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

For screen- redacted

Technology appraisal committee B [15 February 2024, 2nd evaluation meeting]

Chair: Charles Crawley

Lead Team: Tony Wootton, Stuart Williams, Warren Linley

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Technical team: Harsimran Sarpal, Adam Brooke, Richard Diaz

Company: MSD

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Belzutifan for treating tumours associated with Von Hippel-Lindau disease

Supplementary slides

- ❑ **ACM1 recap**
- ✓ Draft guidance recommendations
- ✓ Issues from ACM1 and committee's conclusions
- ❑ ACM2
- Consultation responses
- Company's expert elicitation
- Issue: population misalignment
- Issue: model outputs, time on treatment, treatment waning, HRQoL & severity
- Cancer Drugs Fund

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Abbreviations; HRQoL, health-related quality of life

Draft guidance (DG) recommendations

"Belzutifan is **not recommended**, within its marketing authorisation, for treatment of adults with VHL disease who require therapy for VHL associated RCC, CNS Hb, or pNET, and for whom localised procedures are unsuitable or undesirable"

Abbreviations: CNS Hb, central nervous system haemangioblastomas; pNET, pancreatic neuroendocrine tumour; RCC, renal cell carcinoma; VHL, Von Hippel Lindau

Issues from ACM1 and committee's key conclusions

Key uncertainties		EAG's view-resolved
Decision problem	Generalisability of MK-6482-004 population to the DP/marketing authorisation population uncertain	No
Clinical evidence	ITC approach and using the propensity-score weighting method were highly uncertain: explore alternative methods	No
Cost effectiveness	Model input parameters and assumptions lack face validity	No
	Modelled ToT for belzutifan until progression or until side effects	No
	Extensive sensitivity analyses and testing alternative assumptions on treatment waning effect across tumour types	No
	The company's approach to surgery-associated disutility values uncertain: explore of multiplicative approach and use validated disutility values against literature for similar outcomes	No

Abbreviations; DP, decision problem; HRQoL, health-related quality of life; ITC, indirect-treatment comparison; ToT, time on treatment

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Abbreviations; HRQoL, health-related quality of life

Response to draft guidance consultation

- Company
- Action Kidney Cancer
- UK Kidney Association
- VHL UK/Ireland
- 85 web comments

Overview of company's consultation response

Changes to company's assumptions from ACM1

- **Clarification to committee conclusions**
  - Conducted expert elicitation survey
  - Validation of model outcomes
- **Updated model**
  - Immediate surgery removed; implemented surgery at 4 months only in SoC arm
  - TTS for RCC cohort in SoC arm based on pre-treatment period of MK-6482-004 rather than VHL Natural History Study
  - Revised disutility for ESRD/dialysis (and erythroderma) and applied using a multiplicative approach
  - Cohort weighting based on clinical expert elicitation survey
- **Increased PAS**

Abbreviations: ESRD, end-stage renal disease; PAS, patient access scheme; RCC, renal cell carcinoma; SoC, standard of care; TTS, time to surgery; VHL, Von Hippel-Lindau

Consultation Responses 1/3

Action Kidney Cancer

- Inclusion within CDF would help resolve uncertainties and would allow access to belzutifan
- Belzutifan is an innovative new treatment for VHL disease, with a new mode of action which will negate the need for clinical visits for an infusion every 2-3, thus improving both patient's and carer's quality of life

UK Kidney Association

- Disagree with draft recommendation: belzutifan should be made available for people with VHL
- Consider trial size and inclusion criteria were sufficient for a rare condition
- Urges the committee to consider 2 points:
    - the significant reduction in operative procedures shown in study and
    - ethical challenges in conducting further studies when there is clear evidence of belzutifan effectiveness and safety

Abbreviations: CDF, Cancer Drugs Fund; HST, Highly specialised technology; RCC, renal cell carcinoma; SoC, standard of care; VHL, Von Hippel-Lindau

Consultation responses 2/3

VHL UK/Ireland

- The committee failed to understand the severity of experiencing multiple VHL symptoms over a life-time, leading to complex surgery decision
- Not enough emphasis placed on the quality-of-life improvement belzutifan offers to VHL patients addressing potential complications of dialysis, inclusion dependency, vision impairment and paralysis
- Raised a question about denying belzutifan for CDF and considering it as an opportunity to gather real-world evidence while providing access to people in need

Abbreviations: CDF, Cancer Drugs Fund; HST, highly specialised technology; VHL, Von Hippel Lindau

Consultation responses 3/3

Web comments

- Consequences and financial burdens of VHL on individuals, their family and carers are being greatly overlooked
- Feel disappointed and mentioned discrimination in draft recommendations against those with a rare disease when belzutifan is available in Scotland
- Frustration over lack of access to belzutifan in England and Wales despite its success elsewhere, highlighting the need for alternative options when surgery is not viable
- Comments highlighted the real unmet needs for non-surgical treatments, as surgery is the main treatment
- People highlighted that repeated surgeries from multiple tumours are associated with significant morbidity and accumulated disability with every surgery
- Belzutifan is a life-changing drug for VHL patients, will make a huge difference to current prognosis, prevent secondary illnesses, emotional distress and trauma

"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"

"Neurosurgeon has said he doesn't want to operate on tumour because of the position of the tumour"

"My extended family members may have to reduce working hours or give up to help us"

Abbreviations: VHL, Von Hippel-Lindau

NHS England submission

- “Belzutifan should continue until disease progression or unacceptable toxicity occurs”
- “According to the wording of the marketing authorisation: it should be when the patient and the clinician agree that localised procedures for whichever cancer are unsuitable or undesirable”
- “Without introducing any perverse incentives as to when the time at which treatment with belzutifan is initiated”
- “Commission the use of belzutifan in a pragmatic way which reflects the marketing authorisation and the diversity of the patient population”
- Example:
  - A person who discontinues the drug on account of disease progression… would not preclude re-treatment in future for cancer within the same or different organ
- “NHS England will not commission the use of intermittent elective treatment break to give patients ‘holidays’ from therapy”

Defining VHL treatment eligibility for RCC, pNET & CNS Hb

MA: 'Belzutifan is indicated for treatment of adults with VHL disease who require therapy for VHL associated RCC, CNS Hb, or pNET, and for whom localised procedures **are unsuitable or undesirable**'

	MK-6482-004	Post trial population
CNS		VHL disease-associated CNS tumours requiring surgery/ intervention
RCC	no RCC tumour greater than 3.0 cm that requires immediate surgical intervention*	RCC tumour >=3.0 cm and/or requiring surgical intervention
pNET		pNET tumour greater than 2cm in the head or 3cm in the tail, requiring surgical intervention

Comments from clinical expert elicitation

Multisystem involvement – complex multi-system involvement and significant CNS Hb presentation (synchronous)

Company proposed positioning

- "**inoperable (no chance of success)"** – otherwise resulting in neurological complications and death
- "**precipice of organ failure**" – otherwise resulting in full bilateral nephrectomy, end stage renal disease and dialysis
- "**precipice of organ failure**" – otherwise resulting in full pancreatectomy, brittle or Type 3c diabetes and complications

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* People may have VHL- associated tumours in other organs

See supplementary slide

Abbreviations: CNS Hb, central nervous system haemangioblastomas; MA, marketing authorisation; pNET, pancreatic neuroendocrine tumour; RCC, renal cell carcinoma; VHL, Von Hippel-Lindau

Multi-system VHL disease

Clinical expert comments:

- CNS Hb is highly influential & presentation is in around 70-80% of cases
- Multisystem driven by 80% CNS Hb, 15% RCC and 5% pNET: reasonable
- Out of 60 people with VHL, 2-3 would be eligible for belzutifan: people with a large comprehensive **craniocervical junction Hbs** that requires surgery where the risk of life-changing morbidity is high

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

Table: updated cohort weightage

Multi-system VHL disease: ≥2 organs affected with VHL-related tumours, CNS Hb involvement and/or on the precipice of organ failure

- CNS Hb: inoperable with no chance of successful treatment (neurological complications & death)
- RCC: people likely to lose their last organ (full bilateral nephrectomy, end-stage renal disease and dialysis)
- pNET: on the precipice of losing pancreas (full pancreatectomy, brittle or Type 3c diabetes and complications)

Krishnan et al 2006: reported surgical outcomes of 3 cases of large Hbs (4 × 3, 4 × 5 and 5 × 5 cm) at the craniocervical junction (compressing the brainstem)
Results: Follow-up 3 (1 case) and 4 years (2 cases) after surgery showed no relapse
Conclusion: Micro neurosurgical removal of large Hb at the craniocervical junction with limited preoperative embolization is advisable. Despite initial challenges, long-term outcomes appeared promising

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Please explain the criteria for multi-system VHL disease.
Please describe CNS HBs where the outcomes of surgery will be good and poor.

Abbreviations: CNS Hb, central nervous system haemangioblastomas; PICA, posterior inferior cerebellar artery; pNET, Pancreatic neuroendocrine tumour; RCC, renal cell carcinoma; VHL, Von Hippel-Lindau

Population misalignment b/w DP & MK-6482-004 (1/2)

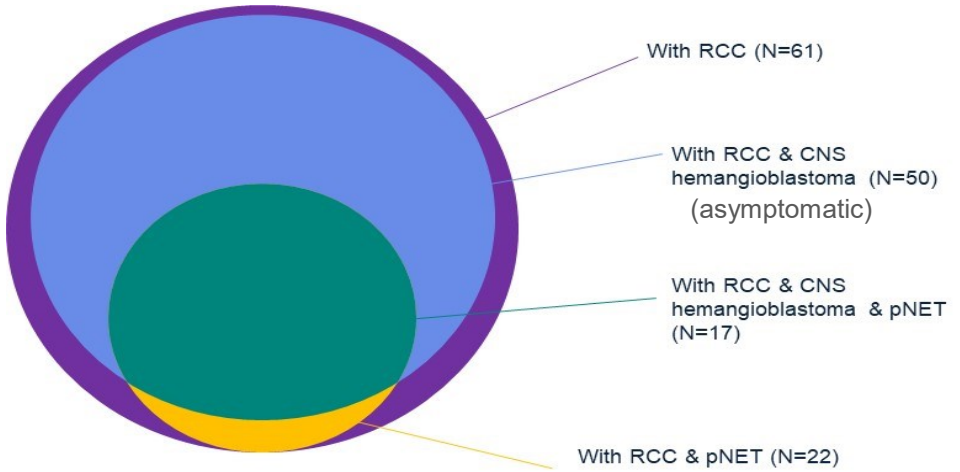
ACM 1:Generalisability of MK-6482-004 population to DP/ MA population uncertain

Company

- Clinical experts: only 3% would be eligible for belzutifan
- Clarified some people in MK-6482-004 had severe disease:
  - only 1 RCC but had left total nephrectomy, right partial nephrectomy, and distal pancreatectomy
  - 2 RCC tumours and 8 CNS Hbs (1 in brain stem)
  - 2 RCC tumours and 6 CNS Hbs; Whipple's procedure, partial nephrectomy, 2 craniectomies & spinal resection

EAG

- Company suggests belzutifan eligible people align with DP i.e., focus on multisystem and CNS Hb involvement and/ or people on the precipice of organ failure
- MK-6482-004 included people with at least 1 RCC tumour and other tumours while DP permitted any tumour combination
- Consider company narrowed its DP population to align with MK-6482-004 in terms of tumour distribution (80% of people have both CNS Hb and RCC tumours)
- Consider MK-6482-004 alignment with DP and applicability to belzutifan eligibility remain uncertain



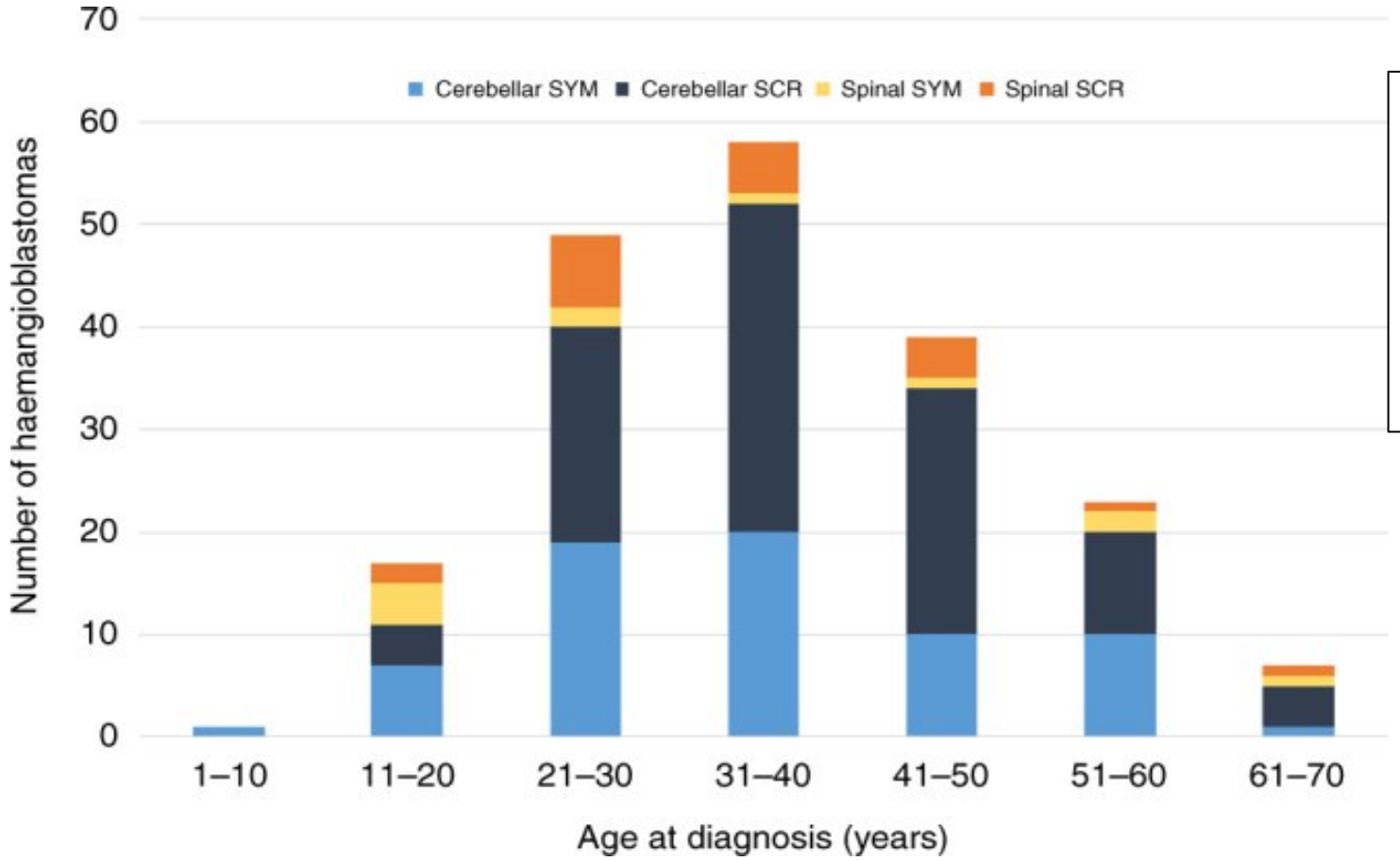
Tumour type, n (%)	No of tumours		
	1-2	3-4	≥5
RCC	42 (69%)	15 (25%)	4 (7%)
CNS Hb	17 (34%)	15 (30%)	18 (36%)
pNET	20 (90%)	2 (9%)	0 (0%)

Table: MK-6482-004 number of VHL tumours

Is the company's updated population aligned to DP/MA population?

Abbreviations: CNS Hb, central nervous system haemangioblastomas; DP, decision problem; IPD, individual patient data; MA, marketing authorisation; pNET, pancreatic neuroendocrine tumour; RCC, renal cell carcinoma; VHL, Von Hippel-Lindau

Age and Distribution of CNS Hbs



National audit of VHL disease in UK (Maher et al 2022), n= 183

Location of CNS Hbs= 217 tumour

- cerebellum: 82% (176)
- spine: 16% (35 tumours)
- brain stem: 2% (4 tumours)

What proportion of people with VHL tumours will be eligible for belzutifan?
For which group of people with CNS Hbs surgery would be undesirable?

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Abbreviations: CNS Hb, central nervous system haemangioblastomas; SCR, Screening; SYM; symptomatic; VHL, Von Hippel-Lindau

Clinical expert elicitation survey

9 experts*
Answered survey

Endocrinologist 2; Neurosurgeon 2; Urologist/ Oncologists 1; Consultant geneticists 4

Developed

Survey designed by MSD asked 3 questions

Validation

Responses validated by 2 experts

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

Small subset of VHL patients, on brink of organ failure/loss and unable to undergo further surgical or local interventions

Experts agreed that they will use belzutifan for people with CNS Hb and multi-systemic VHL, citing declining risk/benefit ratio and inability to undergo multiple interventions

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?

Experts identified multi-systemic disease VHL patients as a distinct group, alongside CNS Hb, pNET & RCC

Many considered CNS Hb the primary tumour due to its significant impact on disability and QoL

Breakdown: multi-systemic:40-50%, CNS Hb:40-50%; RCC: 5%, retinal Hbs: 5%

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?

RCC; metastatic disease or dialysis /renal replacement therapy and death within 5 years

pNET; brittle or type 3c diabetes, risk of infections and intense follow-up

Quality of life deteriorates and the need for increasingly risky surgery. Will have progressive motor decline, needing care with daily living and eventually death. Develop multisystem disease involving CNS, eyes, pancreas and kidneys

Abbreviations: CNS Hb, central nervous system haemangioblastomas; pNET, Pancreatic neuroendocrine tumour; RCC, renal cell carcinoma; VHL, Von Hippel-Lindau

EAG comments on clinical expert elicitation

- The survey method lacked clarity in several aspects:
  - how experts were approached
  - interview format and method used for aggregating responses
- Mismatches were found when comparing individual responses, validation by two experts and model validation by one expert
- Possibility of two cohorts was mentioned: those on the brink of organ failure and those with multi-systemic VHL disease
- Noted inconsistencies in survey structure, and protocol: raising doubts about the consistency and reliability of reported outcomes
- Suggested Delphi methods or the Sheffield Elicitation Framework (SHELF) for transparency

NICE manual section 3.3.21
"Structured methods are preferred because they attempt to minimise biases and provide some indication of the uncertainty."

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Is the committee satisfied with the company's expert elicitation survey?

Abbreviations: VHL, Von Hippel-Lindau

Establishing relative treatment effect 1/2

ACM 1: ITC approach and using propensity-score weighting method were highly uncertain, with alternative methods explored

Company

- No additional ITC using STC method would have addressed the committee's uncertainties because underlying data to inform an STC-based ITC would be same as that of MAIC-based ITC in original submission
- Removed immediate surgery assumption and implemented a 4-month delay to surgery in SoC arm
- Clarified that the company's model starts at treatment decision point, addressing concerns about the exclusion of people requiring immediate surgery in MK-6482-004

EAG

- 4-month delay to surgery only applied to SoC; most people in SoC will receive surgery (90% for RCC and pNET, and 100% for CNS Hb): but has a minor impact on results
- Reiterated difference between intervention and comparator populations still exist: a 4 month delay should also be applied to the belzutifan arm because:
  - belzutifan may be effective for some people but not all people with VHL disease
  - surgery timing for belzutifan should match the SoC i.e., surgery for non-responsive belzutifan people after 4 months
- Consider the proportion of these people could be large as median TTR varies across VHL cohorts

Abbreviations CNS Hb, central nervous system haemangioblastomas; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; pNET, pancreatic neuroendocrine tumour; RCC, renal cell carcinoma; standard of care; STC, simulated treatment comparison; TTR, time to response; VHL, Von Hippel-Lindau

Establishing relative treatment effect 2/2

Table: Results MK-6482-004

Outcome	Results		
	RCC	CNS Hb	pNET
Primary outcome			
Overall response rate (95% CI)	63.9% (50.6%, 75.8%)	44.0% (30.0%, 58.7%)	90.9% (70.8%, 98.9%)
Secondary outcomes			
Time to response (median) Months (95% CI)	11.1 (2.7 to 30.5)	[redacted]	[redacted]

EAG

- Markov traces show low surgery rates in belzutifan arm based on MK-6482-004 while people in SoC arm undergo surgery, affecting subsequent cycles
- Provided hypothetical scenarios analyses:
  - based on median TTR assuming 50% of people in pre-surgery health state at cycle 16 in belzutifan arm of the model would receive last resort surgery at 4 months
  - removing last-resort surgery from the model in both arms

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Is it appropriate to assume a 4-month delay in surgery only in SoC arm not for belzutifan arm?

Abbreviations CNS Hb, Central nervous system haemangioblastomas; CI: confidence intervals; DP, decision problem; pNET, pancreatic neuroendocrine tumour; RCC, renal cell carcinoma; VHL, Von Hippel Lindau; SoC, standard of care

Modelled output: life years accrual for belzutifan vs. SoC (CNS Hb)

Time spent in each modelled health state and QALYs generated

Belzutifan

SoC

Table: Quality-adjusted life years – undiscounted

Technology	Pre-surgery	Event-free after surgery	Metastatic disease	Disutility: primary tumour	Disutility: secondary tumours	Total
Belzutifan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviation: Central nervous system haemangioblastomas; VHL, Von Hippel Lindau; SoC, standard of care

Are the model outputs plausible?
Is it plausible that net benefit of surgery would be indicated by these figures?

Modelled output: life-years accrual for belzutifan vs SoC (RCC)

Time spent in each modelled health state and QALYs generated

Belzutifan

SoC

Table: Quality-adjusted life years – undiscounted

Technology	Pre-surgery	Event-free after surgery	Metastatic disease	Disutility: primary tumour	Disutility: secondary tumours	Total
Belzutifan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviation:; RCC, renal cell carcinoma; VHL, Von Hippel Lindau; SoC, standard of care

Are the model outputs plausible?
Is it plausible that net benefit of surgery would be indicated by these figures?

Modelled output: life years accrual for Belzutifan vs. SoC (pNET)

Time spent in each modelled health state and QALYs generated

Belzutifan

SoC

Table: Quality-adjusted life years – undiscounted ACM2

Technology	Pre-surgery	Event-free after surgery	Metastatic disease	Disutility: primary tumour	Disutility: secondary tumours	Total
Belzutifan	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: pNET, Pancreatic neuroendocrine tumour; VHL, Von Hippel Lindau; SoC, standard of care

Are the model outputs plausible?
Is it plausible that net benefit of surgery would be indicated by these figures?

Time on treatment

ACM 1: Modelling using belzutifan continued until progression or until side effects

Company

- VHL disease does not follow the typical link between treatment and progression found in most cancers
- In VHL, progression in non-linear and surgical outcomes have a greater impact than metastases
- Modelled ToT based on PFS: but consider not appropriate and modelling ToT until side was not feasible in time provided

[redacted]

EAG

- Modelling ToT based on patient-level/ PFS survival has minimal impact on results but choice of parametric distribution has
- Gompertz results in no patients on belzutifan after [redacted] years and [redacted] years while Weibull suggest [redacted] years and [redacted] years for ToT data and PFS data respectively
- EAG raises the question of the plausibility of long-term belzutifan administration, noting potential increases in ICERs

[redacted]

NICE technical team

- Modelling ToT using PFS does not answer the committee's concerns because ToT from MK-6482-004 was not reflective of DP/MA population

Which approach does the committee think more appropriate?

Abbreviations: PFS, progression-free survival; ICER, incremental cost-effectiveness ratio; ToT, time on treatment; VHL, Von Hippel Lindau;

Derivation and implementation of HRQoL

Baseline utility health states
(derived from VHL HRQoL study)

Health state	Belzutifan	SoC
RCC	0.762	0.728
CNS Hb	0.751	0.695
pNET	0.790	0.728

Apply long-term disutility values – applied using multiplicative values

Complication	Percentage of cohort applied	Disutility
Chronic pain	30.8%	-0.195
Cerebral vasculature occlusion or stroke	85.0%	-0.37
Seizure	20.5%	-0.27
Neurological complications	87.2%	-0.27

Example in CNS Hbs

Example: utility values

Complication	Utility value	Source
Dialysis	0.5-0.7	Cooper et al 2020
Total pancreatectomy	0.872	Casadei et al 2016

Apply short-term complications related to surgery (applied for 4 weeks, up to 3 surgeries per patient) – minimal impact on disutility values

Estimated effective utility values in company base case SoC (QALY/LYG over the time horizon)- undiscounted

Health state	SoC
RCC	[redacted]
CNS Hb	[redacted]
pNET	[redacted]

Is the company's approach to modelling HRQoL appropriate?

Abbreviations: CNS Hb, central nervous system haemangioblastoma; HRQoL, health-related quality of life: LYG; life years gained; pNET, pancreatic neuroendocrine tumour; QALY, quality-adjusted life year; RCC, renal cell carcinoma; VHL, Von Hippel Lindau; SoC, standard of care

Severity modifier – calculation and application

ACM 1: unable to apply severity due to uncertainty in underlying assumptions

Company

- Request the committee to view belzutifan through a rare disease lens
- Despite potentially lower QALY weight, due severity of VHL disease and challenges in capturing its full impact; justifies the highest severity modifier (1.7)

Cohort	Expected total QALYs (general population)	Total expected QALYs with VHL(SoC)	QALY shortfall		QALY weight
			Absolute	Proportional	
RCC	18.15	[redacted]	[redacted]	[redacted]	1.2
CNS Hb	18.15	[redacted]	[redacted]	[redacted]	1.2
pNET	18.15	[redacted]	[redacted]	[redacted]	1.2

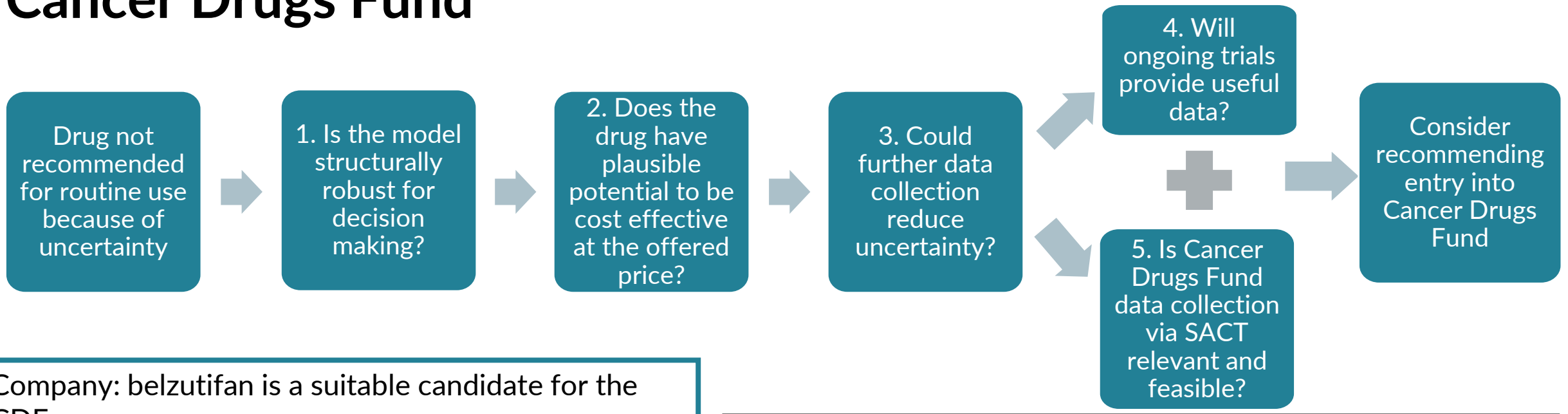
EAG

- Agreed with the company's updated severity modifier calculations of 1.2
- Consider numerous uncertainties are still present in current cost-effectiveness analyses
- Reducing the ICER does not eliminate or make the uncertainties irrelevant

What is the appropriate severity modifier for belzutifan?

Abbreviations CNS Hb, Central nervous system haemangioblastomas; pNET, pancreatic neuroendocrine tumour; QALY, quality adjusted life years; RCC, renal cell carcinoma; VHL, Von Hippel Lindau; SoC, standard of care

Cancer Drugs Fund



Company: belzutifan is a suitable candidate for the CDF

- Proposed 5-year managed access period and commit to:
  - conduct real-world studies to address any remaining gaps in SoC arm
  - collect baseline characteristics, duration of treatment, long term effectiveness and safety & outcomes (i.e. rate of surgery, rate of metastasis, etc in MHRA licensed population

EAG

- 3% of people with VHL would be eligible for belzutifan which equates to 39 to 19 eligible using EMA and Maher estimates
- Suggests validating the prevalent population eligible for belzutifan each year within the Cancer Drugs Fund
- Questioned whether HRQoL data be added to clinical outcomes as these data will used to inform the model

Is belzutifan a candidate for CDF?

Abbreviations: CDF, Cancer Drugs Fund; HRQoL, health related quality of life; MA, marketing authorisation; SACT, Systemic Anti-Cancer Therapy; SoC, standard of Care

Cancer Drugs Fund

ACM 1: Belzutifan did not meet the criteria to be considered for inclusion in the Cancer Drugs Fund

Key uncertainty	Can CDF data collection help reduce uncertainty?
Patient selection and interpretation of marketing authorisation	• Baseline characteristics of prevalent population, surgical history may not be comprehensive but potential for review of MDT notes of new entrants • Prevalent population (3% estimate) equates to 39 to 19 patients. Unclear if there would be different rate of incident population
Clinical effectiveness outcomes	• Up to 5 years of response rates, overall survival, rate of surgery (not currently collected comprehensively in SACT) • No relative efficacy
Duration of treatment	• Discontinuation and reasons for discontinuation collected in SACT
Natural history of VHL	• Company suggests RWE study, not relevant for CDF consideration
Utility and severity of disease	• Linked to Natural History, not relevant for CDF consideration

What is the committee's view on belzutifan's suitability for the CDF?

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Abbreviations: CDF, Cancer Drugs Fund; MA, marketing authorisation; RWE, real world evidence; SACT, Systemic Anti-Cancer Therapy; SoC, standard of Care

Other considerations

Equality considerations

- Stakeholders noted that belzutifan is already available in Scotland and people in England and Wales do not have access to belzutifan constitute a source of inequality
- Stakeholders identified people from deprived areas, with language, learning or cultural barriers, or those with disabilities may be at a disadvantage

Innovation

- Belzutifan is a first-in-class treatment that works via a novel mechanism of action (inhibition of hypoxia-inducible factor alpha [HIF-2α])

Are there any further equality considerations not previously discussed?

Questions for clinical experts

- What proportion of people with VHL CNS Hbs tumours will be eligible for belzutifan? See slide
- What proportion of people with VHL tumours will be eligible for belzutifan?
- For which group of people with CNS Hbs surgery would be undesirable? See slide
- Please explain the criteria for multi-system VHL disease. See slide
- Please explain the nature of CNS Hb surgery and associated outcomes. See slide
- Is the company's updated population relevant to the DP/MA population? See slides

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Abbreviations:CNS Hb, central nervous system haemangioblastomas; DP, decision problem; MA, marketing authorisation; SoC, standard of care; VHL, Von Hippel Lindau

Cost-effectiveness results

All ICERs are reported in PART 2 slides

- Company base case
- EAG was unable to define the base case due to uncertainties

Committee decision making slide

Assumption	Question for committee
Population misalignment	Is the company's updated population relevant to the DP/MA population? See slides (12-14)
Company's ITC	Is the company's updated approach to ITC using pre-treatment MK-6482-004 data appropriate? Is assuming a 4-month delay for only the SoC arm appropriate? See slide (18)
Model outputs	How plausible are the model outputs? See slides (20-22)
Health related quality of life	Are the utilities modelled appropriately and suitable for decision-making? See slide (24)
Time on treatment	Is the committee satisfied with the company's response? See slide (23)
Severity modifier	What is the appropriate severity modifier for belzutifan? See slide (25)
Cancer Drugs Fund (CDF)	Is belzutifan a candidate for CDF? See slide (26-27)

Abbreviations: DP, decision problem; ITC, indirect treatment comparison; MA, marketing authorisation; SoC, standard of care; VHL, Von Hippel Lindau

Supplementary slides

- Recap ACM1: slides
- Consultation responses
- Company's expert elicitation exercise
- Key issues
- Cancer Drugs Fund
- Other considerations

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Belzutifan (Welireg, MSD)

Table: Technology details

Marketing authorisation	'Belzutifan is indicated for treatment of adults 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'
Mechanism of action	• Belzutifan targets hypoxia inducible factor (HIF) - 2α • By blocking the activity of HIF-2α, Belzutifan slows down worsening of VHL and improves symptoms
Administration	• Oral: 120 mg (3X 40mg tablets once daily with or without food) • Treatment should continue until disease progression or unacceptable toxicity occurs
Price	• List price, £11,936.70 for 90 tablets (40 mg) • Average cost of treatment : [redacted] • There is a proposed simple patient access scheme (PAS) discount for Belzutifan

Abbreviations: VHL, Von Hippel-Lindau

Decision problem (1/2)

Recap

	Final scope	Company decision problem/EAG comments
Population	Adults who require therapy for RCC, CNS Hb, or pNET tumours caused by VHL, for whom localised procedures are unsuitable/ undesirable	Adult patients with VHL disease who require therapy for VHL associated RCC, CNS hemangioblastomas, or pNET, and for whom localised procedures are unsuitable or undesirable **Company and EAG** agreed misalignment between the DP/MA and MK-6482-004 study populations
Intervention	Belzutifan	Belzutifan **In line with the NICE scope**
Comparators	**RCC, CNS Hb & pNET:** • SoC without Belzutifan **RCC:** • For advanced or metastatic disease, monotherapy or combination therapy with immunotherapies or kinase inhibitors **pNETs** • For unresectable/metastatic disease, monotherapy with lutetium oxodotreotide or combination with everolimus and sunitinib	For VHL associated RCC, pNET, and CNS hemangioblastomas: • Current SoC without Belzutifan **Company** considered no treatments for advanced or metastatic disease are relevant as comparators because these would be used after treatment with Belzutifan

Abbreviations: CNS Hb, Central nervous system haemangioblastomas; DP, decision problem; MA, marketing authorisation; pNET, Pancreatic neuroendocrine tumour; RCC, renal cell carcinoma; SoC, standard of care

Decision problem (2/2)

	Final scope	Company decision problem/EAG comments
Outcomes	• Overall survival • Progression-free survival • Response rates • Tumour size reduction • Reduction in number of surgical interventions • Adverse effects of treatment • HRQoL	• Response rates • Reduction in number of surgical interventions • Adverse effects • Progression-free survival • Tumour size reduction **Company** • Overall survival was not a designated predefined outcome in the MK-6482-004 • HRQoL not collected in MK-6482-004 • OS and HRQoL derived from other sources **EAG** • Outcomes driven based MK-6482-004 data: **Not in line with NICE scope**

Abbreviations: HRQoL, health-related quality of life

Key clinical trial: MK-6482-004

EAG: MK-6284-004 population not representative of DP population

	MK-6482-004	
Design	Phase II, open label, single-arm	
Population	People with VHL disease who have at least one measurable RCC tumour	
Intervention	Belzutifan	
Duration	Until unacceptable treatment-related toxicity or unequivocal disease progression	
Primary outcomes	Overall response rate (complete or partial defined RECIST 1.1)	
Secondary outcomes (used in model)	• Duration of response, time to response, progression-free survival, time to surgery, adverse events	
Key Inclusion exclusion criteria	Inclusion • Diagnosis of VHL disease • At least 1 measurable solid RCC tumour and no RCC tumour greater than 3.0 cm that requires immediate surgical intervention	Exclusion • Had a surgical procedure for VHL disease or any major surgical procedure completed within 4 weeks prior to study enrolment • **Had an immediate need for surgical intervention for tumour treatment**
Locations	Multicentre, 11 sites in Denmark, France, UK and US	

Abbreviations: RCC, renal cell carcinoma; VHL, Von Hippel Lindau; VEGF (vascular endothelial growth factor

Baseline characteristics: MK-6284-004

EAG: MK-6284-004 population not representative of UK target population

Table: MK-6284-004 baseline characteristics

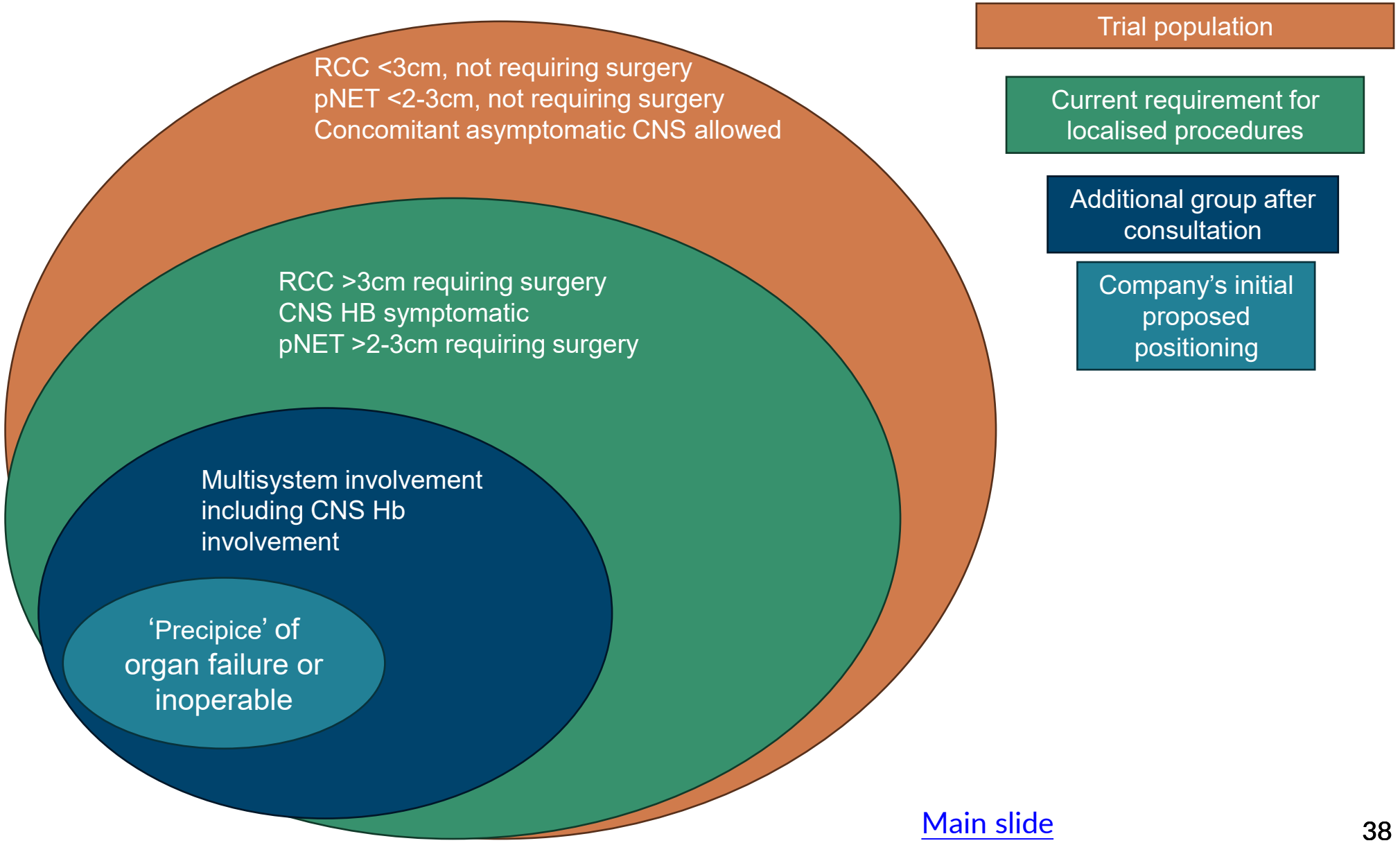
Baseline characteristics		Belzutifan (n=60)
Age (mean), years at time of VHL diagnosis		31.3 (14.29)
VHL subtype, n (%)	Type 1	51 (83.6)
	Others (Type 2A,2B & missing)	10 (16.4)
VHL-associated Non-RCC tumours, n (%)	Pancreatic lesions	32 (52.5)
	Pancreatic lesions; pNETs	22 (36.1)
	Adrenal lesions (pheochromocytomas)	3 (4.9)
	CNS Hb	51 (83.6)
	Endolymphatic sac tumours	1 (1.6)
	Epididymal cystadenomas	10 (16.4)
	Retinal lesions	17 (27.9)
	Other	2 (3.3)
Number of prior Surgeries	n	59
	Mean (SD)	5.5 (3.34)

NICE

Are these baseline characteristics generalisable to NHS clinical practice?

Abbreviations: CNS Hb, central nervous system haemangioblastomas; pNET, Pancreatic neuroendocrine tumour; RCC, renal cell carcinoma; VHL, Von Hippel Lindau; SD, standard deviation

Company's proposed population



Main slide

Abbreviations: CNS Hb, central nervous system haemangioblastomas; pNET, pancreatic neuroendocrine tumour; RCC, renal cell carcinoma; VHL, Von Hippel-Lindau

Treatment effect waning

ACM 1: extensive sensitivity analyses and testing alternative assumptions on treatment waning

Company

- Treatment effect waning period for CNS Hb and pNETs assumed equivalent to RCC due to small sample sizes of discontinued people CNS Hb and pNETs subgroups in MK-6482-004
- Clinical experts find CNS Hb response compelling and agreed with the company's approach
- Consider treatment effect waning cannot start earlier than the trial follow-up period, which already accounted for discontinuation and potential loss of treatment effect waning
- Conducted sensitivity analyses and tested alternation assumptions around treatment waning

EAG

- Highlighted that treatment effect waning still assumed equal across RCC, CNS Hb and pNETs cohorts but acknowledged clinicians find the approach plausible
- However, questions about what happens to people after waning periods end that if tumours return to their initial size and what will be the options:
  - immediate surgery or retreatment with belzutifan (if plausible) which is not included in model which would increase the ICERs
- Noted modest impact on the results based on the company's on sensitivity analyses

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Is the committee satisfied with the company's response?

Abbreviations: CNS Hb, central nervous system haemangioblastomas; ICER, incremental cost-effectiveness ratio ; pNET, pancreatic neuroendocrine tumour; RCC, renal cell carcinoma; VHL, Von Hippel Lindau; SoC, standard of care

Derivation and implementation of HRQoL

ACM 1: use multiplicative approach for disutilities and utility values validated against literature

Health state	Belzutifan	SoC
RCC	0.762	0.728
CNS Hb	0.751	0.695
pNET	0.790	0.728

Response-adjusted utilities in non-metastatic health states

Company

- Acknowledged the uncertainties and updated its model with:
  - using a multiplicative method for combining disutilities
  - comparing the utilities on dialysis with an age- and sex-matched expectation from the general population

EAG

- Estimated disutility from concurrent complications:- [redacted] with additive approach, [redacted] with multiplicative approach respectively
- Additive approach expected to yield more negative disutilities, consistent with observed results. However, the difference between approaches is minor

Table: Long term complication disutilities

Complication	Disutility values	
	ACM1	ACM2
ESRD (long-term RCC complication)	-0.527	-0.422
Chronic kidney disease	-0.136	
Hernia	-0.200	
Chronic pain	-0.195	
Cerebral vasculature occlusion or stroke	-0.370	

Are the utilities modelled appropriately?

NICE

Abbreviations: ESRD: end stage renal disease; HRQoL, health-related quality of life; pNET, pancreatic neuroendocrine tumour; RCC, renal cell carcinoma

NICE National Institute for Health and Care Excellence

Thank you.