, requiring patients and their accompanying family members or carers to travel long distances, sometimes with an overnight stay. This has financial implications for the family in terms of travel and accommodation expenses and time off work. Belzutifan is a tablet that can be taken at home, thereby negating the need for clinic visits for infusions every 2-3 weeks and their associated impact on quality of life and cost to the patient and family.
6	Currently, English cancer survival rates trail behind other comparable European countries, including Denmark, Ireland, and Norway. If NHS England is to improve patient outcomes, including patient experience as well as overall survival, it is vital that innovative new treatments are made available to patients to allow them treatment options and the best care possible. If these drugs are not made available, it leaves English and Welsh patients at a disadvantage in terms of the availability of innovative cancer treatments; these patients are discriminated against and are likely to die prematurely compared to North America, Australia and Scotland, where there is greater choice of effective treatment options.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	VHL UK/Ireland
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment	None

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companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	VHL UK/Ireland strongly disagrees with the TSOP decision not to review belzutifan (Welireg) for VHL via the HST route which would have given much greater flexibility around some of the uncertainties outlined in the draft guidance. The NICE website states: *The HST Programme is designed to be used in exceptional circumstances and its purpose is to evaluate technologies for very rare diseases that have:*

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	1. *small numbers of patients* 2. *limited or no treatment options* 3. *challenges for research and difficulties with collecting evidence, because of the uniqueness of the disease.* On the published Highly Specialised Technologies (HST) criteria checklist, criteria 1 and 4 were NOT MET for this appraisal. 1. *NOT MET Criteria 1: The disease is very rare defined by 1:50,000 in England* At the 1st committee meeting 8th November 2023, NICE themselves quoted on their own slides *"Prevalence between 1 in 68,000 to 91,000 in England with 842 people in the UK"* https://www.nice.org.uk/guidance/indevelopment/gid-ta10817/documents (Supporting Documentation (Published 23/08/23). This clearly MEETS their own criteria set for rare diseases. VHL UK/Ireland therefore considers it unacceptable and grossly unfair that this criterion was not met. The rarity is further supported by criteria 2 being MET where the estimate that no more than 300 people in England are eligible for the technology in its licensed indication and no more than 500 across all its indications, is accurate. 2. *NOT MET Criteria 4: There are no other satisfactory treatment options, or the technology is likely to offer significant additional benefit over existing treatment options.* VHL UK Ireland strongly disagrees with the reasoning for this decision on several counts, and it shows a complete lack of understanding of the complexity of VHL and its impact on the patient and their carers. Now the committee has heard more about VHL, we think this should be reconsidered in conjunction with the following feedback: • Each tumour type and its surgical treatments have been considered in isolation (PNET/RCC/CNS) and there has been no recognition of the fact that VHL patients can have a combination of all three manifestations (and others not within the indication), simultaneously, concurrently, and recurrently. There is also no recognition of the cumulative human effect of the great many surgeries some patients must risk/endure in their lifetime and the subsequent impact on both their physical and mental well-being and that of their carers. • The suggestion that a patient living with kidney failure, dialysis or type 3c diabetes can still maintain some quality of life is offensive, especially when they could need a combination or all of these. Prof. Drake highlighted the truly devastating impact of living without a pancreas gland at the committee meeting. • The suggestion that surgeries for CNS tumours are 'often successful' but may 'seem undesirable', is offensive. 'One' CNS surgery might 'seem' undesirable but multiple surgeries that carry catastrophic risks every time and can often result in severe neurological deficit or death is terrifying for patient and carer.

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	With each successive surgery, there is a sense that you are simply putting off the inevitable and the odds are always against you. • The suggestion that there are further treatment options for metastatic disease in VHL is inaccurate. These treatments are widely accepted in the medical field as ineffective. They are only used as a last resort because there is no other option. • The criticism of medically SIGNIFICANT trial data because of its mismatch to the MHRA marketing authorisation, and the suggestion that belzutifan would 'not treat the underlying disease', is weak, and dismissive of a trial that produced excellent results to the targeted tumours AND in addition, other types of tumours. There is no recognition of the fact that this drug is a well-tolerated, innovative, multisystemic treatment that is transforming the lives of VHL patients in the real world. 3. Finally, although not listed as a formal criterion on the checklist, NICE states the HST route is also used where there are '*challenges for research and difficulties with collecting evidence, because of the uniqueness of the disease*.' • VHL/UK Ireland feels that the consultation paper from NICE is arguing EXACTLY this in section 3.16. The committee has indicated it is not confident in the data provided by the company but also that it would not be possible for the CDF to collect the data either. • VHL does not follow any typical trajectory and no two patients are the same regarding their manifestations, locations, frequency, progression rates and surgical outcomes. One patient may have no surgery during their whole lifetime, another may have 40+ including multiple loss of organs and dire QOL consequences such as paralysis, dialysis, type 3c diabetes and sometimes a combination of all of these. • Even in the same family, where the genetic mutation is exactly the same, no two patients will have the same manifestations. This, coupled with a lack of data collections in the VHL population in general makes the economic modelling extremely challenging, which has been acknowledged on multiple occasions by NICE and the EAG. Therefore, VHL is an ideal candidate for the HST route. Based on all of the above, VHL UK/Ireland fails to see why belzutifan was not accepted into the HST route; the charity believes that this would have provided the flexibility needed to enable the committee to make a positive decision on funding. VHL UK/Ireland believes that belzutifan for VHL could meet all of the HST criteria listed in point 28 for a Minister's referral and can see significant additional benefits from prescriptions routinely being made via chosen specialist centres, therefore avoiding any regional discrimination/inequalities with regard to access: https://www.nice.org.uk/media/default/about/what-we-do/nice-guidance/nice-highly-specialised-technologies-guidance/hst-interim-methods-process-guide-may-17.pdf

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2	Para 3.1 of the Draft Guidance. VHL UK/Ireland considers that the Committee, through the EAG, has failed to comprehend the severity of having several multiple symptoms of VHL concurrently, consecutively and recurrently over a whole lifetime. This is a common factor of VHL disease. This situation then leads to decisions having to be made as to not only when each surgery is advisable, but also which type of surgery is to be given priority over another (with minimum recovery time in between each one). Belzutifan will have a simultaneous effect on multiple tumours. Every patient's health path is different, so trying to make a meaningful generic health model is extremely challenging because of the uniqueness of the disease. Calculations of averages, when related to the surgical outcomes that can have life-changing effects or even death are meaningless when compared to prescribing belzutifan that can, for the first time ever, stabilise multiple tumours (and multiple tumour types) from progressing concurrently, and shrink tumours sometimes to the point of No Evidence of Disease. The need for surgeries may be avoided indefinitely.
3	Para 3.2 of the Draft Guidance states that surgery and other localised procedures are the main treatment options for people with VHL – we would argue that they are the **ONLY** current options available. There is a **huge unmet need** for an alternative to surgery for VHL patients, particularly if that surgery is dangerous or undesirable. In 2019, the technology behind this drug was considered sufficiently innovative to be awarded the Nobel Prize in Physiology or Medicine. An article about Nobel Prize https://pubmed.ncbi.nlm.nih.gov/36650918/ states that: "*The first report of VHL disease was in 1894, meaning the development of a specific drug for this disease took almost 125 years".* The charity believes one of these Nobel Prize winners, Sir Peter J Ratcliffe has made his own comments on this consultation. It would be a travesty if VHL patients in England, (also Wales and Northern Ireland if those countries follow the NICE decision) were now denied access to this medication.
4	Para 3.4 of the Draft Guidance - Belzutifan marketing authorisation and positioning. Please see comments by Dr. Eric Jonasch at point 14 below in respect of this aspect of the appraisal.
5	Para 3.5 of the Draft Guidance - Relevant Population. The original trial was designed for RCC patients only and proved far more successful than originally envisaged, in that CNS tumours and pNETs also reduced in size or disappeared altogether. The draft guidance is critical of this mismatch and VHL UK/Ireland feels that patients are being severely discriminated against because of this positive outcome. Patients who required imminent surgery were (quite correctly) not allowed onto the trial, as there was no guarantee that the drug would be successful, but now this seems to be causing issues with the decision-making in terms of the requirements of the MHRA approval.
6	3.16 of the Draft Guidance – Cancer Drugs Fund. The following statement "*The committee also noted that the Cancer Drugs Fund may provide the opportunity to collect additional data to address some uncertainties about belzutifan's efficacy in clinical practice. But it thought that whether this would provide data to address the issues of its comparative effectiveness compared with standard care was uncertain"* suggests that

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	even with the use of the CDF to collect more data, the committee does not feel that this would be sufficient yet is highly critical of MSD for not being able to produce the data either. This suggests that the committee's decision is already finalised, regardless of any other data which may become available, and members are not prepared to even attempt the gathering of further data to prove/disprove the economic modelling. This committee therefore must acknowledge that VHL is a disease which has extreme challenges for research and difficulties with collecting evidence because of the uniqueness of the disease, which is a criterion for the HST Programme. VHL UK/Ireland cannot see why the CDF approach has been denied, when it is the ideal way to gain the further real-world evidence that the committee has asked for, whilst also giving patients most in need access to the drug.
7	3.17 Other Factors. The use of the natural history study is in place of a control arm to the trial, but it should be noted that VHL patients have **NEVER** seen natural regression of tumours. It is also important to note that had belzutifan been approved for the HST route, there would have been greater flexibility in the ICERs.
8	VHL UK/Ireland considers that VHL is probably the most severe and complex disease that NICE has ever been asked to assess. It seems that there is a problem in understanding that belzutifan does not treat the VHL genetic disease, but is extremely effective in treating the symptoms caused by having the genetic condition.
9	The models used fail to account for belzutifan acting on tumours in parallel, whereas surgeries have to be done serially with recovery time in between; also, the psychological impact of multiple surgeries over time is increasingly cumulative, leading to the possibility of a complete mental breakdown. There is very little data available to quantify this aspect of a VHL patient's life – a sentiment which is reflected in our interview with Dr. Eric Jonasch who is already successfully prescribing belzutifan for his patients in the USA. Please see point 14 below.
10	VHL UK/Ireland notes that there is a blocking difficulty in reconciling models of two studies which had different patient profiles and suggests a more pragmatic approach is required as has been used by other worldwide establishments in already approving belzutifan. For example, Australia approved on 20 December 2022, with the comment that *"The pivotal study for this submission, Study 004, was a single arm study with endpoints of ORR and DOR. The lack of a comparator group is considered acceptable in the context of a rare and serious disease for which there is no systemic therapy established as a standard of care. The natural history study supports that spontaneous shrinkage of a tumour that meets RECIST criteria is unlikely, therefore, tumour shrinkage can be attributed to belzutifan. The small sample size of 61 is acceptable in this setting and is accounted for in the statistical analysis plan"* https://www.tga.gov.au/sites/default/files/2023-09/auspar-welireg-230913.pdf
11	There is major omission with the committee failing to take into account the large amount of real-world patient data presented in two VHL UK/Ireland patient surveys. This includes information including (but not limited to):

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	VHL UK/Ireland conducted a survey amongst patients already using belzutifan in June 2023 (VHL UK/Ireland Patient/Carer belzutifan (Welireg) Survey June 2023- Summary (vhl-uk-ireland.org)) It shows that ALL respondents surveyed experienced some form of stability (61% on one or more tumour/s), slowdown of growth (66% on one or more tumour/s), reduction in size (66% on one or more tumour/s), and in some cases disappearance of some tumours (27% at least one tumour). Belzutifan will therefore limit the need for multiple, high risk, invasive, life limiting (and sometimes life threatening) surgeries. The survey shows 80% of patients already using belzutifan (Welireg) believe they have avoided imminent surgeries. The survey also shows improvements in quality of life for both patients and carers for current users of belzutifan. 68% of patients said it had improved their own quality of life and 88% carers reported theirs had improved. The summary shows expected positive outcomes to social/ leisure activities (70% patients/88% carers), independence (68% patients/75% carers), relationships, work/career, education, and ability to travel. It also demonstrates that belzutifan will have a positive impact on the mental health of both patient (84%) and carer (88%), reducing worry about VHL (82% patients/75% carers) and being more able to plan for the future (82% patients/88% carers). The results published online in the link above include several personal testimonies from patients using belzutifan and how it has impacted their lives, in their own words (e.g. “I was facing a challenging pancreatic tumor surgery. Taking belzutifan has reduced the size of those tumors. I will gladly trade the fatigue and headaches for keeping my pancreas”).
12	VHL UK/Ireland feels that the appraisal has continued to be weighted towards Clear Cell Renal Cell Carcinoma (ccRCC), despite the widening of the MHRA approval to include CNS Haemangioblastomas (HBs) and Pancreatic Neuroendocrine Tumours (pNETS). CNS HB’s carry the greatest morbidity; pNETs carry the same metastatic risks as RCC. Although the clinical experts are extremely knowledgeable on RCC, Professor Drake’s addition was very last minute despite him holding regular VHL clinics and being the only clinician present at the committee who has seen VHL patients in the last ten years. With the disease having such complexity, we feel that the clinicians should have included a neurologist and an endocrinologist, as well as urology and oncology specialists. We also note that there is a bias towards RCC on the NICE website pathway to the belzutifan appraisal – VHL RCC is not currently treatable with the drugs that are currently available to treat non-VHL related RCC. VHL should have its own pathway, as for example, does cystic fibrosis, which is listed as a “highly-complex disease”. https://www.nice.org.uk/guidance/conditions-and-diseases/cystic-fibrosis https://www.nice.org.uk/guidance/conditions-and-diseases/cancer/renal-cancer VHL UK/Ireland recommends that the current legacy bias of belzutifan being placed under "cancer/renal-cancer" should be removed. It currently gives a very false impression of the potential of this "paradigm shift" drug. This can be done by having "von Hippel-Lindau" as a new website navigation path: https://www.nice.org.uk/guidance/conditions-and-diseases/vhl-von-hippel-lindau and puts it on par with cystic fibrosis. Furthermore the new path will provide for expansion for any more specific future VHL drug appraisals.

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13	VHL UK/Ireland does not feel that enough emphasis is being placed on the quality-of-life improvement which belzutifan will provide for patients. It is true that a patient without kidney function can have dialysis; but when you add that to the possibility that the same patient may have a life-long insulin dependency, vision impairment or partial paralysis, the cumulative effect can be devastating. These issues are not either/or situations for VHL patients, each patient can suffer from a range of these conditions simultaneously. This lack of appreciation is also emphasised by Dr. Eric Jonasch – see point 14 below. It is unclear to VHL UK/Ireland that in the comparison of belzutifan instead of surgery, the cost comparison has included the total POSITIVE value of the life-changing IMPROVEMENT that can occur from belzutifan versus the total NEGATIVE value of the life-changing DEGRADATION of surgery over the patient's lifetime.
14	On 19th December 2023, a team from VHL UK/Ireland charity spoke with Dr Eric Jonasch, MD Anderson Cancer Centre, Texas, USA. Dr Jonasch is a physician researcher focused on von Hippel-Lindau disease and renal cell carcinoma. Dr. Jonasch has led the VHL Clinical Center at MD Anderson Cancer Center in Houston Texas for 21 years. He has also served on the Board of the VHL Alliance. He is involved in clinical care, clinical research and in basic research on von Hippel-Lindau disease. Dr. Jonasch led the registrational clinical trial testing belzutifan in patients with von Hippel-Lindau disease. The questions and responses are summarised as follows: **Q. How many VHL patients do you see?** Around 150 patients currently **Q. How many of these are using belzutifan (Welireg) ?** Approx 50 patients **Q. At what point are you starting patients on belzutifan? What are the qualifying criteria?** I'll give 2 book end examples (to avoid suggesting restrictions) A person I **would not** recommend treating with belzutifan: A person in their early-mid 20's, with 1 RCC that looks around 2.5-3cm and so looks like it is going to need some sort of intervention in the near future. Possibly some other tiny hemangioblastomas but nothing that looks like it might be causing any problems for the foreseeable future whereby performing a procedure here, you are going to reset the clock for a significant period of time and sparing them going on systemic therapy. A person I **would** recommend treating with belzutifan: Late 30's/Early 40's. Several hemangioblastomas, PNET, multiple renal lesions, may have had prior interventions and they're basically facing a whole series of procedures that would be needed over the next few years. That person is a great candidate for belzutifan. Another exception where I

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	would use it is patients who have retinal hemangioblastomas which are close to the nerve and where there would be significant risk to their sight to perform a procedure. **Q. How many of those patients fall within the UK Marketing Authorisation (MA) for belzutifan (Welireg), which may be different from the USA's approach:** *("Treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for VHL-associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumours (pNET), and for whom localised procedures are unsuitable or undesirable.")* This is where shared decision making between the patient and physician will come into play as it is so different from person to person. There are some individuals (for example) who are very averse to surgery, that don't want to have procedures done to them, for whatever reason. There are some individuals who are more open to that (surgery). So, this should be dictated by the needs of a particular patient in conjunction with a discussion with a physician. **Q. What difference does it make to them clinically and to their QOL?** For a health authority to say 'Oh, they can just have surgery', well maybe we should ask them how they'd feel about that. The quality-of-life affects the post-surgical recovery. Chronic pain after being subjected to multiple procedures, productivity impact, psychological impact to have to submit oneself to these multiple procedures. Collectively we have done a bad job of measuring the subjection to multiple procedures in the VHL patient population. The psychological burden cannot be ignored and must be put into consideration. **Q. Do you believe what you have seen in the trials/in practice would apply to the UK MA (there is a concern that the gap between the trial data which understandably excluded any patients who needed surgery to avoid metastatic RCC and the UK MA population). Do you think it would be effective still at a later stage? Would it have time to take effect and avoid surgery?** You absolutely do not want an individual developing metastasis (e.g. stage 4 RCC). This a highly undesirable and inappropriate outcome for individuals with VHL disease. There are reasons why this may happen, but it is quite undesirable, and you want to intervene before there is a risk of that. There are buffers in place (via guidelines) to hopefully avoid this scenario (although there are reasons why it can happen). When a patient has (multiple) manifestations that are not necessarily lethal individually but are all potentially problematic in the near future, this is very good example where a systemic therapy is highly appropriate. **Q. What response time are you seeing typically for each tumour type?** Within the 3-12 months range (it varies on the lesions. Hemangioblastoma quite quickly, RCC slightly slower).

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Belzutifan for treating tumours associated with von Hippel-Lindau disease [ID3932]

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	Q. Do you have any quotable stats showing pre belzutifan (Welireg) and post belzutifan (Welireg) surgical procedures? Figure 1D (New England Paper Belzutifan for renal cell carcinoma in von-Hippel-Lindau disease) clearly shows the number of procedures leading up to initiating therapy reduce from 20 (of 61 patients so essentially 1 every 3 years per patient) to almost zero. So, it is reducing the number of procedures these people need. There are updates in abstract from with follow ups to that data – showing a slight increase in the number of procedures but it is still vastly lower than preinitiation (of belzutifan). (Dr Jonasch forwarded this link with permissions to share after the meeting). **Q. How long are patients staying on belzutifan (Welireg)? If they have surgery, are they stopping?** There is a wide spectrum of tolerability. Majority of patients from the trial remain on the drug. Very few have stopped because of progression. Vast majority of them had multiple lesions. You may get one rogue lesion; we then treat that one surgically and maintain them on the drug because everything else is under such good control. We are seeing younger individuals who are very physically active etc who find that as the main side effects are fatigue (3 main are fatigue, Hypoxemia, less with under 50s and anaemia to varying degrees), even when the other two are controlled, fatigue is subjective. Some find the degree of fatigue unacceptable and may choose the surgery over the drug because they don't like the way it makes them feel. It is a minority but a distinct group I have observed. **Q. Why did people drop out of the trial?** The USA health care system can be a challenge. Even though the trial is effectively 'free', patients still have to travel (often cross state, with accommodation etc) to the participating medical centres which can make staying in the trial for years quite burdensome for years and years, (financial and general disruption). They may restart off study on the drug, but it is patient choice. I literally have a number of patients who could simply not afford to stay on the study. **Q. What about dosage amendments on the study?** That is the problem with CTCAE grading – grade 1 or 2 fatigue does not warrant a dosage reduction but in real life that can be a draining existence. So, in the real world, we are being much more liberal in dose adjustments and reductions to allow individuals to match the quality of life to their desired activity levels. Re the study it is the case that dosage reduction was not an option on the trial and why some patients came off it. **Q. Would you use belzutifan for metastatic RCC?** We don't have data re whether VHL metastatic patients react to standard therapies in the same way a non VHL RCC patient does – my gut feel is, they don't respond as well to standard therapies which I think has to do with the biology of a VHL patient. Too few data

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	points to be sure. Should we be considering Belzutifan as front-line therapy if these individuals develop metastatic disease, is a question we don't have an answer for yet, but it could be a reasonable choice. **Q. Some reference to costings were made during the discussion:** From a $ perspective pricing is extremely high but what's so intangible in the VHL community is to quantify the burden of surgery on patients living with VHL. It is not effectively quantified anywhere currently. Hard to justify from financial perspective. Likely more scans and monitoring (at least initially). It's beyond the cost, it's the Aggregate quality of life in a subset of individuals who would otherwise be tortured by repeated surgical procedures and the aftermath. For individuals of multiple surgeries, what does that do to their ability to function in society? What does it do to their mental and physical state? Consequences of multiple surgeries on the individual? **Q. Do you think the impact of each individual surgery added together is more than the sum of each individual surgery?** Yep. Reviewers really need to think about what life would be like if they had 6 major surgeries, say 3 to the brain, 1 to their pancreas and 2 to their kidneys. what would life be like ? **Q. In your opinion, as a physician, what did life look like for VHL patients before belzutifan vs now?** It has provided a very meaningful alternative to surgical procedures. It is not an absolute replacement, but it is a choice that has had a profound impact on a subset of individuals, from a quality and I think even quantity of life perspective. We are still looking at what we need to do next, but it is a dramatically positive addition to the choices that we have and it is essential.

Insert extra rows as needed

Checklist for submitting comments

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- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
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Belzutifan for treating tumours associated with von Hippel-Lindau disease [ID3932]

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- Do not use abbreviations.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Prof William Drake

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Belzutifan for treating tumours associated with von Hippel-Lindau disease [3932]

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	None
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Prof W Drake

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	My clinical opinion, based on a large vHL practice, is that local manifestations of vHL should be dealt with by local means (surgery or, in the case of screen-detected small cerebellar lesions, stereotactic radiation). This applies to almost all patients in my clinic. I have 2-3 patients (out of 60) for whom I believe medical therapy with Belzutifan would be appropriate. They are those for

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	whom the next surgical intervention for already-operated on pancreatic/renal disease would result in being anephric (dialysis-requiring) or apancreatic; and those for whom a large, compressive cranio-cervical junction haemangioblastoma requires surgery where the risk of life-changing morbidity (paralysis, ventilatory support, unable to feed) is unacceptably high. I totally understand (and definitely respect the academic expertise involved) the need to generate economic models of disease, but in this particular disease I believe it is just too difficult to do that in a clinically meaningful way. Such a small proportion of vHL patients requiring Belzutifan could be monitored effectively by a national panel (or MDT) that could meet virtually to review cases and advise.
2	
3	
4	
5	
6	

Insert extra rows as needed

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- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	UK Kidney Association

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nothing to disclose
Name of commentator person completing form:	Professor Patrick Maxwell

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	While I commend the committee on its thorough evaluation of the evidence, I consider that it is wrong that this approved and effective medicine should not be available to NHS patients with VHL disease.

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2	The committee highlighted that the main trial was small. However, the trial involved 61 patients, which I would regard as an impressive size of trial in a condition that is so rare. In addition, the committee highlighted that the criteria for inclusion in the study were different from the marketing authorisation. However, I consider it was appropriate that the trial focussed on patients who did not need surgery at the time of recruitment, whereas a decision to initiate treatment of an NHS patient will be in a different context.
3	A specific point that I would like the committee to consider is that in the MK-6482-004 study, Figure 1D shows a reduction from about 26 operative procedures a year over two years prior to starting belzutifan, to 2 (or fewer) procedures per year over two years on treatment. I regard this as compelling evidence that belzutifan reduces the need for complex and expensive procedures that carry significant risk.
4	A second specific point that I would ask the committee to consider is that the feasibility of further studies will be very challenging from an ethical standpoint, since there is clear evidence that belzutifan is effective in stabilising and shrinking VHL related tumours in the kidneys, pancreas and CNS, and that it is safe.
5	
6	

Insert extra rows as needed

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Single Technology Appraisal

Belzutifan for treating tumours associated with von Hippel-Lindau disease [3932]
Comments on the draft guidance received through the NICE website

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Has all of the relevant evidence been taken into account?

Yes

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I thought you could have done a broader study involving more people because the summary I made from reading the documents was that there was not enough evidence, or gaps in your evidence.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I found it was not clear on who your small group of participants are to be able to answer if there is any direct discrimination.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

I am unsure. This drug has shown many benefits and improvements in America.

The Recommendations advise of a small study. Why were not more VHL patients invited to participate in the Study? You could have got a greater and better understanding of the benefits for your decisions. Scotland has already approved Belzutifan for VHL - Scotland and England are under the same NHS so this is conflicting.

Dear Nice,
I am saddened to read that you are to decline the use of Belzifen for treating Von Hippel-Lindau in England. From reading all the documents, I gather the general refusal is due to the cost of this drug.

I was also saddened to read in the draft guidance consultation that in study MK-6482-004 you did not collect any quality of life data. This would have been a big factor because quality of life is a huge factor in human life.

My father had VHL, he was de novo and I unfortunately inherited it. My father had brain tumours, multiple eye tumours and had to have both kidneys removed meaning he was on dialysis. He died 3 years after diagnosis, when I was 10. I am now 37.

Since then, I have had multiple eye tumours and surgeries resulting in lots of complications and being left with little sight in one eye. If I lose the sight in my left eye, it will be very detrimental. I'll have to give up my job and I would not be able to drive, I'd need someone with me when leaving the house, thus meaning I will become isolated in my home, which will impact my mental health and those around me.

I have also had a partial nephrectomy due to RCC. I was fortunate to have had it all removed, but the recovery was brutal. I needed several months off work and needed a lot of care. I know this will return and I can't imagine how hard it will be to recover being older.

I also have tumours in my spine and one tumour in particular at the location of the cervical medullary junction. My neurologist has clearly stated the he is loathed to intervene at this location because it is like spaghetti junction and he has told me that intervention would cause permanent and catastrophic consequences for me. The same consequence will occur if it continues to grow. This area will mean that if the tumour continues to grow like it has, or surgical intervention is done, I will be paralysed from the neck down and incontinent. Belzuitfan really is my only option and hope.

In the report there was mention of people have scan anxiety. I don't have scan anxiety, I have 'diagnosis fear' from the impact of the strain on the NHS system meaning consultants and radiographers are under extreme pressure and pushed to their limit. On top of being diagnosed of tumours in different areas, I also find it very traumatising to be informed of results in letters. For example, I was diagnosed with RCC and then shortly after I was diagnosed with a spinal tumour via a letter! I had kept saying I hadn't seen any previous reports on my spine – it had never been scanned. I was devastated to be informed this way.

Since then I have fought hard to get the care I deserve and that scans are reported to me in a humane way. Such as have the scan, see your consultant for the results and then ask questions there and then concerning

it. Rather than see your consultant, look over the previous year's results, go for my scans and then get diagnosed with brain tumours, kidney cancer via a letter! Have lots of unanswered questions, unable to speak to consultant so left to dwell on the results until you see the consultant a year later. This is a very traumatic experience. I am often referred to in a jokey way from the NHS as the patient who likes to have results delivered in a 'special way'. No, it is a humane way!

I have often been misdiagnosed, so much that I have been previously advised that I have grounds for formal complaints. Most recent, I was wrongly diagnosed with RCC for over 2 years!! And they wanted to operate on me!

These wrong diagnoses' lead to childbirth decisions being taken away from me at the last minute because all consultants were confused. This was traumatic for me and preventable.

Taking Belzutifan could mean that I don't have to have so many regular scans, not have as much growth, relieve strain on the NHS and provide a better care all over for the NHS/NHS staff and the NHS patients. I also would not be in the position of being wrongly diagnosed so many times!

I have two children. I was decline for PGD at the time and unfortunately both my children have VHL. I had hoped that Belzuifan would have given them a better life.

If my CMJ tumour continues to grow like it has and I can't be offered Belzutifan, then I am facing the following consequences in the not too distant future:
- I would be paralysed from the neck down, including incontinence. I currently lead an active normal lifestyle.
- Being paralysed, I'd have to leave my job. I currently work part time around childcare, but previously full time and I plan to go back to work full time when my children are older.
The following changes would have to be made as well, and please take in to consideration the cost of all these implications, on top of having to leave my job (a loss of £30kpa alone)
- I may need to be in hospital for a significant amount of time meaning that I would be taking up bed space that can be avoided by being on belzutifan.
- My husband would have to leave his employment (a loss of £40kpa) and become my full-time carer.
- We would both have to claim benefits. I would have to claim high rate PIP for daily living and mobility, and my husband would have to claim Carers Allowances. We would have to claim Universal Credit, housing cost element and limited capability. We currently do not claim any benefits, other than Child Benefit which all parents receive under the income threshold. This would be a significant reduction in our income, meaning we would rely heavily on the government even more to support us, source hardship funding from local government, food parcels, free school dinners for

children, take out loans to support our basic needs as a family which may lead to it being written off under IDVA.

We would have to sell our home, but the small amount of equity that comes from the property would be eaten up very quickly by the significant cost of my care and equipment (ie hoists, hospital bed, carers for the rest for my life).

We may not qualify for social housing at first due to the sale of our property, would we have to be street homeless? We couldn't afford to pay for my around the clock care and also pay a mortgage and bills with the current cost of living. What gives? The Government would have to help us, the cost being on them.

- I would need around the clock care, meaning that we would also have to employ carers because my husband would not be able to do this all by himself as he would need to also care for our children (who may also be recovering from surgery) and also need respite too.
- My home will need to be adapted if it can be, but most likely we would have to sell our family home to be able to find a property that will cater for my disabled needs – which wouldn't be possible due to the housing crisis we are facing as a nation. Would I have to stay in hospital, or be sent to a hospice for care whilst I wait for my own home to be suitable? Thus I would be bed blocking, assessments would need to be undertaken from Occupational Therapists. This is not cheap! I would also be missing out on my support from my family and children. The impact this will have on not only my mental health but my families will be permanently catastrophic.
- When you are diagnosed with Von Hippel-Lindau as a child, you are declined for all life insurance policies so it is even more important to preserve quality of life so that we can continue living in our home and repaying our mortgage, contributing to the economy as we do currently.
- I would need to continue care under several neurologists as more tumours begin to grow. This is several consultants in one hospital and then also being referred to see other consultants in other hospitals too which specialise in Brain/ Spine surgery.
- We would need to change our car for a disabled access one, which is purchased via PIP. I would also be awarded a disabled parking badge.
- Not being able to move, I'd need treatments to improve circulation, such a chiropodist and massure.
- My care would involve rehab and having regular physiotherapy to help strengthen muscle weakness and focusing on breathing – a cost to the NHS.
- I would need a psychologist as I am sure dealing with this new life will be devastating. A psychologist would likely be needed for my partner, separate to me due to a conflict of interest for the professional, and also a family psychologist for my children to help them process and understand what is happening to me and our family. My extended family may also seek psychologist/ counselling services to help cope as they will be directly affected to. This would be sought through the GP/NHS service.

- My extended family members may have to reduce working hours or give up to help us.
- Medication may be prescribed to myself, partner and family due to not sleeping, depression, PTSD. Would I have suicidal thoughts? Most definitely. This may also affect the mental health for my children and then the outcome for their future in what they can achieve looks very bleak because their mental health is severely affected.
- If my mental health was so severely affected, I may be awarded the severely mentally impaired which would me that I would be exempt from paying council tax for the rest of my life, meaning that other tax payers and government incur the costs.
- I would need care from specially trained nurses, as I will likely have a catheter, to help with my care alongside the carers, involving the many medicines I would need to help function daily. I may have to be fed through a tube or have a tracheostomy fitted.
- I would need speech and language pathologist if I developed issues with swallowing or with communicating.
- I would be high risk of infection and may have regular stays in hospital to fight infections.
- I would need social services/workers involvement, mental health workers/CPN, family/child services involvement such as MASH referrals which include the schools and the safeguarding team to ensure my children are cared for because I won't be able to do this, and they will be labelled as vulnerable children.
- Our family life would be compromised, my children, whilst also dealing with their own health issues, they may not want to be at home due to how stressful and dysfunctional it becomes, and turn to a life of crime or violence, or lead a generation change of life of 'living on benefits'.

All of this is based on just ONE tumour for just me, but as we know VHL causes multiple tumours over and over again. You remove it and it comes back, maybe in another location but it keeps coming back over and over again. I do believe that stress causes tumours to grow and the above situation is so highly stressful that I know I would develop more and more tumours, requiring more surgery, other treatments, and be closely monitored with scans from 3 months plus. How much extra does this cost the NHS?

Please take into consideration all the cost this will have to the NHS and government on a permanent basis if Belzutifan is not approved. The cost of all the professionals alone, from GP to specialist consultants is significant. This is just an example of one tumour in one person affecting so many organisations, services, treatments. This is not good. It is a catastrophic domino effect across several services.

On top of this, my two children will also have the monitoring and surgery. Without Belzutifan, I feel VHL will destroy my family life and ultimately destroy me mentally and physically. As Scotland has already approved the use of the drug for VHL, we would look at moving to Scotland and leaving all the support we currently receive from family members.

Approving this drug will not only improve the quality of life for many people affected by VHL (carriers or carers), but it will also have a positive impact on the NHS system too, such as benefiting all individuals in the country that have late diagnosis of things such as cancer due to waiting times in the NHS.

Happy individuals, who are also supported, will do far greater things in life that will benefit the economy, rather than adding to the drain on benefits/NHS system (wait times are already over 1 year, we would be adding to that timescale) if it is not approved.

The initial cost is expensive but over time you would hope that manufactures would reduce the cost to produce it, as it becomes more well documented for all its benefits and use. Yes, some people may develop side effects, some may discontinue using it, but from researching the use of Belzutifan in America, a lot of people have few side effects that they can manage themselves because of the improvements its gives to their health. I often read on the VHL American facebook group that people taking Belzutifan for a long period of time have experienced tumours and cysts, completely disappearing, decreasing in size or that they have remained stable. They also document that they have had no new growths anywhere else! This is not only giving VHL patients a better quality of life, or can continue leading a normal active life to pension age and beyond, it also relieves a lot of pressure on the NHS system, Doctors, Consultants, Nurses, and all other services involved in treating one tumour.

I understand the committee comments about not approving for lack of evidence v funding. However, I would like to know why in the UK, where England and Scotland are all under the same NHS system, why Scotland is able to approve Belzutifan, but not England? What was evidenced in the study done in Scotland for it to be approved straight away? Was it any different to England? Why was it passed first time there and not in England? Shouldn't the Scotland study be included as part of this decision in England? Can it be used to fill the gaps of evidence that is reported in the document?

Why wasn't a trial covering more people from all over the country with differing needs, tumour locations and qualities of life completed, so that the committee are basing decisions on the evidence they require, not assumptions and then keep quoting there was not enough evidence? There are other serious illnesses like VHL that have medication approved, why is it not the case for VHL?

VHL is a long standing illness and classed as a disability. It certainly feels like the current refusal decision is discrimination, be it location discrimination or genetic discrimination.

The report describes VHL as being rare and there not being enough clinical evidence. Why were not more individuals invited to participate in the trails to obtain more clinical evidence?

The report also states that Belzutifan can stop or turn back growth of tumours, avoid surgeries, lowers risk of metastasis and reduces the need for dialysis. Knowing that this will happen to every single VHL patient, this drug saves so much money in the long run.
The report kept reiterating throughout about there being uncertainties in the evidence, use of several assumptions and not facts. Have the benefits been fully captured?

A question for the committee; how would you feel if you had VHL? How would reading this report make you feel? What would you do?

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

- Has all of the relevant evidence been taken into account?

The trial only considered the clinical elements of the participants. It didn't include the quality of life of the patients, their carers and families.
It also did not consider a cost analysis that offset the cost of the drugs with a reduction in surgeries, out patient care, and the associated savings for the welfare and social care system.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The guidance talks about the reduced life expectancy for those with VHL. What is does not include is that their quality of life is not the same. 60 for those without VHL is very different to life with VHL.
My cousin is almost blind due to the tumours on her eyes. This drug could reduce the tumours and prevent her from becoming legally blind - preventing her from having a disability. By rejecting the use of this drug - you're effectively condemning her to a disability on top of this incurable disease.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

The difference between the conclusions of NHS England and NHS Scotland should be reviewed, to provide a common guidance for the entire UK. Your conclusion will spur people to undertake medical migration to Scotland to receive life changing treatment. Not an easy decision when carers are typical close family members.

You're considering the uncertainties and the costs as if this treatment would apply to millions rather than hundreds. The uncertainties of current treatments far outweigh the uncertainties of this drug.

You've not considered the savings for surgeries, out patient care, and the burden on the welfare system. Your guidance has been drawn up solely by medical and clinical experts. That's too narrow, you also need people in these discussions that can consider the social care, welfare, and mental health costs/benefits.

For those that suffer with VHL - there are so few breakthroughs. This is a game changer drug which could change their lives for the better. Read them the uncertainties, and let them make and informed choice. Why strip them of that choice.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No, consideration should have been given to the size of the trial and the size of the respective number of people this drug will benefit.

The summaries talk about the uncertainties - which would be valid if this drug was aimed for millions of people. But for the small group of people suffering with VHL - where there is already so much uncertainty, no cure, and so little medicine that actually helps their condition - the uncertainties of your summary seem trivial.

How do your interpretations differ to NHS Scotland? Why have they approved the used of Belzutifan for use on VHL. Did they see different evidence? Did they performa a more comprehensive trial?

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Has all of the relevant evidence been taken into account?

I'm not a medical professional, however from my understanding relevant evidence has been discussed.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I'm not a medical professional, however I believe the Belzutifan drug will be life changing for VHL patients as it would avoid the costs of having to go through multiple surgeries and potentially suffering from debilitating needs as a consequence or funding for aftercare support and treatments. The drug can also benefit patients emotionally and mentally and I think this needs to be further supported in this case and not just reviewed by cost effectiveness.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I'm not a medical professional, however I don't believe there is any discrimination against these groups of people.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

I'm not a medical professional. The recommendations are suitable and sound to my understanding.

I do believe the Belzutifan needs to be carefully re-considered for the mental and emotional welfare of VHL patients and their surrounding support network. This treatment can be ground breaking and avoid putting patients through any unnecessary stress and worry with surgeries and having to potentially live with debilitating needs or intense aftercare programmes afterwards.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

I am a consultant endocrinologist and I set up and lead the Newcastle Joint VHL multidisciplinary clinic team. In this capacity, I look after a cohort of at least 40 VHL patients (adults and children).

VHL is a complex inherited condition which results in the development of tumours in multiple organs, most commonly the kidneys, the central nervous system (CNS), the pancreas and the adrenals. While some of these tumours are benign, some are malignant and even the benign tumours can result in significant morbidity, due to their location, for example in the CNS. There are currently no medical therapies for VHL-associated tumours and therefore the mainstay of treatment is surgery. Repeated surgeries are often required across the lifespan. Each surgical procedure is potentially associated with significant morbidity and people with VHL often "accumulate" disability through repeated procedures. Having VHL is therefore associated with a significant reduction in quality of life for many patients.

There is a real unmet need for non-surgical treatment options for some people with VHL and belzutifan has been developed with this in mind.

Generally, I see surgery remaining the treatment of choice for most VHL-associated tumours, as one would not generally deploy a systemic treatment option if a "local" disease control measure would be suitable. Where I think belzutifan will be of value is for a very select cohort of individuals with VHL where a further surgical procedure will result in loss of organ function or significant neurological disability. To be specific, by this I mean:
a) that the patient with a progressing renal lesion, greater than 3cm in size, will be rendered anephric and dialysis dependent by surgery;
b) that the patient with a progressing pancreatic neuroendocrine greater than 2cm in size (or mutlifocal progressing pNET) will be left without a pancreas following pancreatectomy and be rendered insulin-dependent and requiring pancreatic enzymes lifelong;
c) that the patient with a progressing CNS lesion resulting in symptoms and progressing neurology is likely to be rendered more neurologically disabled by surgery/radiotherapy.

Across the cohort of individuals with VHL that I currently take care of, I feel that belzutifan would be of value to 1 or 2 individuals who meet the above criteria.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

- Has all of the relevant evidence been taken into account?

Yes

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Yes

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

No

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Yes

- Section 1 – Recommendations, point 1.1

I have stage 3 kidney disease I have already had a right nephrectomy. I have just been informed that my remaining kidney is stable but more complex. The worry and anxiety that this information has caused has had an emotional and physiological effect on me and my family(both my daughter suffer also with RCC) .Belzutifan would reduce the risk of having surgery and potentially starting dialysis. I have also been told I have a brain tumour and 30.5mm cyst that is growing , the consultant is monitoring my balance and other symptoms, when they get worse surgery is the only option.

- Section 2 – Information-about-belzutifan, point 2.1 ‘Marketing authorisation indication’

Myself 63 and my 2 daughters 38 & 35 have VHL and we all have had collectively 6 operations on our kidneys. We live with the knowledge that one day we will all have to have kidney dialysis and then await kidney transplants. We all have many pancreatic tumours and I have already had part of my pancreas removed , when our pancreas’s stop working efficiently, we are expecting to be diabetic and be insulin dependant. We have 2 MRI scans a year each with contrast on kidney and pancreas.

- Section 2 – Information-about-belzutifan, point 2.2 ‘Dosage in the marketing authorisation’

The results of reducing mine and my daughter’s brain, kidney and pancreatic tumours out weighs the side effects of the Belzutifan. Belzutifan will give me and my daughters a better quality of life, we have not had a life without worry since being diagnosed with VHL in 2006.

- Section 2 – Information-about-belzutifan, point 2.3 ‘Price’

We have gone through over 20 operations including , 12 brain operations, 6 (full and partial) kidney surgeries, collectively. My pancreas and splenectomy and eye tumours lazered. The money the NHS has paid and is paying and will continue to pay for all scans (12+ each year) and surgeries, consultations etc. this is phenomenal . Also the money spent on CBT on numerous occasions and also PIP and ESA when the need has arisen. Not forgetting the worry of our main carer ,my husband who carries and supports us. He is our rock. Without him we would be again reliant on the NHS generosity for extra care and transport needs.

- Section 3 – Committee-discussion, point 3.1 'The condition'

I am the first sufferer in our family and my first operation was in 1986. But it is my daughters who have suffered more and as each generation VHL becomes more problematic. As VHL sufferers we suffer from numerous side effects and these will only get worse with future operations, so having the opportunity to be considered and hopefully selected for Belzutifan will be a life line for us.
Quote from text "The clinical experts stated that, with more effective treatment, there is potential for people with the condition to live longer and have a better quality of life."

- Section 3 – Committee-discussion, point 3.2 'Unmet need'

Quote "The patient experts explained that avoiding multiple surgeries could greatly improve physical and mental wellbeing, and improve quality of life for both people with VHL and their carers. "

This would be such a relief to avoid more surgery. Belzutifan would give myself and my family a chance to be able to plan a holiday in advance, to think and plan for a future not having to worry about more surgery all the time

- Section 3 – Committee-discussion, point 3.2 'Existing treatment'

Quote. "For CNS hemangioblastomas, MRI scans of the head are done every 12 to 36 months. "

Personally because one of my brain tumour has grown last year I had 3 scans , as I am being closely monitored (as always when tumours start to grow.) Belzutifan will stop so many scans.

- Section 3 – Committee-discussion, point 3.3 'Existing treatment'

Quote" MRI or ultrasound examinations of the abdomen are done every 12 months for RCC tumours and pNETs."

In mine and my daughters case we have an MRi every 6months with contrast on kidney and pancreas costing the NHS.

- Section 3 – Committee-discussion, point 3.3 ‘Belzutifan marketing authorisation and positioning’

Quote. “The committee noted that there may be intervals of 4 months between a tumour reaching the treatment threshold and the decision to proceed with surgery. It also noted that belzutifan is positioned for when people have had surgery for tumours that reached the treatment threshold and are having active surveillance until the next surgery that could lead to potential organ loss is needed”

This waiting is horrendous, when you know that things are starting to happen nothing helps with the anxiety. We just put our lives on hold and suffer. My younger daughter suffers greatly with anxiety and on one occasion we had to take her to a&e with an uncontrollable shaking leg we thought her spine tumour had grown she had numbness and pins a needles too. The result was that her anxiety had got to such a level with her worrying about me and my elder daughter (we both had had news that we had to both go in for surgery) and this is how her anxiety manifested.

- Section 3 – Committee-discussion, point 3.5 ‘Clinical-effectiveness evidence’

This would be amazing if our tumours could be reduced in size. What a relief.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

My husband has suffered from VHL for 31 years and has had several tumours/body parts removed. His 2 sons also inherited the condition and have already lost their adrenal glands. When we heard of this drug we were so happy that his life may be prolonged as he does not have much left that can be removed from his body where he can survive.

The drug has been passed in the US for sometime now and the success stories we have seen have been so positive and given us so much hope. Again, when we heard it had been passed for Scotland our hopes were raised again.

To read this document is heartbreaking and because my husband lives in England he doesn't have the same right to life as someone in the US or Scotland. This is so unfair and really is a postcode lottery to whether you have the chance of a longer life. Please please please reconsider this decision and give my husband and his 2 boys the chance of a longer life.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

- Has all of the relevant evidence been taken into account?

I would not have thought so considering we are not allowed this life changing drug in this country

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

What price do you put on someone life. A life time of operations living on benefits, not being able to work and finally an early death is not cost effective either

- Are the recommendations sound and a suitable basis for guidance to the NHS?

It may have been a good idea to actually ask people with this awful disease how they would feel about having this drug. Which as fr as I am aware is the first one that actually helps us. VHL charities have 'invented' so many drugs that were supposed to be for us but do help other cancer sufferers but not us.
Please just give us a chance to change our lives like they have done in Scotland.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

It seems to me that people with LVH should be allowed to use this drug. Especially if surgery carries great risks.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

We are in the process of starting our own family and we require extensive PGT-M IVF to avoid passing on the gene. This is a beautiful but daunting prospect with risks and limited success rates, if successful, which is a huge IF, we will have to privately fund any further children we wish to have.

This adds to the weight of living with the condition and challenges we face to protect our children and future generations.

Belzutifan would be life changing for my partner and her family. It would mean peace of mind for the most part without fear of numerous tumours and life altering surgeries.

It would provide hope, of which we are seeing in other parts of the world for other patients, using this drug. Not only would it reduce the prospect of extensive surgeries, organs and key functionalities missing, it would support our mental health.

In light of this, we are heartbroken at the results of the NICE review. If NICE approves in the next review, it would be the best thing we could possibly hope for, along with so many other patients.

When I first met my partner it was her strength that brought us so close together. She is the strongest and most caring person I know and I would do anything to see her have every possibility to have as much hope to battle this disease. As we start our own family it makes me think that there is so much hope that this drug will bring and the VHL community will be one step further to tackling this disease.

I could not wish for anything other than this being passed by NICE in its next round, I'm so sad it hasn't already.

Thank you for listening to our story. [redacted], partner of [redacted] - celebrating 10 years this year following her successful whipple operation, it would be an amazing thing to have this approved in the same year.

Please.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

My wife's best friend was diagnosed with VHL just over 4 years ago.
It couldn't have happened to a nicer person, it shocked us all.

She's the kind of person you need to have in your life, she is funny, has a flair for colour and style and is generous to boot.

If this drug has been approved in Scotland then there is no question that this should be approved here.
If not, we're all moving to Scotland.

Do the right thing, approve this drug, let these people living with VHL really live their lives as we are free to live ours.

Give them the fighting chance that they deserve!

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

I am a husband, & at times carer, to a VHL warrior. I've seen first hand the hurt, discomfort & pain this disease can cause. From lengthy stays in hospital, to months of recovery at home. I've seen both the mental & physical impacts it has on my wife.

Belzutifan would make such a difference to my wife & other's lives just from having another option to life saving surgeries, let alone the other benefits that come from taking the drug & the tumours it targets. It would be extremely disappointing if NICE weren't to change their recommendation.

Name	[redacted]

Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

- Has all of the relevant evidence been taken into account?

Yes

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Yes

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

By not giving people the choice to have this medication you are stopping their rights of choice and in doing so, they could be come disabled in my nieces case blind; when this drug could prevent this, if taken early.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Yes

My brother in law had VHL, my niece and two great nephews have it too. In 1990, [redacted] had a very good job, he had a lovely home and family, then, VHL came into their lives.

Within a short space of time, [redacted] had lost both his kidneys because VHL had damaged them so much. [redacted] was then on dialysis, unable to work because he had no strength, was ill a lot and couldn't walk well. They had to start claiming benefits

Within 2 years, [redacted] had died! My sister was left with two young daughters, 10 and 12 and had to claim Widows allowance. It was a dreadful time for them all.

Not long after [redacted] kidney removal, They were told their youngest daughter [redacted] also had VHL…

Her first question when her dad died was "am I going to die too?"

Fast forward many years…. [redacted] is 38, she has very little sight in her right eye, has had part of her left kidney removed.. she has tumours throughout her body and feels like a walking time bomb!

She knows that it's quite likely that in the future, she could be on dialysis, she knows that if her left eye goes the same way as the right one, she could be totally blind, most worryingly, she has tumours in her spine which in the future may require surgery and her consultant says for the one at the base of her brain, the operation could leave her paralysed from the neck down. She is a mum to 2 beautiful boys who sadly both have VHL and will need constant monitoring throughout their lives. [redacted] has a partner, they both work, [redacted] is part time until the boys are older. They don't claim any benefits.

Welireg is the wonder drug! It's [redacted] best chance of avoiding surgery and have a chance of a better life. It shrinks the tumours meaning patients don't need so many scans, consultant appointments and NO expensive treatments.

Without it, if [redacted] were to need surgery, especially on the most worrying tumour, which could leave her paralysed, think of the cost to the NHS and the benefit system. Neither [redacted] or her fiancé would be able to work because [redacted] would need constant care, they would be on benefits, extra carers would also be needed, changes to their house etc… it would be a huge financial burden on government resources and would well outweigh the high cost of approving Welireg.

The insurance companies in America have realised this and Scotland has as well.

I'm amazed that the drug can't be recommended for use in the UK… I know it's expensive but this should not affect the fact that for VHL patients, it could definitely improve the chances of living a good life which in the long run is more economically viable and, I'm sure the cost of the drug will eventually decrease.

Surely if one part of the UK has recognised this, then England and Ireland should do so too, my niece and the many others like her in the UK, should not have to be considering moving to Scotland to be able to obtain this life saving drug! I support my niece and her family a lot, this would not be possible if they moved to Scotland. In the UK we should all be treated the same!

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified

Conflict	No
Notes	
Comments on the DG:	

- Has all of the relevant evidence been taken into account?

Hopefully

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

It will always come down to cost but should be about helping us unfortunate people with vhl

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Hopefully not

- Are the recommendations sound and a suitable basis for guidance to the NHS?

It Scotland NHS any different to the rest of the UK???

Please let's get this belzutafan approved for the whole of the UK not just Scotland please

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

Dear whom this may concern,

My name is [redacted] I am 25 years old student adult nurse with a diagnosis on Von Hippel-Lindau Disease. I was diagnosed at the age of 6 as a result of genetic testing due to my father being diagnoses with VHL following emergency brain surgery at the age of 39. It is also believed my grandmother who was 32 when she passed away had VHL. Along with myself and my father, two of my three sisters have a diagnosis of VHL, aged 27 and 21. My third sister who is my twin does not have VHL.

Following my diagnosis with VHL my childhood, teenage and early adult years have consisted of regular full body surveillance imaging to identify new cystic lesions and tumours. Currently I am known to have a pancreatic neuroendocrine tumour, pancreatic cysts with the biggest measuring 5cm on the head of my pancreas, spinal hemangiomas on my C6 and T1 vertebrae, multiple retinal hemangiomas which are treated with laser upon diagnosis, hemangioblastoma of the brain and multiple renal cysts.
My pancreatic neuroendocrine tumour is currently under investigation, awaiting a second endoscopy with the possibility of needing a pancreaticoduodenectomy (Whipple procedure) in the new year to remove the PNET along with the large pancreatic cyst. For all my other lesions I am currently undergoing MRI scans every 6 months at the Royal Free Hospital in London.

In the near future I am hoping to be able to have children of my own. It is known that with VHL can lead to tumour growth. With Belzutifan the risk of having to have major surgery during pregnancy or post birth could be mitigated.

If Belzutifan was to be approved for use within England it would make a huge difference to my current prognosis and my future. It would allow me to continue in my new career as a registered nurse without the worry of prolonged time away from practice to recover from major and life changing surgery. It would prevent me from developing secondary illnesses such as lack of sensation in my arms and legs or loss of strength from spinal surgery, whipple associated diabetes mellitus and digestion difficulties or the emotional distress and trauma from undergoing brain surgery. It would allow my father to have a better prognosis in regard to his current renal cell carcinoma as well as the multiple hemangioblastoma on his brain. It would provide treatment for my sisters Pancreatic Neuroendocrine Tumour and mean I would no longer have to administer painful and debilitating injections to my sister every 4 weeks to ensure she too doesn't have to have the Whipple Procedure. This medication would allow me the opportunity to live a 'normal' and happy life with my parents, sisters and my husband. Approving this medication will positively impact myself, my sisters and my father as VHL patients but it will also change the lives of my mother, my twin sister, my husband and the partners of my sisters. They will not have to undergo the emotional distress and guilt of having to watch us suffer and struggle with VHL and the complications this can lead to.

We ask that you consider the overall positive impact that Belzutifan would have for all individuals suffer from the consequences of VHL, both directly as patients or indirectly as the patients loved ones.

Thank you for taking the time to read my comment. I hope it gives you an insight into just one of the many families that are relying and hoping desperately that Belzutifan is approved for use within England under the National Health Service.

Thanks,

[redacted]

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

VHL has been in my family for at least 3 generations. My Grandmother died of it before I was born, and my father died due to several CNS Hbs at the age of 56. During his life he had 10 brain surgeries, 4 surgeries on his spine and countless surgeries on his eye, not to mention the gamma ray treatment he had in the early 2000's, the post surgery rehab, and all of the treatments for the complications associated with the effects of both the tumours and the surgeries. When he died, he had been in hospital for over a year, it was a very painful time for him and his whole family and community. The impacts on him were immense; following each surgery he would deteriorate further in terms of his mobility, bowl and bladder function, sensory issues, mental health and many other things. The discussion mentioned that surgery could result in 'neurological deficit or paralysis', this does not, in my opinion, adequately describe the myriad impacts of multiple brain surgeries on every aspect of one's life.

In terms of the impact on us, his family, we spent much of my childhood by his beside in hospital, and lost my father at the age of 18 to this horrible disease. When I became an adult and had the option of having a genetic test, waiting for the results was one of the most terrifying times of my life; would I be destined for a life marked by a condition with no treatment, constantly worrying whether a niggle here or there was a brain tumour? I do not have VHL, but only through the luck of the genetic draw. My twin brother does have VHL, and before the age of 35 he has had 4 brain surgeries, 1 spinal surgery and several procedures on his eye. He currently has one tumours on his brain stem, spine and pancreas. He is suffering terribly from the effects of these. They makes him so sick that at times he is not able to get out of bed for more than a week, and this can happen several times in a month. He has lost an incredible amount of weight through this, and we cannot begin to imagine the damage that this is doing to his body aside from the growth in his brain. His surgeon is not keen to operate on the tumour on his brain stem due to the significant risks that this surgery poses. This is having a huge impact on his life and at the moment there seems to be no end to his suffering. If this drug is not approved he may not have the option of surgery and may have to live with his current symptoms and potentially be looking at a tragically shortened life lived in pain. I cannot overstate how significant the impact on his life, and all our family's lives, would be if he had this as a treatment option rather than relying on risky, expensive surgery. He would be able to make long term plans, be able to

enjoy holidays, family days out, progress in his job and spend less time in the hospital. Most importantly he would have hope.

My family has cost the NHS a lot of money. My father, brother, two cousins and uncle have all suffered from VHL and have had operations to remove brain tumours. We have lived with this condition for generations with no treatment options, and we have dreamed of one day having something that will help with its effects. My brother has been told that he will be a good candidate for Belzutifan treatment should it be approved. To know that there is a treatment that could help my brother but it has been refused would be completely devastating. The discussion notes that “the recommendation would not restrict access for some people over others. No other equality or social value judgement issues were identified”. I understand that Scotland is a separate jurisdiction in relation to such decisions, but those affected by this decision will certainly not feel this way when our neighbours within the UK are able to access this drug if it is not approved in England. In the committee’s conclusion they say that they could not be confident of the additional benefits of Belzutifan. As someone who has been, and will continue for the rest of my life to be, deeply affected by VHL I would suggest that any benefit is a substantial improvement from the current treatment options which are non-existent.

Belzutifan may be costly, but the costs are nothing compared to the overall costs, financial, direct, indirect, tangible and intangible of living with VHL. Please, please, please approve funding for Beltzutifan to be made available on the NHS.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

Disappointment is the first word that comes to mind when I read the initial thoughts of NICE not recommending Belzutifan for use on the NHS with regards to VHL patients.

From the age of 15 (19 years ago) I have suffered from the affects that VHL can have on your life. My diagnosis came from going in for surgery to remove a brain tumour. Since then I've had a further 3 brain tumours removed, my left adrenal gland removed, full Whipples procedure & an edoscopy procedure to open my bile duct that had narrowed following this, causing recurring bouts of Pancreatitis.

This is a lot for a child & then young adult to suffer throughout their life, from the time away from school to the lengthy periods I've had to take sick from work - not to mention the long periods of time in hospitals recovering from

surgery. VHL has had a huge impact on both my mental & physical health - to this day I suffer daily with fatigue, memory loss, lower levels of hearing in my left ear...just to name a few things.

Having another option rather than surgery would be amazing for me. Seeing the success that this drug has had where it's available is so encouraging to see but would be damaging if it wasn't available in England.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

Dear whom this may concern,

My name is [redacted]. I am 27 years old with a diagnosis on Von Hippel-Lindau Disease. I was diagnosed at the age of 6 as a result of genetic testing due to my mother being diagnosed with VHL following emergency brain surgery at the age of 33.

Following my diagnosis with VHL my childhood, teenage and early adult years have consisted of regular full body surveillance imaging to identify new cystic lesions and tumours. To which in my teenage years I had to have 2 surgeries to remove my adrenal glands due to pheochromocytomas developing on both sides, to which now I have to take steroids on a daily basis for the rest of my life due to the surgeries. Currently I am known to have 2 hemangioblastomas of the brain, 2 spinal hemangiomas on my T3 and T4 vertebrae and multiple renal cysts. For all my lesions I am currently undergoing MRI scans every 6 months at the Queens Medical Centre, Nottingham.

If Belzutifan was to be approved for use within England it would make a huge difference to my current prognosis and my future. It would prevent me from developing secondary illnesses such as lack of sensation in my arms and legs or loss of strength from spinal surgery or the emotional distress and trauma from undergoing brain surgery. It would allow my father to have a better prognosis in regard to his current renal cell carcinoma as well as the multiple hemangioblastoma on his brain. This medication would allow me the opportunity to live a ‘normal’ and happy life with my parents and my fiancé.

Approving this medication will positively impact myself and my mother as VHL patients but it will also change the lives of my father and my fiancé. They will not have to undergo the emotional distress and guilt of having to

watch us suffer and struggle with VHL and the complications this can lead to.

We ask that you consider the overall positive impact that Belzutifan would have for all individuals suffer from the consequences of VHL, both directly as patients or indirectly as the patients loved ones.

Thank you for taking the time to read my comment. I hope it gives you an insight into just one of the many families that are relying and hoping desperately that Belzutifan is approved for use within England under the National Health Service.

Thanks,
[redacted]

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Has all of the relevant evidence been taken into account?

My journey started on the 12th April 2019; my Husband's 30th Birthday. We flew to New York, "the city where dreams are made of". Following our "red eye" flight and upon landing, I felt extremely dizzy/ unbalanced and understandably fatigued. Never having flown this far before, I assumed that perhaps it was an after affect of the long flight, lack of sleep and general anxiety with flying itself – sleep was the answer, or so I thought… The dizziness continued and worsened for the entirety of our special trip, including our return and over the following weeks, which turned to months. I went to the out of hours GP, who suggested that I had an inner ear infection, which they prescribed antibiotics for. I completed the course, the symptoms continued, never easing. I eventually got another GP appointment, and whilst the assumption was "nothing ominous", I was referred for an MRI scan on my ear.

I had the initial scan on Tuesday the 15th of October 2019, and was called back for a repeat scan on Thursday the 17th of October; this time with contrast. I was worried about having a cannula fitted (something I'm quite accustomed to now), so I asked my Husband to come with me. The scan took place in a mobile MRI unit, and as it was October, it was very cold. Once the scan was complete, my Husband and I were promptly met at the foot of the stairs, to the van, by a gentleman who asked the Radiographers whether they'd sent the images to majors… I had no idea what this meant, and still naively thought that we were being greeted, to be shown the way out… While we walked from the van to the building, he asked me how I

was, to which I replied jokingly, “surviving”, and that was only with reference to the fuss I’d previously made over the cannula.

We were taken to a small room, there was one chair in the middle, which he asked me to sit on. My Husband ([redacted]), stood at my side. The man crouched down to my level and asked me whether I knew why I had been called back for a repeat scan. I said no, but that I thought it was because they hadn’t gotten a clear enough image the first time, so wanted to complete it again… I then asked, why? Even while typing this now, my whole body vibrates with rushing adrenaline and great anxiety… He gave me this unfortunate look, the kind you might give to a child upon learning that Santa isn’t real! He paused, took a short inhale, followed by, “we have found a shadow on your brain.” When I get anxious, my chest and throat turn red and blotchy.

You don’t need a mirror to know when this is happening, you can feel it start in the pit of your stomach and radiate upwards; much like a volcano I suppose… it’s happening now. I felt this rush of heat, followed by instant cold, although my skin felt damp, as though I’d been exercising – sweaty. I remember sliding from the chair, to the floor and lay silently and afraid, in a little ball. Of the two of us, [redacted] is the talker and he is this positive pillar of strength, nothing ever phases him and nothing ever silences him. He didn’t say a word, nothing... I looked at him, desperate for his positive affirmation, nothing… I think that’s when the realisation of the severity of “there’s a shadow on your brain”, truly set in.

What felt like hours, was probably only a couple of minutes. I spoke for the first time, asking whether I was going to die. I repeated it over and over and over; there was no reassurance from the Consultant, only, “we’ll cross that bridge when we come to it.” I felt as though I was watching myself from someone else’s perspective, it didn’t feel like me, this surely couldn’t be happening to me?! I’m sensible. I don’t do drugs or smoke, I drink alcohol, but I don’t abuse it and I eat relatively healthy, OK the odd burger here and there – this CAN’T be happening to me! Why me? Why me? Over and over in my head.. Oddly, it was at this point the Consultant delivered the next line, “listen, you’re probably going to be questioning yourself a lot and wondering why this is happening to you”.. He was right! I was! He continued, “… but you can’t think like that.” I started to cry, and so did [redacted]. The Consultant “gave us a minute” and left the room. We didn’t speak, we couldn’t speak – neither of us knew what to say. I could hear every noise in that room. I could hear my own heartbeat, and I swear I could hear [redacted] too.

The Consultant returned. I was now sitting, leaning up against the wall. He felt my pulse, I don’t know why… I asked him again whether I was going to die, hoping desperately for some reassurance this time, he repeated what he’d said earlier. I stressed that I needed to tell people, I’d need to let them know about this. He asked, “like who?” And with my voice small and shaking, I replied, “my Mum.” I said again, this time crying out, “I need to tell my Mum.” He smiled, a half smile, breathed out a small chuckle and rolled

his eyes; I think this was his way of reminding himself that even thirty something year olds, still need their Mothers…

I stepped out the room and I called my Mum. I didn't know what to say. She knew I had a Hospital appointment that morning, so she would likely be expecting a call from me at some point. She knew about the fuss I'd been making over the thought of a cannula; she'd have been waiting for a story of the events that unfolded, and she'd hear of my relief that it was all over with now. "Hello [redacted], how'd you get on?" I somehow kept it together… "Hello Mum, I need you to come home from work." … The phone fell silent. She knew something was wrong and asked me "why?"; her voice, fearful, of my response.

"They've found a shadow on my brain."

[redacted] and I returned to my Mum and Dad's house. Their drive looked like the forecourt of a car auction – everyone was there: my brother, sister in law, best friend, Aunt's, Uncle's, cousins, my Mum & Dad; It was obvious that word had got around and that this news had affected more than just myself alone. My Niece and Nephew were not there, they were too young to understand. The thought of seeing their little faces broke my heart the most.

I work at our local Hospital as an [redacted]; her areas of expertise sits within Women's and Children's and Cancer & Diagnostics. I love my job and have always found it interesting, new and exciting, however, I couldn't face the thought of going to work anymore, and was signed off for a month in November 2019. I had slipped into a depression, I was paranoid of everybody, including my Mum and Husband. I wouldn't talk to friends and I didn't want to see anybody. I quit all social media accounts and hid myself away. I stopped wearing makeup, I didn't brush my hair or teeth anymore, I never showered and I stayed in my pyjamas every day. I have since learned that at one point, my Husband thought he might wake one morning, to find that I had committed suicide.

Following a "plotting scan", at Queen's Hospital, late one Sunday evening; it was evident that the tumour had grown following my earlier scan in October. I was rushed in for a pre op appointment, a full body scan and Neurosurgery 4 days later – Thursday 28th November 2019. Up to which point, I had never had any surgeries before. My paranoia worsened, my depression worsened and my anxiety was through the roof. I remember the CNS at the pre op telling me to "calm down" and that my blood pressure was incredibly high. How does one, being prepped for one of the biggest surgeries, calm down?

The surgery went ahead, and was thankfully a success. I was discharged on Sunday afternoon and was prescribed only Paracetamol to ease any pain. The recovery was long and hard. The depression, anxiety and paranoia continued. My relationship with my family and Husband suffered. I argued with my parents and [redacted] out of paranoia. My brother said that he didn't know whether he could trust me with his kids anymore. I wasn't

[redacted], I don't know who I was. I was signed off for a further month from work and returned early January. Following the quick succession of trauma, I was prescribed Sertraline; a tablet which has since become my lifeline. I have also received both single and couples counselling.

Since the start of my journey in April 2019, I have been diagnosed with VHL. I am the only member of my family to have it. I have birthed a healthy baby boy, who has thankfully avoided the gene mutation. My mental health has largely improved, but it will never fully recover. I am traumatised by this and I carry it with me everywhere I go. It is the first thing I wake up to and the last thing I think of at night. The tumour removed from my brain, has now returned and it has since been discovered that I have several tumours elsewhere – eyes, inner ear, pancreas and spine.

The tumours are closely monitored and I pray every day that there is little change to any existing, and that no more grow, although I know I am kidding myself…

At present, there are discussions being had about the tumour (endolymphatic sac) in my inner ear, as this has also shown some growth recently. I have undergone several balance and hearing tests, and passed with flying colours, however, because of its position and the fact that it is growing, Dr's want to operate to remove it. This will mean that I will lose my hearing completely in my right ear and potentially have my driving licence revoked, because of the long term impact this will have on my balance. As it is currently, I can hear perfectly fine and I am unaffected physically by the position of the tumour, so to lose my hearing would be devastatingly unnecessary, especially if there were medication available to slow growth.

If Belzutifan was available to someone like me, it would reduce much of my angst and anxiety regarding growth, and ultimately prolong future surgery, which itself carries its own risk. Before I had neurosurgery, I was warned of the potential outcome, one of which was rehabilitation and to learn to walk and talk again. Thankfully it did not come to this, but this thought will continue to plague me, should I need to have neurosurgery again. Perhaps, I won't be as lucky next time.

I have had a few rounds of laser eye surgery to remove tumours (hemangioblastoma), which have too been successful, however, know of VHL patients that have undergone similar treatment, repeatedly; resulting in the removal of their eye/s, losing the ability to be able to see. The thought of this happening to me eventually, paired with the idea of not being able to physically see my Son grow into a young Man, kills me. And when you consider the ear problematises I mentioned earlier; could one imagine being completely blind and deaf? Life wouldn't be worth living.

I understand that Whipple surgery, used to treat pancreatic tumours (NETs), leaves many VHL patients without the use of their stomach. In fact, usually, the stomach is removed. Removal of Kidney tumours, ultimately leads to

potential kidney failure, and finally spinal tumours – the loss of the use of limbs and the need for a wheelchair.

As mentioned, I am a fully capable wife and mother. I have worked in fulltime employment since the age of 18, and have continued with my fulltime NHS position, despite having my baby. I can drive, I run to stay in shape, recently completing a sponsored 10K for VHL Alliance. I wear glasses for VDU use and I am of perfect hearing. I remain flexible and can perform intricate yoga positions. I am able to do this, whilst in reasonable good health, all while aware that my tumours are increasing in size, with the inevitable deadlines for surgery and its multiple complications & added consequences, looming over me.

If NICE do not approve Belzutifan, they are potentially leaving me without sight, without sound, without the ability to walk and talk and without organs; altering mine and my families lifestyle. I wouldn't be able to work. I would need constant care. My home would need to be adapted, and my personal life and relationships with those that I love, would undoubtedly suffer. Without sounding dramatic, I have been to the depths of Hell with my mental health and I have made a promise to myself, for both my Son and Husband's sake, to never, ever, return to that place again.

All of the above, in my opinion, has to be an absolute last resort. There are magic beans, we just need access to them…

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Has all of the relevant evidence been taken into account?

No

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender

reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

No

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No

As an active supporter of the UK VHL Community, I regard this draft guidance as a good example to show the need for the National Institute for Health and Care Excellence (NICE) and the Company to revise its appraisal processes for an orphan rare disease. They should try to follow the principles of the UK Rare Diseases Framework and the Innovative Licensing and Access Pathway (ILAP) that were to expedite the approval process for the benefit of patients.

It is unbelievable that after this press release published on 26 February 2021 by the MHRA “First Innovation Passport awarded to help support development and access to cutting-edge medicines” we are at this current appraisal stage.

Instead of active collaboration and cooperation to expedite an approval, it seems that the opposite has occurred. The complexity of VHL is quite unique but the company was required to find data and fit to data models that were designed for only simple disease models.

In the past 3 years, VHL patients have continued to suffer life-changing surgeries and sadly a few have tragically died from the disease.

It seems that the NICE Committee wish to restrict any prescribing discretion of VHL expert physicians, and the Company is reluctant to change its pricing model.

There is a wealth of VHL data available from NHS patients in the UK that could have been used to determine the likely immediate and medium-term belzutifan prescription profile and therefore the financial costs associated with belzutifan treatment.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

More stress should have been given on the following positive effects of providing Belzutifan now for VHL patients:
1. Having a treatment available that delays the effects of VHL would greatly increase the productivity of patients and their families. Worry and stress of tests, surgeries, constant uncertainty and unavoidable disabilities has a multiplicative negative impact on patients and families' work and life.
2. From the current progress of cancer research, it is very highly likely that in future many cancers will be managed by a combination of early testing and drugs that help delay the diseases' worst impacts on individuals. Belzutifan is clearly a drug that delays the worst aspects of VHL related cancers. The NHS should use this golden opportunity to us the VHL patient community to better understand how this new Technology can change the way the health service can keep cancer at bay in a group of people. This would be a valuable learning opportunity for future planning. It wont be long before there are many drugs available that are used to slow down cancer and keep patients healthy and productive.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No, the recommendations are not sound. Refusing to provide a drug that clearly works for a group of people that have a horrible experience of uncertainty that negatively impacts their and their families' lives is a bad decision from the point of view of a patient, but also is not a good signal to our society. Help us develop drugs that will save lives only for people rich enough to afford it. What is the point of helping the drug companies develop drugs if they charge so much for them that the NHS cannot pay for them. The drug companies should receive a fair payment for their product but this absurd situation does not help anyone. I think NICE should tell Merck that the drugs are too expensive and indicate a price that is acceptable.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

Patient Perspective- imagine loosing a parent and 3 siblings to VHL. Having one kidney removed, partial nephrectomy on remaining kidney and numerous ablation. Then to find you have another tumour in remaining part of the kidney that they can’t operate on without loosing the kidney resulting in dialysis or the risk of tumour spreading due to its size. Knowing there is a drug being used successfully in other countries for RCC but this isn’t an

option in the England . Having VHL is hard enough to manage mentally but imagine not been able to access Belzutifan that could potentially save your kidney and prevent dialysis. This drug is needed to give patients a chance to prolong their chances and an alternative when an operation isn't a viable option.

I have had 2 major operations at 35, whippple procedure and tumour removal from C7 spine. These are major operations, costly on the NHS, long recovery and affect you mental health. Having Belzutifan could help many people with VHL and would give us more hope having this available in the right circumstances.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

I am a patient with VHL 36yrs F, I have had surgery on my spine and my family pattern of VHL means that it is likely that I might need further surgeries for CNS including brain tumors.

You can imagine the upheaval that surgery had on my life. I was out of work and look time to recover. Thankfully the location of my tumour meant that the surgeon was able to operate successfully.

I cannot imagine what my cousin [redacted] must be going through. He has had multiple brain surgeries, causing side effects, neurological impact, and social impacts. He now has a brain tumour that the consultant has said is too dangerous to operate on.

He is suffering from debilitating symptoms including vomiting, nausea, balance issues and neurological pain. He has been informed that he may have access to an effective treatment that has the potential to reduce these symptoms. Now the rug has been pulled away from him. The only other option is to be resigned to a life where these complications persist and his tumour may grow, causing further discomfort and untold impact on his family.

One wonders at what point his situation become most desperate and he has to give up. Or if there is no option other than to perform life threatening surgery (incurring massive potential costs to the NHS)

I would like to register my appeal for the decision to not make this drug available to people like my cousin. I am urging the panel to reconsider given

this example and the many other examples of VHL patients, families, friends and carers.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

I think that more thought should be put into this decision, as the benefits of Belzutifan should be considered as an alternative option to surgery. Patients with Hippel-Lindau disease have been waiting for a medicine such as this to be approved for use in England and Wales.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Has all of the relevant evidence been taken into account?

No. Belzutifan was approved for use in VHL by the FDA over 2 years ago. In addition to the original trial cited in the draft recommendation, there have been additional studies on its use since being approved for VHL. None of these have not been taken into consideration at all in the NICE draft recommendation. For example, in May 2023 the Journal of Clinical Oncology Vol 41, 16, published a study "Real-world outcomes and safety in patients with VHL associated tumors receiving belzutifan". The conclusion of the study: "Our real-world outcomes analysis of patients with VHL-associated tumors who are treated with Belzutifan shows an improved objective response when compared to the initial clinical trials, which is promising for patients. The analysis based on our real-world data shows the superior objective response in VHL-associated RCCs with Belzutifan, with a manageable safety profile. These findings reinforce Belzutifan as an effective treatment option for this patient population but warrant confirmation in a larger sample".

Another study published in the Journal of Neuro-oncology (Vol 165, 2) in November 2023 also recommended its use in VHL based on a small study "The outcome of central nervous system hemangioblastomas in Von Hippel-Lindau (VHL) disease treated with belzutifan: a single-institution retrospective experience". The Conclusion: "Belzutifan appears to be an

effective and safe treatment for CNS hemangioblastoma in VHL patients. Further clinical trials to assess the long-term effectiveness of the medication are required".

There are case studies which show how effective it can be with a short duration of treatment. Surely this must be preferable to surgery or no treatment in a potentially fatal disease? For example, in the journal CNS Oncology Vol 11, (3) "First clinical experience with belzutifan in von Hippel-Lindau disease associated CNS hemangioblastoma" showed significant reduction in tumour size after just 2 months, and a second patient after 3 cycles of treatment.

Were additional studies taken into account when Scotland evaluated its use for VHL, and that is why it has been recommended in Scotland? Why has the NICE committee not looked into what other research has taken place since Belzutifan was approved by the FDA??

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No. How can a cost be put on someone's life? The suggestion that the existing study is not relevant or sufficient because it was not a randomised controlled trial is a poor interpretation of the evidence. It is not uncommon for trials to have one arm without a control group when a potentially fatal condition is being investigated. It is often considered unethical to not offer a life saving treatment to ALL those taking part in a study with a life threatening condition.

An interpretation of cost of treatment has been made without stating at what age NICE expects treatment to start and for how long? As a comparison where are the costs for treating cancers such as brain tumours, kidney cancer and pancreatic cancer? Both the surgery involved and cost of drugs.

And what cost assessment has been made for the treatment and well-being of family and friends? Has anyone involved in this draft guidance have any idea of the stress caused by watching a loved one with VHL? There is no consideration at all in the document regarding those who support those living with VHL. For example, "Family members of cancer patients were less employed (57.9% vs. 63.0%, $p<0.001$), more functionally limited (20.2% vs. 16.5%, $p=0.032$), and had lower self-rated health ($p=0.023$) compared with sex and age-matched control subjects. They also had a significantly higher level of stress (79.7% vs.76.1%, $p=0.008$), and history of depression (12.9% vs. 10.2%, $p=0.035$)"

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Yes. Where is there any mention in these recommendations regarding the England Rare Diseases Action Plan 2023 to improve the lives of those living with rare diseases??? Is anyone on this committee even aware of the Action Plan or read it? Point 4 of the plan (available on the .gov.uk website) says: Priority 4: improved access to specialist care, treatment and drugs.

There is clearly discrimination in the draft recommendations for Belzutifan for VHL against those with a rare disease. It has already been approved for the treatment of VHL in the USA and Scotland, so why not by NICE? If half the population were affected by VHL or dying of it, would they still be recommending that Belzutifan not be prescribed? There would be a public outcry.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Not at all. A close friend has VHL and has already had 4 brain tumours removed and part of his kidney. He now has a tumour on his brain stem which is too dangerous to attempt surgery. So how can the recommendation be made that says it is more cost effective to have surgery than medication? When surgery is far too dangerous. With cancer treatments if surgery has not been successful or sufficient the patient is commonly offered chemotherapy. There is no other treatment known to be successful for reducing VHL related tumours. What is the difference between these 2 groups of patients? Are the lives of cancer patients more valuable than those of VHL?? Of course not.

It does not appear that all the relevant evidence was taken into account when NICE drew up their recommendations. (See answers to questions, especially in relation to studies conducted on its effect since the approval for its use for VHL by the FDA over 2 years ago). There have been several studies since its approval, which do not appear to have even been looked at.

I would also question why the draft recommendation is against its use in England when it has already been approved in the USA and Scotland?

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

- Has all of the relevant evidence been taken into account?

The evidence cited all appears to be from the original trials by the developing phamaceutical company. It was licensed by the FDA in August 2021 and no evidence from Belzutifan's subsequent use in the USA appears to have been taken into account. There have also been at least two other studies, in IMay 2023 and November 2023, which have not been referenced. Based upon the above I do not believe that all relevant evidence has been taken into account.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I am not satisfied that, even if NICE argues that a monetary value can be placed on a human life, all criteria have been taken ino account. I am sure that the cost of foregone tax revenues from early retirees (such as myself), the cost of carers giving up their own employment to care for patients, the costs of cancer treatments, the costs of treating related ailments (depression etc), amongst many other costs, cannot have been fully accounted for. I would also question the assumptions that must have been made as to the age at which someone is placed on the drug, what percentage of the VHL population is prescribed the drug, and how long they remain on it.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

I do not believe the recommendations are a sound basis for guidance. During the course of my care within the NHS, many specialists (neuro-oncologists, eye doctors, kidney surgeons, cancer geneticists) have expressed excitement about the use of Belzutifan as an additional option in the treatment of the condition. They are all aware of the body of evidence as to its effectiveness, and its licensing in Scotland and by the FDA. Are all of these specialists, Scotland, and the FDA incorrect, or is this proposed NICE recommendation weighted more to the saving of costs?

I am a VHL patient who has had brain surgery to remove a haemangioblastoma, stereotactic radiotherapy on another haemangioblastoma (this one near my brainstem), a partial nephrectomy of my right kidney and numerous instances of laser treatment of haemangiomas in my eyes. I do, however, have one haemangioma on an optic nerve, which cannot be treated in this manner. I am a Chartered Accountant who has decided to give up work at 60 years of age due to the constant stress of living with VHL (particularly the regular scans and treatments). Prior to this I was very productive in my career, paying significant annual income tax and national insurance - I wonder whether NICE has taken this type of factor into account in the cost side of their cost-benefit analysis? Living with VHL has also left me feeling quite depressed

as I have entered my 60s (a factor significantly exacerbated by the prospect of being denied access to Belzutifan). This proposed recommendation flies in the face of all other views of Belzutifan's benefits (e.g. being approved for use in Scotland and being approved by the FDA in the USA). This would be a significant step backwards in the licensing of new drugs for patients with rare diseases and conditions, and contains tests which new drugs to treat rare conditions are, by definition, extremely unlikely to meet. I believe this discriminates against people unlucky enough to suffer from a rare condition, simply because it is more expensive to treat. The available evidence is that Belzutifan is effective, but the committee seems to err on the side of saving costs as opposed to allowing access to the drug and contributing to the body of evidence, not to mention improving the lives of patients - this is, I believe, discriminatory. It also goes totally against the Government's 2021 UK Rare Diseases Action Plan, one aim of which is the following:

"improving access to specialist care, treatments and drugs". As a major test of that action plan this recommendation would be a notable failure - All evidence to date suggests that Belzutifan is effective in the treatment of patients with VHL, it has been lapproved in Scotland and by the FDA, yet NICE is proposing not to approve it.

- Section 1 – recommendations, point 1.2 ‘Belzutifan marketing authorisation and positioning’, “Clinical-effectiveness evidence from a small study suggests that belzutifan reduces tumour size. It also suggests that it increases the amount of time people have before their condition gets worse, but by how much is uncertain.There are also uncertainties in the economic model, as well as assumptions that likely favour belzutifan. So, it is not clear what the most likely cost-effectiveness estimates are for belzutifan and it cannot be recommended for routine use.Even though some of the uncertainty in the clinical-effectiveness evidence could be addressed in the Cancer Drugs Fund, the cost-effectiveness evidence suggests that belzutifan is not likely to be cost-effective. So, belzutifan is not recommended for use in the Cancer Drugs Fund”

Due to the rarity of the condition (VHL), and the fact that Belzutifan is a relatively new drug, is this not an unavoidable situation, where any new drug will, by definition, fail the longer-term benefit test? I believe this could be stated about almost anything that is new and can only draw from a small population. It would appear that VHL patients in England are unlikely to benefit from new drugs if they are to be evaluated on this basis since the two factors stated (long-term benefit and likely cost-effectiveness) can never be known unless the drug is used over the longer term. I do not believe that there is any evidence to date which would indicate that the benefit is only short-term. Surely this favours its use over the longer term?

- Section 3 – committee-discussion, point 3.3 ‘Existing treatment’

I am a VHL patient and have had surgery to remove a brain tumour, Stereotactic Radiotherapy on a further brain tumour, laser treatment on eye

haemangiomas and a partial nephrectomy due to a cancerous tumour on my right kidney. I have a haemangioblastoma near to my brain stem that would be very dangerous to operate on, and a haemangioma on my optic nerve in my left eye which, due to its location, is otherwise untreatable. Belzutifan is the only prospect I have for treating these.

- Section 3 – committee-discussion, point 3.4 ‘Belzutifan marketing authorisation and positioning’

Please refer to my comments on "3.3". I believe there is very little subjectivity,over and above the normal subjectivity involved in clinical decisions, and these decisions would be made by surgeons and specialists who understand the risks and benefits of each option being considered. Belzutifan gives them another weapon in their arsenal. These are professionals who are employed to regularly make decisions regarding the best means of treating patients and I believe this section significantly underplays their expertise. There is no returning from an operation going awry due to a tumour being too close to the brain stem, or the loss of sight in an eye, when another available option (Belzutifan) has been denied to the medical team.

- Section 3 – committee-discussion, point 3.9 ‘Establishing relative treatment effect’

This is a very technical section but appears to be dismissing Belzutifan on the basis that it would be an all-or-none solution for all patients diagnosed with VHL and is addressing the statistical outcomes of being on Belzutifan against the possibility, but not the certainty, of other clinical interventions being necessary due to not being on Belzutifan. It does not appear to cover the statistical outcomes solely for patients where other clinical interventions have been exhausted, or are considered too risky (but the patient has reached the stage where some intervention is necessary).

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Has all of the relevant evidence been taken into account?

From a family member of someone with VHL the stress that is caused by the many hospital attendances for appointments many times a year and when any pain or symptoms occur one always wonders if a tumour is

growing. The amount of scans done a year would be costing the NHS a lot of money and time. The tumours in eyes can cause sight loss if in the pupil etc and the laser treatments are costly and time consuming (some have to be done under general anaesthetic).

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

All the appointments that someone with symptoms and tumours has to attend along with the many scans and ongoing treatments. After treatment of tumours regular scans every 3 months.

Young people with VHL are aware that whatever the adult goes through they will probably go through as well which can be very scary for them. The treatments can cause disabilities which need extra help costing for long term care

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Has all of the relevant evidence been taken into account?

No please see my comments below.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No please see my comments below.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Please see my comments below

Are the recommendations sound and a suitable basis for guidance to the NHS?

No please see my comments below

Please read this to the end. Thank you.

As a retired Senior NHS nurse of nearly 40 years experience I write these comments with a clear understanding of how NHS funding operates within the guidelines set by NICE & appreciate the time spent by all members of NICE who have been involved in this evaluation. I have read many of the documents associated with the evaluation – something I have been well used to doing as part of my nursing background, as I was involved in many NICE consultation documents at local level during that time.

My understanding of the conclusion is that Belzutifan is not recommended by NICE for use in England & Wales, as it is not cost effective. I strongly dispute that decision. Scotland, where I now live, has approved the drug for use and the decision by NICE does not give equality to the whole of the UK. I am not commenting as a former nurse but as someone who has knowingly spent the last 54 years as part of a family living & dying with VHL. I recognise that my responses are emotional but they are factual and I will attempt to give NICE an idea of the impact of VHL as well as some estimated costs (not all as I do not know the cost at that time) to the NHS to date for my family.

My grandmother died in 1966 aged 55 from metastases of ‘renal carcinoma’ following a nephrectomy. Although only a small child, I remember that she lived for many painful months following surgery requiring care from the NHS until she died. Obviously, this was at cost to the NHS which I am unable to be a figure on. VHL was not mentioned as the cause until many years later as a result of genetic counselling & a ‘look back’ exercise by the Consultant at the time.

In 1970 my profoundly deaf sister, B, aged 17, presented at the optician with a retinal haemagioblastoma & was referred to an ophthalmologist. She underwent removal of her eye & spent the rest of her life fearing the same in her remaining eye, as her eyes were also her ears & without sight she would not have been able to communicate. B maintained that if this happened she would commit suicide as life would be unbearable. The Ophthalmologist had heard of VHL & referred her for brain scans which showed multiple cerebral haemagioblastoma & it was confirmed that B had VHL. There were no specialist centres or experts at this time & exactly the same as now, management, was symptomatically based. As a family we were not told of the familial/genetic link at this stage. As knowledge & expertise improved over the years B received excellent care. Her NHS interventions included: Repeated scans ranging from ultrasound, CT to MRI; Laparoscopic sterilisation at aged 19 as she was advised not to have children due to the ‘brain tumours’ - another devastating blow to her & her husband who both wanted a family; Bilateral nephron-sparing nephrectomies; multiple medications over the years; Brain surgery aged 47 to remove one of the most troublesome tumours that was affecting her mobility. There were also many medications to control symptoms over the

years. Additionally, B developed multiple spinal lesions which affected her ability to walk. She worked as a support social worker for the Deaf, teaching parents of deaf children sign language & supporting other deaf people. B had to be medically retired due to her ill health which obviously cost the 'State' money & took a skilled person out of the workforce. B also received benefits in the form of Disability Living Allowance. B's brain surgery at aged 47 was carried out as the tumours were continuing to grow & no other option was available. B haemorrhaged on the operating table, never woke up, spent 3 days on a ventilator and died.

My mother, M, did not know she had VHL until she presented with bilateral renal tumours at the age of 44 in 1978. She received experimental treatment at the time, of ablation of her kidneys, which failed. It was at this stage she was informed that VHL was genetic & could have been passed to her 4 children by her. She knew that B already had VHL but the status of the other 3 was unknown. M did not live long enough to know if her other children had inherited the VHL gene. The renal tumours rapidly spread & M died aged 47 after receiving terminal care for over a year with the associated financial costs to the NHS. Her two youngest children were aged 12 and 9 years.

My sister, A, was 9 years old when I had to tell her that our mother had died. A, received repeated screening for VHL for many years until she was able to be cleared of VHL by the genetic test developed by Dr Eamonn [redacted]. The NHS tests were many, as were the Consultant appointments at cost to the NHS.

I similarly was repeatedly & regularly screened & cleared of VHL aged 38 by Dr [redacted]. However, in the preceding years I had a laparoscopic sterilisation in my 20's and part of my decision making was that my VHL status was unknown. After witnessing VHL, I would have been unable to shoulder the burden of passing on the faulty gene. Additionally, I was a live donor of a kidney to my brother. My belief is that a kidney retrieval cost is approx. £15k but this does not take into account the on costs of pre-op work up tests/medical time/sick time from the NHS & loss of workforce productivity/post op GP care. I continue with annual GP care for blood tests/BP etc.

My brother, D, only had one renal screen when my mother was alive and did not wish to be monitored after that. He presented with a testicular tumour aged 29, had an orchidectomy (cost £2k) and was confirmed to have VHL. D is still alive aged 54 but the financial cost to the NHS has been huge (some of estimated cost in brackets). D has many features of the VHL syndrome including: testicular tumour, brain haemangioblastomas, spinal haemangioblastomas, pancreatic lesions, renal cell carcinomas. He is also partially deaf & wears bilateral hearing aids. It is difficult to keep track of all the NHS interventions he has had over the years but these include: MRI's(£2250), Ultrasound (£200), CT scans (£175) /X-rays/blood tests – all in multiples thereof ; Bilateral nephrectomies at different times due to RCC (£60k); Renal dialysis for 3 years (average cost £32,700 per year); Renal

transplant (£17k plus £19k on costs for 1st year post op); to date 17 years of immunosuppressants (cost £5k per year) plus anti-hypertensives, PPI's, analgesics; Spinal blocks for pain management; Repeated hospital admissions for infections due to being immunosuppressed; Immunisations; Consultations are numerous & ongoing with: VHL team, Nephrologist, Neuro-surgeon, Rheumatologist (has osteoporosis due to dialysis), Orthopaedic team, Neuro Physician, Radiologist, General Surgeon, ENT, GP, Practice Nurse, Phlebotomist, Pharmacist, CCU team – to name but a few. D also had Stereotactic Radiotherapy (gamma knife) for two of his brain lesions. In 2023, one of his brain lesions was assessed & deemed not suitable for gamma knife treatment due to the amount of fluid surrounding the tumour. He therefore had to undergo brain surgery (£23k) to remove the tumour before it became too big to operate on. It was especially traumatic for D, but also all the family, who had witnessed B's death due to the same surgery. D had surgery & was rapidly discharged home. At 3 days post-op, he was on the operating table again undergoing emergency surgery for a perforated bowel, probably likely due to the steroids he takes daily for his transplanted kidney & the additional operative steroids received during brain surgery, causing fragility of his gut. A Hartman's procedure was carried out & he now has a stoma. Immediately, post op he was in CCU for 10 days (cost average £2k per day) spending time on a ventilator, total failure of his transplanted kidney and the family being prepared by the staff, for him to die. He didn't die such is his sheer bloody-mindedness to live. He now has regular appointments with the CCU follow-up team due to the trauma of being ventilated & is being assessed by the surgeons for stoma reversal at a later date. He is also on the waiting list for spinal surgery to try & relieve some of the pain he endures on a daily basis. None of the above take into account the cost of Disability Living Allowance whilst on dialysis, loss of productivity to the workforce & sick pay; inability to pay tax & NI whilst not working. His VHL continues to dominate our lives on a daily basis.
We know that many with VHL have many more manifestations and suffer or have suffered as do their families.

In conclusion, as acknowledged by NICE, VHL is a rare disease and therefore by default the number of patients who may be suitable for Belzutifan will be small.

The USA is much further ahead with use of Belzutifan and people with VHL are positively benefitting with tumour shrinkage.
Scotland have already approved Belzutifan for use and if NICE do not approve for use in England & Wales then there will not be equality of access to Belzutifan across the UK. This may prove to be discriminatory to those not living in Scotland, such as my brother.

The decision not to approve Belzutifan is not sound or a suitable basis for recommendation to the NHS nor cost effective.

Treating appropriate VHL patients with Belzutifan, as needed, will save the NHS & wider public purse costs in the long term, as the burden currently is huge, as I have tried to illustrate with the story of my family.

Any medication which gives people with VHL an alternative to invasive surgery, lifelong disability or at worst death, is such a glimmer of hope in an otherwise bleak future and as such I urge NICE to reconsider their decision. There is so much more that I could add emotionally but where do I stop…..VHL never stops.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

I am addressing the consultation on the use of Belzutifan from the perspective and context of a family living with VHL and caring for a family member with VHL, and from a non-medical academic perspective, considering the arguments made against approval of the drug Belzutifan, made in the consultation documents. VHL has an ongoing impact on my immediate and wider family; we have experienced the trauma and need to support our family member through the loss of a kidney, and now the ongoing annual event of scans to monitor tumours at those sites associated with VHL, the stress of awaiting the outcome of those scans to know whether we are at the stage of further surgery being required, or findings to indicate metastasis, all of which has significant psychological impact on members of my family of all ages.

For all individuals living with VHL, multiple surgery is the only current treatment response available in England through the NHS, and the availability of Belzutifan gives opportunity for alternative treatment and the hope that this brings.

There is also a key point to be made that multiple surgeries on multiple organs have a dramatic effect on patient quality of life, given that removal of a tumour also means removal of healthy tissue onto which the tumour is attached, with consequential debilitating effects on kidney function, digestive system (pancreas) and speech, balance, swallowing, even to the point of paralysis for brain/spine tumours.

Given evidence of the effectiveness of the drug demonstrated in its use in the USA and Canada, and its approval for use in Scotland, it seems invalid and discriminatory to deny it to the rest of the United Kingdom on the basis of financial modelling, supposed uncertainties in evidence of the effectiveness of the drug and challenges in decision-making within clinical practice.

Name	[redacted]
Role	Not specified

Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

As somebody who is a close friend to a sufferer of VHL, I have witnessed the chaos and fear and toll this disease can take on a person, it would be extremely detrimental to deny people of England this drug. It has an extreme impact on daily living but most importantly for me, mental health. And as mental health is at forefront of a lot of issues in our current world, and extreme numbers of suicide. Wouldn't it be far better to give people, the people who have this disease, most likely not people who make this decision the right to better mental health by granting them a drug that could improve their physical health at same time. We need to stop putting money first, and start putting people first. Treat people with kindness and how anybody would want to be treated, medically, spiritually, therapeutically, wholey! Treat the whole person.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

- Has all of the relevant evidence been taken into account?

Definitely Not! You should have talked to more families affected by vhl!! My comment is a copy of my daughters testimony.

Welireg is her best chance of having a better quality of life... yes, its expensive but vhl patients are in a minority and compared to the savings to the NHS, and due to the fact that its being prescribed in Scotland, it should be passed in the UK. My family should not be worrying about our daughter and her family moving to Scotland where we won't be able to support or see them!

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I don't think so... this trial is a farce, a waste of tax payers money as you've not targeted the right patients. It was clear its all about cost!

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

By not approving this drug when the USA and Scotland have already done so, uou have discriminated agent every VHL patient in the UK!

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Definitely not... you did the trial on adrenal gland cancer when the USA and Scotland did it on Renal cancer patients.

The results are biased because of the cost... very few patients have been consulted. The savings to the NHS in the long term have not been given, only the cost of the drug. I have written to my MP and will encourage others to do so too!

Dear Nice,
I am saddened to read that you are to refuse use of Belzifen for treating Von Hippel-Lindau in England. From reading all the documents, I gather the general refusal is due to the cost of this drug.

I was also saddened to read in the draft guidance consultation that in study MK-6482-004 you did not collect any quality of life data. This would have been a big factor because quality of life is a huge factor in human life.
My father had VHL, he was de novo and I unfortunately inherited it. My father had brain tumours, multiple eye tumours and had to have both kidneys removed meaning he was on dialysis. He died 3 years after diagnosis, when I was 10. I am now 37.Since then, I have had multiple eye tumours and surgeries resulting in lots of complications and being left with little sight in one eye. If I lose the sight in my left eye, it will be very detrimental. I'll have to give up my job and I would not be able to drive, I'd need someone with me when leaving the house, thus meaning I will become isolated in my home, which will impact my mental health and those around me. I have also had a partial nephrectomy due to RCC. I was fortunate to have had it all removed, but the recovery was brutal. I needed several months off work and needed a lot of care. I know this will return and I can't imagine how hard it will be to recover being older.
I also have tumours in my spine and one tumour in particular at the location of the cervical medullary junction. My neurologist has clearly stated the he is loathed to intervene at this location because it is like spaghetti junction and he has told me that intervention would cause permanent and catastrophic consequences for me. The same consequence will occur if it continues to grow. This area will mean that if the tumour continues to grow like it has, or surgical intervention is done, I will be paralysed from the neck down and incontinent. Belzuitfan really is my only option and hope.

In the report there was mention of people have scan anxiety. I don't have scan anxiety, I have 'diagnosis fear' from the impact of the strain on the NHS system meaning consultants and radiographers are under extreme pressure and pushed to their limit. On top of being diagnosed of tumours in different areas, I also find it very traumatising to be informed of results in letters. For example, I was diagnosed with RCC and then shortly after I was diagnosed with a spinal tumour via a letter! I had kept saying I hadn't seen any previous reports on my spine – it had never been scanned.
I was devastated to be informed this way. Since then I have fought hard to get the care I deserve and that scans are reported to me in a humane way. Such as have the scan, see your consultant for the results and then ask questions there and then concerning it. Rather than see your consultant, look over the previous year's results, go for my scans and then get diagnosed with brain tumours, kidney cancer via a letter! Have lots of unanswered questions, unable to speak to consultant so left to dwell on the results until you see the consultant a year later. This is a very traumatic experience. I am often referred to in a jokey way from the NHS as the patient who likes to have results delivered in a 'special way'. No, it is a humane way!

I have often been misdiagnosed, so much that I have been previously advised that I have grounds for formal complaints. Most recent, I was wrongly diagnosed with RCC for over 2 years!! And they wanted to operate on me! These wrong diagnoses' lead to childbirth decisions being taken away from me at the last minute because all consultants were confused. This was traumatic for me and preventable. Taking Belzutifan could mean that I don't have to have so many regular scans, not have as much growth, relieve strain on the NHS and provide a better care all over for the NHS/NHS staff and the NHS patients. I also would not be in the position of being wrongly diagnosed so many timesI had hoped that Belzuifan would have given them a better life. If my CMJ tumour continues to grow like it has and I can't be offered Belzutifan, then I am facing the following consequences in the not too distant future:
- I would be paralysed from the neck down, including incontinence. I currently lead an active normal lifestyle.
- Being paralysed, I'd have to leave my job. I currently work part time around childcare, but previously full time and I plan to go back to work full time when my children are older.
The following changes would have to be made as well, and please take in to consideration the cost of all these implications, on top of having to leave my job (a loss of £30kpa alone)
- I may need to be in hospital for a significant amount of time meaning that I would be taking up bed space that can be avoided by being on belzutifan.
- My husband would have to leave his employment (a loss of £40kpa) and become my full-time

carer.
- We would both have to claim benefits. I would have to claim high rate PIP for daily living and mobility, and my husband would have to claim Carers Allowances. We would have to claim Universal Credit, housing cost element and limited capability. We currently do not claim any benefits, other than Child Benefit which all parents receive under the income threshold. This would be a significant reduction in our income, meaning we would rely heavily on the government even more to support us, source hardship funding from local government, food parcels, free school dinners for children, take out loans to support our basic needs as a family which may lead to it being written off under IDVA. We would have to sell our home, but the small amount of equity that comes from the property would be eaten up very quickly by the significant cost of my care and equipment (ie hoists, hospital bed, carers for the rest for my life). We may not qualify for social housing at first due to the sale of our property, would we have to be street homeless? We couldn't afford to pay for my around the clock care and also pay a mortgage and bills with the current cost of living. What gives? The Government would have to help us, the cost being on them.
- I would need around the clock care, meaning that we would also have to employ carers because
my husband would not be able to do this all by himself as he would need to also care for our children (who may also be recovering from surgery) and also need respite too.
- My home will need to be adapted if it can be, but most likely we would have to sell our family home to be able to find a property that will cater for my disabled needs – which wouldn't be possible due to the housing crisis we are facing as a nation. Would I have to stay in hospital, or be
sent to a hospice for care whilst I wait for my own home to be suitable? Thus I would be bed blocking, assessments would need to be undertaken from Occupational Therapists. This is not cheap! I would also be missing out on my support from my family and children. The impact this will
have on not only my mental health but my families will be permanently catastrophic.
- When you are diagnosed with Von Hippel-Lindau as a child, you are declined for all life insurance policies so it is even more important to preserve quality of life so that we can continue living in our home and repaying our mortgage, contributing to the economy as we do currently.
- I would need to continue care under several neurologists as more tumours begin to grow. This is several consultants in one hospital and then also being referred to see other consultants in other hospitals too which specialise in Brain/ Spine surgery.
- We would need to change our car for a disabled access one, which is purchased via PIP. I would also be awarded a disabled parking badge.
- Not being able to move, I'd need treatments to improve circulation, such a chiropodist and massure.weakness and focusing on breathing – a cost to the NHS.- I would need a psychologist as I am sure dealing with this new life will be devastating. A psychologist would likely be needed for my partner, separate to me due to a conflict of interest for
the professional, and also a family psychologist for my children to help them process and understand what is happening to me and our family. My

extended family may also seek psychologist/counselling services to help cope as they will be directly affected to. This would be sought through the GP/NHS service.
- My extended family members may have to reduce working hours or give up to help us.
- Medication may be prescribed to myself, partner and family due to not sleeping, depression, PTSD.
Would I have suicidal thoughts? Most definitely. This may also affect the mental health for my children and then the outcome for their future in what they can achieve looks very bleak because their mental health is severely affected.
- If my mental health was so severely affected, I may be awarded the severely mentally impaired which would me that I would be exempt from paying council tax for the rest of my life, meaning that other tax payers and government incur the costs.
- I would need care from specially trained nurses, as I will likely have a catheter, to help with my care alongside the carers, involving the many medicines I would need to help function daily. I may have to be fed through a tube or have a tracheostomy fitted.
- I would need speech and language pathologist if I developed issues with swallowing or with communicating.
- I would be high risk of infection and may have regular stays in hospital to fight infections.
- I would need social services/workers involvement, mental health workers/CPN, family/child
services involvement such as MASH referrals which include the schools and the safeguarding team to
ensure my children are cared for because I won't be able to do this, and they will be labelled as
vulnerable children.
- Our family life would be compromised, my children, whilst also dealing with their own health issues, they may not want to be at home due to how stressful and dysfunctional it becomes, and turn to a life of crime or violence, or lead a generation change of life of 'living on benefits'.
All of this is based on just ONE tumour for just me, but as we know VHL causes multiple tumours over and over again. You remove it and it comes back, maybe in another location but it keeps coming back over and over again. I do believe that stress causes tumours to grow and the above situation is so highly stressful that I know I would develop more and more tumours, requiring more surgery, other treatments, and be closely monitored with scans from 3 months plus. How much extra does this cost the NHS? Please take into consideration all the cost this will have to the NHS and government on a permanent basis if Belzutifan is not approved. The cost of all the professionals alone, from GP to specialist consultants is significant. This is just an example of one tumour in one person affecting so many organisations, services, treatments. This is not good. It is a catastrophic domino effect across several services.
On top of this, my two children will also have the monitoring and surgery. Without Belzutifan, I feel VHL will destroy my family life and ultimately destroy me mentally and physically. As Scotland has already approved the

use of the drug for VHL, we would look at moving to Scotland and leaving all the support we currently receive from family members. Approving this drug will not only improve the quality of life for many people affected by VHL (carriers or carers), but it will also have a positive impact on the NHS system too, such as benefiting
all individuals in the country that have late diagnosis of things such as cancer due to waiting times in
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- I would need speech and language pathologist if I developed issues with swallowing or with communicating.
- I would be high risk of infection and may have regular stays in hospital to fight infections.
- I would need social services/workers involvement, mental health workers/CPN, family/child services involvement such as MASH referrals which include the schools and the safeguarding team to
ensure my children are cared for because I won't be able to do this, and they will be labelled as vulnerable children.
- Our family life would be compromised, my children, whilst also dealing with their own health issues, they may not want to be at home due to how stressful and dysfunctional it becomes, and
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consideration all the cost this will have to the NHS and government on a permanent basis if Belzutifan is not approved. The cost of all the professionals alone, from GP to specialist consultants is significant. This is just an example of one tumour in one person affecting so many organisations, services, treatments. This is not good. It is a catastrophic domino effect across several services.

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to Scotland and leaving all the support we currently receive from family members. Approving this drug will not only improve the quality of life for many people affected by VHL (carriers or carers), but it will also have a positive impact on the NHS system too, such as benefiting all individuals in the country that have late diagnosis of things such as cancer due to waiting times in the NHS.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

I am a VHL patient, who has lost a parent to VHL and has had to watch siblings go through major surgeries and assist them through their recovery. VHL is more than a cyst/tumour or even cancer. It is a life changing condition that impacts all parts of your life and the life of your loved ones. Your life revolves around the next scan or doctor's appointment and the outcome of those appointments. At the start of every year, I wonder if I will get through the year without a single medical intervention and if I dare make any plans for that year. The amount of anxiety and lack of self-confidence created by VHL should not be underestimated. Belzuitifan has been approved in a number of countries where VHL patients, in most need, are benefitting from this drug and beginning to have some hope and plan for the future. The VHL community in the United Kingdom deserve the opportunity to access this life changing drug. We are more than just a cost effectiveness model.

- Section 3 – Committee discussion, point 3.1 'The condition' "Von Hippel-Lindau disease (from now, VHL) is caused by a mutation in the VHL gene. This gene is responsible for producing a protein that controls cell growth. A mutation in the gene can cause cells to grow abnormally, leading to cysts or tumours developing in different parts of the body, such as the kidneys, brain and pancreas"

It is important to note that cysts/tumour also develop in the eyes and spinal cord. I feel eyes should be mentioned as this is one our major senses and VHL can lead to loss of sight. I personally have lost sight in my right eye and have had it removed due to VHL. Numerous eye surgeries since the age of 14 till 47 has had a huge impact on all aspects of my life.

- Section 3 – Committee discussion, point 3.3 'Existing treatment' "The clinical experts explained that surgery is highly effective in most cases for all VHL tumours, with the most benefit for VHL-associated RCC. But surgery can result in organ loss after multiple surgeries or morbidity, depending upon the primary VHL-associated tumour.2

Surgery may be effective in removing VHL tumours in some cases, however it has not been made clear how surgery impacts a patient's overall life. The surgery itself is only part of the procedure. Consideration has to be given to the preparation for surgery and then the recovery process.

A patient who has dependents not only has to prepare themselves for surgery but also needs ensure dependents are cared for before, during and following any surgery. It is especially difficult if some of those dependents have VHL themselves and have a watch a parent/sibling go through surgery.

- Section 3 – Committee discussion, point 3.1' Company's model structure and outputs' "he committee considered that the model included 3 cohorts with overlapping evidence and that the assumptions used in the model were not based on firm evidence. It would have preferred to see a model structure based on the natural history of VHL disease rather than individual tumours and the surgery associated with them. It noted that the relative efficacy derived from the ITC"

VHL is a complex disease, which would be extremely difficult to demonstrate in a financial model due to the different/multiple manifestations in each individual patient. I do not feel this would fit into any "standard" finance model. NICE should work collaboratively with the company to understand the model and it's complexes and agree on a model that works for both parties (and benefits VHL patients).

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

- Has all of the relevant evidence been taken into account?

I'm no medical professional so i can only speak from the position of a Husband, whose wife lives with VHL. Having reviewed the recommendations that have been provided by the Clinical and patient experts and its very clear insight into the affects VHL can have on patients and their families. The recommendations also highlight the lack of treatment options that clinicians can offer patients.

I'd like to provide you with a snippet from the life of my wife, [redacted], who lives with this condition to strengthen the points made in the recommendations and provide some real-life perspective of the condition. [redacted] is an active, bright and bubbly 34-year-old lady who is mother to our amazing 2-year-old son, [redacted], who for me, is pivotal in saving my wife's life and getting her the critical treatment required.

In 2019,[redacted] had surprised me with a trip to New York for 4 nights. Previously, [redacted] had struggled with dizziness following a flight that would typically ware off within a day. This time, the dizziness had not shifted. This persisted for a few weeks after the holiday. Our GP referred [redacted] to ENT who carried out a balance test. Following the balance test, the consultant requested an MRI scan which identified a Hemangioblastoma in the cerebellum.

Following the find,[redacted] was referred to Queens Hospital in Romford. The team had touched on the fact that [redacted] could potentially have a rare condition known as VHL. They proceeded to test her eyes, pancreas and kidneys. A subsequent tumour was identified on the pancreas, but Ophthalmology did not identify any tumours in the eyes.

[redacted] neurosurgeon had always advised proceeding with an operation to remove the tumour but a subsequent MRI scan had shown that the tumour had grown by half a centimeter, so the decision was taken to rush her in for emergency left cerebellar surgery. This had taken a massive toll on [redacted] mental health, which had taken a significant crash to a low that I had not seen in the 10 years we had been together.

Following [redacted] surgery, she was referred to the lower GI team to assess the tumour on her pancreas. This was the start of a long journey, seeing many professionals to seek various test samples and discussions on whether to test [redacted] for the VHL gene. This all came at a time when the covid-19 pandemic struck the world. We were passed between Queens Hospital and Colchester Hospital, who were trying to avoid sending [redacted] for VHL testing.

With all this going on, and not really knowing much about VHL, we carried on with our lives and decided to try for a baby. It was when [redacted] fell pregnant that the midwives finally made the call for the VHL testing to be undertaken as they needed to know if this may have any effect on the

pregnancy. Following this, [redacted] was referred to GOSH for genetic testing.

The midwives had requested the assistance of a consultant to monitor [redacted] throughout her pregnancy. Another MRI scan had found 2 new tumours in the spine which came to light when [redacted] was in labor. Not knowing what to do, the team were in contact with the specialists at Queens hospital. The decision was made to deliver the baby via c-section under general anesthetic.

Our healthy baby son was born. They took a sample of his cord blood at the request of GOSH and sent this off for testing as we were made aware during the pregnancy that there is a 50% chance, he could have the gene. Once [redacted] was discharged, it was a few weeks later when GOSH had informed us that [redacted] did have VHL, but our baby did not have VHL. Following testing of [redacted] family, it was apparent that she was de novo. Following this diagnosis, [redacted] was referred to the VHL Clinic at St Bartholomew's Hospital under the care of Prof Drake in the VHL Clinic. Since being under the clinic, we have discovered further tumours in the eyes, ear, the return of the tumour in the cerebellum, along with the 2 in the spine, 1 on the pancreas and tumours on the kidneys. The diagnosis has had a profound impact both on [redacted], myself and the family. [redacted] has struggled to come to terms with the condition and the impact this condition will have on her life. She has had counselling and takes anti-depressants to help her live a stable life. We know one day our son will start to ask questions, but we will put the inevitable discussion off for as long as we can.

[redacted] has been under the VHL clinic for a few years which have been life changing for us all. She is under moorfields eye hospital where they are currently monitoring the tumours in her eyes following various laser treatments and 1 operation in both eyes.

Currently, [redacted] has an endolymphatic sac tumour which has doubled in size since 2019 but is still classed as small. The ENT consultant has advised that they operate to remove the tumour at the cost of losing her hearing and vestibular function in the ear. What makes this so difficult is that [redacted] has passed the hearing tests and balance tests. An operation to remove the tumour would leave her worse off. We are currently exploring the option of radiotherapy but will likely see the same outcome with this.

This snippet hopefully provides a better understanding of how complicated the life of a VHL patient already is. The condition causes untold stress, anxiety and constantly leaves you wondering what will happen next.
If Belzutifan was made available on the NHS for professionals to prescribe, it would provide a great deal of assurance that the growth of the tumours would slow down, it would help avoid several major life changing surgeries and provide a newfound confidence in patients knowing that operations are no longer the main source of treatments. We know Belzutifan is not the cure to the condition, but providing patients with longer periods before requiring

surgery will be a game changer. It will give so much back to patients lives and allow them to live without fearing they can't go on holiday, expand their family or put big plans on hold in fear of another major surgery.

I fully appreciate there are concerns about the longevity of taking Belzutifan but i do believe that in some cases, the option of Belzutifan would far outweigh the decision of surgery that would possibly result in loss of organ function of a deterioration in the quality of a patient's life.

If NICE were not approving this drug, this would be a huge disappointment to the various patient settings this drug is being aimed at. Belzutifan has the potential to provide a lifeline to many patients that currently face the daunting option of surgeries that will impact their mental health, their physical health and will potentially onset further medical conditions which will cost the NHS more money to treat.

I really hope NICE will follow in Scotland's decision and approve this drug as it will provide so much hope, positivity and further hope that we may find more treatments, or even a cure to this terrible condition.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I'm not sure I agree with this. In the current climate, Operations are favored as the success rate of an operation in most cases is the most effective treatment. This comes at a cost to the patients' health, effectiveness of organs and has a massive impact on the patient's mental health.

A drug such as Belzutifan that costs around £11,000 a year surely would prove to be a cost-effective treatment that already has demonstrated benefits. If loss of organs was the outcome of a surgery, then the NHS would have the cost of treating another condition that could have been avoided.

In the case of my wife, [redacted] she has an Endolymphatic sac tumour in her inner ear. Her ENT consultant wants to remove the tumour whilst it's still classed as "small" which we've been told will result in the loss of hearing and vestibular function being damaged. The cost of this operation would be a deterioration in her mental health, further cost to the NHS to support [redacted] post op to treat the new symptoms and the constant worry of if she has the same thing happen in the other ear.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No, they are not. They do not give a full account of every case. I feel this judgement weighs too heavily on the side of cost. You must consider the many stories you will undoubtedly read from other patients, families and friends of VHL patients and consider this before deciding. Most of us pay

into the NHS, don’t ask much of it but could really do with the NHS’s support for conditions such as this.

In the case of my family, most of us work in the NHS. We hardly ever need to visit our GP, hardly ever go to hospital (apart from work) and never need to use any of the other NHS services other than when my wife was pregnant or counselling. I feel that not approving Belzutifan to an organization I pay in to is a deeply concerning given the number of VHL patients, the impact this will have and the fact I pay my national insurance and wish to be heard.

I fear a rejection in the use of the drug would lower an already low faith in the NHS and see people up-root to new places where they feel they may get better for VHL such as Scotland or abroad, causing yet more stress and anxiety.

- Section 3 – Committee-discussion, point 3.1, ‘committee-discussion’

This section has pretty much covered everything i would want to contribute to the panel.

I'd like to add that due to the rare nature of VHL, patients who are not under a VHL clinic will often face mentally challenging and worrying circumstances when being referred to clinicians that do not have a good understanding of the condition. This made my wife's pregnancy very complicated and at times, scary as doctors where very clear that they did not know about the condition.

With this lack of knowledge, i feel that sometimes, clinicians make decisions that a VHL expert may otherwise disagree with.

Because the condition is rare, there is not many places in the UK that deal with it. This often results in traveling great distances to hospital settings that offer clinics for the condition. This can also result in many visits for various scans and referrals made within the VHL clinic.

- Section 3 – Committee-discussion, point 3.2, ‘Unmet need’

I'd like to echo the comments in this section. My wife had surgery to remove a hemangioblastoma. Since then, the tumour has grown back. Unless there are other treatment options, this would likely result in another surgical procedure to remove the tumour.

This would cause an enormous amount of anxiety not only for my wife, but myself (Husband), our son and wider family.

My wife currently has a tumour in the inner ear. This tumour is still classed as "small" and currently not causing any issues following extensive balance/hearing tests within ENT. Because there are currently no alternative treatments for the tumour, the team want to operate to remove the tumour. This would result in the loss of her hearing, loss of the balance

following nerve damage and the added recovery time physically and mentally.

I would also like to add that at Barts Hospital, the consultant that my wife is under in ENT has only performed this operation a few other times so does not have a great deal of confidence. This has had a great mental impact on my wife's wellbeing.

- Section 3 – Committee-discussion, point 3.3, 'Existing treatment'

I would like to add that although the operations are generally successful in removing the tumour, you have already highlighted that there are likely loss of organ function or other risks from these procedures.

I would also like to stress the mental impact this has on patients. The operation my wife had on her cerebellum to remove her tumour came at a great cost to her mental health. Following the removal of this, and subsequent diagnosis of VHL, it's taken her many years to get back on her feet. She and myself have been through various sessions of counselling and my wife takes anti-depressions to help her live with this condition.

We were lucky that she did not require any rehabilitation, but that is no guarantee that next time, she would not be so lucky. There will be many patients who have had far worse invasive procedures that delay recovery, going back to work and living a normal life.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

- Has all of the relevant evidence been taken into account?

Yes

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I feel that the sacrifice VHL sufferers have to go through in order to live a "normal" life including multiple scans, pain, surgeries and constant fear is that this alongside time, finances and reliance on the nhs for the above could be greatly reduced with belzutifan.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I feel it discriminates people with VHL as without belzutifan they are highly likely to need multiple surgeries and therefore time away from family and work commitments and adding pressure on financial situations and asking their employer to accommodate this time for them. It's affects a far wider range of people.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

I feel that belzutifan would free up vital scans and surgery time for others to while giving VHL sufferers a better life.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

My husband had VHL and died in 2006. We dreamt of a drug that would help to reduce the haemangioblastomas and improve his enjoyment of life. My son, a Charge Nurse, has VHL and has had four ops and six haemangioblastomas removed from his head and one from his spinal cord. He also has had much laser treatment to his eye.

At present he has an haemangioblastoma near his brain stem and one in a syrinx in his spine. His Surgeon is not wanting to operate on his brain stem tumour (he has already had on op on this site) as the risks are so great and it could be sorted/ massively helped by Belzutifan. This tumour is causing him to vomit very frequently.

I understand that Belzutifan has already been licensed for use with VHL in Scotland. The above is only a snippet of one persons suffering with VHL. Please, please licence Belzutifan for use in England too so that many can be helped and symptoms relieved.

I believe that the use of Belzutifan for VHL will help reduce the numbers of operations needed and consequently reduce post up complications needing readmission thereby reducing overall cost to the NHS.

Please licence the use of Belzutifan for VHL patients.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

The decision not to recommend Belzutifan is frankly shocking and deeply saddening, particularly because you do seem to cite a knowledge of many of the challenges faced by patients and caregivers with VHL from multiple aspects.

You even cite "The committee noted that there is an unmet need for treatments that could improve outcomes and quality of life for people with VHL. It concluded that the current unmet need could be addressed by belzutifan because it has the potential to preserve or delay the loss of organ function and the associated morbidity."

It's as though you heard what the advocates said, but didn't care enough because the cost is high.

You claim that you had questions about the comparison populations, but these are very small population sizes as far as samples go, are you not holding these to an unfair standard when the results of the drug's efficacy are so clear?

As someone with VHL, this decision reeks of ablism, effectively saying that there is a price tag on a human life, and many of those with VHL just aren't worth it. The quibbles about sample comparisons feels like a scapegoat.

Are we not deserving of some semblance of a normal life, if one is possible for us? Why should we not be afforded the ability to live a full life or at least resist our condition for many years more, or be given another tool in the arsenal of treatment options available to improve our chances of success against this disease that you clearly have no idea what it's like to live with?

As a VHL patient in Canada, I've had a vast array of harrowing and painful years and treatments throughout my life, and at the young age of my later 30's I was told that my neurosurgeons were no longer able to operate on my countless spinal cord haemangioblastomas. I was quickly progressing to being quadriplegic, and other chemotherapies and radiation were either not possible or tried and failed. Belzutifan was not yet approved for use in Canada (though now is), and I was out of options. I was scared for my life and was realising I was going to need to figure out when to decide to pursue medically assisted death before the day would come when I could no longer administer my existing medical therapy requirements that VHL has given

me over the years (addisonian and insulin-dependent, digestive enzyme therapies to eat, etc). I had lost hope entirely and ready to give up.

Then my neuro oncology team was able to procure a special access to Belzutifan to combat the growth of my spinal haemangioblastomas, and it has provided revolutionary change for me. It has provided stability and even considerable shrinkage in my innumerable spinal lesions, allowing me to walk again, regain my arm and grip strength, eliminate my back pain, restored bladder independence, and also shrink a kidney lesion before it grew to surgical necessity and eliminate a paraganglioma entirely from scan view. Not only this, I've found my love of life again, restoring hope that I might live a fulfilling existence.

I have been on Belzutifan for nearly 2 years, and it continues to provide benefits to me. I am so fortunate to have been able to begin this therapy when I had, or else I may not be here today.

I am so saddened that my friends with VHL in the UK are potentially not going to be able to have the same access to a drug that has given me my life back. Because of this decision/delay, how many others without other treatment options available are going to lose their lifelong battles with VHL, or suffer outcomes that will tax the NHS for the rest of their lives? Or leave the patients unable to work, in constant pain, or reliant on in-home supports for their activities of daily living?

I implore you to reconsider your decision to not recommend Belzutifan for those with VHL in the UK.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

They place too great emphasis on uncertainties given how much benefit to patient outcomes are occurring with the drug.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

I see the logic of them, but I feel you are denying life to many VHL patients by your overly critical interpretation of audience samples and comparisons.

- Section 3 – Committee-discussion, point 3.2, ‘Unmet need’, “The committee noted that there is an unmet need for treatments that could improve outcomes and quality of life for people with VHL. It concluded that the current unmet need could be addressed by belzutifan because it has the potential to preserve or delay the loss of organ function and the associated morbidity.”

How can you make this comment acknowledging that this very drug could serve the unmet need and actually change lives, but then not approve its use?

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Has all of the relevant evidence been taken into account?

No. The evidence has not taken into account the VAST disparities in presentation of VHL – with some patients very significantly impacted far more than others.

The statement evidence suggests at the most severe end of the spectrum that patients “might have a number of tumours in different organs”.

It does NOT describe patients who have a long history of tumours and repeated surgeries (some with over 20 surgeries) for both recurrent tumours in the same organ as well as tumours in other organs, nor does it describe patients facing multiple concurrent surgeries. And it does not describe those patients for whom surgical intervention is not viable.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

he committee concludes that there is “no plausible cost-effectiveness estimate on which to base a decision”, and the impact is that those patients who are worst impacted by VHL, and who face either the increased risks associated with repeated ongoing surgery, or who do not have a viable surgical option are excluded- this is in itself discriminatory. This “highly complex” cohort of VHL patients is therefore significantly and adversely discriminated

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No. The absence of a statistically relevant sample size, and assumption of an “average” VHL patient within any cohort is highly dangerous. No account has been taken of patients who are worst impacted by VHL. An assessment that does not take specific account of this highly complex VHL cohort is unsuitable

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

The recent award of the first Innovation Passport, intended to expedite the development and accessibility of state-of-the-art medicines (as stated in UK Government News), is in stark contrast with the discussions and recommendations of the committee about Belzutifan. I disagree with the assertion in section 3.9 of the "Belzutifan for treating tumours associated with von Hippel-Lindau disease" document, under Project Lead Vonda Murray's guidance (NICE Guidance), which notes that "the committee acknowledged that the relative treatment effect was highly uncertain".

As a 26-year-old British citizen contending with von Hippel-Lindau (VHL) disease, and being the sibling of a fellow VHL patient, [redacted] who is successfully undergoing treatment in the US by accessing Belzutifan through my parents' medical insurance, I am compelled to express my profound disappointment at the disparity between the UK's proclaimed commitment to enhancing access to innovative treatments and the actual situation regarding Belzutifan.

My own experience with VHL began in 2020 when I was diagnosed following an emergency surgery to remove a life-threatening haemangioblastoma in my cerebellum. A subsequent operation was necessary two months later to excise another haemangioblastoma from my spinal cord, which, if left untreated, would have caused paralysis. Following the second surgery, I was rehospitalized due to a suspected spinal cord leak, increasing the risk of a more complex reoperation.

These surgeries were not merely physically demanding; they resulted in a significant interruption in my professional life, and VHL has left an emotional imprint. Although I take pride in having graduated with an MSc in Data Science and secured a position as a data scientist, I struggle with depression and anxiety about my future with VHL.

The anxiety is heightened by the presence of another tumour in my spinal cord, which, as per my last MRI 10 months ago, did not necessitate surgery. The possibility that I might need an operation after my next MRI in two months is daunting, especially considering the tumour's central location, which makes surgical access potentially harmful to the spinal cord. Access to Belzutifan would likely prevent such an operation. At 26, I am no longer eligible for coverage under my parents' US insurance, and to prevent paralysis, self-funding treatment would impose a severe financial strain.

My brother [redacted] underwent cerebellum and brain stem surgeries in 2022. Post-surgery, he was left having to deal with multiple brain and spinal cord tumours. Particularly alarming was a tumour at C2, which grew notably from 3.5x3mm in 2020 to 8x5.5mm in 2022, presenting a life-threatening risk and without Belzutifan would have required an operation in early 2023. Faced with Belzutifan's unavailability in the UK, even on a self-pay basis, our family was forced to seek treatment in the USA. We obtained a Belzutifan prescription in September 2022, incurring a substantial personal cost of $32,000 per month. This unsustainable expense led my parents to relocate to the US and secure employment there, a decision fraught with stress and uncertainty.

The effect of this medication on [redacted] has been extraordinary. Four months after starting Belzutifan, MRIs indicated the disappearance of several spinal cord tumours and a significant reduction in the size of the critical C2 tumour, thereby eliminating the need for the anticipated surgery in 2023. It is encouraging to witness [redacted] living a full life despite his VHL.

I wish to have access to Belzutifan to ensure I will not become a burden to my family and fellow citizens due to paralysis. I truly desire to continue my professional development as a data scientist and actively contribute to the economy and society.

Given that Belzutifan has been crucial in helping my brother avoid a life-threatening situation and could potentially spare myself and other UK citizens from paralysis and severe emotional distress, I implore your institution to champion the availability of this medication for all individuals in the UK suffering from severe VHL complications.

Sincerely, [redacted]

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

I can't think of a reason why any advancement in medicine, especially with such positive results as this, would be denied to anyone.
Let alone a drug that could go on to lengthen and save lives of people living with such a horrendous condition as VHL.

The year I turned 30, the year me and my three best friends turned 30, I thought wow, now we're really living.

We're so young still, we've put some years under our belt, we've just been testing the water, now it's our time to really get things going.
Then towards the end of that year, I had my husband sit me down after I'd just finished a night shift, hand me a coffee and say "[redacted] is ill...really ill."

My best friend of 15 years had a tumour, she had to have an operation, there were risks involved, but this was only the start. We're a few years down the road now from that moment, and I've learnt a lot about VHL in the hopes that in some way I can help [redacted].
I still can't quite understand the condition, but what I really can't get my head around is, why her.
She wouldn't hurt a fly, she's done nothing wrong, she doesn't deserve this.
She deserves to live, as we all do.
She deserves the freedom of living the mundane, but she is now constantly having to think about that next appointment or consultation or scan.
So she's always thinking something is going to show up, as it has been doing.

These new drugs can give her, and all the others living with VHL, the chance to live as we do, elongate their lives, give them a real fighting chance.

If it has been approved in Scotland then we know it's not a matter of safety.
If it's a matter of funding then I emplore you, get the funds, make it happen, let my best friend live, and I mean really live.

Please give her this chance.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

In the committee biographies, there was no mention of anyone with a background in ethics or bioethics, and of the 25 members, only 1 mentioned having a background in oncology, and 1 in neurology.

It would have been prudent given the subject to consider a higher involvement with those having specialties in Neuro/Oncology and also to consider Ophthalmology Nephrology and Endocrinology input as well. While I don't doubt that the people involved are well suited to medical considerations of all kinds, given the rarity of VHL and the specificity of systems involved, it would have been more reassuring to see a higher representation of those who typically make up our medical teams. To me this would reflect that 8% of the committee would be someone who is likely

to be involved in our day to day assessments, planning, and care management, yet making the decision on access to this life changing medication.

- Has all of the relevant evidence been taken into account?

No. The experiences of those who are using Belzutifan were excluded from many parts of it's research process and results. This should not be taken lightly given the challenges of a small community with a rare disorder. I believe this component, which could be manageably collected (e.g. Submissions by providers managing VHL care, or from participants at a collaborative event such as the VHL summit could be considered to remedy this gap) could provide valuable insight which may have been able to sway the opinion of the committee which currently seems to have closed the door based on small availability rather than any proof of harm or damage.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No. Throughout the document the committee repeatedly acknowledges the challenges they have with the available evidence and their reluctance to use it for a variety of reasons. Given that the committee themselves openly acknowledge that they don't find the evidence presented to be appropriate to use to make decisions, it seems a strange decision that they are then defaulting to a decision of "cannot recommend" given the prior acknowledgement and understanding that with rare disorders that may have disproportionately skewed research data based on collection and also small(er) sample sizes, or where a variety of symptoms or disciplines cross in research.

Acknowledging that this is the case and deciding as a committee to deny this opportunity rather than open it to the individualized decision making of multi-disciplinary teams that care for families with VHL is a statement from NICE itself to our community. Knowing that the committee believes the evidence is insufficient and also that we experience very invasive alternatives if there are any to be offered at the time, how are we as a community to receive the response instead of a positive reflection of including Belzutifan within a scope that allows the specialists we work with to know if the benefits will outweigh the risks for us as individuals?

We cannot say that the summaries are reasonable interpretations when the document reads of all the potential benefits being acknowledged, saying the research is too complicated to evaluate specifically, and then make a decision to deny patients the opportunity to weigh the available research as an individual under team care.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender

reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Some questions that came to mind for me, working in Canadian health care would be there is no disclosure within the committee regarding the input from the protected populations. While I would hope that members of the committee are members of these outlined groups, there was no identification within the document of how or where input specific to the hardships people may face other than the underdeveloped section 3.18.

"It also noted that people from deprived areas, with language, learning or cultural barriers, or those with disabilities may be at a disadvantage." Approval of Bezultifan would be an opportunity to alleviate some of that burden as it offers one more alternative treatment, one that requires less intervention and is more readily accessible .

"The committee agreed that, if belzutifan were recommended, the recommendation would not restrict access for some people over others." This statement is based on equality when health care needs to be striving to a vision of equity. I supposed the statement is factual in the way that there are already such significant barriers for some people to access health care in the first place, by the time someone has navigated the system enough to find their way to Belzutifan, there are likely multiple levels of privilege that have paved the way and hopefully there would not be a restriction of access. This begs the question though how the choice to restrict access is further holding the barriers that would help remove some of the inequities people in our community are already facing.

"No other equality or social value judgment issues were identified." Regarding the members of the committee making the decision, we cannot say there are no judgement issues identified if we do not know the process to ensure inclusion. If there is nobody who is disabled on the committee, or there was not intentional inclusion of opinion from someone in the disabled community, a judgement issue has been identified. In that case we are making decisions about marginalized populations without their input.

The above list would be particularly relevant for those with VHL regarding the following;

Age- those with VHL have a higher than normal mortality. Any access we have to care paths (as deemed individually appropriate) that would help us reduce the rate of mortality would be beneficial. Denial of a medication that has known and proven benefits is a decision to continue to limit our lifespan. This was particularly relevant with regards to the included and excluded age brackets for the research on Belzutifan.

Disability is exceptionally prevalent within the VHL community and there was a lot that was left to be desired in this document. Again, the withholding of Belzutifan is an active decision to increase the rate, length, and

complexity of our disabilities while fully knowing the external supports required within health care to care for those with these needs.

- Section 3 – Committee-discussion, point 3.2, ‘Unmet need’

This section is accurate, there is a massive unmet need for those living with VHL. While the population sizes overall may be small, it is a significant strain to access specialist care on top of the daily symptom and care management.

Considering this unmet need is acknowledged within the scope of this review, it is discriminatory to suggest withholding access to a solution that is likely to be of assistance AND in the absence of other available options, is not only an acknowledgement and active continuation of the unmet need, but also a further burden on an already struggling health care system when we are knowingly denying an effective course of care which will result in much heavier and more frequent use of system resources.

- Section 3 – Committee-discussion, point 3.3, ‘Existing treatment’

A personal anecdote, not a single one of our family's VHL surgical managements have gone as planned or within the normal time frame for a hospital stay. Each "48 hour stay" has extended into weeks or months of complex post operative care, including one resulting in moderate paralysis requiring a 3 month inpatient spinal rehabilitation that was booked with a 48h management plan. Ensuring that surgical intervention is not looked upon as a benign option, or always as the first choice is crucial to understanding how disappointing it is to see NICE denying a viable alternative to those living with VHL. It was only after this life-altering "routine surgery" that Belzutifan was approved for us, and I can tell you that we could have lived without that experience knowing it was available for us to use prior but we were not approved because that surgery was "the easier option".

I can fully acknowledge that this may read as too personal. "Well, surely things didn't go to plan" however the last multiple surgeries in our family had grown more increasingly complex and our neuro-surgeon was regularly open that he was growing very uncomfortable with the risk but was denied other options including Belzutifan at the time. We were also denied alternative forms of chemotherapy and radiation based on clinical risk, and so we were left with what alternative? I ask you to strongly consider that the request for access to Belzutifan in this controlled way, may truly be the last remaining option for some and you are deciding that as a whole they are not worth consideration when you decline it's approval for use in this scope. While I wish every person with VHL had the opportunity to experience the positive effects of Belzutifan, I can understand needing to balance the benefits and risks also, however I believe this is best done within the teams we work with who see us regularly, understand our individual needs and will be the ones dealing with the outcomes including discussion of end of life care plans for someone in their 30's because a committee wouldn't allow

them the scope to make that clinical decision and use that life changing medication when required.

- Section 3 – Committee-discussion, point 3.4, ‘Belzutifan marketing authorisation and positioning’

I cannot imagine any new medication that does not come with these challenges. Weighing the benefits and risks carefully for each individual case is important when we are still learning about medication uses. However, using this as rationale to potentially deny access to those who would benefit when their medical team agrees with this course of care demonstrates a cruelly ableist view from the committee.

- Section 3 – Committee-discussion, point 3.10, ‘Company's model structure and outputs’

If the committee will have opinions on the research models being "too complex", including specific rubrics within the document would have been appreciated. It looks as though the committee is opting to discount a large proportion of the research available, however the complexity of sifting through research on a small group of people living with a significantly life altering rare disease is worth the time.

- Section 3 – Committee-discussion, point 3.13, ‘Health-related quality of life’

To me this is an exceptional research loss as in our family the value and quality of life changes we have experienced while using Belzutifan have been incomprehensible. I truly did not think I would experience access to this type of medication for VHL within my lifetime, and the positive impact it has had in our family has been nothing short of miraculous. From pre-surgical motor function decline impacting daily living including employment pause, post surgical paralysis and discussing palliative care options, and now not only return to daily living, mobility, and quality of life including ability to be employed and out of hospital. I am dumbfounded that this type of information was excluded from data collection.

I certainly hope it will be collected as time and experience with Belzutifan continues, and I can only hope that NICE will not look back in hindsight and wonder why they denied the potential for improvement to those when it was available, accessible, and if indicated by medical teams.

- Section 3 – Committee-discussion, point 3.14, ‘Severity’

Reading this section as an outsider, it is concerning. You are able to acknowledge the incredible severity and variety within the VHL community, as well as the impact on those living with it. You can also acknowledge that some assumptions had to be made because those with VHL often fall into multiple categories vs one eg: RCC/pNET. Yet, knowing that these will only

increase the severity for those living with VHL, instead it seems to be a blatant disregard of that experience in favour of calculations and underlying assumptions based on standard care. Anyone with VHL will tell you, there is no standard when living with this disease! A little bit of compassion that statistics should be a part of consideration but not all, would go a long way.

- Section 3 – Committee-discussion, point 3.15, ‘Uncertainties in the evidence and the company's modelling assumptions’

The final paragraph simply reads cost over health care. "within the range normally considered an effective use" , yet when we are comparing the price of the medication to multi-disciplinary team salaries, long term stays in the hospital, while considering the reduction of income for patients and thus reduction on tax dollars that support the health care system itself, where exactly is the financial incentive not to use Belzutifan if and when clinically indicated by a care team?

- Section 3 – Committee-discussion, point 3.16

We accessed Belzutifan via a cancer drug fund with an individualized application, and it is the only reason we are able to afford it, and also the only thing that has kept our family out of palliative care currently.

The idea that this potential avenue of funding would be excluded across the board is disheartening.

- Section 3 – Committee-discussion, point 3.17, “Other factors”

This is an unacceptable acknowledgement that a debilitating genetic disorder has complex research needs, and yet decisions to withhold a new medication across the board rather than with individual assessment were made with full understanding of this deficit.

- Section 3 – Other factors, point 3.18, “Equalities”

In this section you outline that that treatment is innovative, approved, and that clinical experts show that it offers a change to stop and even reduce tumours, surgical intervention, metastatis and dialysis. The multiple benefits are acknowledged and yet the committee declined it's recommendation based on "no additional benefits". I will challenge those on the committee to consider what their expectations are for a medication that is new to the market? What more would you like to see in order to deem it suitable to be offered when there are no other alternatives? What is the criteria you will use given that you are denying something that has shown benefit for an incredibly complex disorder with limited alternatives, particularly when we know we will be heavily reliant on other health care supports including access to imaging, surgical care, oncology, dialysis etc. Denial of a possibility to utilize this medication will keep us exceptionally reliant on other forms of management that are known to run their course of efficacy and leave us with no alternatives.

- Section 3 – Other factors, point 3.19, “Innovation”

In this section you outline that that treatment is innovative, approved, and that clinical experts show that it offers a change to stop and even reduce tumours, surgical intervention, metastatis and dialysis. The multiple benefits are acknowledged and yet the committee declined it's recommendation based on "no additional benefits". I will challenge those on the committee to consider what their expectations are for a medication that is new to the market? What more would you like to see in order to deem it suitable to be offered when there are no other alternatives? What is the criteria you will use given that you are denying something that has shown benefit for an incredibly complex disorder with limited alternatives, particularly when we know we will be heavily reliant on other health care supports including access to imaging, surgical care, oncology, dialysis etc. Denial of a possibility to utilize this medication will keep us exceptionally reliant on other forms of management that are known to run their course of efficacy and leave us with no alternatives.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

As a UK citizen and a daily user of Belzutifan, my experience highlights a disappointing disconnect with aspirations to enhance access to groundbreaking treatments, as exemplified by the awarding of the first Innovation Passport https://www.gov.uk/government/news/first-innovation-passport-awarded-to-help-support-development-and-access-to-cutting-edge-medicines) and the committee discussion and recommendation regarding Belzutifan.

In particular, I disagree with the supposition in 3.9 in this of the "Belzutifan for treating tumours associated with von Hippel-Lindau disease" with Vonda Murray as Project Lead https://www.nice.org.uk/guidance/indevelopment/gid-ta10817 that "the committee noted that the relative treatment effect was highly uncertain".

I can attest to the impact of Belzutifan as a 23-year-old UK citizen. Thanks to Belzutifan, I can now complete my engineering BSc and, instead of worrying about becoming a paraplegic or dying at a young age, I look forward to a fulfilling life. After what I have experienced, I now value life more than I imagined and am proud that I can contribute to economic growth, rather than be a burden to my family and fellow citizens.

I am fortunate to have access to Belzutifan through my parents' endeavor to get help in the USA. I am disappointed that myself and fellow UK citizens with VHL cannot get access to such life-saving medication in the UK.

I was diagnosed with VHL in 2020 after my older brother had an emergency operation to remove a life-threatening haemangioblastoma located in his cerebellum, followed by a further operation two months later to remove a spinal cord haemangioblastoma, which, if untreated, would have left him paralysed.

In April 2022, I had a brain tumour removed surgically, followed by an operation in June 2022 to remove a dangerous tumour on my brain stem at the top of my spinal cord. After undergoing these operations, I was to left deal with complications related to the growing 15 brain tumours and 7 spinal cord tumours that I had before the Belzutifan intervention.

My MRIs showed that without intervening medication it was inevitable that I would have to undergo several operations. If the tumours located centrally in my spinal cord were removed surgically, I would have had to cope with severe neurological consequences. I was advised by neurosurgeons that the tumour I have at C2 that grew from 3.5x3mm in 2020 to 8x5.5mm in 2022 would have been life-threatening as surgical intervention could have removed my ability to breathe and swallow independently.

As a result, after learning that Belzutifan was not available in the UK even on a self-pay basis due to administrative issues, at enormous personal cost my family sought treatment in the USA. My parents arranged and paid for consultations at MD Anderson in Houston, Texas, and in September 2022, we secured a prescription for Belzutifan. We paid $32,000 per month to secure Belzutifan for a number of months. To make access to Belzutifan more financially sustainable, my parents had the courage to take the risk of moving to and finding jobs in the US. The whole ordeal was incredibly stressful as there was so much uncertainty as navigating the US health system to secure delivery of Belzutifan required personal funds and emotional resilience.

As a result of my parents' endeavours, I began to take Belzutifan in October 2022. Results from the MRIs performed 4 months after commencement show that several spinal cord tumours had disappeared, and the largest and most dangerous spinal cord tumour at C2 had reduced in size by 50%. I attest that I am in good physical and emotional health with no noticeable side effects.

Thanks to my parents, I feel privileged that I can lead a full life despite having VHL. As long as my parents have the strength to be employed in USA I will have access to Belzutifan till I am 26 years old. Since Belzutifan has helped me avoid a life-threatening situation, I call upon your institution to recommend that this medication is made available to all people with severe VHL complications in the UK.

Sincerely, xxxxxxxxx

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

Happy, confident, bubbly. That was my sister in law before her life was turned upside down by the diagnosis of VHL. She puts on a brave face but behind that exterior she isn't the same person. Do you know that feeling when you wake one morning from a bad dream in a panic but then you remember it was a dream, a sense of relief comes over you and you can relax? My sister in law doesn't get to feel that anymore because that dread, that weight is always there. Looking forward to something, your mind allows you to get excited for just a second before you are crudely brought back to reality with a crash. Imagine these feelings every single day. Imagine seeing someone you love so much go through this and you feeling useless because all you can do is watch and not really understand the full, real impact on them both mentally and physically. Imagine there being medication available to help make your life better, to give you some tiny amount of comfort, to ease some of your fears. Now imagine being told that you can't have it. It's not a lot to ask for to compensate for the huge sacrifice to your life by having regular appointments, tests, scans, constant worry, being told that you will lose your hearing and potentially your sight and possibly worse. I wonder if the decision to refuse this drug in England would be the same if it had to be made by the people who have to live through this hell, every single day. Look beyond the red tape and bureaucracy and when you make the final decision imagine your life as someone diagnosed with VHL.

- Has all of the relevant evidence been taken into account?

Yes

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Yes

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

No

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Yes

Name	Not specified
Role	Not specified
Other role	Not specified
Organisation	[redacted]
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Has all of the relevant evidence been taken into account?

No - I am writing about my niece, a real live person living in fear for her life, not a statistic. The impact her diagnosis had on me has been immensely sad and worrying. I have seen this lovely, vivacious young woman become a timid, anxious, nervous and sadly depressive soul. With all this to cope with, she still fits in a full time job (for the NHS no less), the raising of her beautiful two year old son with the help of her wonderful husband and miraculously does charity work for her cause. Her son, by the grace of God, does not carry this cruel VHL gene, which she only found out about after an agonising wait.

No one should watch a loved one suffer incessantly but it seems we have no choice. At present, after having a tumour removed from her head, which has subsequently grown back, and her eyes operated on, she is trying to cope with the fact that a growth within her inner-ear is growing and will definitely need to be removed. This surgery will leave her deaf in this ear and disfigured, this growth which the doctors advised to leave alone. Perhaps with the new drug, it would have bought her more time.

Her main concern is seeing her precious son [redacted] grow up and to raise him well but also her ability to hold down an important job and be a good wife. Imagine living in this continuous state of anxiety day in, day out. Belzutifan will slow the growth of her tumours so instead of living in fear under the endless threat of the inevitability of more tumours, and risks with more major surgeries, this 32 year old (young) woman, can meet the milestones we all want for her and that she wants for herself.

Let's all try to close our eyes and put ourselves in her position. Who would want to live like this, even for half an hour? Imagine every day not knowing the next stage of progression and knowing that Belzutifan is there and will help you make it, to see your son grow up and even take away the mental anguish of major invasive surgeries.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

There is enough clinic effectiveness for this drug to be available in Scotland.

What is the cost of the surgeries and after care. How much money is lost from the economy because conventional treatments could mean people have to leave the workforce.

What difference Belzutifan will make to their life?

This new drug would be life changing, not just for [redacted] but also for her family and support network.

It's would remove this horrendous cycle of monitoring, waiting, operations.

It would give them a chance of a more normal life.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I don't know where to start. I feel anger, sadness and most of all let down by a system I have paid into my whole life. I feel very confused why the NHS wouldn't want to help the so many people suffering with this dreadful disease in England. I feel quite despondent that the NHS wouldn't want to slow down these terrible growths and tumours, and even prevent surgeries. Why has it been approved in Scotland when if you are English you are left to deal with your fate all alone? How can this not be discriminatory against a group of people? The people with VHL in England? Well, I say to you, the surgeries are not the answer. They leave people blind, deaf, disfigured and without vital organs, and most of all, because of their life sentence of fear, their quality of life is non-existent! Just one person having to live like this, is one too many. If you have a conscience, please, please, please reconsider your recommendations..

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No - all of the above make these recommendations to the NHS unsound. VHL sufferers in England need and deserve more than just major invasive surgeries, that piece by piece take away their quality of life until there is nothing left!

Name	[redacted]
Role	Not specified

Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

I am a retired GP. My Husband and twin daughters and my nephew have VHL ,so I have first hand knowledge about this devastating diagnosis.
My husbands mother and his brother died of this condition in their 50s requiring a large amount of care from the NHS as they both became paraplegic because of inoperable spinal and brain hemangioblastomas .
My nephew who is now 35 ,has multiple hemangioblastomas and has already had multiple neurosurgical interventions. He has a brainstem tumour which is making him vomit every few weeks and is interfering with his job as a senior nurse in recovery at our local hospital. He also has multiple hemangioblastomas in his spinal chord , pancreas and other places . His neurosurgeon has said he doesn't want to operate on his tumour because of the position of the tumour.

I have reviewed the NICE documents and feel that for a case such as my nephew's , a drug treatment would save the NHS money in the long run.
I feel that there are a few patients deserving of the medical option like my nephew and that NICE should review the treatment case by case basis

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

I was disappointed to learn of this provisional outcome. Although I understand (but do not necessarily agree with) the analysis I think there are additional matters which have not received sufficient consideration or which have received consideration but where the potential patient impact has not been fully appreciated.

In particular I should like to highlight youth of the patient and severity of the disease. In considering severity, I am particularly concerned about denying potentially effective treatment to young patients who are no only threatened by cancer risk, but also by neuro-ocular manifestations. In the event that these (haemangioblastoma) are not (readily) amenable to surgery the patient is faced with a true nightmare of accruing neurological deficit and/or loss of sight together with the threat of a catastrophic event.

My reading of the experience to date (and my knowledge of mechanism) leads me to believe that Belzutifan would reduce these risks and I think the benefits of this to (albeit rare) severely affected patients have been underestimated. It might also be predicted that mutation-based resistance would be unusual in these settings.
I would also like to comment on novelty. This is an entirely new mode of treatment. As such there are unknowns on the upside, which do not appear to have been properly considered.
A additional argument (which is not patient-centric), but nevertheless needs to be considered is the need for some bias in support of innovation within the UK..

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

I contest the assertion made in section 3.9 of the "Belzutifan for Treating Tumours Associated with Von Hippel-Lindau Disease" document, overseen by Project Lead Vonda Murray (as per NICE Guidance), which states, "the committee recognised that the relative treatment effect was considerably uncertain". This perspective starkly contradicts our own experiences with Belzutifan, which has shown outstanding effectiveness in managing VHL-related tumours. Furthermore, the recent conferral of the first-ever Innovation Passport, intended to expedite the development and availability of advanced medical treatments (as reported in UK Government News), stands in marked contrast to the committee's cautious approach towards Belzutifan. In light of this disparity, I earnestly appeal to the committee to re-evaluate their stance on Belzutifan, taking into consideration its proven efficacy and the forward-thinking ethos of the Innovation Passport initiative.

As a British citizen and father of two sons, [redacted] (26) and [redacted] (23), who are diagnosed with VHL, I have observed firsthand the significant impact this disease has on patients and their families. My perspective is shaped not just by personal experience but also by an awareness of the wider repercussions of your recommendations on the VHL community.

I was 50 when diagnosed with VHL, following [redacted] emergency cerebellar surgery. My VHL-related complications have been relatively minor, but witnessing my sons' battles has been deeply distressing.
[redacted], diagnosed with VHL in 2020 after his emergency surgery, has undergone multiple procedures, including a vital operation for a spinal cord tumour. His journey has been marked by physical and emotional hardships,

disrupting his career as a data scientist and causing considerable anxiety about his future.

[redacted] ordeal has been equally troubling. He had surgeries for brain and brain stem tumours in 2022, and was left facing a particularly concerning tumour at C2, which was due for a potentially life-threatening operation in 2023. The growth of this tumour underscored the urgency of accessing Belzutifan, a drug unavailable in the UK. Faced with this dilemma, we decided to seek treatment in the USA in September 2022. Initially paying out of pocket, we obtained a prescription for [redacted] in the USA and spent $32,000 monthly for Belzutifan. To make this sustainable, we risked relocating and finding employment in the US. This entire experience has been incredibly stressful, as my wife and I upended our lives to navigate the US health system to ensure [redacted] could receive Belzutifan and lead a normal life.

Belzutifan has been remarkably effective for [redacted]. Within months, several spinal cord tumours vanished, and the critical C2 tumour significantly shrank, negating the need for life-threatening surgery. [redacted], now 26, is not covered under our US insurance, and we, as a family, face the daunting task of self-funding his treatment, an overwhelming financial burden. His ambition to continue contributing to society as a data scientist is overshadowed by the fear of paralysis and the emotional toll of VHL.

Moreover, [redacted] and I are currently under the care of Dr [redacted], MD, Associate Professor of Medicine at Massachusetts General Hospital Cancer Center, Harvard Medical School. He has prescribed Belzutifan to several VHL patients. Dr [redacted] represented to me that he is astounded by the medication's effectiveness, which has produced unprecedented responses in oncology, transforming patients' lives. He expressed that it is a tragedy that VHL patients outside the US lack sustainable access to Belzutifan, highlighting the avoidable pain and suffering of an effective drug with little or no side effects.

In conclusion, I respectfully implore the committee to reconsider its stance on Belzutifan for VHL, considering the extensive implications of its decision on patients' lives, their families, and the healthcare system. The ultimate objective should be to guarantee equal access to effective treatments, in line with the UK's ambition to be at the forefront of healthcare innovation.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	Not specified
Comments on the DG:	

- Section 3 – Committee discussion , point 3.20, “Recommendation”, “The committee's concerns about the clinical evidence and cost-effectiveness model meant that it was not confident about the results presented. It concluded that it would like the uncertainties to be addressed and that belzutifan could not be recommended.”

Would you please reconsider your recommendation not to approved Belzutifan for NHS use. I have VHL and had to endure over 20 operations, on my brain, spine and eyes, this has greatly affected my health, I have lost 50% of my vision, 50% of my hearing, I have problems with balance, coordination and I have had to surrender my driving license, leading to a loss of freedom. This drug is potentially live changing, it is probably too late for me but would change my nephews life, if we can do anything to slow down the tumours to avoid invasive surgery, we should do it, whatever the cost.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	No
Conflict	Not specified
Notes	
Comments on the DG:	

- Has all of the relevant evidence been taken into account?

All the evidence has not been taken into account. I personally know numerous family members with VHL living in the United States who have access to this drug and have been on it for over two years with NO complications and a massive reduction in tumour size and stabilisation of growth.

The benefits of this drug clearly outweighs the consequences and I feel this drug would practically remove life threatening surgeries and save lives. So I would request you to re consider your conclusion and approve this drug as there is clear real life evidence this drug is highly beneficial for VHL patients.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Yes - As you mention in your guidance the cost effectiveness isn't a huge burden for the NHS and this drug is definitely worth it. It allows the NHS to save on costs of surgeries and treatments.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

You need to factor in VHL causes patients to become disabled and by refusing this drug you could be potentially allowing patients to become disabled in life threatening situations such as a Brain or Spine tumour and eye tumours.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Absolutely NOT. This drug has been approved in the United States in 2021 and most recently in Scotland NHS. As per my comments above the recommendation should be saying "approved for use" as living with VHL isnt easy, back to back surgeries, disabilities, cancer spreading and a short life span all because NICE decide to refuse a drug that is clearly life saving and provides a good quality of life. So please re consider your conclusion and approve this drug ASAP so VHL patients in critical situations can live their life again.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

I am a 31 year old male living in Stamford, Lincolnshire.

My partner (30) has VHL, along with her mother (58) and sister (35). Her grandmother also had VHL and passed away from kidney cancer as a result of the disease a few years ago.

In my partner's family, they have battled pancreatic cancer, brain and spine tumours, and adrenal tumours. My partner has had surgery to remove an adrenal gland due to an adrenal tumour. My partner's sister has to take medication every day since removal of her pancreas after her pancreatic surgery. Her sister has also lost sight in one eye and she is awaiting surgery for an adrenal gland to be removed due to a tumour. Her mum has lost her hearing in one ear and has had an adrenal tumour leading to surgical removal. We live in constant fear of the next tumour and it has affected our mental health immensely. Her sister runs a VHL charity, through which we have met many patients, all of whom have their own struggles dealing with

VHL. Meeting them really highlights how much the disease can impact not only the patients but their family and friends.

We are currently planning our future, which involves having children. This will require extensive PGT-M IVF to ensure that VHL is not passed to any children that we may be fortunate enough to have.

Belzutifan would be life changing for my family and many other patients. It would mean we would not have to face the fear of numerous tumours and life altering surgeries. It would provide hope, of which we are seeing in other parts of the world for other patients. Not only would it reduce the prospect of extensive surgeries, organs and key functionalities missing, it would support our mental health.

In light of this, we are heartbroken at the results of the NICE review. If NICE approves in the next review, it would be the best thing we could possibly hope for, along with so many other patients.

I trust that NICE will take this account, and all other accounts provided, combined with the rare nature of this disease (that although rare, affects lives severely), to ensure the right decision of approval is made.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

I am a 35 year old female based in Lincolnshire, England. I have VHL, along with my mother and sister. My grandmother also had VHL and passed away from kidney cancer as a result of the disease.

My family have faced pancreatic cancer, brain and spine tumours, adrenal tumours. I have to take medication every day since removal of my pancreas my pancreatic surgery, I have lost sight in one eye and I am awaiting surgery for my adrenal gland to be removed due to a tumour. My mum has lost her hearing in one ear and both her and my sister have had their adrenals removed. We live in constant fear of the next tumour and it has affected our mental health immensely. I have met many patients through the charity support groups and it highlights how much can happen to a patient, of which makes the disease even more daunting.

For my sister and I, we require extensive PGT-M IVF to start a family and avoid passing on the gene, of which is a daunting prospect with risks and limited success rates. This adds to the weight of living with the condition.

Belzutifan would be life changing for my family and many other patients. It would mean we would not have to face the fear of numerous tumours and life altering surgeries. It would provide hope, of which we are seeing in other parts of the world for other patients. Not only would it reduce the prospect of extensive surgeries, organs and key functionalities missing, it would support our mental health.

In light of this, we are heartbroken at the results of the NICE review. If NICE approves in the next review, it would be the best thing we could possibly hope for, along with so many other patients.

In 2014, I attended a VHL support group where I met a patient in fairly good health but battling the condition. I met this patient again in 2021; she was now immobile, nearly blind and very affected mentally. I have never seen someone so desperate for this treatment, it was a real testimony to how this drug is life or death. Unfortunately I have also seen patients pass away since 2014, of which they would still be here.

I trust that NICE will take this account, and all other accounts provided, combined with the rare nature of this disease (that although rare, affects lives severely), to ensure the right decision of approval is made.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

My Fiancée and my two sons have VHL.

I have been with my Fiancée for 7 and a half years now and so my experience with VHL is limited to only those years as I had never heard of it before. From mine and my Fiancées experience of it now and the information I have about VHL, I believe that Belzutifan, and from the results of the clinical study of Belzutifan, shows its capability to transform someone diagnosed with VHL's quality of life.

My Fiancée was diagnosed at age 10 after finding out she had inherited it from her father, who sadly passed away at the age of 42, 3 years after being diagnosed with VHL.

Since then, she has had multiple eye tumours and surgeries resulting in lots of complications and being left with little sight in one eye. If she loses the sight in her left eye, it will be very detrimental. She would have to give up her job and she would not be able to drive, she'd need someone with her

when leaving the house, thus meaning she will become isolated in her home, which will impact her mental health and those around her.
She has also had a partial nephrectomy due to RCC. She was fortunate to have had it all removed, but the recovery was brutal. She needed several months off work and needed a lot of care. She knows this will return and She can't imagine how hard it will be to recover being older.
She also has tumours in her spine and one tumour in particular at the location of the cervical medullary junction. Her neurologist has clearly stated the he is loathed to intervene at this location because it is like spaghetti junction and he has told her that intervention would cause permanent and catastrophic consequences for her. The same consequence will occur if it continues to grow. This area will mean that if the tumour continues to grow like it has, or surgical intervention is done, she will be paralysed from the neck down and incontinent. Belzuitfan really is her only option and hope.

Knowing that the tumour in her neck has the potential to disable her in the future and with all the costs and time involved with that scenario, surely the cost of the drug outweighs the continuous cost to the NHS for the rest of her life and to the government as well.

I find it hard that from the same study the drug has been approved elsewhere, especially in the NHS in Scotland, and for some reason it is not in the NHS England. I understand that it will always come down to cost, but I feel that consideration into the long term benefits of this drug for people's lives and the reduced impact it would have to the NHS, would show enough savings to reduce the overall cost of the drug to the NHS and to help sway the decision to approve it.

With my sons also having the same VHL diagnosis, it would give me hope for the future, that with a drug like Belzuitfan being available for VHL patients on the NHS, their quality of life and possible length of their life would be vastly improved.

I implore you to reconsider this decision and approve this wonder drug, as being the only drug that has proven to help reduce tumours in VHL patients, it will change my family's health and outlook on life, plus also many more who deserve the chance as everyone else for a better, longer, happier life.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

- Has all of the relevant evidence been taken into account?

No because the definition of the impact on VHL patients says:
“Some people with the condition might only develop 1 or a few tumours in their whole life, while others might have multiple tumours in different organs”
It does not take into account patients like me who have had life-changing surgery to remove:
Pancreas
Spleen
Duodenum
Gall Bladder
Rather it suggests that tumours might arise at different times in differing organs

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence

It is impossible to say because the data is not transparent.
If the base description of a VHL patient as above is flawed, then the cost effectiveness interpretation must be equally flawed and cannot possibly take account of patients who have had very many surgeries.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

There is a small population of VHL patients who have Highly Complex cases, and this group are being discriminated against by this decision, which is otherwise based on a “typical group of VHL patients” which is ill-defined.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

It cannot be argued that the recommendations are soundly based if they fail to understand the complexity of cases of a small number of VHL patients.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

Speaking as a mother who's daughter is de novo, it came as a great shock when she was diagnosed with VHL back in 2003 when she was 14. She was diagnosed with a brain tumour which was swiftly removed and she was able to leave hospital early for her 15th birthday. We were subsequently told she had VHL which of course we had never heard of before.

She has gone on to have 3 more brain tumours removed, full whipple procedure, adrenal gland removed.

Her kidneys, spine and pancreas tail have tumours which are being monitored and once they reach the appropriate size will hopefully be removed.

Our daughter and son-in-law did not want to pass this condition on, they were offered PGD and now have a healthy, nearly 2 year old who is a great joy, although the pregnancy was marred when she was diagnosed with her 4th brain tumour a few months in. This was removed 6 weeks after giving birth. All the family were on hand to assist with the big upheaval in their lives. She didn't trust herself to hold and carry the baby as she had a tremor in her hands, which still happens occasionally now.

Unless I have misunderstood, currently only 69 people from 500+ in England and Wales are suitable for Belzutifan. I do not know if our daughter would be eligible, but, I do know that if she was it would be wonderful to know that further surgeries and symptoms could potentially be lessened.
I see and feel the effect of scanphobia regularly. If this drug can help other families it should be fully endorsed. I don't understand how other 1st world countries, US, Scotland have agreed it is a good drug, but NICE haven't!
Obviously, I am hopeful you will reconsider this decision and give Belzutifan the all clear in 2024. Thank you for reading.

- Has all of the relevant evidence been taken into account?

I do not feel qualified to answer this question

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I do not feel able to comment

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I don't feel there is any discrimination in any papers I've read.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Again, I do not feel qualified to answer this question.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Has all of the relevant evidence been taken into account?

Definitely not!
The evidence states that the worst affected patients “might have a number of tumours in different organs”.
It takes no account of patients like me who have:
- a long history of tumours and to date almost 30 surgeries in 4 different organs
- multiple tumours currently in multiple organs
- tumours which are not operable or carry a very high risk of mortality, or at best have other complications stemming from surgery, radiotherapy, etc.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Put simply “No”.
The cost effectiveness interpretation doesn’t reflect in any way those patients who are worst affected by VHL – my own case is typically descried as “highly complex” due to the past surgical history, ongoing tumour and cyst presentations and difficulty in further surgery. Instead, it assumes that “most” patients can be satisfactorily treated with surgery- believe me if surgery was an option I would grab it with both hands!

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Yes
The small population of VHL patients who are worst affected and described as Highly Complex are being discriminated against by this decision which does not take into account our medical circumstances and needs

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Definitely not! An assessment that does not take specific account of the highly complex VHL patients is unsuitable, as it is based on flawed assumptions of what a “typical VHL patient” looks like.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

Happy, confident, bubbly. That was my sister before her life was turned upside down by the diagnosis of VHL. She puts on a brave face but brothers know sisters and behind that exterior she isn't the same person. Do you know that feeling when you wake one morning from a bad dream in a panic but then you remember it was a dream, a sense of relief comes over you and you can relax? My sister doesn't get to feel that anymore because that dread, that weight is always there. Looking forward to something, your mind allows you to get excited for just a second before you are crudely brought back to reality with a crash. Imagine these feelings every single day. Imagine seeing someone you love so much go through this and you feeling useless because all you can do is watch and not really understand the full, real impact on them both mentally and physically. Imagine there being medication available to help make your life better, to give you some tiny amount of comfort, to ease some of your fears. Now imagine being told that you can't have it. It's not a lot to ask for to compensate for the huge sacrifice to your life by having regular appointments, tests, scans, constant worry, being told that you will lose your hearing and potentially your sight and possibly worse. I wonder if the decision to refuse this drug in England would be the same if it had to be made by the people who have to live through this hell, every single day. Look beyond the red tape and burocracy and when you make the final decision imagine your life as someone diagnosed with VHL. Has all of the relevant evidence been taken into account?

Yes

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Yes

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any

group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

No

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	
Sounds like a fantastic drug to help cure this disease	

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	Not specified
Comments on the DG:	
VHL has affected my family since I was a child. My dad, after 2 brain tumours was diagnosed with VHL. After that, our family life was flipped upside down. Dad went on to have multiple eye tumours treated and a full nephrectomy meaning he went on to dialysis. He had to leave job and my mum had to return to work whilst looking after him, me and my sister. With support from family we went on a rare holiday to Butlins. I recall my mum saying that my Dad would get upset because he said he just wanted to see his children grow up. He died shortly after. He was 42, I was 12. I was the one who found him dying at home and even now when I am nearly 40, I find it very traumatic to talk about it. Had Belzutifan been approved 30 years ago, he would have lived longer, would have had his transplant that he was only 4 months away from having, he'd of had his wish of seeing his children grow up and as a family we would have had more time together. The stress and devastation of his experience with VHL and death caused to me develop anxiety, nervousness and IBS. I still get problems now which I am under the care of the NHS for.	

VHL still remains in our family, because although my father was the first person in our family to develop it, when my sister and I were tested for VHL, I was negative but unfortunately my sister was positive. My sister has several manifestations and had multiple operations from the age of 7 including eyes, kidneys, spine and brain. She has lost most of her vision in one eye, had kidney cancer and currently has a cervical medullary junction tumour which she has been told that if it continues to grow, or they have to do surgical intervention it will lead to permanent and catastrophic effects for her. She has a family of her own and unfortunately both her children have inherited VHL too.

She is the strongest person I know. Belzutifan needs to be approved in England so that she can preserve the quality of life she has. Likewise for other VHL patients as well.

If my sister is unable to be accepted to take Belzutifan she will become paralysed from the neck down. This will not only severely impact her quality of life and family life; it impacts her extended family, such as me and our mother as well. We are a close supportive family so it directly affects us too.

If my sister becomes paralysed from the neck down, she and her family will need multiple people around them to support them pretty much 24/7. Due to the many complications that come with being a quadriplegic, I may need to reduce my hours at work or leave my employment all together so that I can care for my sister, and her children physically and emotionally. She may not be able to be left alone and my support would help her to try and retain what dignity she'll have left, if any. I may need to take on more of a role as a mother figure for her children as she will be unable to care for them when they are recovering from manifestations of VHL or surgery. I would need to be able to support them emotionally when they ask questions because they don't understand why this is happening to them and trying to process what is happening to their mum.

I have a family myself and it will be hard to juggle and I will feel guilt because a) I didn't inherit the illness b) I don't want to take parental duties away from her, but I know that she would try and protect her children from seeing things we had to experience when we were younger.
Overtime this stress and emotional drain would have a negative impact on me and my family too, it may impact my anxiety and IBS, I may develop depression and need to receive counselling on a regular basis so that I can process the impact on our lives. Thus I am an additional strain on the NHS from VHL .

If my sister can take Belzutifan she can continue working and supporting her family as she does now. Quality of life is paramount. How bad does her situation need to become before she would be suitable for this drug?
VHL doesn't just affect the patient, it affects their families too and we could then all have an additional strain on the NHS due to the manifestations of

VHL, which could be prevented and greatly reduced by approving Belzutifan. We have been through enough.

I understand that the same study has been used in your decision to decline the approval was also used in Scotland who approved the use of it. How does that work? One study under the same NHS system yet one part of the UK approve it and one part declines it. That doesn't feel right.
I understand that the cost of producing the drug is expensive. However, the long term benefits of this drug would reduce the direct impact to the NHS more as a whole for not just the VHL patients but their families too.

Please reconsider your decision, as mentioned it the reports, VHL is a devastating illness and affects more than just the patient and impacts several services in the NHS because of it.

- Has all of the relevant evidence been taken into account?

Yes

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

It doesn't seem right the Scotland have used the same study and approved it under the same evidence.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Unknown

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Unknown

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

My family has been upturned over the past 9 years with several members being diagnosed with VHL. The most recent being my 3 year old son.

In 2015, my mother received a diagnosis of VHL after undergoing a bilateral nephrectomy for renal cell carcinoma. Around 6 months later, I also received a diagnosis of VHL (age 25) and underwent a craniotomy to remove a large hemangioblastoma which had caused a multitude of problems prior. The recovery from these surgeries were long and difficult and further surgeries are expected for myself in the not so distant future.

Hearing of the successes thus far with the Belzutifan trial and the positive outcomes for those that have already started taking the medication, makes me feel hopeful. With Belzutifan, we are hopeful for reduction or even the possibility of eliminating the need for further surgeries. It also gives me hope that my son will not have to go through the same trauma that myself and my mother have.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

My husband had VHL, my daughter and two grandsons have it too.
In 1990, [redacted] had a very good job, we had a lovely home and family, then, VHL came into our life.

Within a short space of time, [redacted] had lost both his kidneys because VHL had damaged them so much. [redacted] I was then on dialysis, unable to work because he had no strength, was ill a lot and couldn't walk well..we had to start claiming benefits

Within 2 years, [redacted] had died! I was left with two young daughters, 10 and 12 and had to claim Widows allowance. It was a dreadful time for us all. Not long after [redacted] kidney removal, we were told our youngest daughter [redacted] also had VHL…

Her first question when her dad died was "am I going to die too?"
Fast forward many years…. [redacted] is 38, she has very little sight in her right eye, has had part of her left kidney removed.. she has tumours throughout her body and feels like a walking time bomb!

She knows that it's quite likely that in the future, she could be on dialysis, she knows that if her left eye goes the same way as the right one, she could be totally blind, most worryingly, she has tumours in her spine which in the future may require surgery and her consultant says for the one at the base of her brain, the operation could leave her paralysed from the neck down.

She is a mum to 2 beautiful boys who sadly both have VHL and will need constant monitoring throughout their lives. [redacted] has a partner, they both work, [redacted] is part time until the boys are older. They don't claim any benefits.

Welireg is the wonder drug! It's [redacted] best chance of avoiding surgery and have a chance of a better life. It shrinks the tumours meaning patients don't need so many scans, consultant appointments and NO expensive treatments.

Without it, if [redacted] were to need surgery, especially on the most worrying tumour, which could leave her paralysed, think of the cost to the NHS and the benefit system. Neither [redacted] or her fiance would be able to work because [redacted] would need constant care, they would be on benefits, extra carers would also be needed, changes to their house etc… it would be a huge financial burden on government resources and would well outweigh the high cost of approving Welireg.

The insurance companies in America have realised this and Scotland has as well.

I'm amazed that the drug can't be recommended for use in the UK… I know it's expensive but this should not affect the fact that for VHL patients, it could definitely improve the chances of living a good life which in the long run is more economically viable and, I'm sure the cost of the drug will eventually decrease.

Surely if one part of the UK has recognised this, then England and Ireland should do so too, my daughter and the many others like her in the UK, should not have to be considering moving to Scotland to be able to obtain this life saving drug! I support my daughter and her family a lot, this would not be possible if they moved to Scotland. In the UK we should all be treated the same!

- Has all of the relevant evidence been taken into account?

I have reviewed this information, as a mother and grandparent of people with VHL, there is no question in my mind that this drug should be allowed in the UK

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I understand the cost but feel that the long term saving to healthcare would be much higher

- Are the recommendations sound and a suitable basis for guidance to the NHS?

The consultation looks at the cost for prescribing the drug but every case of VHL is different and it's therefore difficult to predict what:
1. the personal health risk would be for not being allowed to have the drug.
2. what the long term cost and potential saving would be for treating VHL long term verses not having many of these costs if the drug was allowed, which I greatly hope it will be!

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

I live with VHL and I would like to appeal the decision to not recommend Belzutifan in VHL patients. My mum, my sister and I all have VHL disease and between us we have had 20 major surgeries for brain tumours and RCCs. We have to travel to 4 different hospitals for routine scans, appointments and treatment, the furthest of which is 60 miles away. I have personally had 4 brain surgeries and 3 partial nephrectomies. I now have just 3/4 of a kidney, which means that any more kidney surgeries puts me at risk of needing dialysis. I also still have countless tumours in my brain, spine, kidneys and pancreas. My most recent surgery was in June 2023 for a brain tumour. I was in hospital for 5 weeks with the surgery followed by a very serious case of meningitis. This has meant that I have had a significant amount of time off work (6 months and counting) and I have lasting issues, such as fatigue and balance problems. These operations and our treatment have cost the NHS a significant amount. In addition our quality of life is much reduced due to living with VHL and taking time out for major operations and recovery. It is a challenging disease to live with, it causes serious anxiety from one scan to the next and we need another treatment option to avoid the continual disruption to life. For myself, I am self employed so every time I take time off work for an operation and recovery, I have to get a benefit and I pay no tax or NI at this time. Me and my husband are also going through preimplantation genetic diagnosis (PGD) on the NHS so we do not pass this disease on to our children.

In summary, the data from Belzutifan is promising and I believe it would be a good option for me, my mum and my sister. We have no options other than scans and invasive operations at this point and we desperately need another option. As a patient, I appreciate that it is expensive, however the cost of very invasive operations, treatment, hospital stays, complications from surgery, long-term disabilities and issues due to surgery, loss of earnings in addition to reliance on a benefit while I’m off sick are also very costly. I believe it will significantly benefit our quality of life.

Has all of the relevant evidence been taken into account?

I believe that the cost of patient's current treatment and quality of life needs to be considered further, as well as the need for an alternative treatment option.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I do not believe so from my own experience (Please see my comment). There are significant benefits to Belzutifan as it is a much needed alternative for patients and it will give us a better quality of life. More will potentially be saved due to reduced operations and hospital stays and therefore no resulting complications and long-term issues from surgery, less scans and treatment, no need for dialysis etc. and in addition, individuals like myself will be able to earn more and pay more tax and NI due to less disruption to life.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

No

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

I am a 44yr old man with VHL, who has been on Belzutifan for 6 months – with great results so far. New scans indicate tumor reduction. In the past 15 yrs, I have had surgeries to the brain, spinal cord, kidney and gamma knife treatment on the brain (x2!). These have all been either life or lifestyle saving interventions, however I have also had multiple eye surgeries to correct side effects of brain surgery, I live with chronic pain in my arm, am deaf in one ear and have poor balance. I am writing as an individual and am not part of any lobby group and have never been associated with a VHL charity. My view is that Belzutifan is life changing and should be available to anybody who needs it (where their doctor thinks it appropriate).

My comments speak to the everyday reality of living with VHL for me and for my family and the importance of continuing to test and learn how to better manage the condition, even if the known benefits are only short term.

- Draft Recommendation does not consider mental health benefits (& hope) for patients. VHL patients live with a sword above their heads. Scanning and testing is (thankfully) frequent, but every scan comes with a huge fear. Belzutifan changes that. In my case, every scan now comes with the hope and expectation of tumor reduction, rather than growth. The reality for many VHL patients is that they don't need their condition to get better. It only needs to not get worse. Belzutifan mostly delivers this, at least for a while. Patients are realistic. Belzutifan is not a cure. VHL has no cure. However, Belzutifan can ensure symptoms don't develop into something serious. In that respect, it acts like a cure and this is a huge mental health benefit. VHL chips away at you over time. Every few years, there is something else to deal with and eventually one of those things will be big enough, to change your life. Life expectancy of VHL is 49-59, (depending on what you read). This becomes irrelevant when on Belzutifan. It is reducing my tumors, keeping me cancer free, keeping me off dialysis and away from the operating table. My outlook has changed and I can make longer term plans. A true game changer.

- It's not just about me, it's about my family – Part 1. Everything I said about the mental health implications for the individual, applies also to my wife and daughters. Every scan and test comes with huge fear for them too. Any benefit of Belzutifan therefore applies to them. We can plan as a family over a longer term and make longer term commitments. VHL also impacts on family planning decisions, which would be radically simplified by the availability of a drug which makes a very serious disease, easier to manage.

- It's not just about me, it's about my family – Part 2. As with any genetic condition, VHL disease is not fairly distributed among the population. Due to the 50% prevalence of the gene, individual families can become devastated. Although I am the first formally diagnosed case in my family, it explains a lot of our family history. We are now aware of other confirmed cases of VHL within my family. I am not sure how often NICE recommends to withhold life or lifestyle sustaining drugs on the basis of economic viability, however special consideration should be given to genetic conditions due to impact on entire families and not just the individuals. This disease can be brutal and devastating for specific families.

- It will get better long term with further data and continued investment: I realize the benefits I am currently experiencing may be short lived and that ongoing long term positive impact of Belzutifan is uncertain. I was diagnosed with VHL at 26 and was the first formal diagnosis within my extended family. My diagnosis was the first time I ever heard of VHL. At that time, I recall somebody saying "in 20 years, there will be a tablet for that!" I remember not really believing it – yet here we are. I believe in continuous improvement. The drug is not perfect right now. I experience strong side effects of the drug (anaemia) which are manageable. I believe that new iterations of the drug will reduce side effects and improve long term effectiveness. We can only learn more and more about the long term

effectiveness of the drug by having more people use the drug. I would also not like to see further investment and research move away from Belzutifan, due it not being made available to those who need it.

• Draft Recommendation does not clearly articulate a downside to funding Belzutifan now: While long term benefits are uncertain, the downside to funding it now and learning is not clear. There are clear short term benefits to patients, their families and to the health service. The draft recommendation make it seem like a decision to fund the treatment would be final, however my understanding is that NICE is free to revisit this decision in future. There is no clear rationale to deprive some desperate patients now, because of uncertain long term benefit. Surely, the right thing to do is fund it now, and revisit in future, rather than block it now, and revisit in future. If the main reason for blocking the recommendation is an uncertain long term economic model, the recommendations should show at least how it has considered the basic economic principle that if the treatment proves ineffective over time, demand for the drug and therefore cost and instance of prescription will reduce. This means long term risk of funding the drug should be minimal. The recommendations should address this point.

In summary, patients who need Belzutifan, should have access to Belzutifan now. This gives them benefit in the short term and provides more data for long term learning.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Has all of the relevant evidence been taken into account?

Yes

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

access to Belzutifan is a drug essential to anybody with VHL and should be free on the NHS at this cost

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender

reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I am the father of 2 woman in their 30's who have VHL, they both have successful careers, pay taxes & NI to a greater degree than the average population & want this to carry on, the ability to contribute positively to society & enjoy good health & start families and live a decent long life.
my youngest suffered from a Pheaochromocytoma on her adrenal gland when she was 18 and had this removed in a very serious operation, currently she is showing no further sysmptoms.
my eldest daughter lost the sight in one eye at 13, now takes daily medication after the successful removal of a pancreatic malignant tumour in incredibly serious surgery, I still worry about this. she has now also developed a Pheaochromocytoma on her adrenal gland which awaits serious surgery.

My ex wife also had a Pheaochromocytoma on her adrenal gland which was removed, and a tumour in her inner ear which left her daef in that ear and without the ability to hear in that ear & with vertigo & lost the ability to drive in the dark, she has inactive tumours on her spine and had many tumours laser removed from her eyes the cost for all these surgeries, etc has been immense to the system and also us
both my daughters wish to start a family but will need to go theough the exhaustive PGT-M IVF process to ensure their children don't inherit the disease as well. this disease has very much dominated our family's lives, casued immense stress, upset & hurt - the continual fear of what might just be starting to happen in their bodies if incredible & the USA has shown that Belzutifan would give us a life changing hope for my family & other VHL sufferers & to see that NICE has denied its use on the NHS is just the worst news for us & is heartbreakingly disappointing - as a carer you live your life HOPING nothing will occur but get on with the difficult consequesnces when it does - this drug's use could save my family from the prospect of serious surgery's, limiting life's function as it has with my daughter & ex wife and as much affected their mental health

I sincerley hope that NICE takse this into account, even though the disease is very rare the impact it has on sufferes is huge and needs to be addressed & the drug to be allowed

- Are the recommendations sound and a suitable basis for guidance to the NHS?

no, the use of Belzutifan should be authroised under NICE guidelines

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified

Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

- Has all of the relevant evidence been taken into account?

Yes

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Yes - on going major surgeries sometimes multiple times per year for VHL patients is a huge cost not to mention complications from these surgeries. Having the belzutifian drug to help shrink tumours would be more cost effective long term for the NHS

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation

I feel that without the drug my family especially my young son who has had 2 brain tumours a spinal tumour and is struggling with mobility issues is going to have a huge impact on our mental and physical well being, we saw a little light and had hope that belzutifan would allow us a better quality of life. Especially after seeing the positive results that it has had on VHL patients in the countries it is available. I feel we are not be treated fairly and very upset that there is a drug that could change our life so much and we are not able to access this

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

I am a VHL patient with renal cell carcinoma, brain and spine haemangioblastomas and numerous manifestations on my adrenal gland, pancreas and liver. VHL has had a dramatic effect upon my family for several decades. When I was 22 years old (my sister was 20), we helped to care for and watched our father die from metastatic RCC, at the age of 45, caused by VHL. Our grandfather also died of the same disease at the age of 48 and several other members of our family have passed away over the aforementioned decades. I am well aware that I may ultimately be facing the same outcome because of VHL.

Against this backdrop I have been closely involved in the appraisal process of belzutifan. I cannot express how extremely disappointed I am with the way in which the appraisal has been conducted and the draft guidance which was issued following the first committee meeting.

Belzutifan was the first drug to receive an ILAP passport in 2021 which was presented as a new pathway intended to give patients “quicker access to cutting-edge treatments and therapies” following on from the huge success in developing a vaccine for COVID-19. Yet here we are, some THREE YEARS on from that trumpeted announcement, with NICE, the EAG and the Company still arguing over the modelling and costings relating to the drug. I believe that the appraisal process has been grossly unfair because:

- My opinion is that the complexity of VHL disease, and how it affects multiple organs at the same time, consecutively and concurrently, has not been fully understood or appreciated. The immense cumulative effect that this has on a patient’s quality of life is incalculable.
- Everyone understands the benefit of belzutifan to the patient, but I have perceived a lack of communication and indeed, animosity, between NICE/the EAG and the Company over the last three years, which in my opinion, has been a major factor in the inability to obtain a positive outcome. In the meantime, VHL patients continue to suffer and some patients who may have benefitted from the drug have sadly died during this time.
- The existing models used in the appraisal process are inappropriate when applied to such a rare and complex disease as VHL, where the trajectory and manifestations are unique for every patient. Members of the same family with the same genetic mutation will each have different manifestations at different times in their lives. I am a classic example of this – although I too have RCC, I showed no symptoms until I was 53 years of age despite my father and grandfather dying in their 40’s. I now only have one kidney, several tumours on the remaining kidney and face the prospect of needing dialysis at some point.
- As a patient looking at the appraisal system, I cannot understand why belzutifan was deemed ineligible for the HST route. I feel that two years have been wasted in discussing this issue, yet at the first committee meeting NICE quoted rarity figures which were within their own requirements for the HST process.
- I feel that it is unreasonable that the committee also refused access to the Cancer Drugs Fund. If sufficient evidence is not available at the current time to approve funding for belzutifan, surely the CDF would be an

opportunity to gather further information, which is widely available within the VHL community and NHS Genetic Centres.
The USA, Canada, Australia and Scotland have now approved belzutifan for use and a more flexible approach appears to have been taken by these countries, as they accept that VHL is a rare disease and therefore information is difficult to obtain for the appraisal process. I feel that patients in England (also Wales and Northern Ireland, who follow England's lead for funding approvals) are being discriminated against – surely, UK citizens should all have access to the same medications?

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Has all of the relevant evidence been taken into account?

The UK Cancer Genetics Group is responding to the NICE consultation on Belzutifan on behalf of the cancer genetics community. Clinical geneticists have decades of experience in caring for individuals and families with Von Hippel Lindau Syndrome (VHL) through tertiary multi-disciplinary clinics which offer both screening and co-ordination of management for the multi-systemic features of VHL.

We believe that there are a number of areas in which additional evidence might be relevant to this decision making process in the NHS.

1) UK Clinical Infrastructure and VHL patient population

We note the concerns of the NICE committee of the differences between MK-6482-004's population to the marketing authorisation population. We also note the use of the US based VHL natural history cohort in this application. The UK National Health Service already has a co-ordinated number of tertiary VHL clinics with decades of experience in the surveillance and management of patients with VHL. The UK has co-ordinated national audits to standardise the management of VHL patients across the NHS.
Evaluation of tumour surveillance protocols and outcomes in von Hippel-Lindau disease in a national health service | British Journal of Cancer (nature.com)

The UKCGG has received emails from our members across the UK leading these clinics with clinical examples of patients they felt would benefit from Belzutifan in whom they did not feel this consultation adequately captured the potential cost effectiveness.

The UK Cancer Genetics community have more specific criteria of patients who they feel would benefit most from Belzutifan in a cost-effective way compared with the criteria assessed in this document. Estimates from real world clinic data indicates that around 2% of all VHL patients would be strong candidates for Belzutifan if it were available in 2024. The strength of the collaborative UK Cancer Genetics community who manage the tertiary care VHL clinics means that organisation into national or super-regional MDTs would be straightforward and easy to implement to standardise both eligibility criteria for Belzutifan and drug access and monitoring across the NHS. A key exemplar of this regional infrastructure and delivery of care for complex genetic disorders would be the specialised NHS organisation of services for patients with Neurofibromatosis Type 2 (NF2), particularly considering delivery of Avastin/bevacizumab therapy.

We do not feel that the UK VHL population who would most benefit from Belzutifan has been appropriately considered and we do not feel that the efficiencies of the cancer genetics community (and their partner specialists) in standardising delivery of a treatment service for VHL were properly considered

2) Eligibility criteria

a) General

We note the concerns of the NICE committee of the potential for the positioning and use of Belzutifan in the treatment pathway could be open to interpretation. The UK Cancer Genetics community feel that their clinical expertise in the management of these patients enables a tighter definition of patients to whom access to the drug should be considered. These patients all have complex disease, usually multi-system. They have been advised that surgery is going to be hazardous/not possible, for example, patients with multiple CNS haemangioblastomas that have required multiple surgeries in the past where significant burden of additional tumours remain and further surgery would lead to significant morbidity if they progressed. The multi-system nature of the condition means that considering each organ system independently is likely to under-estimate the health economic benefit of the drug which has been shown to impact tumour growth across different organ sites.

Discussions focused on renal cell carcinoma (RCC), central nervous system haemangioblastomas (CNS Hbs) and pancreatic neuroendocrine tumours (pNETs) due to the submission and trial evidence available. VHL encompasses additional significant associations which impact on morbidity in patients, including retinal angiomas leading to blindness and endolymphatic sac tumours requiring neurosurgery, and whilst these would not be primary indications for belzutifan treatment at present (although this should be kept under review), in complex patients with multisystem disease unresponsive to current treatment approaches, these features can further complicate standard patient management and exacerbate disability. There is some evidence that a subgroup of patients with retinal disease in whom

conventional treatment is ineffective or hazardous (optic disc lesions) and who usually have multisystem disease would likely benefit from Belzutifan (see addendum). We do not feel that the data on retinal disease has been properly considered in this consultation with respect to cost effectiveness of Belzutifan in VHL.

We appreciate that it is very difficult to obtain evidence on cost-effectiveness of a treatment in a rare disease such as VHL, where the underlying genetic change may cause different types of tumours across systems. However, we are concerned that the current evidence does not account for the potential impact on Belzutifan across multiple tumour types causing cumulative major morbidities in our patient cohort.

We feel that it is possible to consider more specific eligibility criteria both for the complexity of patients we would like to treat and to account for the multi-system impact of the drug.
Authorisation for the limited number of patients meeting stringent complex criteria in whom other treatment modalities are likely to have extremely high morbidity, through a highly regulated national network supported by existing infrastructure to gather further real-world data, should be considered by the committee (similar to services for delivery of Avastin/bevacizumab therapy in NF2).
This would enable NHS services to gather the evidence required to make cost effectiveness decisions in this complex setting where the applied models are inadequate and associated with a large degree of uncertainty.

Addendum on Retinal disease

Retinal haemangioblastomas (angiomas) affect up to 70% of VHL patients. They most commonly develop early in the third decade of life, although can occur in childhood. The tumours can be multiple and/or bilateral. They are usually located in the temporal periphery of the retina. However, they also develop in the posterior pole (1%) and optic disc (8%). The standard treatment for peripheral retinal angiomas is argon laser photocoagulation or cryotherapy. However, optic disc angiomas, in particular, are notoriously challenging to treat. Indeed, treatment itself can lead to visual field defects (including central scotomata). As the lesions progress, sight-threatening complications can develop. These include tumour-associated oedema and exudate, retinal detachment, rubeosis iridis (neovascularisation of the iris), uveitis, and glaucoma. Complex eye disease can require monthly intervention; children often require a general anaesthetic to facilitate treatment.

One case series that suggests that around 3% of VHL patients with eye disease are legally blind. Visual impairment and blindness carry a significant economic burden and are associated with considerably reduced quality of life. Given the impact of VHL more broadly on both of these measures, treatments to preserve vision and prevent blindness are particularly important.

Clinical trials have not tended to focus on efficacy in treating eye tumours as a primary outcome. The body of relevant literature is therefore relatively small. However, the existing literature suggests that Belzutifan does prevent progression of eye disease and/or lead to visual improvement in treated patients. In terms of the drug's mode of action and the underlying pathophysiology of VHL-related tumours, this would be expected. Of particular relevance to those with advanced eye disease, there are case reports of success in reducing fluid and exudate.

In summary, the trials show:

- Belzutifan for Renal Cell Carcinoma in von Hippel-Lindau Disease – this is a phase 2 open label single group trial. The median follow up was 21.8 months. 16 eyes (12 patients) with retinal haemangioblastomas were included. 100% were graded as showing improvement following treatment with belzutifan. Belzutifan for Renal Cell Carcinoma in von Hippel–Lindau Disease | NEJM
- Oral HIF-2α inhibitor Belzutifan for ocular von Hippel Lindau disease – this is an open label single arm phase 2 study. 29 eyes with at least one retinal haemangioblastoma. Following treatment with belzutifan 55% improved, 41% were stable, 3% were not evaluable. No eye was graded as progressed and no new retinal haemangioblastomas occurred. Oral HIF-2α inhibitor belzutifan for ocular von Hippel-Lindau (VHL) disease | IOVS | ARVO Journals

There are 3 relevant patient reports in the literature:

Two cases of von Hippel-Lindau syndrome-associated retinal hemangioblastoma treated with belzutifan - PubMed (nih.gov)

- Two cases of Von Hippel-Lindau syndrome associated retinal haemangioblastoma treated with Belzutifan.
i. Patient 1 - had a 10% reduction in the largest tumour diameter, an 8% reduction in thickness, improving subretinal fluid , intraretinal oedema and retinal traction after 4 weeks of treatment.
ii. Patient 2 - 45% reduction in thickness of tumour (near optic disc), resolved subretinal fluid and greatly improved subretinal fluid and traction). Another lesion showed 12% reduction in diameter and 36% reduction in thickness. Treatment for 2.5 years.
- No new lesions occurred in either patient.

Successful Treatment of Von Hippel-Lindau (VHL) Disease-Associated Retinal Capillary Hemangioblastoma (RCH) with Belzutifan in a Pediatric Patient - PubMed (nih.gov)
Paediatric case report (2023) - 4/12 treatment with Belzutifan led to regression in size and less perfusion to the haemangioblastoma in a patient where standard treatment plus Avastin had failed.

We do not feel that the data on retinal disease has been properly considered in this consultation with respect to cost effectiveness of Belzutifan in VHL.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

We note the concerns of the committee around the models provided with respect to interpretations around time for surgical interventions and assumptions favouring Belzutifan. We understand the difficulties in applying standard cost effectiveness models to this condition. We do not believe that this consultation is accurate in capturing the real-world cost effectiveness of the drug in our patients most likely to benefit from Belzutifan which includes multi-system disability including significant working age disability removing individuals from the working economy.

If the eligibility criteria for Belzutifan encompass stringent complex criteria, then those who meet them will be the most severely impacted in terms of quality of life and the economic cost of their care will be the most significant. They are likely to have undergone repeated surgeries, which will have aimed to balance the need for organ preservation and the prevention of metastasis. They may also have significant care needs and become unable to care for affected relatives. The committee raises concern about the comments on double counting; for example, in relation to ‘stroke’ and ‘neurological complications’. There are a broad range of neurological complications that can occur in VHL. Use of either term in isolation for this severely affected population is likely to underestimate disutility. If anything, for complex cases, the impact of the disease on quality of life has been underestimated.

It is important to note that due to the nature of the tertiary VHL services it will be possible to collect data on an ongoing basis to re-evaluate these models and assist in term decision making.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

The Scottish medicines consortium has approved the use of Belzutifan following in-depth engagement with patients and clinicians. This means there is now a discrepancy in access within the UK. We will have families in which some individuals can access the drug when their relatives cannot.

We note that many of the concerns of the committee around the evidence to support the use of Belzutifan, and the cost effectiveness model are a result of the rarity and complexity of the condition. This results in difficulty in obtaining trial and comparative real-world data on outcomes for different treatment modalities in a very rare disease with a complex multisystem

phenotype. Inherited genetic conditions are often multi-system since the causative genetic variant is present in every cell in the body from conception. As experts in rare disease tumour predisposition, we wish to highlight that NICE authorisation processes do not appear to be suitably adapted to the complexities of genetic rare disease such as in this context. We believe this is discriminatory on the basis that individuals with rare genetic disorders are disadvantaged by the NICE health economic assessment process purely due to the rarity of their genetic variation and propensity towards rare forms of complex disability.

We have further concerns that this consultation may be discriminating against our patients on the grounds that they have significant disabilities which this evidence does not consider, particularly blindness and mental health issues, including addiction, due to the progressive nature of their condition.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Our concerns that this consultation does not well capture the UK VHL cohort who would benefit from Belzutifan in a cost-effective manner, means that we do not believe these recommendations to be sound and a suitable basis for NHS guidance.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

My cousin and her 2 children have VHL. I can't believe that after the USA and Scotland doing similar trials and finding enough valuable evidence to recommend the use of Belzutifan for VHL patients, another part of the UK, England, has NOT passed it for use.

It shouldn't be a postcode lottery; people shouldn't have to be considering moving to Scotland, sacrificing their family life and support systems (ie relatives.. who currently save the NHS a fortune in care bills).
Has this trial concentrated on finding a way out of approving it because of the cost? It seems like it.

Has this trial spoken to many VHL patients to assess how this miracle drug would improve their quality of life and no doubt lengthen it.. I don't feel it has.

Has this trial considered how much money the NHS could save in future years... no! Whereas, its common sense that if the drug shrinks the tumours

and means less annual scans, less long term care.. versus the initial cost.. there can only be one outcome... REVERSE YOUR DECISION!
Please, please take this all into consideration! The USA and Scotland have and can see it makes sense. Eventually, the cost of this new drug will decrease...

It's peoples lives that's at stake and surely England should be the fore runner in approving Belzutifan.

My cousin has a tumour at the point where the brain meets the spinal cord.. her consultant has said that if he has to operate, its likely she will be paralysed.. OMG, think of the cost (mental health, stress quality of life etc)... it could be so easily prevented! Pass this drug, I implore you. Imagine it was someone in your family.. you would all be fighting for Belzutifan to be approved.
Please Reverse the decision!

- Has all of the relevant evidence been taken into account?

No, I don't feel it has.
VHL patients in England should have all been contacted and also people in Scotland who have been allowed access to Belzutifan.. the benefits and saving to the health service would have stood out and well exceeded the initial cost of this drug

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I don't feel either interpretations support the huge amount of evidence to prove the initial cost verses the incredible amount of NHS money that would be saved in the years to come.
Surely, the evidence can't dispute this.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Read what I've said before..
VHL patients and their families are being discriminated against and have put them in a situation that they have to consider moving to Scotland.. its unconscionable that England can't approve it yet Scotland has already passed it!

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No, no no! You say not enough evidence yet there's plenty out there.. the USA and Scotland found enough to see the benefits far outweigh the initial cost.

It's said VHL is rare...a small minority have it so it wouldn't cost the NHS much as less people to treat but in the long run, this group of people being allowed to take Belzutifan can save millions!

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Are the recommendations sound and a suitable basis for guidance to the NHS?

In our clinic in UCLH we see around 35 patients. As the disease the progresses they are likely to have several inoperable tumours in different sites. The need for recurrent brain surgeries is fraught with potential devastating side effects, speech defects, mobility deficits , and paralysis can result. Patients often need numerous surgeries for palliative care to reduce swelling in the brain. This drug would reduce the need for these repeated interventions at end of life, this would not only increase the quality of life and dignity of patients but also be an economically viable alternative to multiple surgeries.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Regarding age discimination: my 78-year-old husband is thought to be the oldest living VHL survivor. Should further VHL tumours be revealed, I hope that he would not be discriminated against for treatment on the grouinds of his age. In any event, it is thought he may not survive further surgeries thus leaving Belzutifan his only option - if it is available on the NHS at that time.

I live with the possibility that my husband and/or my daughter would not survive further surgeries, should they be required. Belzutifan would obviate immediate surgery should this be the only alternative.

Name	Nathaniel Mason
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Has all of the relevant evidence been taken into account?

It is not clear whether the draft guidance or the evidence it is based on considered the following :
- Reduced psychological welfare and time cost associated with VHL for family members and others caring for VHL patients around surgery
- Reduced economic contribution of VHL patients because of ongoing, lifetime risks posed by the condition under current treatment options. The current treatment options deter riskier but potentially more economically productive livelihood strategies, for example establishing and growing a business. It is not clear that such effects are captured in the economic modelling or disutility values applied in the analysis. As a VHL patient who has had four surgeries (bilateral total adrenalectomy, endolymphatic sac tumour, resection of CHS Hbs and stereotactic radiosurgery for another CNS Hbs), I have established a business but am significantly deterred from growing it (and therefore employing others, increasing tax potential etc.) by the risk that I will have long periods of ill-health and inability to work, associated with recovery from surgery and/ or complications following surgery.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No comment

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Outside the above factors, NICE's decision not to recommend Belzutifan in this case, in contrast to the SMC's recent decision, creates a postcode lottery situation between those living in different parts of the UK. This will

affect my family directly, since my sister, who also has VHL, lives in Scotland, while I live in England.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

While the recommendations clearly find issue with the economic modelling and therefore cost-effectiveness, the evidence on clinical effectiveness seems stronger, and the committee appears to be less equivocal here. I can only hope that further and stronger evidence regarding both cost and clinical effectiveness will be provided, and that NICE is able to reconsider its draft decision. The decision not to recommend does not reflect my own lived experience of the psychological distress, physical pain and discomfort and mortality risk associated with VHL under current treatment options.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Has all of the relevant evidence been taken into account?

VHL Europa strongly disagrees with the TSOP decision not to review belzutifan (Welireg) for VHL via the HST route which would have given much greater flexibility around some of the uncertainties outlined in the draft guidance.

The NICE website states:
The HST Programme is designed to be used in exceptional circumstances and its purpose is to evaluate technologies for very rare diseases that have:
1. small numbers of patients
2. limited or no treatment options
3. challenges for research and difficulties with collecting evidence, because of the uniqueness of the disease.

On the published Highly Specialised Technologies (HST) criteria checklist, criteria 1 and 4 were NOT MET for this appraisal.

1. NOT MET Criteria 1: The disease is very rare defined by 1:50,000 in England

At the 1st committee meeting 8th November 2023, NICE themselves quoted on their own slides “Prevalence between 1 in 68,000 to 91,000 in England with 842 people in the UK”
https://www.nice.org.uk/guidance/indevelopment/gid-ta10817/documents

(Supporting Documentation (Published 23/08/23). This clearly MEETS their own criteria set for rare diseases. VHL Europa therefore considers it unacceptable and grossly unfair that this criterion was not met.

The rarity is further supported by criteria 2 being MET where the estimate that no more than 300 people in England are eligible for the technology in its licensed indication and no more than 500 across all its indications, is accurate.

2. NOT MET Criteria 4: There are no other satisfactory treatment options, or the technology is likely to offer significant additional benefit over existing treatment options.
VHL Europa strongly disagrees with the reasoning for this decision on several counts, and it shows a complete lack of understanding of the complexity of VHL and its impact on the patient and their carers. Now the committee has heard more about VHL, we think this should be reconsidered in conjunction with the following feedback:

- Each tumour type and its surgical treatments have been considered in isolation (PNET/RCC/CNS) and there has been no recognition of the fact that VHL patients can have a combination of all three manifestations (and others not within the indication), simultaneously, concurrently, and recurrently. There is also no recognition of the cumulative human effect of the great many surgeries some patients must risk/endure in their lifetime and the subsequent impact on both their physical and mental well-being and that of their carers.
- The suggestion that a patient living with kidney failure, dialysis or type 3c diabetes can still maintain some quality of life is misplaced, especially when they could need a combination or all of these. Prof. Drake highlighted the truly devastating impact of living without a pancreas gland at the committee meeting.
- The suggestion that surgeries for CNS tumours are ‘often successful’ but may ‘seem undesirable’, is offensive. ‘One’ CNS surgery might ‘seem’ undesirable but multiple surgeries that carry catastrophic risks every time and can often result in severe neurological deficit or death is terrifying for patient and carer. With each successive surgery, there is a sense that you are simply putting off the inevitable and the odds are always against you.
- The suggestion that there are further treatment options for metastatic disease in VHL is inaccurate. These treatments are widely accepted in the medical field as ineffective. They are only used as a last resort because there is no other option.
- The criticism of medically SIGNIFICANT trial data because of its mismatch to the MHRA marketing authorisation, and the suggestion that belzutifan would ‘not treat the underlying disease’, is weak, and dismissive of a trial that produced excellent results to the targeted tumours AND in addition, other types of tumours. There is no recognition of the fact that this drug is a well-tolerated, innovative, multisystemic treatment that is transforming the lives of VHL patients in the real world.

3. Finally, although not listed as a formal criterion on the checklist, NICE states the HST route is also used where there are 'challenges for research and difficulties with collecting evidence, because of the uniqueness of the disease.'

- VHL Europa feels that the consultation paper from NICE is arguing EXACTLY this in section 3.16. The committee has indicated it is not confident in the data provided by the company but also that it would not be possible for the CDF to collect the data either.
- VHL does not follow any typical trajectory and no two patients are the same regarding their manifestations, locations, frequency, progression rates and surgical outcomes. One patient may have no surgery during their whole lifetime, another may have 40+ including multiple loss of organs and dire QOL consequences such as paralysis, dialysis, type 3c diabetes and sometimes a combination of all of these.
- Even in the same family, where the genetic mutation is exactly the same, no two patients will have the same manifestations. This, coupled with a lack of data collections in the VHL population in general makes the economic modelling extremely challenging, which has been acknowledged on multiple occasions by NICE and the EAG. Therefore, VHL is an ideal candidate for the HST route.

Based on all of the above, VHL Europa fails to see why belzutifan was not accepted into the HST route; the charity believes that this would have provided the flexibility needed to enable the committee to make a positive decision on funding.

VHL Europa believes that belzutifan for VHL could meet all of the HST criteria listed in point 28 for a Minister's referral and can see significant additional benefits from prescriptions routinely being made via chosen specialist centres, therefore avoiding any regional discrimination/inequalities with regard to access: https://www.nice.org.uk/media/default/about/what-we-do/nice-guidance/nice-highly-specialised-technologies-guidance/hst-interim-methods-process-guide-may-17.pdf

Furthermore, some small numbers of VHL patients with metastatic disease have responded incredibly well. One 41 year old German patient entered a clinical trial of belzutifan in Maastricht, the Netherlands with metastatic renal cell carcinoma, and 42 metastatic lesions in his brain, liver and lungs. Luckily he was randomised in August 2021 to the highest dose (200mg daily) and has experienced few side effects. He had been told that he had to put his affairs in order in preparation of death, yet today he is a fit patient advocate, and has only 3 tumours detectable, all of which are stable.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No. Pricing is extremely high but we need to quatify the burden of surgery in the VHL community. It is not effectively quantified anywhere currently.

The burden of disease is beyond the cost. The Aggregate quality of life in a subset of individuals who will undergo repeated surgical procedures with subsequent recovery periods. For individuals of multiple surgeries, what does that do to their ability to function in society? What does it do to their mental and physical state? Consequences of multiple surgeries on the individual?

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

VHL Europa believes that belzutifan for VHL could meet all of the HST criteria listed in point 28 for a Minister's referral and can see significant additional benefits from prescriptions routinely being made via chosen specialist centres, therefore avoiding any regional discrimination/inequalities with regard to access: https://www.nice.org.uk/media/default/about/what-we-do/nice-guidance/nice-highly-specialised-technologies-guidance/hst-interim-methods-process-guide-may-17.pdf

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No. VHL Europa, a federation of 13 national patient group organisations, feels that there are substantial problems with the recommendations:
1. This appraisal is weighted towards renal cell carcinoma, despite MHRA approval to include the most morbid of all VHL lesions, CNS haemangioblastomas as well as pancreatic neuroendocrine tumours (pNETs). VHL Europa recommends that belzutifan should no longer be categorised as "cancer/renal-cancer" and moved to "von Hippel-Lindau" as a new website navigation path: https://www.nice.org.uk/guidance/conditions-and-diseases/vhl-von-hippel-lindau.
2. there is no consideration on the quality of life improvement. 5 studies on QoL in VHL have demonstrated substantial distress associated with tumour growth and surgical interventions.
3. Para 3.1 of the Draft Guidance. VHL Europa considers that the Committee, through the EAG, has failed to comprehend the severity of having several multiple symptoms of VHL concurrently, consecutively and recurrently over a whole lifetime. This is a common factor of VHL disease. This situation then leads to decisions having to be made as to not only when each surgery is advisable, but also which type of surgery is to be given priority over another (with minimum recovery time in between each one). Belzutifan will have a simultaneous effect on multiple tumours.

Every patient's health path is different, so trying to make a meaningful generic health model is extremely challenging because of the uniqueness of the disease. Calculations of averages, when related to the surgical outcomes that can have life-changing effects or even death are

meaningless when compared to prescribing belzutifan that can, for the first time ever, stabilise multiple tumours (and multiple tumour types) from progressing concurrently, and shrink tumours sometimes to the point of No Evidence of Disease. The need for surgeries may be avoided indefinitely.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

Dear Sir/Madam,

I would like to make a submission for Belzutifan to be approved in England and available for the NHS.

My partner, who is in her twenties, was diagnosed with Von Hippel-Lindau Disease (VHL) at the age of 6. Her two sisters, in their early twenties, and their father also suffer from this condition

I have borne witness to the way this disease has dominated and adversely affected the lives of these four people. My partner suffers from pain on a daily basis due to the tumours on her liver, spleen, kidneys, pancreas, spine and eyes. She will inevitably have her left eye removed due to the invasive and ineffective treatment which has already failed to save her sight. She now has monthly lanreotide injections in an attempt to control the growth of tumours on her organs. This causes her terrible side-effects and severely diminishes her quality of life. Without Belzutifan there is a likelihood she will also need to undergo the Whipple procedure.

My partner is a Civil Servant, her first sister is a Nurse and the other works within the Police Service. These individuals work hard in difficult and essential occupations and they wish to continue doing so. VHL is a pernicious disease which, over years, debilitates the sufferer through the build up of multiple tumours and cysts, reducing their ability to work and live as we do.

Belzutifan is being used in other countries and is already improving the lives of VHL sufferers, giving hope that they can properly control this disease and improve their life-expectancy.

Please can you give proper consideration into making this drug available, so my partner, her family and others like them can hope to live as normal a life as possible.

Yours faithfully,

[redacted]

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Has all of the relevant evidence been taken into account?

I do believe all the relevant evidence has been taken into account, however from a personal point of view it is hard to put into words the emotional impact living with VHL has on your life knowing what the future could hold from reading all of the facts and figures. The way the condition is summarised is so depressing and I don't want that to be my narrative. If there is a drug that will eliviate the symptoms before they even occur or reduce tumors that are pre-existing then I think people should have the option to be able to avail of this. 4/6 members of my immediate family members have the condition and all have been effected in some way or another, the males (my father and brother) suffering more than my sister and I, interestingly. That being said the emotional and psychological impact on our family as a whole has been imense,even for those who don't have VHL. From hundreds of hospital appointment, days missed at work, surgeries, quality of life and the not knowing whats around the corner, VHL very much dictates this household. My brother's 18 month child is now awaiting testing for VHL, even this is a step in the right direction as my mother was denied testing for me and my siblings for years as the children's hospitals in Dublin (CHI) refused to do so. This was a 6 year delay which could have had serious impacts on our quality of life in the future.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Although I understand that money rules please consider each person with the disease deserves the right to a long worry free life just as much as the next person, regardless of age, sex, location, history or status.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I would like to see everyone with VHL included in the treatment, and not exclusively if they are waitring on a surgery and have a pre-existing tumor that needs removing. To me it makes more sense if the drug was used to prevent even getting that far. Life shouldn't be about constantly worrying about tumors but preventing them from ever growing. Living in Ireland also shouldn't exclude a person from recieveing belzutifan.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

The recommendations seem to be very thorough and a suitable basis for guidance to the NHS. It seems as though evry aspect has been covered.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

My name is [redacted]. I am 27 years old with a diagnosis of Von Hippel-Lindau Disease. I was diagnosed at the age of 6 as a result of genetic testing. This was due to my father being diagnosed with VHL following emergency brain & kidney surgery as a consequence of renal cell carcinoma . My Grandmother died at the age of 32 from VHL, following a missed diagnosis. Along with myself and my father, two of my three sisters have a diagnosis of VHL. They are aged 25 and 21. Another sister, who is a twin, does not have the condition.

Following my diagnosis with VHL my childhood, teenage and early adult years have been consumed by hundreds of hospital appointments to monitor and treat cystic lesions and tumours; both malignant and benign.

To date I have tumours and cysts on my eyes, liver, spleen, kidneys, pancreas and spine.

At the age of 17, whilst studying for my A-levels, I experienced the beginning of a retinal detachment in my left eye. This was due to the 50+ tumours which had developed in this eye. These needed lasering, and in turn caused the retinal detachment. I had surgeries in 2016, 2017, 2020 and two emergency surgeries in 2022 to try and save my sight. The last two surgeries in 2022 were unsuccessful and I experienced a full retinal detachment in April 2023. Since then, I have experienced constant pain in my left eye, which is now visibly starting to shrink due to the lack of blood flow. At the age of 27, my appearance has completely changed and I have been told my eye will need removing to help me manage the daily pain I experience. I have an untreatable tumour on the optic nerve of my right eye.

I have been told that I will lose the vision in this eye if the tumour becomes problematic.

In 2018, a PET scan identified a pancreatic neuroendocrine tumour (PNET). This was monitored, along with the innumerable amount of cysts that cover my pancreas. In 2022, following routine imaging, my pancreatic NET and cysts started to show significant growth. I was told that a Whipple procedure would be needed. This is an extremely invasive surgery and would serious diminish the quality of my remaining life. I started lanreotide injections in April 2023, at the same time as experiencing the retinal detachment. This was an attempt to halt the tumour growth and avoid the Whipple procedure, so I could focus on saving my eye sight. These injections, taken monthly, cause significant side effects including weight loss, digestion issues and keep me house-bound for the first 3 days after I've taken them. For someone in their 20s this has been hugely impactive, as I am unable to attend work in person and have to regularly cancel plans with friends and family because I am unable to leave the house due to the symptoms. I am monitored through 6 monthly MRI and yearly PETs as to the progress of my PNET. If the lanreotide injections are unsuccessful, I will need to have a Whipple procedure.

For all my other lesions, I am currently undergoing MRI scans every 6 months at the Royal Free Hospital in London.

As I am writing this, I am sat waiting for my sister to come out of a endoscopy to confirm if she has a PNET and if she will need the Whipple procedure. I am due to have a call with my Urologist this afternoon as my kidney tumours are growing significantly and showing signs of renal cell carcinoma. My only treatment option available is surgery.

If Belzutifan was to be approved for use within England it would make a significant difference to my current prognosis and my future. It would allow me to continue in my career as a Civil Servant without the worry of prolonged time away to recover from major and life-changing surgery. It would prevent me from developing secondary illnesses such as lack of sensation in my arms and legs or loss of strength from spinal surgery, whipple associated diabetes mellitus and digestion difficulties or the emotional distress and trauma from undergoing other invasive surgeries.

It would allow my father to have a better prognosis for his renal cell carcinoma as well as the multiple hemangioblastoma on his brain, one of which is causing pressure to his brain stem. It would allow my younger sisters to not experience the same life changing diagnosis and treatments that myself and my father have had to endure. This medication would allow me the opportunity to live a 'normal' and happy life alongside my parents, sisters and my partner.

Approving this medication will not just positively impact myself, my sisters and my father as VHL patients, but it will also change the lives of those closest to me and all of those who care and support my family. They will not

have to undergo the emotional distress and guilt of having to watch us suffer and struggle with VHL and the complications this can lead to.

We ask that you consider the overall positive impact that Belzutifan would have for individuals who suffer the consequences of VHL, both directly as patients or indirectly as our loved ones.

Thank you for taking the time to read my comment. I hope it gives you an insight into just one of the many families that are relying, and hoping desperately that Belzutifan is approved for use within England under the National Health Service. It is encouraging to see that Scotland have approved its use within the NHS and I hope that the rest of the UK can follow.

- Has all of the relevant evidence been taken into account?

No

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Please see comments

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Section 1 – Recommendations point 1

As an onlooker and occasional full time carer for patients suffering from VHL it is hard to understand why treatments like this are not recommended.

The impact surgeries have and the day to day impact on life is considerable both physically and mentally. It is very difficult to have what might be considered a normal life. Any treatment that might have a beneficial impact is considered to be vital to anybody in this position.

- Section 1 – Recommendations point,1.1, “recommendations”

As a husband and father of two adult daughters I would like this to be reconsidered. My wife and daughters have VHL diagnosed 17 years ago and have already had numerous brain surgeries and kidney surgeries with tumours still remaining in both. The future will inevitably be dialysis so any possible treatment that delays or prevents this must be made available if at all possible so that clinicians can use it if appropriate for the individual case.

- Section 2 – Information-about-belzutifanpoint, point 2.3

s a family we average at least one major surgery per year as well as numerous scans and consultations at five different hospitals some of which are over 50 miles from home. This comes at great expense to both the NHS and ourselves. I could not quantify the cost but it will be considerable. Although the cost of this treatment would appear to be high it would be considerably reduced by the amount potentially saved in other areas. Also due to the rarity of the condition this treatment would be less than the overall cost of treatments for other conditions.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

How VHL has impacted you personally. I have put my heart and soul into this document and pray that it is read!

Learning that my precious daughter [redacted] has VHL, has mentally and physically destroyed me and my life is now one of incessant fear of losing my beautiful girl. When she was born on [redacted], after an 11 year gap from my first baby, her brother [redacted], hearing the midwife telling me I had a beautiful, healthy baby girl was the best news in the World, [redacted] had asked for a baby sister for Christmas, and we were all over the moon. I checked her all over and she was perfect!

Now my most cherished memory of the day she was born, and all of my happy memories of her childhood through to adolescence, and even her

birthdays, are marred because my beautiful perfect baby wasn't healthy, she had VHL and because babies are not tested for VHL, this disease would lay silent until she was 30 years old and given the earth-shattering news on 17th October 2019 that she had a brain tumor and had to have major invasive surgery to remove it. All her life she had had this cruel disease and I never knew. This mortified me and I was terrified that my beautiful girl was going to die. During the diagnosis of the brain tumour, VHL was briefly mentioned but she was told not to google it, because she probably didn't have it!

Life was unbearable in the weeks leading to her surgery as [redacted] tried to come to terms with this overwhelming news. She couldn't eat, she couldn't sleep, she lost all sense of self-worth and I was petrified she would take her own life. She would tell me that she just wanted to run away. But how do you run away from yourself? Then, when the news came that the tumour had grown and the surgery had to be brought forward, I had to stand helplessly by and watch my beloved girl crawl on the floor screaming in sheer panic and despair, and I could do nothing to comfort her.

On the day of the surgery 28th November 2019, at 6:30 am, [redacted], [redacted] (her husband) and myself arrived at Queens Hospital in Romford and [redacted] took [redacted] to book in. I remained in the waiting room, which was decorated for Christmas and songs were playing on the hospital system – a happy atmosphere, or so it should have been - and apart from the hospital cleaning staff, I was alone. [redacted] returned a few hours later and said they had found another tumour on her pancreas that she would be referred to Gastroenterology at a later date. The surgery on her brain was going ahead and she had gone down to theatre. [redacted] returned to be closer to [redacted] and I began the long anxious wait for the surgery to be over.

At 9.00 am [redacted], who works in Romford, arrived to be with me and at 11:00 am my sister and brother-in-law arrived. My husband [redacted] couldn't be with us but continued to ring throughout the day – we were all so worried, and were desperately waiting for good news but at 5:00 pm when [redacted] returned to us and said [redacted] was still in surgery, I was beside myself with worry and extremely concerned that something was dreadfully wrong. But after a further agonising period of waiting and no news, [redacted] rang the contact number and was eventually told [redacted] was out of surgery, this had gone well, and she was awake and in recovery. We all celebrated that [redacted] had come through the horrific surgery. [redacted] then went off again to be with her but [redacted] and I were told we could not see her, and whilst I was so thankful that the surgery was over and my darling girl was ok, I was crushed that I could not be with her. We left the hospital and began the 65-mile journey home.

During the night [redacted] rang me and I was overjoyed to hear voice, but she was very anxious as she had been taken off her pain management of Morphine, practically as soon as she had got on to the Ward and given only Paracetamol. She had overheard some worrying comments from the clinical staff, that lead her to believe that she was going to die and that I was actually at the hospital in the next room to her. She said she could hear me was crying because I had been given this dreadful news. [redacted] left Queens hospital on 30th November 2019 because she could not deal with her fears and anxieties and wanted to be with her loved ones because she truly believed she was dying. The weeks that followed saw her mental health suffer as her mood swung from high to suicidal, and she had to be put on anti-depressants, which she still takes.

Prior to the diagnosis of the brain tumour, [redacted] and [redacted] had been trying for a baby and approximately six weeks after her surgery, when she met with her Consultant in the Outpatients clinic, she asked him if she was ok to continue with their plans. He told her she was just a person prone to "cysts" and to get on with her life and start a family. But whilst she dearly wanted to have a baby and move on, the discovery of the tumour on her pancreas made this impossible for her and she became more and more paranoid that she was dying and that I knew this and was keeping it from her.

Her appointment with the Gastroenterologist for the tumour on her pancreas was in February 2020 and it was at this appointment that she was told she was being referred for VHL testing. However, the world went into lockdown because of the COVID Pandemic, and the referral did not take place until she was pregnant with [redacted] in 2021, and her midwife insisted on it. But by the time she had the test and received confirmation that she had the VHL disease, and equally worring, that her unborn baby had a 50/50 chance of having the vicious disease, she was nearing the end of her pregnancy. Therefore, not only did she have to come to terms with the enormity of having VHL, but she also struggled with the burden of guilt that she had passed this on to her precious baby.

[redacted] was born on [redacted] [redacted] 2021 at 6:04pm, by emergency C-section because whilst [redacted] went into labour in the early hours, it was put off because another two tumours on her spine were discovered, and it was not considered safe for her to have the epidural birth she had hoped for. Her mental anguish was to continue for another agonising nine weeks after [redacted] birth, until she was given the wonderful news, we had all been praying for, that [redacted] did not have the faulty VHL gene.

My husband [redacted], [redacted] and I were all tested for VHL and were all found to be negative. But all the time I was waiting for my result, whilst this would have had terrible repercussions for my sisters, nieces and nephews, I prayed I had the faulty gene. It breaks my heart to see my daughter, whom I worship, in this incredibly lonely place.

That my beautiful daughter has VHL is continually on my mind from the moment I wake up in the morning to the moment I fall asleep at night and waking me during the night with the most dreadful scenarios imaginable. I feel I have failed her because there was nothing, I could do to protect her from the disease, and am helpless seeing her struggle with the mental torture, anxiety and paranoia that her life has become because of VHL. I dread the MRI scans and each hospital appointment she must attend, always fearing the worst. But because I cannot show my fears to her, I put on an act that everything will be alright, so my life is full of deceit! This is draining and has affected my mental health; I too take anti-depressants and have done since this nightmare of the VHL life sentence began.
So far she has had major invasive surgery for a brain tumor – since which another tumor has grown - and several laser treatments for eye tumors. She also has tumours on her pancreas, spine, and in her inner ear. The latter having shown signs of growth and she has been told by her Specialist that surgery is the only option. But apart from the risk of her having to undergo major invasive surgery for a second time and relive the trauma that we went through with her first surgery, there are negative post-op consequences:

1) She will lose her hearing completely in that ear, which currently is 100%.
2) The nerves in her face will be damaged changing her facial appearance, likened
to that of a Stroke victim.
3) Her balance will deteriorate.
4) She probably won't be able to drive again.

But why should this be? Surgery is not the only option – Belzutifan is an option, so why subject her to unnecessary drastic invasive major surgery, with all its dire significances, when she could be given the treatment and spared from this and other inevitable surgeries that loom ahead? How many times must she suffer this intolerable situation, when there is another way?

[redacted], as do I, and all the VHL victims and their families and friends, that live with the reality that is the VHL disease day in, day out, deserve better care then "the current clinical standard of care (SoC)" i.e. more and more invasive surgeries, they deserve and have the right to peace of mind, a better quality of life and hope for the future. Not the foreboding prospect of existing tumour growth, new tumours, multiple major surgeries that eventually result in organ loss, and God forbid, metastasis. They deserve the same duty of care and treatment with Belzutifan, as their fellow VHL victims in Scotland.

Further research could see Belzutifan going from strength to strength with more breakthroughs into VHL.

I live in fear for my daughter's life and I beg my late mum and dad, to watch over her and keep her safe. I pray to God and make bargains with him, that I will do anything, if he could only grant a miracle that will make everything right again and take away all this wretchedness that makes our lives a living

hell. If anything were to happen to my beloved [redacted], I don't know what I would do, I would be torn between my husband and son and being with [redacted], because I could not live without her.

What difference you think belzutifan (Welireg) will make to your/their life It would mean the World and both [redacted], and I would be elated and have a new lease of life that instead of being sentenced to life in this desolate void, we would be free to be happy again, make plans and look forward to the future without fear. It would mean that VHL will at last have been recognized and something positive was being done to help the thousands of VHL victims.

How you will feel if NICE do not change their recommendation Distraught that my daughter's life isn't considered important and not deserving of treatment that her fellow VHL victims in Scotland are receiving!

Total loss of faith in the NHS and left wondering just what good it is, if not to approve new innovations into future medical care, when it is so desperately needed.

VHL is a vicious silent killer, and people should remember that "There but for the grace of God go I." No one knows just how many people have VHL because the test for it is only given if a patient displays certain signs, and even then, as in my daughter's case, the test was delayed, not only because of COVID but also, whilst the powers that be deliberated on whose budget the cost of the test should come out of i.e. the GP in Primary care who made the referral in the first instance, the relative department Nuerology in Secondary care etc.

The refusal to authorise Belzuifan in England is an affront to many people of England that have contributing now and those that have contributed all their working life, to keeping the NHS going, not only to provide medical care but to support and fund such innovations as Belzutifan, not create barriers. Surely this is discrimination between one group of people and another. Belzutifan is a game changer for all VHL victims and their devoted, tormented families.

Please give us all the chance of happiness and a near normal life and authorize the use of Belzutifan.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

How VHL has impacted you personally.he fact that my daughter has VHL and watching her struggle with the terrors that this causes her: 24 hours a day, seven days a week, 52 weeks a year, absolutely cuts me to the core. I would move heaven and earth for her to make her well again but am powerless and she is condemned to suffer.

What difference you think belzutifan (Welireg) will make to your/their life To see her happy again and worry free from the endless hospital visits and constant monitoring, would be a life changer and the most important thing in the World to both of us. It would be like winning the lottery.

How you will feel if NICE do not change their recommendation Angry and let down by an institution that I have spent my whole life paying into and at a time when you really need it most, can sit and make decisions about my daughter's miserable life, based on statistics and refuse to offer her a ray of hope.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

How it impacted on me personally? I am writing about a close member of my family who has been diagnosed with VHL, regretfully a young woman aged 32 who is very much loved and treasured by all around her. A hardworking full-time mother to a 2-year-old son, a wife, daughter and sister. It has been horrific for her (and all of us supporting her) to witness this dreadful disease unfold taking its toll on her mental health and her supportive family. To watch her face up to her illness after horrific brain surgery and try to educate everyone about this disease has been inspiring. To watch her maintain optimism when more tumours were found in her pancreas and spine, and lasered from her eyes. Soon she will need invasive surgery again for a tumour in her right inner ear, rendering her deaf and disfigured. To watch her pray for her new-born son to be redeemed from this dreadful fate. To watch her fight to maintain her hope, positiveness and mental health when more are found and left to be monitored only to grow, can only be described as torture for her and all of those around her. To hear of the loneliness, she feels is heart breaking. It has been a devastating journey that we are hoping can now be controlled.

What difference Belzutifan will make to their life? That common sense had prevailed and that the VHL sufferers in England are also important, not penalised, but given every chance of a normal life as possible, that they richly deserve.

If you felt like you were living with a timebomb, many timebombs inside you, how would you feel if a new drug was developed that could slow the tumours and potentially stop them in the first place, only to be told, this 'miracle' although approved in Scotland, was not being approved in England. I say again, how would you feel? Imagine that you are living life waiting for the next trauma of scans, uncertainty, surgeries, recoveries. Imagine having a 2-year-old son to look after and an important NHS job to hold down whilst juggling all that worry and hopelessness. Imagine if all this trauma could be avoided with the use of a drug.

How I will feel if NICE do not change their recommendation? It would be a travesty. A complete injustice to all decent, hardworking people. This travesty is heightened by the fact that some areas in the UK are deemed worthy of this drug while those in England aren't. Surely one person suffering to this extent, is one person too many!

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

How it impacted on me personally? I am writing about my cousin, a now 35 year old woman, mother to a beautiful 2 year old son, lovely wife, daughter and sister, hardworking and generous to the core. My baby cousin who I have watched grow up and seen her through many milestones in life, milestones everyone deserves. It saddens me that she has recently been diagnosed with VHL after discovering a tumour in her brain. No one can imagine the shock or the impact it has had on her close core of a family but also on us, her extended family! I have had to watch my adored 'baby' cousin endure horrific surgeries cutting this tumour out, her scaring, invasive eye surgery, invasive scans only to find more growths, her struggle to come to terms with this disease and why this has happened to her, and then finally facing it and fighting it by campaigning and through her charity work. She has done this with such bravery and grace, she an inspiration, but it has inevitably affected her mental health.

I feel the worst of times was when she had to wait to see if her beautiful son carried this vicious gene. As a mother of three, I do not know where she found the strength. Surely it is every mother's hope to see their children progress and move through life in the best possible way. Thankfully, he was saved from such an horrific, anxious life living under a dark cloud of fear, as is her life. Her illness has made me reflect on her courage but also the legacy we leave our children. My mum, my sister and my aunt all walked in her shoes when we were waiting to see if it was in our bloodline. Imagine if I

had passed such a cruel disease on to my children? Although this wasn't the case, I am left feeling what a lonely place this must be for her.

What difference Belzutifan will make to their life? I know we never know what our fate is but I take care of myself and would like to think I will be around to see my children graduate, get married, ride a bike, learn to drive, reach milestones (all that they wish for). I feel that my cousin's mental health is constantly being affected by this fear and worry that she will not be around for her son's milestones. She holds a responsible job in the NHS, a valuable role. She longs to provide for her son with a lovely home, and all mother's want to provide but how can she do this with the constant threat of terrifying surgeries that leave her out of action both emotionally and physically for months, years on end. Belzutifan offers her hope and optimism after years of fear and lack of control. Proven to slow the growth of tumours and even turn them back, this would inevitably give my cousin more time experiencing good health, reducing her anxiety and inevitable depression. She is currently waiting for a disfiguring ear operation to remove a fast-growing tumour, which doctors say will leave her deaf in that ear. That is without the trauma of the actual invasive surgery and the impact this has on her mental health and the worry and concern of all of those around her. Why can't she have access to something that would slow this down or possibly control these tumours permanently? This drug would give her hope for the future and a long healthy life that everyone deserves.

How I will feel if NICE do not change their recommendation? Despair. A complete lack of hope and faith in the human spirit. Why does Scotland get the privilege of this drug and England doesn't?

How would I feel if you did change your decision? Relief! I would feel that everything was right in the world, a world where good, hardworking people get the support they deserve. After all, my cousin and all her family (our family) are hardworking people who pay into the NHS and have done for a long time. I would feel that we live somewhere that it is fair, and that for the first time in years, my cousin had a fighting chance at a long, healthy, joyous life.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	
How it impacted on me personally? I have watched my wife and our close family hit rock bottom after the diagnosis of our niece to VHL. At the age of 32, she has already endured major brain surgery to remove a tumour, eye surgery, invasive scans and monitoring, and is about to endure surgery to her right inner ear, which will leave her deaf in that ear and disfigured. She	

is a young mum and treasured daughter. These surgeries are not all of it though. There is the mental aspect of this disease. Her parents and sibling, along with my wife, have witnessed terrible breakdowns and sustained depression both around and building up to the surgeries. One cannot imagine what it feels like living in constant threat of yet another growth that is to be monitored long term only to result in the inevitable. My words here cannot even capture the things I have seen in our family, the traumas, the upset, the joys when all is thought to be well, only for the joys to be shattered, when the nightmare begins again. How my niece maintains her job (very important in the NHS ironically!), her marriage, her charity work for this cause, and continues still, to be a brilliant mum, is anyone's guess.

What difference Belzutifan will make to their life? Whilst we have all been on this journey together so far, it seems there is a solution or perhaps a ray of hope that this is not the future destiny for our family. This new drug would be life changing, not just for [redacted], but also for her long-suffering family. All of this could be behind us, with a future that looks brighter, longer and free from this horrendous cycle of events.

How I will feel if NICE do not change their recommendation? I am getting older now and have lived a life of good health, happiness and reasonable prosperity. Doesn't everyone deserve good health and the right to a stress-free life if there are drugs out there to allow this? It's true of people suffering with VHL in Scotland so why not here[redacted] is only young. Give her and her young family a chance of happiness please!

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

How it impacted on me personally? I have a large extended family and my cousin has VHL. It's like a life sentence of constant tumours, surgeries, waiting time, anxiety and trauma. My cousin is young and has this ahead of her for her whole life. I admire her charity work and 10k runs to raise awareness and funds. She is also a mum. I would not want to grow up with my mum constantly ill, worried or worse, possibly not around.

What difference Belzutifan will make to their life? This drug would slow down or stop the tumours meaning less trauma, horrific surgeries, endless monitoring of growths causing stress and poor mental health and disfigurement. All for a few pills? It makes perfect sense. Everyone says prevention is better than cure, after all.

How I will feel if NICE do not change their recommendation? I think it would make me lose my faith in this country, especially when it has selected

Scotland as ‘worthy’ of the drug, but not England. I don’t think I would want to invest my future in such an unfair place.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	
How it impacted on me personally? I was [redacted] bridesmaid at her wedding 10 years ago. She is my mum’s younger cousin. She was my mum’s first baby that she loved. They have a special bond. I have seen [redacted] grow into a lovely mum and wife. I found out she had a brain tumour when I was young but old enough to understand the impact it had on our close family. Everyone was devastated but showed support to get it removed and try to help [redacted] move on. Then we realised this was going to keep happening because she had VHL. I am only 14 but I cannot imagine what this must feel like, constantly waiting for the next round of discovering them and then waiting for them to develop. And then have to have them removed and recover all over again. It makes me feel sad but also lucky that my mum, Nana, Aunt and Great Aunt aren’t affected because I don’t know how I would feel if it was in our genes. [redacted] must be so lonely. What difference Belzutifan will make to their life? I try to imagine what it must be like to live with such a thing hanging over you like [redacted] and to remain positive and happy. I know she throws herself into her charity work and being a great mum. We know there are drugs to help her and I want them to let her have them. To help her mental health, to slow the tumours so she will be around when her son gets older. I know I want my mum and dad at my wedding and when I graduate but just to take me to school and help me grow up. How I will feel if NICE do not change their recommendation? It all seems very unfair to me. I feel like we are all being let down. All my family try hard to do the right thing and look out for people and by working hard. [redacted] deserves her chance.	

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	

- Has all of the relevant evidence been taken into account?

Yes

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

I thought you could have done a broader study involving more people because the summary I made from reading the documents was that there was not enough evidence, or gaps in your evidence.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

I found it was not clear on who your small group of participants are to be able to answer if there is any direct discrimination.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

I am unsure. This drug has shown many benefits and improvements in America.

The Recommendations advise of a small study. Why were not more VHL patients invited to participate in the Study? You could have got a greater and better understanding of the benefits for your decisions. Scotland has already approved Belzutifan for VHL - Scotland and England are under the same NHS so this is conflicting.

Dear Nice,
I am saddened to read that you are to decline the use of Belzifen for treating Von Hippel-Lindau in England. From reading all the documents, I gather the general refusal is due to the cost of this drug.

I was also saddened to read in the draft guidance consultation that in study MK-6482-004 you did not collect any quality of life data. This would have been a big factor because quality of life is a huge factor in human life.

My father had VHL, he was de novo and I unfortunately inherited it. My father had brain tumours, multiple eye tumours and had to have both kidneys removed meaning he was on dialysis. He died 3 years after diagnosis, when I was 10. I am now 37.

Since then, I have had multiple eye tumours and surgeries resulting in lots of complications and being left with little sight in one eye. If I lose the sight in my left eye, it will be very detrimental. I'll have to give up my job and I

would not be able to drive, I'd need someone with me when leaving the house, thus meaning I will become isolated in my home, which will impact my mental health and those around me.

I have also had a partial nephrectomy due to RCC. I was fortunate to have had it all removed, but the recovery was brutal. I needed several months off work and needed a lot of care. I know this will return and I can't imagine how hard it will be to recover being older.

I also have tumours in my spine and one tumour in particular at the location of the cervical medullary junction. My neurologist has clearly stated the he is loathed to intervene at this location because it is like spaghetti junction and he has told me that intervention would cause permanent and catastrophic consequences for me. The same consequence will occur if it continues to grow. This area will mean that if the tumour continues to grow like it has, or surgical intervention is done, I will be paralysed from the neck down and incontinent. Belzuitfan really is my only option and hope.

In the report there was mention of people have scan anxiety. I don't have scan anxiety, I have 'diagnosis fear' from the impact of the strain on the NHS system meaning consultants and radiographers are under extreme pressure and pushed to their limit. On top of being diagnosed of tumours in different areas, I also find it very traumatising to be informed of results in letters. For example, I was diagnosed with RCC and then shortly after I was diagnosed with a spinal tumour via a letter! I had kept saying I hadn't seen any previous reports on my spine – it had never been scanned. I was devastated to be informed this way.

Since then I have fought hard to get the care I deserve and that scans are reported to me in a humane way. Such as have the scan, see your consultant for the results and then ask questions there and then concerning it. Rather than see your consultant, look over the previous year's results, go for my scans and then get diagnosed with brain tumours, kidney cancer via a letter! Have lots of unanswered questions, unable to speak to consultant so left to dwell on the results until you see the consultant a year later. This is a very traumatic experience. I am often referred to in a jokey way from the NHS as the patient who likes to have results delivered in a 'special way'. No, it is a humane way!

I have often been misdiagnosed, so much that I have been previously advised that I have grounds for formal complaints. Most recent, I was wrongly diagnosed with RCC for over 2 years!! And they wanted to operate on me!

These wrong diagnoses' lead to childbirth decisions being taken away from me at the last minute because all consultants were confused. This was traumatic for me and preventable.

Taking Belzutifan could mean that I don't have to have so many regular scans, not have as much growth, relieve strain on the NHS and provide a

better care all over for the NHS/NHS staff and the NHS patients. I also would not be in the position of being wrongly diagnosed so many times!

I have two children. I was decline for PGD at the time and unfortunately both my children have VHL. I had hoped that Belzuifan would have given them a better life.

If my CMJ tumour continues to grow like it has and I can't be offered Belzutifan, then I am facing the following consequences in the not too distant future:
- I would be paralysed from the neck down, including incontinence. I currently lead an active normal lifestyle.
- Being paralysed, I'd have to leave my job. I currently work part time around childcare, but previously full time and I plan to go back to work full time when my children are older.
The following changes would have to be made as well, and please take in to consideration the cost of all these implications, on top of having to leave my job (a loss of £30kpa alone)
- I may need to be in hospital for a significant amount of time meaning that I would be taking up bed space that can be avoided by being on belzutifan.
- My husband would have to leave his employment (a loss of £40kpa) and become my full-time carer.
- We would both have to claim benefits. I would have to claim high rate PIP for daily living and mobility, and my husband would have to claim Carers Allowances. We would have to claim Universal Credit, housing cost element and limited capability. We currently do not claim any benefits, other than Child Benefit which all parents receive under the income threshold. This would be a significant reduction in our income, meaning we would rely heavily on the government even more to support us, source hardship funding from local government, food parcels, free school dinners for children, take out loans to support our basic needs as a family which may lead to it being written off under IDVA.
We would have to sell our home, but the small amount of equity that comes from the property would be eaten up very quickly by the significant cost of my care and equipment (ie hoists, hospital bed, carers for the rest for my life).

We may not qualify for social housing at first due to the sale of our property, would we have to be street homeless? We couldn’t afford to pay for my around the clock care and also pay a mortgage and bills with the current cost of living. What gives? The Government would have to help us, the cost being on them.

- I would need around the clock care, meaning that we would also have to employ carers because my husband would not be able to do this all by himself as he would need to also care for our children (who may also be recovering from surgery) and also need respite too.
- My home will need to be adapted if it can be, but most likely we would have to sell our family home to be able to find a property that will cater for my disabled needs – which wouldn’t be possible due to the housing crisis

we are facing as a nation. Would I have to stay in hospital, or be sent to a hospice for care whilst I wait for my own home to be suitable? Thus I would be bed blocking, assessments would need to be undertaken from Occupational Therapists. This is not cheap! I would also be missing out on my support from my family and children. The impact this will have on not only my mental health but my families will be permanently catastrophic.
- When you are diagnosed with Von Hippel-Lindau as a child, you are declined for all life insurance policies so it is even more important to preserve quality of life so that we can continue living in our home and repaying our mortgage, contributing to the economy as we do currently.
- I would need to continue care under several neurologists as more tumours begin to grow. This is several consultants in one hospital and then also being referred to see other consultants in other hospitals too which specialise in Brain/ Spine surgery.
- We would need to change our car for a disabled access one, which is purchased via PIP. I would also be awarded a disabled parking badge.
- Not being able to move, I'd need treatments to improve circulation, such a chiropodist and massure.
- My care would involve rehab and having regular physiotherapy to help strengthen muscle weakness and focusing on breathing – a cost to the NHS.
- I would need a psychologist as I am sure dealing with this new life will be devastating. A psychologist would likely be needed for my partner, separate to me due to a conflict of interest for the professional, and also a family psychologist for my children to help them process and understand what is happening to me and our family. My extended family may also seek psychologist/ counselling services to help cope as they will be directly affected to. This would be sought through the GP/NHS service.
- My extended family members may have to reduce working hours or give up to help us.
- Medication may be prescribed to myself, partner and family due to not sleeping, depression, PTSD. Would I have suicidal thoughts? Most definitely. This may also affect the mental health for my children and then the outcome for their future in what they can achieve looks very bleak because their mental health is severely affected.
- If my mental health was so severely affected, I may be awarded the severely mentally impaired which would me that I would be exempt from paying council tax for the rest of my life, meaning that other tax payers and government incur the costs.
- I would need care from specially trained nurses, as I will likely have a catheter, to help with my care alongside the carers, involving the many medicines I would need to help function daily. I may have to be fed through a tube or have a tracheostomy fitted.
- I would need speech and language pathologist if I developed issues with swallowing or with communicating.
- I would be high risk of infection and may have regular stays in hospital to fight infections.
- I would need social services/workers involvement, mental health workers/CPN, family/child services involvement such as MASH referrals which include the schools and the safeguarding team to ensure my children

are cared for because I won't be able to do this, and they will be labelled as vulnerable children.
- Our family life would be compromised, my children, whilst also dealing with their own health issues, they may not want to be at home due to how stressful and dysfunctional it becomes, and turn to a life of crime or violence, or lead a generation change of life of 'living on benefits'.

All of this is based on just ONE tumour for just me, but as we know VHL causes multiple tumours over and over again. You remove it and it comes back, maybe in another location but it keeps coming back over and over again. I do believe that stress causes tumours to grow and the above situation is so highly stressful that I know I would develop more and more tumours, requiring more surgery, other treatments, and be closely monitored with scans from 3 months plus. How much extra does this cost the NHS?
Please take into consideration all the cost this will have to the NHS and government on a permanent basis if Belzutifan is not approved. The cost of all the professionals alone, from GP to specialist consultants is significant. This is just an example of one tumour in one person affecting so many organisations, services, treatments. This is not good. It is a catastrophic domino effect across several services.

On top of this, my two children will also have the monitoring and surgery. Without Belzutifan, I feel VHL will destroy my family life and ultimately destroy me mentally and physically. As Scotland has already approved the use of the drug for VHL, we would look at moving to Scotland and leaving all the support we currently receive from family members.

Approving this drug will not only improve the quality of life for many people affected by VHL (carriers or carers), but it will also have a positive impact on the NHS system too, such as benefiting all individuals in the country that have late diagnosis of things such as cancer due to waiting times in the NHS.
Happy individuals, who are also supported, will do far greater things in life that will benefit the economy, rather than adding to the drain on benefits/NHS system (wait times are already over 1 year, we would be adding to that timescale) if it is not approved.

The initial cost is expensive but over time you would hope that manufactures would reduce the cost to produce it, as it becomes more well documented for all its benefits and use. Yes, some people may develop side effects, some may discontinue using it, but from researching the use of Belzutifan in America, a lot of people have few side effects that they can manage themselves because of the improvements its gives to their health. I often read on the VHL American facebook group that people taking Belzutifan for a long period of time have experienced tumours and cysts, completely disappearing, decreasing in size or that they have remained stable. They also document that they have had no new growths anywhere else! This is not only giving VHL patients a better quality of life, or can continue leading a normal active life to pension age and beyond, it also

relieves a lot of pressure on the NHS system, Doctors, Consultants, Nurses, and all other services involved in treating one tumour.

I understand the committee comments about not approving for lack of evidence v funding. However, I would like to know why in the UK, where England and Scotland are all under the same NHS system, why Scotland is able to approve Belzutifan, but not England? What was evidenced in the study done in Scotland for it to be approved straight away? Was it any different to England? Why was it passed first time there and not in England? Shouldn't the Scotland study be included as part of this decision in England? Can it be used to fill the gaps of evidence that is reported in the document?
Why wasn't a trial covering more people from all over the country with differing needs, tumour locations and qualities of life completed, so that the committee are basing decisions on the evidence they require, not assumptions and then keep quoting there was not enough evidence?
There are other serious illnesses like VHL that have medication approved, why is it not the case for VHL?
VHL is a long standing illness and classed as a disability. It certainly feels like the current refusal decision is discrimination, be it location discrimination or genetic discrimination.

The report describes VHL as being rare and there not being enough clinical evidence. Why were not more individuals invited to participate in the trails to obtain more clinical evidence?
The report also states that Belzutifan can stop or turn back growth of tumours, avoid surgeries, lowers risk of metastasis and reduces the need for dialysis. Knowing that this will happen to every single VHL patient, this drug saves so much money in the long run.
The report kept reiterating throughout about there being uncertainties in the evidence, use of several assumptions and not facts. Have the benefits been fully captured?

A question for the committee; how would you feel if you had VHL? How would reading this report make you feel? What would you do?

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	No
Notes	
Comments on the DG:	
I am a 33 year old male based in Lincolnshire, England. Both my sisters have VHL, along with my mother. My grandmother also had VHL and passed away from kidney cancer as a result of the disease. While being fortunate enough to not inherit VHL, I have witnessed my family	

face pancreatic cancer, brain and spine tumours, adrenal tumours.

My family live in constant fear of when/if the next tumour arises and as a family member is so hard to witness this turmoil, even when they're in good health.

When unfortunate enough to be in poor health, I've witness my family undergo numerous treatments and procedures of which my mum has lost hearing in one ear, both my sister, and mum, have a adrenal gland removed, my other sister have her pancreas removed, as well as losing sight in one of her eyes.

It was a huge blow to hear of the results of NICE review, as for the first time in my life, there appeared to be real hope and a way of living with this disease in a significantly more treatable way.

I trust that NICE will take this account, and all other accounts provided, combined with the rare nature of this disease (that although rare, affects lives severely), to ensure the right decision of approval is made.

Name	
Role	[redacted]
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	Not specified
Notes	No

Comments on the DG:

I am a 34 year old female based in Lincolnshire, England. I am getting married in July to my partner whose family has VHL. Although he did not inherit VHL, his mum and both sisters have VHL. His grandmother also had VHL and passed away from kidney cancer as a result of the disease.

His family have faced pancreatic cancer, spine and brain tumours and adrenal tumours. They live in constant fear of the next tumour developing and VHL affects all aspects of their lives, daily. Concerns around starting a family; worries of getting unwell and the impact upon their health, economics, relationships etc. just to name a few.

Belzutifan would be life changing for them (and all VHL patients) providing hope, reducing fear, and supporting both their physical and mental health. We were absolutely heartbroken after the first review and we can only hope that NICE approves it in the next review. It would be the very best thing to happen for my extended family and it makes me emotional to think that they could possibly be given this opportunity.
Thank you.

Role	[redacted]

Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	Not specified
Notes	No

Comments on the DG:

I am a 31 year old female based in Lincolnshire, England. I have VHL, as do my mum and sister. My grandmother also had VHL and passed away from kidney cancer as a result of the disease.

My family have faced pancreatic cancer, brain and spine tumours, adrenal tumours, kidney tumours and retinal tumours. My sister had pancreatic cancer at the age of 25 - she underwent life changing surgery, takes daily medication and lives in fear of the cancer returning. I was 20 when she went through this and it was a traumatic experience for our family, I later underwent therapy and was diagnosed with PTSD following my sister's illness and surgery.

My sister has lost sight in one eye and my grandmother was fully blind due to VHL related tumours. My sister found out she had an untreatable tumour in her retina at the age of 11 and has had to live with her vision reducing in that eye ever since, now it is fully gone. We can only hope that her healthy eye remains unaffected.

Both my mum and myself have had adrenal glands removed. I was diagnosed with my adrenal tumour at the age of 17 and underwent surgery between exams for my final year A levels. My sister currently has an adrenal tumour that she is waiting to be removed. My mum had her adrenal tumour diagnosed and removed when I was a young baby. I recently found an old report from when I was at nursery that was a tough read - it detailed how the trauma at home was clearly upsetting me. I can only wonder what long term effects going through this at such a young age would have on a person.

My mum has lost her hearing in one ear due to a brain tumour. She had surgery for this when I was 16. I vividly remember my mum being poorly in bed on my 16th birthday and turning up to school crying.

I currently have 3 small brain tumours that are not of immediate concern but are being monitored. It is daunting, to say the least, to think of what might come from these in the future. Brain surgery is terrifying to think about but the nature of VHL means that I would have to consider myself lucky if a tumour is even deemed operable. Last year I had a spell of severe headaches that terrified me as I thought it may be a result of the brain tumours. It turns out it was just a migraine, but the stress and worry caused by this possibly being VHL-related meant that my migraine lasted for 6 weeks.

That is just a very brief summary of the medical history of my immediate family. We have no idea what the future could bring for any of us - good

health, blindness, cancer, brain surgery, wheelchair bound, death? Our relatives without VHL, as well as partners and friends, also have their own perspective and life long concerns. As both a patient with VHL and a relative of someone with VHL, it is a constant mental battle.

I am a scientist and work for the NHS - I recently relocated back to my home town but unfortunately my new place of work is also now the hospital that I have had annual screening at for most of my life and where myself and my mum and sister have had surgery. I am on extended leave at the moment and am in the process of handing my notice in as I underestimated how triggering it would be to work in the same hospital that I have such bad, traumatic memories in for both myself and my family. This unfortunately will be me leaving the NHS for good as the nature of my work is quite closely linked with my medical past and while I have no control over VHL, I can only try control where I work. It is just another way that VHL impacts my life.

If myself or my sister want to start a family in the future, we would require extensive PGT-M IVF in order to ensure our children do not inherit VHL. Now that I am of an age where I need to start seriously considering this, I am finding it extremely tough and triggering.

I have attended VHL screening appointments for as long as I could remember. I never imagined something like Belzutifan being available. When I received my formal diagnosis of VHL at the age of 15, I thought I would never have children as I didn't want to risk my children inheriting the condition. But preimplantation genetic testing is now an option and it has changed everything for the future. I would hope that Belzutifan can do the same - it could change the future of how we mentally and physically deal with VHL. When the inevitable tumours arise for myself and my mum and sister, the fact that we may be able to avoid potential extensive surgeries is remarkable. Not having to watch your relatives lose organ by organ and worrying about what is left in tact, will the next tumour arise on a remaining healthy organ? As mentioned previously, it could also provide hope for previously inoperable tumours. The mental toll of all this, the physical battle and recovery, lengthy unpleasant hospital stays, the disruption to your life, the concern for our partners and relatives. I cannot put into words the hope that Belzutifan would bring us. It is a game changer, it is hope for the future, it is something we didn't dare to dream of.

When I received the results of the NICE review, it felt like a physical punch to the gut. I appreciate costs always have to be considered, but I see news and literature articles for much much more expensive drugs for much rare conditions that get approved. I can only imagine the cost that the numerous individual surgeries VHL patients go through (and all the after care involved) amounts to. That is before considering the mental toll on patients and their relatives (which is unquantifiable). This is made even worse by seeing the positive and life changing impact the drug is having for VHL patients in other countries - it cannot be a post code lottery like this.

My message to you is purely from a personal perspective, I can’t even begin to cover the wider impact this would have on other VHL patients (a lot of which, quite frankly, have had it much worse than me). I have to keep hope that NICE will consider all the evidence and everyone’s opinions and come to the right decision here and approve the drug.

Thank you for taking the time to read my comments.

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Belzutifan for treating tumours associated with Von Hippel-Lindau disease [ID3932]: EAG critique of consultation response

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Introduction

This document provides the External Assessment Group's (EAG's) critique of the materials submitted to the National Institute for Health and Care Excellence (NICE) in response to the Appraisal Consultation Document (ACD)[1] issued following the first technology appraisal committee meeting for belzutifan for treating tumours associated with Von Hippel-Lindau (VHL) disease. Materials were submitted by the company plus several other stakeholders: Action Kidney Cancer; VHL UK Ireland; UK Kidney Association; Professor W. Drake (clinical endocrinologist); and a collection of comments submitted by service users and their relatives/carers (web comments). The EAG noted the large volume of information submitted overall and in particular, the many changes made to the economic model. Following discussion between NICE and the EAG, it was agreed that the EAG critique should focus on the company's ACD response as well as comments from clinicians and organisational stakeholders.

The following sections are structured according to the source of comments, and the comment number where applicable. Since a number of comments are opinion-based without substantiation, the EAG has focused on those where potentially new sources of information are mentioned or specified changes to the input, method and estimates from the economic model.

EAG critique of company's response

Comment 1: Company's overview

Please see below for the EAG critique.

Comment 2a: Relevant population

Section 3.14 of the ACD ("*Severity*") outlines the committee's considerations of appropriate quality adjusted life year (QALY) severity weighting for different tumour types: renal cell carcinoma (RCC), central nervous system haemangioblastomas (CNS Hbs) and pancreatic neuroendocrine tumours (pNETs). As part of their deliberations, the committee indicated an appreciation of "*the substantial impact of VHL*" and concluded that "*it was unable to apply an appropriate severity weight based on the calculations presented by the company because of uncertainty in its underlying assumptions.*"[1] In their response to the ACD, the company stated that: "*It appears the committee may think the MK-6482-004 population does not have 'severe' disease. We acknowledge that summary statistics obscure essential detail about the severity of the patients in MK-6482-004*" (p.8) and in an attempt to address this, provided individual participant data (IPD) at baseline for age, sex, ethnicity, medical history, tumours present at trial initiation and prior therapy for VHL-associated disease (Appendix 3).[2]

The EAG do not consider that there is clear evidence that the committee has misunderstood the level of disease severity in the MK-6482-004 trial population. Either way, the EAG is uncertain how the baseline IPD are helpful in increasing understanding. The company suggest that the patients eligible for belzutifan, which the EAG argue would be equivalent to the decision problem (DP) population, according to UK clinical experts, are those with *"…multisystem and CNS Hb involvement and / or patients on the precipice of organ failure."*[2] The company then go on to say that these patients are well represented in the belzutifan trial. As stated in the EAG report and acknowledged in the ACD, one of the problems with the belzutifan trial as a source of evidence for the DP was that the DP permitted any combination of tumours whereas the trial required at least one RCC tumour as well as possibly other types. The company provide further clarification that the relevant population is like the belzutifan trial in that 80% of patients have both RCC and CNS tumours. Therefore, it appears that the company have now narrowed the DP to be more like the belzutifan trial at least in terms of tumour distribution.

This also appears to be consistent with a cohort of patients eligible for belzutifan identified by clinical experts. However, it is crucial to note that this cohort appear to be distinctly different to the cohort *"on the precipice of organ failure"*, which is inconsistent with the company modelling of standard of care (SoC), where most patients received immediate surgery. No further data on the trial presented by the company can mitigate this problem because the data are not on the patients who need immediate surgery: indeed, they were excluded from the trial. Of course, the company have also implemented a delay of 4 months to surgery in the model (only for patients receiving SoC) to mitigate this problem. The EAG would therefore argue that the DP population has been narrowed further to those patients who need surgery in 4 months, which does seem to align with clinical expert opinion recorded in the ACD that: *"…belzutifan will provide an option for people…are waiting for the surgery…that…would be at about 4 months."* (p. 8)[1] Unfortunately, it is unclear the degree to which the trial patients align with this, and crucially this still only applies to SoC in the model because the assumption of most patients receiving surgery immediately or at 4 months does not apply to those in receipt of belzutifan. In fact, the EAG would continue to argue that the best estimate of the rate of surgery without belzutifan in patients who are eligible for belzutifan would be that during the pre-treatment phase of the belzutifan trial i.e. without the imposition of a substantial increase by assuming that nearly all patients receive it at any time including four months.

Comment 2b: Comparator data

The EAG consider that the use of the pre-treatment phase to estimate rate of surgery, as requested by the EAG, is a valuable alternative to the Natural History data. However, as stated in Section 2a, there remains a bias if only patients with the comparator are assumed to have surgery, even if delayed for 4 months.

Comment 2c: Outcomes

No further comment from the EAG.

Comment 2d: Establishing relative treatment effect

The company noted the following statement from Section 3.9 ("*Establishing relative treatment effect*") of the ACD: "*After matching, this made it easy to compare outcomes because the populations were likely to be more balanced*".[1] The company commented as follows:

"*It would be more correctly understood that this should mean that 'After matching it is easier to compare outcomes between treatment with belzutifan and standard of care because the populations from which the adjusted outcomes data are now derived are now similar*'."[2]

During the stakeholder response phase, the EAG had suggested that the above sentence be deleted and replaced with the following text:

"*As stated in TSD 18, this method of population adjustment using non-randomised trial data requires that all effect modifiers and prognostic factors are accounted for. This assumption is very strong, and largely considered impossible to meet. Failure of this assumption leads to an unknown amount of bias.*"[3]

Related to this, the EAG wishes to highlight that the indirect treatment comparison (ITC) only applies to the RCC cohort. In addition, the EAG suggests that the effect of the immediate surgery assumption on the model results needs to be clearly explained.

The company has removed the immediate surgery assumption from the model and a 4-month delay to surgery has been implemented instead, as recommended by clinical experts. It should be emphasised nevertheless that, as it happened with the immediate surgery assumption, the 4-month delay in surgery is only applied to the SoC arm. A great majority of patients in SoC (90% for RCC and pNET, and

effectively 100% for CNS Hb) will still receive surgery, but this has been delayed by 4 months. The delay itself has a relatively minor impact on the model results: the company base-case (including delayed surgery in SoC) incremental QALYs for the weighted cohort reported in the model is [redacted], whereas if no delay in surgery (for SoC patients only) is assumed, the incremental QALYs equal [redacted].

The underlying issue whether the modelled SoC patients are the same as those modelled in the belzutifan arm remains thus unresolved. The purpose of the immediate or 4-month delayed surgery was to account for patients who were "out of options", so that this surgery was considered as a last resort. Based on the presented evidence, and the discussions during the Committee meeting, the EAG considers this assumption reasonable, but it should also be applied to patients in the belzutifan arm. Because this did not happen in the originally submitted model, nor in the updated model, the EAG considers that the cost effectiveness results are still biased in favour of belzutifan.

The EAG argues that, at model start, patients in both arms should be equal. Therefore, patients in the belzutifan arm are also in need of last resort surgery. Because belzutifan is assumed to be effective, *some* patients will be able to avoid this last resort surgery, but not all of them: the EAG assumption is that if 4 months is selected as "waiting time" for having last resort surgery in the SoC arm, this should be the same in the belzutifan arm, where the last resort surgery should be applicable only to those patients who did not respond to belzutifan treatment in 4 months. The proportion of patients in the belzutifan arm who might receive last resort surgery could be large, as can be deduced from Table 1, where it can be seen that for the median time to response (TTR) was 11.1 months, [redacted] and [redacted] for the RCC, CNS Hb and pNET cohorts, respectively. This means that at 4 months, more than [redacted] of patients have not achieved response in any of the cohorts; however, the exact proportions are unknown. Furthermore, Table 1 shows that 22 patients (36%), [redacted] and [redacted] did not achieve response at all in the RCC, CNS Hb and pNET cohorts, respectively. This shows that in the CNS Hb cohort, which seems to be the leading cause for surgery (80% as indicated above), [redacted] of these patients did not respond to belzutifan treatment at all in the MK-6482-004 trial.

Table 1: Summary of MK-6482-004 study efficacy results (1 April 2022 data cut-off)

Outcome	Summary of results
RCC (all patients, N=61)	
Overall response rate (ORR)	63.9% (95% CI: 50.6%, 75.8%)
Disease control rate (DCR)	98.4% (95% CI: 91.2%, 100.0%)
Duration of response (DOR)	Median DOR not reached (range: 5.4+ to 35.8+ months)
Time to response (TTR)	Median TTR was 11.1 months (range: 2.7 to 30.5 months) among 39 participants with response
Progression-free survival (PFS)	[redacted]
Time to surgery (TTS)	NE
Subgroup of patients with CNS hemangioblastoma (n=50)	
ORR	44.0% (95% CI: 30.0%, 58.7%)
DCR	90.0% (95% CI: 78.2%, 96.7%)
DOR	Median DOR not reached (range: 3.7+ to 38.7+ months)
TTR	[redacted]
PFS	[redacted]
TTS	NE

Outcome	Summary of results
Subgroup of patients with pNET (n=22)	
ORR	90.9% (95% CI: 70.8%, 98.9%)
DCR	100% (95% CI: 84.6%, 100.0%)
DOR	Median DOR not reached (range: 11.0+ to 37.3+ months)
TTR	[redacted]
PFS	[redacted]
TTS	NE

This is Table 3.13 in the EAG report[4] which in turn was based on Table 15 and Section B.2.7 of the CS[5] and the company's response to clarification question A.22.[6]
95% CI = 95% confidence interval; CNS = central nervous system; CS = company submission; DCR = disease control rate; DOR = duration of response; NE = not evaluable; ORR = overall response rate; PFS = progression-free survival; pNET = pancreatic neuroendocrine tumour; RCC = renal cell carcinoma; TTR = time to response; TTS = time to surgery

As previously mentioned, the EAG considers it reasonable to assume that patients not responding to belzutifan treatment in 4 months should receive surgery to make them comparable to patients in the SoC arm of the model. The Markov traces in the model show that the proportion of patients in the belzutifan arm receiving surgery is low, since this is based on the surgery rates observed in the MK-6482-004 trial. In the SoC arm surgery rates are also initially low (even though higher than in the belzutifan arm, which is in line with the presented evidence), but at 4 months patients in the model are "forced" to have surgery, so that at model cycle 17, the proportion of patients undergoing surgery is applied to the subset of patients who remain in the pre-surgery health state at cycle 16 (for example, for the RCC cohort [redacted] of the patients were in the pre-surgery health state at cycle 16, whereas at cycle 17 this was [redacted] only, reflecting the assumption that 90% of the pre-surgery in SoC patients got surgery). Since a similar assumption is not applied in the belzutifan arm, the EAG considers that a more severe patient population is the SoC arm is being assumed in the model. In their critique of Comment 4b, the EAG presents the results of a *hypothetical* scenario analysis where it was assumed that 50% of patients in the pre-surgery health state at cycle 16 in the belzutifan arm of the model would receive last resort surgery. While the EAG would like to emphasise that this scenario is hypothetical, the EAG also considers that it could be informative for the Committee, as it shows how the model outcomes might change when including the last resort surgery assumption for belzutifan patients. Acknowledging that this is still an imperfect scenario (many uncertainties are still present), the EAG believes that it provides a better approximation to what is believed to represent the DP population, as we understand it. Finally please note that, because the median TTR is achieved [redacted], it could be argued that assuming a 50% of delayed surgery for non-responders in the belzutifan arm might still be [redacted] for belzutifan.

Comment 3: Economic model

Comment 3a: Model structure and outputs

The company provided additional clarification based on the ACD comments. The EAG has no further comments regarding the model structure.

Comment 3b: Time on treatment

The company modelled time on treatment (ToT) based on progression-free survival (PFS) to address comment 3.11 in the ACD.[1] This scenario, assuming a Gompertz distribution, results in an incremental cost-effectiveness ratio (ICER) estimate of [redacted] per QALY gained.

It should be noted that modelling ToT based on either fitted (patient-level) ToT or PFS data does not have a large impact on the model results. What does impact the model results is the parametric distribution selected to model ToT. The Gompertz distribution, selected for the base-case analysis, [redacted] compared to the other distributions; meaning that at approximately [redacted] no patients are on belzutifan treatment. Any other distribution has [redacted]. Since the observed ToT data [redacted], none of the distributions included in the model seem to capture this shape very well. For example, by assuming a Weibull distribution, ToT reaches 0 at approximately [redacted]. The ICERs in these scenarios are [redacted] and [redacted] per QALY gained, respectively. The EAG cannot assess the plausibility of the Weibull (or any other) extrapolation for ToT but would like to highlight the issue whether belzutifan should be administered in the long-term. If that would be the case, the ICER can be substantially increased according to the economic model.

The company also mentioned that modelling ToT until side effects was not feasible in the timeframe to provide these responses as it was not a pre-specified analysis in the trial. Therefore, the EAG has no comments on this aspect.

Comment 3c: Treatment waning

The treatment effect waning period for the CNS Hb and pNET cohorts is still assumed to be equivalent to the RCC cohort. This is due to the small sample size of discontinued patients in the CNS Hb and pNET subgroups in the MK-6482-004 trial, which makes it unfeasible to provide a better estimate in these two cohorts. Therefore, the EAG considers that this limitation is still present in the company's model. However, the company indicated that clinicians considered the approach to treatment effect waning plausible for the CNS Hb and pNET cohorts.

The company conducted additional scenario analyses to test alternative assumptions of the treatment effect waning period in the CNS Hb and pNET cohorts (for the RCC cohort no additional assumptions were tested). The ICERS ranged from [redacted] to [redacted] per QALY gained, suggesting a modest impact on the model results.

The company reiterated that treatment effect waning cannot begin earlier than the trial follow-up period, since this accounts for discontinuation and potential loss of treatment effect that occurs during this period. The EAG wonders however what should happen to patients after the waning period has finished and tumours have eventually reverted to their initial size. It could be argued that in that case, patients should receive "immediate" surgery or re-treatment with belzutifan (if that would be clinically plausible). None of these two options are included in the current model, which are expected to considerably increase the ICER.

Comment 3d: Health-related quality of life

The company made two changes regarding the implementation of health-related quality of life (HRQoL) in their economic model, following the Committee comments in Section 3.13 of the ACD:[1]

- A multiplicative method (as opposed to an additive one) for combining disutilities.

- The disutility value for end-stage renal disease (ESRD)/dialysis was deducted from 1 in the previous model. This was replaced by comparing an absolute estimate of the utility on dialysis with an age- and sex-matched expectation from the general population.

These changes were in line with the Committee's preferences. The EAG observed in the model that with the additive approach the estimated disutility from concurrent complications was estimated to be [redacted], whereas with the multiplicative approach the new this was [redacted]. This is in line with the expectation that the additive approach would result in more negative disutilities, but it should also ben noted that the difference is minor.

Comment 3e: Severity

The company indicated that a severity weight of 1.7 should be applied despite that the absolute and proportional QALY shortfall estimates (calculated by the company) suggest a severity weight of 1.2. The company argues that given the rareness of the disease and the poor patient outcomes, the application of a lower severity weight is unreasonable and unfair. The company also referred to the NICE methods guide (paragraph 6.2.11), where it is stated that severity modifiers that are not included in the estimated QALYs "*can be taken into account qualitatively through committee discussion or quantitatively through QALY weighting*".[7] The company is of the opinion that this might be the case and that the severity of the disease is not completely captured by the absolute and proportional QALY shortfall estimates.

The EAG considers that, based on the absolute and proportional QALY shortfall calculations, which are based on the currently available data, the applicable severity weight should be 1.2. However, it is up to the Committee to decide whether other factors not captured by the data are relevant and a higher severity weight should be applied. In any case, the company reports an updated base-case ICER of £[redacted], which is below the thresholds of £51,000 and £36,000 per QALY gained (reflecting a 1.7 and 1.2 severity weight, respectively). The updated base-case ICER is discussed in the next section.

The company concluded that they [redacted]. The EAG does not agree with this conclusion. As it has been made clear through the company's and EAG's comments, many uncertainties are still present in the current cost effectiveness analyses. Reducing the ICER to acceptable cost effectiveness levels does not imply that these uncertainties disappear or are no longer relevant.

Comment 4: Cost-effectiveness estimates

Comment 4a: Uncertainties in the evidence and company's modelling assumptions

The company referred to Section 3.15 of the draft guidance document to list a number of key uncertainties present in the evidence and company's model. The EAG considers that the majority of these uncertainties have not been resolved:

- The evidence for the generalisability of the MK-6482-004 population to the marketing authorisation (MA) population: unresolved according to the EAG (please see Comment 2a).
- The ITC approach and using the propensity-score weighting method, which were highly uncertain, with alternative methods explored: improved but not resolved (please see Comment 2d).
- The uncertainty in the model input parameters and assumptions and uncertainties in the model outputs: unresolved according to the EAG (please see all previous comments).
- Modelled ToT for belzutifan until progression or until side effects: partially improved with an additional scenario, but the underlying uncertainties are still present (see Comment 3b).

- Extensive sensitivity analyses and testing alternative assumptions on the treatment waning effect across the tumour types: partially improved with additional scenario analyses, but the underlying uncertainties are still present (see Comment 3c).
- The uncertainty in the company's approach to surgery-associated disutility values, with an exploration of the multiplicative approach and use of validated disutility values against literature for similar outcomes: improved but minor impact on model results (see Comment 3d).

Comment 4b: Summary of updated company cost-effectiveness analysis base-case

The company defined an updated base-case based on the following adjustments:

- Immediate surgery delayed to 4 months (in the SoC arm only).
- Time to surgery for the RCC cohort in the SoC arm is now based on pre-treatment period data (rather than the VHL Natural History Study and a matching-adjusted indirect comparison [MAIC]).
- A revised disutility value for ESRD/dialysis (and erythroderma) was included in the model.
- Disutilities applied using a multiplicative approach (instead of an additive approach).
- Cohort weighting (to calculate an overall ICER) based on clinical expert elicitation.
- A revised patient access scheme (PAS) of [redacted].

The EAG's view on these changes have been explained in previous sections of this document. Table 2 shows the company's updated base-case deterministic cost-effectiveness (CE) results. These indicated that belzutifan was more costly and more effective than SoC in all cohorts. Compared to SoC, in the weighted cohort belzutifan accrued [redacted] incremental QALYs at [redacted] additional costs. Therefore, the ICER in the weighted cohort was £[redacted] per QALY gained. When accounting for disease severity, assuming a QALY weight of 1.2, results on an ICER equal to £[redacted] per QALY gained for the weighted cohort.

The company indicated that one clinical expert highlighted that the life years gained estimated by the model, particularly for the CNS Hb cohort in SoC, are likely to be at the upper end of survival expectations. However, the current model does not include overall survival (OS) as input parameters for the model and due to time constraints, the company was not able to amend this in the model. However, the company's expectation is that modelling lower survival for the CNS Hb cohort in the SoC arm would result in a lower ICER (to what extent is not mentioned). Average utility values were also presented to the same clinical expert who stressed that the utility in SoC patients, particularly in those with CNS Hb, is expected to be very low (which is expected to decline over time as life expectancy shortens). Finally, the expert indicated that utility values for the RCC cohort should account for ESRD/dialysis and additional considerations of VHL disease.

Table 2: Company revised base-case deterministic CE results (belzutifan updated PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)	Severity Adjusted ICER – company*
VHL RCC cohort (weight = 15%)								
Belzutifan	[redacted]	[redacted]	[redacted]					
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VHL CNS Hb cohort (weight = 80%)								
Belzutifan	[redacted]	[redacted]	[redacted]					

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)	Severity Adjusted ICER – company*
VHL RCC cohort (weight = 15%)								
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VHL pNET cohort (weight = 5%)								
Belzutifan	[redacted]	[redacted]	[redacted]					
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weighted cohort								
Belzutifan	[redacted]	[redacted]	[redacted]					
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 8 in the company response to ACD.[2]
* Company's severity adjusted ICERs based on a QALY weight equal to 1.2 for all cohorts.
ACD = Appraisal Consultation Document; CE = cost effectiveness; CNS Hb = central nervous system hemangioblastoma; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LYG = life years gained; PAS = patient access scheme; pNET = pancreatic neuroendocrine tumours; QALY = quality-adjusted life year; RCC = renal cell carcinoma; SoC = standard of care; VHL = Von Hippel-Lindau

Sensitivity and scenario analyses results are reported in Appendix 7 of the company's ACD response.[2] EAG conclusions are similar to those in EAG report, therefore, we refer to the EAG report for further details. The EAG would like to emphasise though that the model results are still sensitive to the selected probability distribution for ToT. The impact of the immediate surgery assumption is discussed separately below, given its importance on the model results. The results of these two scenarios illustrate the importance of properly defining the patient population and the great impact that it might have on the ICER.

Table 3 shows the results of the hypothetical scenario where it was assumed that 50% of patients in the pre-surgery health state at cycle 16 in the belzutifan arm of the model would receive surgery. The rationale for this scenario has been explained above in Section 2d. The EAG considers that this scenario provided a better approximation what is believed to represent the DP population. In this scenario, belzutifan was also more costly and more effective than SoC in all cohorts. Compared to SoC, in the weighted cohort belzutifan accrued [redacted] incremental QALYs at [redacted] additional costs. Compared to the company's base-case, in this scenario the incremental QALYs were considerably reduced whereas the incremental costs were greatly increased, reflecting thus the impact of assuming that last resort surgery will also occur to patients not responding to belzutifan treatment in 4 months. The ICER in the weighted cohort in this scenario was £[redacted] per QALY gained, [redacted]. When accounting for disease severity, assuming a QALY weight of 1.2, results on an ICER equal to £[redacted] per QALY gained for the weighted cohort.

Table 3: EAG hypothetical scenario: last resort surgery at 4 months in belzutifan arm for 50% of patients in pre-surgery (belzutifan updated PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)	Severity Adjusted ICER – company*
VHL RCC cohort (weight = 15%)								
Belzutifan	[redacted]	[redacted]	[redacted]					
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VHL CNS Hb cohort (weight = 80%)								
Belzutifan	[redacted]	[redacted]	[redacted]					
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VHL pNET cohort (weight = 5%)								
Belzutifan	[redacted]	[redacted]	[redacted]					
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weighted cohort								
Belzutifan	[redacted]	[redacted]	[redacted]					
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on economic model submitted as part of the company's response to the ACD.[8]
* Severity adjusted ICERs based on a QALY weight equal to 1.2 for all cohorts.
ACD = Appraisal Consultation Document; CE = cost effectiveness; CNS Hb = central nervous system hemangioblastoma; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LYG = life years gained; PAS = patient access scheme; pNET = pancreatic neuroendocrine tumours; QALY = quality-adjusted life year; RCC = renal cell carcinoma; SoC = standard of care; VHL = Von Hippel-Lindau

Table 4 shows the results of the scenario where last resort surgery is not included in the model calculations. The rationale for this scenario has been explained above in Section 2d. The EAG considers that this scenario might provide a better approximation to the population in the MK-6482-004 trial (even though the trial population did not require immediate – or 4-month delayed – surgery; and the multi-system component of the disease is not captured in the model). In this scenario, belzutifan was still more costly and more effective than SoC in all cohorts. Compared to SoC, in the weighted cohort belzutifan accrued [redacted] incremental QALYs at [redacted] additional costs. Compared to the company's base-case, in this scenario the incremental QALYs were also considerably reduced whereas the incremental costs were greatly increased, reflecting thus the impact of assuming that SoC patients will not require last resort surgery. The ICER in the weighted cohort in this scenario was £[redacted] per QALY gained, [redacted]. When accounting for disease severity, assuming a QALY weight of 1.2, results on an ICER equal to £[redacted] per QALY gained for the weighted cohort.

Table 4: Scenario with last resort surgery removed from SoC (belzutifan updated PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)	Severity Adjusted ICER – company*
VHL RCC cohort (weight = 15%)								
Belzutifan	[redacted]	[redacted]	[redacted]					

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)	Severity Adjusted ICER – company*
VHL RCC cohort (weight = 15%)								
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VHL CNS Hb cohort (weight = 80%)								
Belzutifan	[redacted]	[redacted]	[redacted]					
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VHL pNET cohort (weight = 5%)								
Belzutifan	[redacted]	[redacted]	[redacted]					
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weighted cohort								
Belzutifan	[redacted]	[redacted]	[redacted]					
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on economic model submitted as part of the company's response to the ACD.[8]
* Severity adjusted ICERs based on a QALY weight equal to 1.2 for all cohorts.
ACD = Appraisal Consultation Document; CE = cost effectiveness; CNS Hb = central nervous system hemangioblastoma; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LYG = life years gained; PAS = patient access scheme; pNET = pancreatic neuroendocrine tumours; QALY = quality-adjusted life year; RCC = renal cell carcinoma; SoC = standard of care; VHL = Von Hippel-Lindau

Comment 4c: Cancer Drugs Fund

The EAG has no further comments, but we think that further data collection should help resolving or reducing (some of) the remaining uncertainties.

Comment 5: Other factors

The EAG has no further comments.

Comment 5a: Rarity of disease and applying greater flexibility

The EAG has no further comments.

Comment 5b: Equalities

The EAG has no further comments.

Comment 5c: Innovation

The EAG has no further comments.

Appendices

Appendix 1: Additional clinical expert input elicitation

The main information about the clinical expert elicitation exercise is in Appendix 1 of the company's response and this was cross-referenced throughout other sections of the same document.[2] It is apparent from this that the company relied heavily on expert opinion to inform parameters that had been identified by the committee as uncertainties, in relation to both clinical and cost-effectiveness.

The company claimed that they used "*a structured survey method*", the basis of which was three initial questions posed to clinicians contributing to the management of patients with VHL disease. The company described the following subsequent process: "*These responses were then validated via a virtual teleconference call with two clinical experts who are the service leads for the largest VHL clinics in the UK. Following this validation call, MSD implemented the validated clinical expert input into the model with the intent of validating the new model outcomes with a clinical expert. MSD validated these updated outcomes in a subsequent virtual teleconference with one of the VHL clinical experts on the previous call.*"[2] The three initial questions were:

1. *"Please describe the patients who you would like to treat with belzutifan. Why do you want to treat these specific patients?"*
2. *"Of the patients that you would like to treat with belzutifan, which is the tumour driving this decision? CNS Hb, pNET or RCC? Why is this tumour driving a preference to treat with belzutifan? (In your practice what is the % split of VHL patients by these three 'primary' tumour types. Note, we use primary tumour here to mean tumour driving treatment decision making)"*
3. *"If these patients do not receive treatment with belzutifan, what is the likely course of their disease? Please reference any similar patients you may have treated in the past."*[2]

Several aspects of the survey method were not clear, including:

- how the experts were initially approached;
- degree of independence between the experts and the company;
- whether remuneration was offered to the experts by the company for undertaking the survey;
- format of interviews (e.g., as a group or individually? In person or by telephone/online?);
- and methods used for aggregating the responses.

The company stated that 15 experts had been invited to participate in the survey, of which nine responded. The reasons for declining participation were not stated. The clinical specialties of the nine respondents were: endocrinology (n=2); neurosurgery/neuro-oncology (n=2); uro-oncology (n=1); and genetics (n=4). The company provided summary and as well as eight individual responses (it is possible that one of the individual responses was joint between two people although this was not entirely clear from the account provided).[2] Tabulated information (p.33 of the company's response[2]) suggested that the two clinical experts (Professors Drake and Maher, both VHL service leads) providing the so-called validation were among the nine original respondents and one of these individuals also endorsed the model outcomes.

When comparing findings across the three sources of information (individual responses, validation of responses by two experts and model validation by one expert), some mismatches are apparent. For example, the 3% issue is only mentioned in the validation summary and one estimate is questionable (2 to 3 patients out of 60 does not equate to 3%). Other results may not represent a consensus across respondents although this could be partly explained by some experts only responding within the context of their own specialty (RCC only or CNS Hb only) and this also influenced responses to questions about the distribution of tumour types that would inform the decision to prescribe belzutifan.

In the summary of survey outputs (p.33 of Appendix 1), the possibility of two eligible patient cohorts is mentioned: patients on the brink of organ failure; and "*another cohort of patients…. those with multi-systemic VHL disease (i.e., with ≥2 organs affected with VHL related tumours e.g., a patient with both a pNET and CNS Hb)*".[2] However, elsewhere the company seem to combine the two cohorts: "*…multisystem and CNS Hb involvement and / or patients on the precipice of organ failure*" (p.4 of the company's response document).[2] It is not clear from this whether the company is asserting a population that is narrower again than the one in the company submission (CS), e.g., patients must have multi-systemic VHL disease (≥2 organs affected) and/or multiple CNS Hb in order to be treated with belzutifan.

The company described the survey as "*structured*" however there is an apparent mismatch between questions and answers and the questions shown are fewer than the responses which suggests a lack of structure, protocol or topic guide. Therefore, there is some doubt about the consistency and reliability of the reported outcomes.

Other problems include the lack of independence between the respondents and the company and between different groups involved in the survey. Preferable methods for eliciting expert opinion include those requiring a protocol and pre-defined structure such as Delphi methods or the Sheffield Eliciation Framework (SHELF), the latter being identified by the company[9]) which would have the advantages of greater transparency (e.g., conflicts of interest declared) and results that are more consistent and reliable.

Appendix 2: MK-6482-004 study participant tumour burden and prior treatment history at baseline

The EAG has no further comments.

Appendix 3: MK-6482-004 study baseline individual patient data (confidential)

The EAG has no further comments.

Appendix 4: Updated Cancer Drugs Fund Managed Access Agreement proposal

In section 3.3 of Appendix 4, the company reported the number of prevalent patients eligible for belzutifan each year within the Cancer Drugs Fund, which varied between [redacted] and [redacted] at year 1 as estimated by the company and NICE, respectively.[2]

In the original CS,[5] the company indicated that the total number of people with VHL in England is estimated to be 1,300 using the European Medicines Agency (EMA) estimate, or 620 using the Maher et al. (1991) study.[10] Based on the MA definition, to be eligible for belzutifan, patients must have VHL disease and one of the tumours (RCC, CNS Hb or pNET) and not be suitable for localised procedures, such as surgery. The company further indicated that:[5]

- 46% of patients with VHL have one of the three tumours (although the company considers this likely to be an overestimate, as some people with VHL have more than one tumour at the same time). This percentage is based on the audit published by Maher et al. (1991).[10]
- 20% of the patient population are ineligible for localised treatment, such as surgery (based on clinical feedback the company has requested at the beginning of the submission).

This led to an estimate of between 120 to 55 people eligible for treatment, as reported in the original CS.[5] This is somewhat different to the number of patients reported now to be eligible for belzutifan treatment. However, if the relevant population is approximately the 3% of the total VHL population, as reported by the clinical experts now (what we referred to as Cohort 1), the number of eligible patients would vary between estimated as 39 using the EMA estimate, or 19 using the Maher et al. (1991) study.[10] These estimates are much different to those presented in the company ACD response.[2] The

EAG would like to suggest that the number of prevalent patients eligible for belzutifan each year within the Cancer Drugs Fund should be validated.

In addition, regarding the clinical outcomes to be collected as mentioned in Section 7 of Appendix 4,[2] the EAG wonders whether HRQoL data should be included since these data will be used to inform key model input parameters.

Appendix 5: Summary of transition probability estimation approach from pre-surgery and event-free after surgery health states

The EAG would like to highlight that there are still uncertainties associated to all transition probabilities presented in Table 7 of this appendix.

Appendix 6: Updated QALY shortfall analysis

The EAG was able to replicate the calculations presented by the company. However, as mentioned above, it is up to the Committee to decide whether a severity weight different than 1.2 is appropriate for this submission.

Appendix 7: Updated cost-effectiveness estimates

This company presented and explained the changes made to the economic model. Updated cost effectiveness results are presented but these are discussed above in Comment 3 and 4 of this addendum.

Appendix 8: Treatment effect of belzutifan on key surgical rate outcomes

The EAG has no further comments.

EAG critique of responses from other stakeholders

In terms of reviewing the responses from the non-company stakeholders, the EAG has taken the approach of focusing on those that refer to potential sources of new information (summarised in Table 5 below).

Table 5: Summary of responses from stakeholders other than the company

Summary of comment from stakeholder	Substantiating information	EAG critique
Action Kidney Cancer		
Comment 3: cites references to support the clinical effectiveness and cost-benefit of belzutifan treatment.[11]	The clinical effectiveness data are quoted from the NEJM (2021) paper for MK-6482-004.[12] A link for a cost benefit analysis paper was also provided.[13]	The signposted information about clinical effectiveness is not new. It reports outcome data at the 1 December 2020 cut-off[12] whilst the CS[5] and the EAG report[4] summarise data for the 1 April 2022 cut-off. The cost-benefit reference is an abstract for a poster session and it compared surgeries before and after the trial period. The trial is LITESPARK-004 (same as MK-6482-004). Therefore, these should already be captured in the model.
VHL UK/Ireland		
Comment 11: The committee did not take account of the large amount of real-world patient data presented in two VHL UK/Ireland patient surveys.[14]	Report of a survey conducted by VHL UK/Ireland during June 2023 involving patients already using belzutifan (n=44) and their carers (n=8).[15] The survey report summarised details on patient-reported outcomes including treatment effectiveness (tumours that had stabilised, slowed down speed of growth, reduced in size or disappeared), HRQoL and AEs.	The survey results consisted of patients' and carers' views. Whilst this provides useful contextual information, it is difficult to envisage how it could have contributed formally to the submission, e.g., the data on treatment effectiveness were not verified clinically. Some data (p.4) indicated a potential overlap between the patients in the survey and those recruited to the MK-6482-004 trial (n=5 patients, 11% of those surveyed).[15]
Comment 14: On 19 December 2023, a team from VHL UK/Ireland interviewed Dr Eric Jonasch, MD Anderson Cancer Centre, Texas, USA. Dr Jonasch is described as a physician researcher focused on VHL and RCC and is the lead author for the MK-6482-004 trial report.[12] One of the interview questions was: "*Do you have any quotable stats showing pre belzutifan (Welireg)*	Dr Jonasch signposted Figure 1D in the main MK-6482-004 trial publication in relation to the number of tumour reduction procedures required pre- and post- treatment with belzutifan[12] and provided a link to a conference abstract, whilst suggesting that this reported updated information for the same outcome.[16]	The signposted information is not new. Figure 1D of the main MK-6482-004 trial publication reported the number of tumour reduction procedures at the 1 December 2020 cut off.[12] The conference abstract reported outcome data at the later cut-off of 1 April 2022 however did not show details of pre- and post-treatment tumour reduction procedures as part of this.[16] The EAG

Summary of comment from stakeholder	Substantiating information	EAG critique
and post belzutifan (Welireg) surgical procedures?"[14]		notes that the numbers of patients undergoing pre- and post-treatment tumour reduction procedures was already presented in the CS (Figure 8 of Document B of the CS[5] and reproduced in Figure 3.6 of the EAG report[4]).

AE = adverse event; CS = company submission; EAG = External Assessment Group; HRQoL = health-related quality of life; NEJM = New England Journal of Medicine; RCC = renal cell carcinoma; UK = United Kingdom; VHL = von Hippel Lindau

References

[1] National Institute for Health and Care Excellence. *Belzutifan for treating tumours associated with von Hippel-Lindau disease [ID3932]. Draft guidance consultation*. London: NICE, 2023. 23p.

[2] National Institute for Health and Care Excellence. *Belzutifan for treating tumours associated with von Hippel-Lindau disease [ID3932]. Merck Sharp & Dohme (UK) Limited stakeholder response to draft guidance consultation*. London: NICE, 2024. 103p.

[3] O'Meara S, Qendri V, Krijkamp E, Chen J, Tian X, Patel M, et al. *Belzutifan for treating tumours associated with von Hippel-Lindau disease [ID3932]. EAG response to draft guidance document (as a stakeholder)*. York: Kleijnen Systematic Reviews Ltd., 2023. 2p.

[4] O'Meara S, Qendri V, Krijkamp E, Chen J, Tian X, Patel M, et al. *Belzutifan for treating tumours associated with von Hippel-Lindau disease [ID3932]: a Single Technology Assessment*. York: Kleijnen Systematic Reviews Ltd., 2023. 263p.

[5] Merck Sharp & Dohme (UK) Ltd. *Belzutifan for treating tumours associated with von Hippel-Lindau disease (ID3932): submission to National Institute of Health and Care Excellence. single technology appraisal (STA): document B - company evidence submission (v3.0 - 2 June 2023)*: Merck Sharp & Dohme (UK) Ltd., 2023. 431p.

[6] National Institute for Health and Care Excellence. *Belzutifan for treating tumours associated with von Hippel-Lindau disease (ID3932): response to request for clarification from the ERG*. London: NICE, 2023. 116p.

[7] National Institute for Health and Care Excellence. *NICE health technology evaluations: the manual. Process and methods [PMG36] [Internet]*. London: National Institute for Health and Care Excellence, 2022 [accessed 8.2.22]. 181p. Available from: https://www.nice.org.uk/process/pmg36

[8] Merck Sharp & Dohme (UK) Ltd. Cost-effectiveness model of belzutifan for treating tumours associated with Von Hippel Lindau (VHL) disease. Version: May 2023 (revised September 2023 and December 2023). Excel file provided by Company 11.1.24. 2023.

[9] Williams CJ, Wilson KJ, Wilson N. A comparison of prior elicitation aggregation using the classical method and SHELF. J R Stat Soc Ser A Stat Soc 2021; 184(3):920-40

[10] Maher ER, Iselius L, Yates JR, Littler M, Benjamin C, Harris R, et al. Von Hippel-Lindau disease: a genetic study. J Med Genet 1991; 28(7):443-7

[11] National Institute for Health and Care Excellence. *Belzutifan for treating tumours associated with von Hippel-Lindau disease [ID3932]. Action Kidney Cancer stakeholder response to draft guidance consultation*. London: NICE, 2024. 6p.

[12] Jonasch E, Donskov F, Iliopoulos O, Rathmell WK, Narayan VK, Maughan BL, et al. Belzutifan for renal cell carcinoma in von Hippel-Lindau disease. N Engl J Med 2021; 385(22):2036-2046

[13] Wang L, Bensimon AG, Sundaram M, Xu R, Lai Y, Liu Y, et al. Burden of surgeries and surgical complications in patients with Von Hippel Lindau (VHL) disease before and after treatment with belzutifan. J Clin Oncol 2023; 41(6_suppl)

[14] National Institute for Health and Care Excellence. *Belzutifan for treating tumours associated with von Hippel-Lindau disease [ID3932]. VHL UK/Ireland stakeholder response to draft guidance consultation*. London: NICE, 2024. 12p.

[15] VHL UK/Ireland. VHL UK/Ireland patient/carer belzutifan (Welireg) survey June 2023- summary [Internet]. 2023 [accessed 23.1.24]. Available from: https://vhl-uk-ireland.org/vhl-uk-ireland-patient-carer-belzutifan-welireg-survey-june-2023-summary/

[16] Srinivasan R, Iliopoulos O, Rathmell WK, Narayan V, Maughan BL, Oudard S, et al. LBA69 - Belzutifan, a HIF-2alpha inhibitor, for von Hippel-Lindau (VHL) disease-associated neoplasms: 36 months of follow-up of the phase II LITESPARK-004 study. Ann Oncol 2022; 33(suppl_7):S808-S869