Managed Access Agreement

Belzutifan for treating tumours associated with von Hippel-Lindau disease (TA1011)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund – Data Collection Arrangement

Belzutifan for treating tumours associated with von Hippel-Lindau disease [TA1011]

Company name: Merck, Sharp & Dohme (UK) Ltd

Primary sources of data collection: Ongoing trial of belzutifan in VHL-associated tumours LITESPARK-004 (MK-6482-004); NHS England routine population-wide cancer data sets, including Systemic Anti-Cancer Therapy data set

Secondary sources of data collection: Merck & Co., Inc. global non-interventional study (NIS); Merck Sharp & Dohme (UK) Retrospective case note review; Merck Sharp & Dohme (UK) Multicentre retrospective analysis

NICE Agreement Manager	[redacted]
NHSE Agreement Manager	[redacted]
NHSE Agreement Manager	[redacted]
MSD UK Agreement Manager	[redacted]

1 Purpose of data collection arrangement

1.1 The purpose of the agreement is to describe the arrangements and responsibilities for further data collection for belzutifan for treating tumours associated with von Hippel-Lindau disease [TA1011]. A positive recommendation within the context of a managed access agreement (MAA) has been decided by the appraisal committee.

2 Commencement and period of agreement

2.1 This data collection arrangement shall take effect on publication of the managed access agreement.

2.2 Estimated dates for data collection, reporting and submission for a guidance update are:

End of data collection (primary source)	LITESPARK-004: Q2 2025 NHS Digital data sets: Q2 2028
Data available for development of company submission	Q4 2028
Anticipated company submission to NICE for a guidance update	September 2029

2.3 Merck Sharp & Dohme (MSD) anticipate the results from the additional data collected during the Cancer Drugs Fund period will be incorporated into an evidence submission and economic model by September 2029.

2.4 MSD acknowledge their responsibility to adhere as closely as possible to the timelines presented in this document.

2.5 NICE will, as far as is practicable, schedule the guidance update into the technology appraisal work programme to align with the estimated dates for the end of data collection.

2.6 The NICE guidance update will follow the process and methods applicable to guidance updates that are in place at the time the invitation to participate in the guidance update is issued. These may be different from the process and methods applicable to guidance updates when this technology entered into the managed access agreement.

2.7 As part of the managed access agreement, the technology will continue to be available through the Cancer Drugs Fund after the end of data collection and while the guidance is being reviewed. This assumes that the data

collection period ends as planned and the guidance update follows the standard timelines.

2.8 The company is responsible for paying all associated charges for a guidance update. Note that this includes the 'change fee' if the Company does not provide sufficient notice to NICE regarding changes to the evaluation timelines. Please refer to the NICE website and Charging Procedure for further information.

2.9 The company must inform NICE and NHS England (NHSE) in writing of any anticipated changes to the estimated dates for data collection at the earliest opportunity.

2.10 Any changes to the terms or duration of any part of the data collection arrangement must be approved by NICE and NHSE.

2.11 If data collection is anticipated to conclude earlier than the estimated dates for data collection, for example due to earlier than anticipated reporting of an ongoing clinical trial, the company should note:

- Where capacity allows, NICE will explore options to reschedule the guidance update date to align with the earlier reporting timelines.
- It may be necessary to amend the content of the final SACT or real-world data report (for example if planned outputs will no longer provide meaningful data).

2.12 If data collection is anticipated to conclude later than the estimated dates for data collection, the company should note:

- The company must submit a written request to NICE and NHSE, with details of the extension requested, including an explanation of the factors contributing to the request.

- It may be necessary for the company to mitigate the impact of any delay, and reduce any risks of further delays.
- In the event of an extension, it may not be possible to amend the date of the final SACT or real-world data report, although NICE will explore options with NHSE to provide data over the extended period.

2.13 MSD acknowledge their responsibility to provide an evidence submission for this technology to NICE under all circumstances following a period of managed access.

2.14 In the event that MSD do not make a submission to NICE for the purpose of updating the guidance, NICE and NHSE will require the company to agree to submit the clinical evidence collected during the managed access period, and to participate in an engagement meeting convened by NICE with attendance from NHSE, patient and professional group stakeholders, with the company presenting the clinical evidence collected during the managed access period and an explanation of the decision to proceed with withdrawal of the guidance.

2.15 NICE and NHSE may consider the data collection agreement no longer valid, and withdraw the technology from the Cancer Drugs Fund for the following, non-exhaustive, grounds:

- The primary sources of data are delayed, without reasonable justification.
- The primary sources of data are unlikely to report outcome data that could resolve the uncertainties identified by the technology appraisal committee.
- Amendments are made to the marketing authorisation.

3 Patient eligibility

3.1 Key patient eligibility criteria for the first use of belzutifan in the Cancer Drugs Fund include:

- This application is being made by, and the first cycle of systemic anti-cancer therapy with belzutifan will be prescribed by, a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy.
- The patient is an adult with a VHL germline alteration
- This patient's case has been discussed at a VHL multidisciplinary team meeting which has recommended the use of belzutifan for a VHL associated renal cell carcinoma or a CNS haemangioblastoma or a pancreatic neuroendocrine tumour, AND for which localised procedures are unsuitable or undesirable.
- In the absence of systemic therapy with belzutifan the patient would otherwise proceed to treatment for VHL associated tumour(s) with a localised procedure/procedures which is/are considered by the patient and clinician to be unsuitable or undesirable.
- The prescribing clinician confirms the patient's status with regard to any VHL associated renal cell carcinoma (RCC)
- The prescribing clinician confirms the patient's status with regard to any VHL associated CNS haemangioblastoma
- The prescribing clinician confirms the patient's status with regard to any VHL associated pancreatic neuroendocrine tumour (pNET)
- The prescribing clinician confirms the patient's status with regard to any VHL associated retinal haemangioblastoma(s)

- The patient has not been previously treated with belzutifan or any hypoxia-inducible factor 2 alpha (HIF-2α) inhibitor unless the patient was receiving belzutifan via a company compassionate access scheme and all other criteria on this form are fulfilled.

3.2 The prescribing clinician confirms whether there is any evidence of metastatic disease or not of one of the VHL associated tumours of RCC, CNS haemangioblastoma or pNET.

Note: if there is such metastatic disease, there must still be a localised procedure which is currently indicated and in the absence of treatment with belzutifan is considered to be unsuitable or undesirable.

- The patient is of ECOG performance status 0 or 1.
- Belzutifan is only to be used as monotherapy for treating VHL associated RCC and/or CNS haemangioblastoma and/or pNET.
- For the indication/tumour driving the prescribing decision (the dominant indication/tumour), belzutifan is to be continued until disease progression or unacceptable toxicity or patient choice to stop treatment or the occurrence of an intervention with a localised procedure for that dominant indication/tumour.

Note: NHS England recognises that it may be desirable for treatment with belzutifan to continue beyond disease progression in one dominant tumour with the consequent need for intervention with a localised procedure for this progressing tumour IF there has nevertheless been continued benefit in other equally dominant VHL associated tumours and in which the absence of continued belzutifan would also be subject to the need for an unsuitable/undesirable

localised procedure. In such a patient, Blueteq form BELZUT1b should be completed to continue treatment with belzutifan.

Note: NHS England also recognises that belzutifan which has been discontinued for disease progression or the occurrence of an intervention with a localised procedure for one particular tumour may be later indicated again for another tumour if a localised procedure for that other tumour is considered to be unsuitable or undesirable. In such a patient, Blueteq form BELZUT1b should be completed to restart treatment with belzutifan.

Note: belzutifan cannot be restarted for patients who suffer unacceptable toxicity or choose to stop treatment.

Note: the intention to treat with belzutifan must be with a planned and continued administration of belzutifan until disease progression or unacceptable toxicity or patient choice to stop treatment or the occurrence of an intervention with a localised procedure. Belzutifan is not funded to be used electively in an intermittent treatment schedule with planned 'treatment holidays'.

- The prescribing clinician is aware of the need for monitoring of anaemia, the scheduling of such monitoring and the management of anaemia (including the use of erythropoietin) as set out in sections 4.4 and 4.8 of the belzutifan Summary of Product Characteristics (SPC).

- The prescribing clinician is aware of the need for monitoring of hypoxia, the scheduling of such monitoring and the management of hypoxia as set out in sections 4.4 and 4.8 of the belzutifan SPC.

- The prescribing clinician is aware of all the precautions necessary to prevent embryofoetal toxicity whilst patients are on treatment with belzutifan as set out in sections 4.4 and 4.6 of the belzutifan SPC.

- The prescribing clinician is aware of the potential drug interactions of belzutifan with other medications including hormonal contraceptives as set out in section 4.5 of the belzutifan SPC.

- A formal medical review as to whether treatment with belzutifan continues or not will be scheduled to occur at least by the end of the second month of treatment.

- When a treatment break of more than 6 weeks beyond the expected weekly cycle length is needed, a treatment break approval form will be completed to restart treatment.

- Belzutifan will be otherwise used as set out in its Summary of Product Characteristics.

3.3 Key patient eligibility criteria for the use of belzutifan in the Cancer Drugs Fund in other circumstances (either continuation of belzutifan beyond disease progression in one dominant tumour but with continued benefit in other equally dominant VHL associated tumours or a subsequent restart of belzutifan for a different VHL associated tumour to the one which previously resulted in the indication for belzutifan treatment, and for which localised procedures are unsuitable or undesirable) include:

- This application is being made by, and continuation of or a restart of systemic anti-cancer therapy with belzutifan will be prescribed by, a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy.

- The patient has already received treatment with belzutifan for one VHL associated tumour for which a localised procedure was unsuitable or undesirable.

- There has been **either** disease progression in one dominant tumour but continued benefit in other equally dominant VHL associated tumours or the patient previously discontinued belzutifan on account of disease progression of a dominant tumour and this was followed by a localised procedure to treat this and the patient has now developed a new VHL associated tumour which would otherwise require a localised procedure which is unsuitable or undesirable.

- This patient's case has been discussed at a VHL multidisciplinary team meeting which has recommended the continued use or a re-start of belzutifan for a VHL associated renal cell carcinoma or a CNS haemangioblastoma or a pancreatic neuroendocrine tumour, AND for which localised procedures are unsuitable or undesirable.

- In the absence of systemic therapy with belzutifan the patient would otherwise proceed to treatment for VHL associated tumour(s) with a localised procedure/procedures which is/are considered by the patient and clinician to be unsuitable or undesirable.

- The prescribing clinician confirms the patient's status with regard to any VHL associated renal cell carcinoma (RCC)

- The prescribing clinician confirms the patient's status with regard to any VHL associated CNS haemangioblastoma

- The prescribing clinician confirms the patient's status with regard to any VHL associated pancreatic neuroendocrine tumour (pNET)

- The prescribing clinician confirms the patient's status with regard to any VHL associated retinal haemangioblastoma(s)

3.4 The prescribing clinician confirms whether there is any evidence of metastatic disease or not of one of the VHL associated tumours of RCC, CNS haemangioblastoma or pNET.

Note: if there is such metastatic disease, there must still be a localised procedure which is currently indicated and in the absence of treatment with belzutifan is considered to be unsuitable or undesirable.

- The patient is of ECOG performance status 0 or 1.
- Belzutifan is only to be used as monotherapy for treating VHL associated RCC and/or CNS haemangioblastoma and/or pNET.
- For the dominant indication/tumour belzutifan is to be continued until disease progression or unacceptable toxicity or patient choice to stop treatment or the occurrence of an intervention with a localised procedure for that dominant indication/tumour.

  Note: belzutifan cannot be restarted for patients who suffer unacceptable toxicity or choose to stop treatment.

  Note: the intention to treat with belzutifan must be with a planned and continued administration of belzutifan until disease progression or unacceptable toxicity or patient choice to stop treatment or the occurrence of an intervention with a localised procedure. Belzutifan is not funded to be used electively in an intermittent treatment schedule with planned ‘treatment holidays’.

- The prescribing clinician is aware of the need for monitoring of anaemia, the scheduling of such monitoring and the management of anaemia (including the use of erythropoietin) as set out in sections 4.4 and 4.8 of the belzutifan Summary of Product Characteristics (SPC).

- The prescribing clinician is aware of the need for monitoring of hypoxia, the scheduling of such monitoring and the management of hypoxia as set out in sections 4.4 and 4.8 of the belzutifan SPC.
- The prescribing clinician is aware of all the precautions necessary to prevent embryofoetal toxicity whilst patients are on treatment with belzutifan as set out in sections 4.4 and 4.6 of the belzutifan SPC.
- The prescribing clinician is aware of the potential drug interactions of belzutifan with other medications including hormonal contraceptives as set out in section 4.5 of the belzutifan SPC.
- A formal medical review as to whether treatment with belzutifan continues or not will be scheduled to occur at least by the end of the second month of treatment.
- When a treatment break of more than 6 weeks beyond the expected weekly cycle length is needed, a treatment break approval form will be completed to restart treatment.
- Belzutifan will be otherwise used as set out in its Summary of Product Characteristics.

3.5 The estimated patient numbers per year for this technology within the Cancer Drugs Fund are:

As estimated by the company	Year 1 – [redacted], Year 2 – [redacted], Year 3 – [redacted], Year 4 – [redacted], Year 5 – [redacted]
As estimated by NICE Resource Impact Assessment team	Year 1 – 100, Year 2 – 100, Year 3 – 101

4 Patient safety

4.1 The company and NHSE have the responsibility to monitor the safety profile of the technology and must provide an overview of any new or updated safety concerns to NICE. If any new safety concerns are confirmed, NICE and NHSE will take steps, as appropriate, to mitigate the risk including but not limited to updating the eligibility criteria or recommending that the managed access agreement be suspended.

5 Area(s) of clinical uncertainty

5.1 The appraisal committee identified the following key areas of uncertainty during the course of the appraisal process:

1. Characterising people with VHL who would receive belzutifan in clinical practice (eligible population in line with marketing authorisation and percentage of tumour in each type)
2. Long-term efficacy of belzutifan
3. Treatment waning
4. Time on treatment

5.2 The committee concluded that further data collection within the Cancer Drugs Fund could resolve these uncertainties. For further details of the committee's discussion see section 3 of the Final Appraisal Document.

6 Sources of data collection

Primary and secondary sources of data collection

Primary source(s)	○ LITESPARK-004 ○ Systemic Anti-Cancer Therapy (SACT) dataset ○ NHSE Blueteq data

Secondary sources	○ Merck & Co., Inc. global non-interventional study (NIS) [subject to final confirmation of details and dates] ○ Merck Sharp & Dohme (UK) Retrospective case note review [subject to final confirmation of details and dates] ○ Merck Sharp & Dohme (UK) Multicentre retrospective analysis [subject to final confirmation of details and dates]

Description of sources

6.1 **LITESPARK-004** is a Phase II, open-label, single arm study to investigate the safety of orally administered belzutifan, in 61 patients with RCC associated with VHL disease. The primary end point is objective response in RCC tumours; objective response in non-RCC neoplasms is also assessed.

6.2 **NHSE's Blueteq database** captures the Cancer Drugs Fund population. The lawfulness of this processing is covered under article 6(1)e of the United Kingdom General Data Protection Regulations (GDPR) (processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller). NHSE, through the National Disease Registration Service (NDRS), does have statutory authority to process confidential patient information (without prior patient consent) afforded through the NDRS Directions 2021 issued to it by the Secretary of State for Health and Social Care, and has issued the NDRS Data Provision Notice under section 259 of the Health and Social Care Act 2012 regarding collection of the Blueteq data from NHSE.

6.3 The Systemic Anti-Cancer Therapy (SACT) dataset, is a mandated dataset as part of the Health and Social Care Information Standards. NHSE is

responsible for the collection, collation, quality-assurance and analysis of this dataset.

6.4 Datasets collected and collated by NDRS in NHSE will be a primary source of data collection. NDRS will collect data, including via the SACT dataset, alongside the primary source of data collection.

7 Outcome data

Clinical trial

7.1 The key outcomes to be collected are:

- Overall response rates (ORR)
- Duration of response (DOR)
- Time to response (TTR)
- Time to surgery (TTS)
- Progression-free survival (PFS)
- Safety and tolerability

Follow-up is ongoing in the existing clinical trial LITESPARK-004. Additional data from the clinical trial will resolve uncertainty in the long-term efficacy and safety of belzutifan.

Other data, including SACT

7.2 NDRS in NHSE will collect the following outcomes through SACT unless it is determined by the SACT Operational Group that no meaningful data will be captured during the period of data collection:

- Number of patients starting treatment

- Baseline patient characteristics, including gender, age and performance status
- Treatment duration
- Overall survival
- Subsequent treatments and surgeries

7.3 NHSE's Blueteq system will collect the following outcomes:

- Number of applications to start treatment, or restart treatment according to eligibility criteria listed above
- VHL-associated tumour type(s) to be treated
- Reason for being unsuitable or undesirable for localised procedures (i.e. what is the procedure that a patient would have instead of belzutifan that is unsuitable/undesirable?) [note: this will be a 'free text' field]
- Prior VHL-associated treatment & procedures
- History of VHL disease-related metastasis or advanced cancer
- Baseline patient characteristics

8 Data analysis plan

Clinical trials

8.1 There will be pre-planned annual updates of the LITESPARK-004 study. The final analysis will follow the analysis plan outlined in the trial protocol. The LITESPARK-004 study is an open-label single-group trial and so had no assignment, randomisation, or stratification. Periodic review of the trial data will be performed. Any analysis for the study will only take place after all

patients have had the opportunity to complete at least two imaging assessments on study or have discontinued study therapy by the time of analysis data cut-off. The final analyses for the study will utilise a data cut-off date which will be at least 36 weeks after enrolment of the last patient. Subgroup results may be reported for patients VHL disease-associated renal cell carcinoma AND central nervous system hemangioblastomas, as well as for patients with VHL disease-associated renal cell carcinoma AND pancreatic neuroendocrine tumours.

8.2 Database locks will occur annually in mid-2024 and mid-2025.

Other data

8.3 At the end of the data collection period NHSE will provide a final report which provide analyses based on NHSE's Blueteq data and routinely collected population-wide data, including that collected via SACT. The necessary controls will be put in place to ensure that patient confidentiality is not put at risk. The report will be shared with the company in advance of the planned guidance update. Where SACT is a secondary source of data, availability of the final SACT report will be aligned to the availability of data from the primary source. The end of SACT data collection will be 8 months prior to the availability of the final SACT report to allow for NHS trusts to upload SACT data, data cleaning, and report production.

8.4 For the Merck & Co., Inc. global NIS, [redacted]. The output will be a report on results from a prospective patient registry with the objectives to further characterise efficacy and understand long-term safety, particularly in VHL-

associated RCC and CNS haemangioblastomas. This NIS is subject to confirmation of final details and dates.

8.5 For the Merck Sharp & Dohme (UK) Retrospective case note review, [redacted]. [This retrospective case note review is subject to confirmation of final details and dates]

8.6 For the Merck Sharp & Dohme (UK) Multicentre retrospective analysis, [redacted]. [This multicentre retrospective analysis is subject to confirmation of final details and dates]

9 Ownership of the data

9.1 For the clinical trial (LITESPARK-004) data and the NIS listed above, Merck & Co., Inc. is the owner.

9.2 For the retrospective case note review and multicentre retrospective analysis listed above, Merck Sharp & Dohme (UK) Limited is the owner.

9.3 This work uses data that has been provided by patients and collected by the NHS as part of their care and support. The data are collated, maintained and quality assured by the National Disease Registration Service, which is part of NHSE. The company will not have access to the NHSE patient data, but will receive de-personalised summary data, with appropriate governance controls in place.

9.4 The SACT dataset is a mandated dataset as part of the Health and Social Care Information Standards. All necessary governance arrangements through SACT, and other datasets brought together by NHSE, have been established with NHS Trusts and NHSE.

9.5 Blueteq's Cancer Drugs Fund system data is owned by NHSE. NHSE is responsible for implementing Blueteq data collection and generally for the analysis of these data. The lawfulness of this processing is covered under

article 6(1)e of the United Kingdom General Data Protection Regulations (UK GDPR) (processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller). NHSE, through the National Disease Registration Service, does have statutory authority to process confidential patient information (without prior patient consent) afforded through the National Disease Registries (NDRS) Directions 2021 issued to it by the Secretary of State for Health and Social Care. The lawfulness of NHSE's processing is covered under article 6(1)(c) of the UK GDPR – processing is necessary for compliance with a legal obligation to which the controller is subject (the NDRS Directions).

10 Publication

10.1 The details/authorship of any proposed publications arising from these studies will be planned with the publication of the final study results.

10.2 NDRS will produce a final report which includes analysis of data collected through SACT and from NHSE's Blueteq system. This report will be provided to NHSE and the company at the end of the managed access period. The final report will form part of NHSE's submission to the guidance update, and will therefore be publicly available at the conclusion of the guidance update.

10.3 NDRS will produce interim reports, which will be shared with NICE and the company at regular intervals during the data collection period. These reports will be used to determine whether real-world data collection is proceeding as anticipated, and will not form part of the guidance update.

10.4 Publications of any data from the NDRS reports is not permitted until after the date of publication of the NICE committee papers (on the NICE website) following the first NICE guidance update committee meeting.

10.5 The contribution of all relevant individuals must be acknowledged in any publications regarding the data collection or analyses generated from the

data collection arrangement. Authors will need to contact the NICE Managed Access Team for the full list of relevant individuals.

11 Data protection

11.1 The terms of clause 7 (data protection) of the managed access agreement, that apply between NHSE and MSD UK, shall also apply between the parties to this data collection arrangement in relation to the performance of their obligations under this data collection arrangement

12 Equality considerations

12.1 Do you think there are any equality issues raised in data collection?

☐ Yes ☒ No

13 Data collection agreement: version control table

Date updated	Description of update/changes made
11 November 2024	**Amendment to text in paragraph 8.4** **Original DCA:** The output will be a report on results from a prospective patient registry with the objectives to further characterise efficacy and understand long-term safety, particularly in CHL-associated RCC and CAN haemangioblastomas. **Updated DCA:** The output will be a report on results from a prospective patient registry with the objectives to further characterise efficacy and understand long-term safety, particularly in VHL-associated RCC and CNS haemangioblastomas.

Commercial Access Agreement

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The contents of this document have been redacted as they are confidential

- A glossary of terms relating to managed access agreements in the Cancer Drugs Fund is available here.