National Institute for Health and Care Excellence

Health Technology Evaluation

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

Response to stakeholder organisation comments on the draft remit and draft scope

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Wording	Merck Sharp & Dohme	Given the confusion that has already taken place regarding this appraisal we request that the full marketing indication is re-quoted: Belzutifan for the treatment of adult patients with 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 We note that nowhere in the scoping document is the marketing authorisation for this indication correctly stated. This indication is final and was published in May 2022. We draw attention to three aspects of the indication wording. Belzutifan should be used only in people: 1. Who require treatment. 2. Who have one of the three primary tumours RCC, CNS or pNET. MSD has interpreted this wording to mean belzutifan can be used in patients with a tumour in any one of these primary sites, or in more than one of these	Thank you for your comment. The draft remit wording refers to the marketing authorisation, but does not state it. The technology section has been updated to quote the marketing authorisation directly.

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		primary tumour sites, or in patients with multi-system tumours, so long as one of them is RCC, pNET, or CNS. 3. In whom localised procedures are not suitable or not desirable. The company proposes that the way to consider this clause is: if a localised procedure can successfully be used, it should be. Belzutifan should be retained for patients in whom localised procedures cannot be successfully used.	
	VHL UK/Ireland	The frequency of patients affected with VHL in the UK is ~1 in 70,000 (the 1 in 35,000 is an estimate that includes potential gene carriers who are not currently affected) The scope does not give an accurate picture of the complexity of VHL disease and underestimates the challenges of managing patients with severe disease. For example, the lifetime risk of renal tumours in VHL disease is around 70% which is similar to that for retinal and central nervous system haemangioblastomas. The occurrence of multiple tumours in the kidney, CNS, eyes, though frequent, is not sufficiently acknowledged and the difficulty in treating these is not addressed.	Thank you for your comment. The background of the scope offers a broad overview of the indicated disease. Belzutifan's marketing authorisation is for RCC, CNS haemangioblastomas and pNETs. The background has been updated to more closely reflect VHL.
	Action Kidney Cancer	The wording of the remit needs to make it clear that there is an unmet need for an effective and safe treatment of VHL-associated RCC and VHL patients in general.	Thank you for your comment. This has been reflected in the scope. No action needed.

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Timing Issues	Merck Sharp & Dohme	The urgency of this appraisal to the NHS is very high. UK marketing authorisation for belzutifan in this indication has been received from the MHRA since 31-MAY-2022, following on from belzutifan for this indication being the first to ever have been granted an “Innovation Passport” allowing entry into the MHRA ILAP granted on 26-FEB-2021. There is substantial unmet need in UK patients with VHL disease, who have no effective systemic treatment options and therefore vitally need access to belzutifan in this indication. Advocacy groups supporting VHL patients have actively been following this appraisal now for a number of years and are growing increasing frustrated with the pace at which this appraisal has progressed.	Thank you for your comment. No action needed.
	VHL UK/Ireland	Belzutifan was approved for use in the USA by the FDA on 13 August 2021. VHL patients across the UK are seeing excellent results from America, with some tumours shrinking, and in some cases disappearing, due to belzutifan. Belzutifan is approved by the MHRA for treatment of adults with von Hippel-Lindau (VHL) disease who require therapy for associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumours (pNET), not requiring immediate surgery.Surgery is the current standard procedure for localized tumours with a risk of metastasis or organ dysfunction. Repeated surgeries cause substantial morbidity and have a major impact on quality of life. In respect of patients that have advanced or metastatic disease, who are not suitable for surgery, there are no treatments that are curative and so there is an urgent need for improved treatment options. This drug (belzutifan) may reduce/delay the need for multiple surgeries and other invasive procedures, such as ablation or nephrectomy. There will also be possible reductions in the number of patients requiring dialysis or becoming diabetic through PNETs, for example.	Thank you for your comment. No action needed.

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		Note 1: The most challenging cases of pNET surgeries cause, by erosion of pancreatic function, absolute insulin deficiency. This is actually more challenging than 'conventional' type 1 diabetes because of the absence of glucagon. In addition, they need lifelong pancreatic enzyme supplement to replace pancreatic digestive action. Note 2: There are some RCCs that are very unfavourable anatomically for cryoablation (minimally invasive) therapy. In order to preserve kidney function, there are selected patients whose progression to end-stage renal failure can be prevented by the use of belzutifan.	
	Action Kidney Cancer	High urgency because of the unmet need for a treatment for VHL-associated RCC.	Thank you for your comment. No action needed.
	Genetic Alliance UK	This treatment is considered as a significant step-change in the management of VHL as it has the potential to benefit patients by reducing or preventing the need for multiple surgeries or other invasive procedures. Therefore, it should be appraised quickly to benefit as many patients as possible.	Thank you for your comment. No action needed.

Comment 2: the draft scope

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Additional comments on the draft remit	Merck Sharp & Dohme	Given the confusion that has already taken place regarding this appraisal we request that the full marketing indication is re-quoted: Belzutifan for the treatment of adult patients with 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	Thank you for your comment. The draft remit wording refers to the marketing authorisation, but does not state it. The technology section has

Section	Consultee/ Commentator	Comments [sic]	Action
		We note that nowhere in the scoping document is the MA indication correctly stated. This indication is final and was published in May 2022. We draw attention to three aspects of the indication wording. Belzutifan should be used only in people: 1) Who require treatment 2) Who have one of the three primary tumours RCC, CNS or pNET. MSD has interpreted this wording to mean belzutifan can be used in patients with a tumour in any one of these primary sites, or in more than one of these primary tumour sites, or in patients with multi-system tumours, so long as one of them is RCC, pNET, or CNS. 3) In whom localised procedures are not suitable or not desirable. The company proposes that the way to consider this clause is: if a localised procedure can successfully be used, it should be. Belzutifan should be retained for patients in whom localised procedures cannot be successfully used	been updated to quote the marketing authorisation directly.
Background information	Merck Sharp & Dohme	With regard to the first two sentences of the draft background that states VHL disease "affects about 1 in 35,000 people", it should be explicitly stated whether this is an incidence or prevalence value, and whether it refers to presence of the genetic mutation, identification of tumours, presentation of tumours that need an intervention, or presentation of tumours that need an intervention but where local procedures are not suitable/not desirable (i.e. the population covered by this indication).The source of this estimate should also be provided. This is important so that readers do not mistakenly interpret this as implying that there is published evidence that VHL is a disease that has a prevalence in England of about 1 in 35,000. A definitive national audit of VHL disease in the UK published earlier this year estimated that the prevalence of VHL disease in the UK is likely to be between 1 in 77,340 to 1 in 68,493 (https://doi.org/10.1038/s41416-022-01724-7).	Thank you for your comment. The background section gives a broad overview to the condition in general. It has been updated to more closely reflect the nature of VHL disease.

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		The booklet from University Hospital Southampton referenced in the draft scope is not a primary data source and does not provide a reference for this epidemiological estimate. We request that this reference is not used in the scope. A patient booklet has a very specific function which balances informing and reassuring someone who is often a newly diagnosed patient. Unfortunately for some patients, VHL is a terrible experience that would not be described in stark detail to a newly diagnosed patient. We request a clarifying sentence in the first paragraph of the Background section: *Multiple tumours can present in the same or different systems/organs at the same time.* This unfortunate feature of VHL disease is a key detail to help understand the current burden of disease. The following statement included in this section should be removed: *If tumours are detected early and treated before they grow to a size of approximately 3 cm, in nearly every case the tumour will not come back or spread anywhere else in the body.* This statement is factually inaccurate. For some patients, many tumours will recur in the same or different organs or blood vessels over time following resection. In addition, the patient that can feasibly have their tumour burden	

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		relieved using a single procedure is not covered by the marketing authorisation for belzutifan and therefore the case described in the above statement focuses on the wrong patient type and should therefore be removed. MSD also do not agree with the statement below: *'Most [CNS] tumours can be removed with surgery; however, this may be deferred depending on symptoms'.* The above statement lacks the required nuance to explain the situation in which some patients have inoperable CNS tumours, or that they have operable tumours that would result in catastrophic injury if operated on. For CNS hemangioblastoma, belzutifan should only be used to treat patients whose CNS hemangioblastoma cannot be treated with surgery. Elsewhere in this section of the draft scope it is stated for patients with VHL-associated pNETs that *"Larger tumours can usually be removed successfully by surgery".* We request the word 'successfully' be removed from this sentence. In cases of surgical removal of pNETs, there are often severe adverse effects associated with surgery. Pancreatectomy can result in loss of pancreatic function that will effectively result in full Type 1 diabetes mellitus and such patients will consequently require lifelong insulin therapy and/or pancreatic enzyme replacement therapy. Pancreatectomy may require a splenectomy, and the loss of the spleen in such patients compromises the immune system to such an extent that they must take long-term prophylactic antibiotics to	

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		mitigate the increased risk of severe pneumococcal infection. These surgical interventions cannot be considered “successful” given these severe and permanent impact on patients’ quality of life. It would be inappropriate to omit these relevant nuances when describing these surgeries in the context of the draft scope and appraisal. It is important to stress that this indication is in patients for whom localised procedures are unsuitable or undesirable, as explicitly stated in the marketing authorisation, and so patients who can receive any sort of successful surgical procedure are not ones relevant to this indication. We request the key objective of care for VHL patients is added to the Background information section: *The primary objective of VHL treatment is the careful balance of preserving organ function and preventing tumour metastasis.* We request the sentences in bold are added to scope: *With regular screening, most tumours associated with VHL are detected at an early stage.* ***However, for some patients, tumours cannot be managed by locallised procedures and it becomes very difficult to preserve organ function and prevent the cancer advancing. This is where the marketing authorisation indicates belzutifan should be used.*** The following sentence should be amended in the scope:	

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		For people in whom preventative treatment options fail and they develop *advanced or metastatic tumours, systemic treatments are similar to those used to treat patients with cancers unrelated to VHL.* It would be useful to include in the Background section information on when standard clinical practice in the UK would be to resect the tumour using a localised procedure, namely: • In VHL-associated RCC, this is usually triggered when the tumour reaches 3 cm in diameter. • In VHL-associated pNET, this is usually when the tumour reaches 2 cm in diameter, is continuing to grow and is likely to metastasise despite treatment with somatostatin analogues (therefore somatostatin analogues are given at a stage earlier than the intended position of belzutifan in the treatment pathway and so are not relevant comparators to belzutifan in this indication). • In VHL-associated CNS hemangioblastoma, this is usually when the tumour has grown to a size where it is causing symptomatic disease.	
	VHL UK/Ireland	Under “Background”, “Tumours develop” should read “Multiple tumours develop”. Para 2: “in nearly every case the tumour will not come back or spread anywhere else in the body”. VHL disease is such that, although the same primary tumour may not come back, another one or more primary tumours will arise, requiring further surgeries. These tumours could grow in the same location as previous tumours.	Thank you for your comment. The background section gives a broad overview to the condition in general. It has been updated to more closely reflect the nature of VHL disease.

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		The individual descriptions of each type of tumour do not state that tumours will return in VHL patients, unless, as a last resort, the organ has been removed. It should also be noted that many VHL patients will suffer from tumours in several organs of the body at the same time throughout their lives. For example, a minority of patients could have multiple tumours including: - haemangioblastomas at the cranio-cervical junction that have grown to such a size that the patient is getting compressive symptoms – surgery is hazardous and can result in death. (similarly for patients with brainstem haemangioblastomas and treatment of multiple spinal hemangioblastomas is challenging and associated with risk of paraplegia). - tumours of the kidney whose removal will 'tip the balance' into renal failure. - pNETs whose surgery will condemn them to insulin-requiring diabetes with no glucagon and therefore very difficult diabetes control and the risk of death from hypoglycaemia. Patients like this would be good examples of someone having a major benefit from belzutifan availability. It would greatly improve their chances of avoiding disability or death.	
	Action Kidney Cancer	Belzutifan is the only drug that has been proven effective against VHL RCC tumours and is therefore a revolutionary treatment for these patients. VHL is an inherited condition where 80% of cases are inherited from a parent who has VHL syndrome. VHL affects people of all ages. The psychological impact of having multiple tumours needs to be considered, even for those patients with benign tumours. This also has major implications for young women of reproductive age wanting a family.	Thank you for your comment. No action needed.

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		Systemic treatments for RCC recommended by NICE include immunotherapies such as nivolumab, ipilimumab, pembrolizumab and avelumab; vascular endothelial growth factor (VEGF) tyrosine kinase inhibitors such as cabozantinib, axitinib, pazopanib, lenvatinib and sunitinib; and mammalian target of rapamycin (mTOR) inhibitors, such as everolimus.	
	Genetic Alliance UK	The severity of the condition has not been accurately captured in the background information. Individuals affected by VHL develop multiple tumours throughout their lives, repeatedly. Although the exact same tumour may not arise again, other primary tumours will grow and may be in the same location, unless the organ is removed entirely. Individuals often experience multiple tumours in several organs at one time, leading to compounding health issues that significantly impact quality of life. Undergoing multiple surgeries or other invasive procedures to remove tumours takes a physical and emotional toll on the individual and families and carers. Management for the condition may mean individuals spend significant periods of time travelling to and from hospitals, therefore negatively impacting their employment and/or education.	Thank you for your comment. The background section gives a broad overview to the condition in general. It has been updated to more closely reflect the nature of VHL disease.
The technology/intervention	Merck Sharp & Dohme	Please replace the description of the technology with the actual marketing authorisation wording. The current phrasing is ambiguous and, given the complexity of this disease, it is important to be as consistent with wording and terminology as possible.	Thank you for your comment. The description of the technology has been updated to reflect the marketing authorisation for belzutifan.

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	VHL UK/Ireland	Belzutifan (MK-6482) is a new type of medicine called a “hypoxia-inducible factor 2α (HIF-2α) inhibitor”. VHL tumours frequently have mutations in a gene called the von Hippel-Lindau (VHL) gene, resulting in high levels of a protein called hypoxia-inducible factor, or HIF-2α. This results in a number of changes in the cancer cells and their surrounding environment that favour tumour growth. Belzutifan (MK-6482) blocks the action of HIF-2α.	Thank you for your comment. No action needed.
	Action Kidney Cancer	There is no description of the technology being appraised and how it works. A protein called hypoxia-inducible factor, or HIF-2α, is found in the blood of people with VHL disease. This causes changes in cells resulting in the growth of tumours, some of which are malignant. Belzutifan is a new medicine, called a hypoxia-inducible factor 2α (HIF-2α) inhibitor, which blocks the action of HIF-2α.	Thank you for your comment. No action needed.
Population	Merck Sharp & Dohme	The population is not accurately described. Please use the marketing authorisation wording for this indication, noting in particular: 1. Patients who require treatment. 2. The three primary tumours included in the marketing authorisation. 3. Patients for whom localised procedures are not suitable or desirable. The population stated in the draft scope is “Adults with untreated renal cell carcinoma, central nervous system hemangioblastomas, or pancreatic neuroendocrine tumours caused by von Hippel-Lindau disease” whereas the marketing authorisation for belzutifan in this indication is “for the treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for VHL associated renal cell carcinoma (RCC), central nervous system (CNS)	Thank you for your comment. The population has been updated to reflect the marketing authorisation for belzutifan.

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		hemangioblastomas, or pancreatic neuroendocrine tumours (pNET), and for whom localised procedures are unsuitable or undesirable". The belzutifan marketing authorisation does not specify that the intervention is licenced only in patients whose tumours are "untreated" (patients eligible for treatment with belzutifan in fact are likely to have had multiple previous treatments [i.e. surgeries] prior to initiating treatment with belzutifan). We request this erroneous word be removed from the draft scope. We note the use of the word *untreated*, probably miscategorises VHL as a 'typical cancer'. The cancer paradigm does not work for this disease. While VHL is a very rare disease, it is also a highly heterogeneous disease. Belzutifan's indication wording covers patients with one of three primary tumours. Patients can have multiple tumours in the same or different organs or blood vessels, as long as one of the primary tumours is covered. Patients with complex multi-system tumours may have the worst quality of life and hardest to manage disease. Therefore, while the MSD submission will cover the full indication wording, we expect to discuss subgroups of patients according to their primary tumour site: RCC, pNET, and CNS hemangioblastomas and patients with multi-system tumours.	
	VHL UK/Ireland	We believe that the patient population has been appropriately defined, however we consider that there would be sub-sets of patients with complex conditions that will be selected by their medical teams as appropriate for belzutifan therapy.	Thank you for your comment. No action required.

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	Action Kidney Cancer	The population is defined appropriately.	Thank you for your comment. No action needed.
Comparators	Merck Sharp & Dohme	The comparator to belzutifan in this indication is current management with the standard of care (SoC) without belzutifan. SoC for patients at the point in which belzutifan is indicated is no satisfactory treatment option. Clinicians caring for a patient in this situation endeavour to treat that patient as well as they can. This might include high-risk procedures that are not desirable and/or that are known to have very serious sequelae. Active surveillance is not a suitable comparator as patients for whom active surveillance is an appropriate form of disease management do not 'require treatment'. Patients who are suitable for surgery should have surgery instead of belzutifan. Surgery is an effective option for such patients and belzutifan should not be considered as a treatment option for them. Belzutifan should be considered when surgery cannot be used to control tumour growth. Patients with VHL disease who require therapy for VHL associated RCC, CNS hemangioblastomas, or pNET fall into two categories: • Surgery suitable/desirable – They should undergo active surveillance, then surgery and not receive belzutifan. This set of treatment options	Thank you for your comment. The comparators for belzutifan remain unchanged at this stage. Stakeholders can provide justification around the most appropriate comparators and the committee will consider this during the appraisal.

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		are not comparators to belzutifan i.e., belzutifan will not displace these interventions. • Surgery unsuitable/undesirable - Surgery is not viable as an effective treatment option, therefore treatment with belzutifan should be considered. The current alternative to belzutifan in routine clinical practice in the UK at this stage for these patients is a complex mix of interventions. As this SoC is a sequence of interventions administered when patients' tumours are ineligible/unsuitable for surgery, or progress following each of the various interventions used to manage symptoms, there is not a single treatment strategy (for the entire population or for any tumour site-defined subgroup considered separately) that can appropriately be described as the "best alternative care". The treatment aim of all modalities of current management is to preserve organ function and prevent tumours becoming advanced or metastatic, while maintaining patient quality of life. For patients whose VHL disease-associated RCC, CNS hemangioblastoma, or pNET has grown to an extent where localised procedures would be used in current SoC, available localised procedures may no longer be suitable nor desirable due to an elevated risk of important loss of organ function, adverse effects of the procedure, or anything else that will lead to the patient not being able to live anything like a normal healthy life after the procedure. The circumstances that would make localised procedures unsuitable or undesirable for the tumour(s) in question, or the patient as a whole, are manifold and include (but are not limited to):	

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		• In VHL-associated RCC, when the localised procedure would render the patient renal replacement therapy-dependent. • In VHL-associated pNET, when the localised procedure would lead to loss of pancreatic and splenic function leading to lifelong type 1 diabetes mellitus and being immune-compromised such that the patient will require lifelong insulin therapy, antibiotic therapy and/or pancreatic enzyme insufficiency impacting digestion. • In VHL-associated CNS hemangioblastoma, when the localised procedure would lead to severe neurological or neuromuscular deficits equating to severe permanent disability (this most often arises with tumours located in for example the brainstem where they are difficult to access or operate on without damaging important nearby tissues, potentially leading to significant morbidity and death). In current clinical practice and SoC without belzutifan, for patients with VHL RCC or pNETs for whom localised procedures are unsuitable or undesirable, the interventions they may receive may still include localised procedures. However, instead of preserving organ function and allowing a patient to live a normal healthy life after the procedure, the localised procedures are ones that would (as described above) not be able to preserve organ function, and so result in sequelae that lead to the patients no longer being able to live a normal healthy life. In current UK clinical practice, patients undergo these non-organ-preserving procedures as they are the only treatment option available to keep patients alive, or prevent symptomatic disease progressing to the point where the severe sequelae of such procedures are on-balance preferable, or prevent the patient developing advanced or metastatic disease. • For RCC tumours, the localised procedures that are no longer capable of preserving organ function are radical (i.e. full) nephrectomies.	

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		• For pNETs, such localised procedures that are no longer capable of preserving organ function are Whipple procedures/ pancreatectomies and splenectomies (A Whipple surgery involves removal of the head of the pancreas, a part of the duodenum, some of the bile duct and the gall bladder. The stomach, bile duct and remainder of the pancreas will then be rejoined to the small bowel. The operation usually takes 4-6 hours. Long-term effects of this procedure include but are not limited to diabetes, pancreatic insufficiency, and change in bowel habit). In routine clinical practice in the UK, in such patients there may be an interval between the time when the relevant tumour(s) have reached the threshold necessitating treatment with a localised procedure and the time of the procedure itself. In this interval patients receive symptom management, this should not be confused with active surveillance or watchful waiting. There are also some patients, whose tumours have grown to the aforementioned extent and for whom localised procedures are unsuitable or undesirable, for whom effective localised procedures are practically not possible (regardless of whether these are surgeries that are organ function-preserving/organ-sparing [such patients are not the intended treatment population for belzutifan anyway] or are surgeries that are not organ function-preserving nor organ-sparing [such as radical nephrectomies, pancreatectomies and splenectomies]), due to the relevant tumours being inaccessible when using available surgical techniques, or the risk of death associated with the procedure for the patients in question being too high to countenance.	

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		In patients who have reached this stage of disease but who cannot undergo/survive any form of effective surgical procedure (potentially due to characteristics of the patient such as frailty etc. instead of, or in addition to, characteristics of the tumour), their treatment in current UK clinical practice without belzutifan consists only of symptom management and preservation of life functions until their tumours/disease have progressed to the point where first-line systemic anti-cancer therapies (SACT) for unresectable or advanced cancer are used. This stage of disease is downstream of the position of belzutifan in the treatment pathway i.e., where patients can end up if treatment with belzutifan or current management fails, and so such SACT are not relevant comparators to belzutifan. The SACT which are not relevant comparators to belzutifan in this indication include monotherapy or combination therapy with immunotherapies or kinase inhibitors for RCC, ablative therapies (i.e. cryotherapy) for RCC, radiotherapy for CNS hemangioblastomas, and monotherapy with lutetium (177Lu) oxodotreotide or combination therapy with everolimus and sunitinib for pNETs.	
	VHL UK/Ireland	This new drug is novel and could be used as an alternative first line therapy for selected patients to treat VHL tumours in that it specifically targets HIF-2α. RCC - We believe that it should state that these procedures are likely to be repeated throughout a patient's lifetime, often on both kidneys. It should be noted that each surgery can have the effect of reducing kidney function or causing renal failure. Central Nervous System (CNS) – as above. If belzutifan can be used on selected patients to shrink haemangioblastomas, this will alleviate symptoms and reduce the need for multiple, complex and risky neurosurgeries.	Thank you for your comment. No action needed.

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		Pancreatic Tumours (PNETs) – please refer to the paragraph above.	
	Action Kidney Cancer	Instead of 'kinase inhibitors', use VEGF tyrosine kinase inhibitors.	Thank you for your comment. No action needed.
Outcomes	Merck Sharp & Dohme	While the outcome of overall survival is an important health related benefit, it was not a designated predefined outcome in the MK-6482-004 trial that provides the clinical evidence to support the efficacy of belzutifan in this appraisal. All other outcomes listed in the draft scope are appropriate.	Thank you for your comment. No action needed.
	VHL UK/Ireland	We agree with the listed outcomes on the scope	Thank you for your comment. No action needed.
	Action Kidney Cancer	Add identification of a prognostic/predictive biomarkers and duration of response. Add genetic analysis of the tumours of VHL patients. We are pleased to see overall survival at the top of the list. We are also pleased to see that quality of life is being considered.	Thank you for your comment. No action needed.
Economic analysis	VHL UK/Ireland	The economic analysis will be different for each individual patient.	Thank you for your comment. No action needed.
Equality	VHL UK/Ireland	VHL globally affects people of all backgrounds and ethnicities. Our organisation does not believe the scope and proposed remit need changing in this regard.	Thank you for your comment. No action needed.

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	Action Kidney Cancer	Ensure there is good representation of people from BAME cultures and deprived areas of England and Wales. Ensure equality of access to the clinical trial/drug treatment on the NHS/CDF regardless of where the patient lives.	Thank you for your comment. No action needed.
Other considerations	VHL UK/Ireland	Our organisation does not feel that there are any other considerations to be taken into account.	Thank you for your comment. No action needed.
Innovation	Merck Sharp & Dohme	Belzutifan is a novel, potent and selective inhibitor of HIF-2α. Research into VHL biology that led to the discovery of HIF-2α was awarded the Nobel Prize in Physiology or Medicine in 2019. MSD considers belzutifan to be innovative in its potential to make a significant and substantial impact on health-related benefits and improves the way that current need is met in a manner that constitutes a “step-change” in the management of adults with untreated clear-cell renal cell carcinoma caused by von Hippel-Lindau disease. Belzutifan in this indication was the first to be awarded an Innovation Passport by the Medicines and Healthcare products Regulatory Agency, National Institute for Health and Care Excellence and the Scottish Medicines Consortium under the UK Innovative Licensing and Access Pathway, reflects the innovative nature of this technology in this indication.	Thank you for your comment. No action needed.
	VHL UK/Ireland	Yes, we consider the technology (belzutifan) to be innovative in its potential to make a significant and substantial impact on health-related benefits for selected VHL patients. This is a unique, first in class medication specifically targeting VHL disease and it will provide a significant, ‘step-change’ in the management of the condition. We are unable to specifically comment on the QALY calculation (values). However, our organisation is of the opinion that health related quality of life	Thank you for your comment. No action needed.

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		over time will be substantially improved for selected VHL patients by belzutifan being made available, since (as noted above) repeated surgeries cause substantial morbidity and have a major impact on quality of life. Nature of the data available to the Appraisal Committee: Jonasch E et al. Belzutifan for Renal Cell Carcinoma in von Hippel-Lindau Disease. N Engl J Med 2021 Nov 25;385(22):2036-2046. doi: 10.1056/NEJMoa2103425.	
	Action Kidney Cancer	Yes, belzutifan is the first HIF-2α inhibitor to be approved for VHL-associated RCC and is considered an innovative treatment for all VHL patients.	Thank you for your comment. No action needed.
	Genetic Alliance UK	This treatment is seen as innovative as it has the potential to significantly improve the outcomes for people living with VHL as a first line treatment, rather than monitoring and removing tumours as they arise. This will likely delay or decrease the frequency of surgeries and will therefore significantly improve the quality of life for those affected.	Thank you for your comment. No action needed.
Questions for consultation	Merck Sharp & Dohme	**Question**: Where do you consider belzutifan will fit into the existing care pathway for VHL? **MSD response**: This question has been largely covered above in the response to the Comparators section (see that section for additional details). The place of belzutifan in the clinical pathway is therefore to give patients for whom localised procedures are unsuitable or undesirable (as described previously) an alternative to the localised procedures they would have to otherwise undergo. The objective of the treatment to prevent or reverse symptomatic disease progression and give these patients the opportunity to live a normal healthy life.	Thank you for your comment. Belzutifan has been routed for evaluation via NICE's STA process following consideration against its HST criteria. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		Below are illustrative cases of patients who could be treated with belzutifan in this indication, based on discussions with clinical experts who treat VHL in the UK: • A woman in her 30s with a large inoperable CNS hemangioblastoma who has previously had radiotherapy that was not effective. She has a family and is worried about how she will care for them, she has exhausted her options but is likely to go for an incredibly high-risk operation anyway. • A 32-year-old woman with a 2-year-old child. She has previously had one CNS hemangioblastoma, one pNET, and one RCC each treated with surgery. She now has another pNET on the remaining portion of her pancreas that exceeds 2 cm in size is still growing despite treatment with a somatostatin analogue, and surgery will result in her developing lifelong diabetes. If she does not undergo surgery, she will develop jaundice and metastases. **Question**: Would belzutifan be a candidate for managed access? **MSD response**: [redacted] **Question**: Do you consider that the use of belzutifan can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?	

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		Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. **MSD response**: The results from the MK-6482-004 study showed that efficacious effects of belzutifan in patients with VHL disease-associated retinal hemangioblastomas and pancreatic tumours (not just pNETs). While the marketing authorisation for belzutifan does not cover these tumours, the nature of VHL disease means that patients with VHL disease-associated RCC, CNS hemangioblastomas, and pNETs do often also have these tumours at the same time, and as belzutifan does have an effect on these tumours (as shown in the results of the MK-6482-004 study), then this constitutes a substantial health-related benefit not included in the QALY calculation. Additionally, reduction in inpatients days associated with treatment with belzutifan may have a positive impact on mental health, which, while widely remarked upon by patients with VHL disease, is hard to capture for QALY calculation. Similarly, this is also the case for the feelings of powerlessness that VHL patients feel as they wait for tumours to grow when localised procedures are unsuitable or undesirable. A reduction in anxiety knowing they were taking a daily oral treatment aimed at shrinking tumours would be eminently plausible but again, is hard to capture for QALY calculation. **Question**: NICE intends to evaluate this technology through its Single Technology Appraisal process. We welcome comments on the appropriateness of appraising this topic through this process. **MSD response:** As argued previously, MSD strongly believes that this technology should be evaluated through NICE's Highly Specialised Technology (HST) process, and strongly disagree with NICE's rationale for	

Section	Consultee/ Commentator	Comments [sic]	Action
		deciding that this indication does not meet each of NICE's HST eligibility criteria	

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope