Managed Access Agreement

Etranacogene dezaparvovec for treating moderately severe or severe haemophilia B (TA989)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Innovative Medicines Fund – Data Collection Arrangement

Etranacogene dezaparvovec for treating moderately severe or severe haemophilia B (TA989)

Company name: CSL Behring UK Ltd (the company)

Primary source(s) of data collection: CT-AMT-061-02 (HOPE-B, Phase 3) with Open-label extension trial (OLE)

NICE Agreement Manager	[redacted], Associate Director, Managed Access
NHSE Agreement Manager	[redacted], NHSE Clinical Advisor (Non-oncology)
CSL Behring UK Ltd Agreement Manager	[redacted]

1 Purpose of data collection arrangement

- The purpose of the agreement is to describe the arrangements and responsibilities for further data collection for etranacogene dezaparvovec for treating moderately severe or severe haemophilia B (TA989). 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

- This data collection arrangement shall take effect on publication of the MAA.

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

End of data collection (primary source)	Q1 2030, last patient visit for PhIII HOPE-B trial. [redacted]
Data available for development of company submission	[redacted]
Anticipated company submission to NICE for a guidance update	[redacted]

[redacted]

- CSL Behring anticipates the results from the additional data collected during the Innovative Medicines Fund period will be incorporated into an evidence submission and the updated economic model by November 2027.
- CSL Behring acknowledges their responsibility to adhere as closely as possible to the timelines presented in this document.
- 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.
- 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.

- At the appropriate time NICE will explore and discuss with the company and NHSE if a proportionate approach can be applied to the exit from Managed Access as per NICE Methods.
- As part of the managed access agreement, the technology will continue to be available through the Innovative Medicines Fund after the end of data collection and while the guidance is being updated. This assumes that the data collection period ends as planned and the guidance update follows the standard timelines.
- The company is responsible for paying all associated charges for a guidance update. Further information is available on the NICE website.
- The company must inform NICE and NHS England (NHSE) in writing of any anticipated changes to the estimated dates for data collection and reporting at the earliest opportunity.
- Any changes to the terms or duration of any part of the data collection arrangement must be approved by NICE and NHSE.
- 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 real-world data report (for example if planned outputs will no longer provide meaningful data).

- 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.

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

- In the event that CSL Behring does 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.

- NICE and NHSE may consider the data collection arrangement no longer valid, and withdraw the technology from the Innovative Medicines 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 Monitoring arrangements

- NICE will convene a Managed Access Oversight Group (MAOG) with representation from NICE, NHSE, and the company.
- The MAOG exists to oversee the operation of all aspects of the MAA and to address issues that may arise throughout the MAA term. The MAOG is responsible for monitoring the implementation of the MAA and for recommending actions to support its operation and will meet regularly throughout the data collection period.
- A detailed description of the MAOG function will be available in a Terms of Reference document produced by NICE.

4 Patient eligibility

- Key patient eligibility criteria for the use of etranacogene dezaparvovec in the Innovative Medicines Fund include:
  - Aged 18 years or older
  - Moderately severe or severe haemophilia B
  - Demonstrated absence of Factor IX inhibitors and no previous history of Factor IX inhibitors
  - A pre-existing neutralising antibody titre has been performed and that the patient does not have neutralising anti-AAV5 antibodies above a titre of 1:678 (7-point assay) or 1:898 (9-point assay)

- Baseline hepatic function has been assessed
- The treatment will be delivered by a commissioned haemophilia ATMP treatment hub
- Use is in accordance with the SmPC

o The estimated patient numbers per year for this technology within the Innovative Medicines Fund are:

As estimated by the company	[redacted]
As estimated by NICE Resource Impact Assessment team	Year 1: 10 Year 2: 11 Year 3: 16

5 Patient safety

o The company and NHSE have a 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.

6 Area(s) of clinical uncertainty

- The appraisal committee identified the following key areas of uncertainty during the course of the appraisal process:
  - Long-term treatment durability of etranacogene dezaparvovec
  - Proportion of people that require Factor IX prophylaxis after etranacogene dezaparvovec.
  - The committee concluded that further data collection within the Innovative Medicines Fund could resolve these uncertainties. For further details of the committee's discussion see section 3 of the Final Appraisal Document.

7 Sources of data collection

Primary and secondary sources of data collection

Primary source(s)	○ **CT-AMT-061-02 (HOPE-B, Phase 3) with Open-label extension trial (OLE)**
Secondary	○ CT-AMT-060-01 (Phase 1-2) with OLE. [redacted] ○ CT-AMT-061-01 (Phase 2b) with OLE. [redacted]

Description of sources

- Primary Source: Phase 3 clinical trial (HOPE-B). Open-label, single-dose, multicentre trial to evaluate safety and efficacy of etranacogene dezaparvovec. N=54 patients dosed. The latest data cut-off is at 36-month post-treatment, as provided in Appendix C of the draft guidance company response. [redacted]

- Secondary data source - CT-AMT-060-01: Open-label, uncontrolled, single-dose, dose-ascending designed study enrolled subjects (n=10) with haemophilia B. [redacted]. Eligible subjects were allocated to 2 consecutive dose cohorts and received a single intravenous dose of AMT-060; Cohort 1 (n=5) received the low dose of 5.0×10^{12} centigram/Kilogram (gc/kg) and Cohort 2 (n=5) received the high dose of 2.0×10^{13} gc/kg. [redacted]

- Secondary data source - CT-AMT-061-01 (Phase 2b) with OLE. Open-label, single-dose, single-arm, a multicentre trial was initiated to confirm the Factor IX activity level of AAV5-hFIXco-Padua in adults (n=3) with severe or moderately severe haemophilia B. 3 patients have completed 4 years follow up (July 2023) and none have returned to prophylaxis. [redacted]

8 Outcome data

Clinical trial

Outcome data	Data source	Outcomes measured	Likelihood data collection could sufficiently resolve key uncertainties
CT-AMT-060-01 with OLE (AMT-060) Currently patients are enrolled in an open label extension (OLE) study, [redacted]	Open-label, uncontrolled, single-dose, dose-ascending designed study enrolled subjects (n=10) with haemophilia B. Eligible subjects were allocated to 2 consecutive dose cohorts and received a single intravenous dose of AMT-060; Cohort 1 (n=5) received the low dose of 5.0×10^{12} gc/kg and Cohort 2 (n=5) received the high dose of 2.0×10^{13} gc/kg	***Efficacy*** **Endogenous Factor IX activity** **Utilisation of Factor IX-replacement therapy** **Annualised bleeding rate (Factor IX-requiring); including the following:** • **All bleeds Spontaneous bleeds Traumatic bleeds** • **Joint bleeds** Short form (SF-36) and EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) QoL scores Haemophilia Joint Health Score (HJHS) ***Safety*** Factor IX inhibitors ALT/AST levels Liver pathology (assessed by ultrasound) Alpha-fetoprotein (AFP)	[redacted]
CT-AMT-061-01 (Phase 2b) with OLE Last patient visit expected in September 2023, with data available approximately May 2024.	Open-label, single-dose, single-arm, multicentre trial was initiated to confirm the Factor IX activity level of AAV5-hFIXco-Padua in adults (n=3) with severe or	***Efficacy*** **Endogenous FIX activity** **Total usage of FIX replacement therapy** **ABR (including a further break down**	[redacted]

Patients will then enrol into OLE [redacted]	moderately severe haemophilia B. Single dose of 2.0 x 10^{13} gc/kg	**of the frequency and percentage of spontaneous, traumatic, and joint bleeding events)** Joint health and quality of life (QoL) scores ***Safety*** Observed ALT/AST levels and corticosteroid use for any elevations Antibody formation to AAV5 and human FIX AFP Abnormal findings on the abdominal ultrasound	[redacted]
CT-AMT-061-02 (HOPE-B, Phase 3) with OLE Last patient visit is expected approximately Q2 2025 with final data available after 6 months Patients will then enter into an OLE [redacted]	Open-label, single-dose, multicentre trial to evaluate safety and efficacy of etranacogene dezaparvovec Single dose of 2.0 X 10^{13} gc/kg 54 patients were dosed in HOPE-B. 53 patients have completed 36 months follow-up (July 2023) with 51 patients remaining off prophylaxis.	***Efficacy*** **Endogenous Factor IX expression** **Proportion free from Factor IX prophylaxis** **Annualised consumption of Factor IX replacement therapy** **Estimated ABR** Correlation of pre -IMP anti -AAV5 antibody titres on Factor IX activity levels after dosing Occurrence and resolution of target joints **Proportion of subjects with zero bleeding episodes** Patient reported outcomes: International Physical Activity Questionnaire (iPAQ), EuroQol-5	[redacted]

		dimensions-5 levels (EQ-5D-5L) Visual Analog Scale (VAS), Work Productivity and Activity Impairment Questionnaire (WPAI), Brief Pain Inventory (BPI), Haemophilia Activities List (HAL), and Haemophilia Quality of Life Questionnaire for Adults (Haem - A - QoL) Haemophilia Joint Health Score (HJHS) scores ***Safety*** Changes in abdominal ultrasound Formation of Factor IX inhibitors and recovery Liver enzyme: AST, ALT and proportion requiring corticosteroid use if increases noted Alpha-fetoprotein	
Outcomes in bold will be used to address uncertainty			

Summary of data currently available and data to be available at the end of the managed access period:

Clinical trial	Latest data cut off	Data available at end of managed access period (assuming start in Q2 2024)
CT-AMT-060-01	[redacted]	[redacted]
CT-AMT-061-01 (Phase 2b)	[redacted]	[redacted]
CT-AMT-061-02 (HOPE-B)	[redacted]	[redacted]

Data analysis plan

Clinical trials

Outcome data	Data analysis plan
OLE (AMT-060)	Data will be summarized using descriptive statistics. No formal statistical comparisons are planned. *Analysis populations* The Full Analysis Set (FAS) will consist of all patients previously administered AMT-060 (Study CT-AMT-060- 01) and who enrolled in this study. If applicable, further analysis sets will be defined, such as a Per Protocol Analysis set. *Sample Size* No formal sample size calculation is made. The choice of 10 patients total is based on the total number of patients enrolled in Study CT-AMT-060-01. *Statistical Methods Sko* Primary safety analysis Adverse events, possibly or probably related to previous AAV5-hFIX administration, will be summarized by system organ class and preferred term within each dosing cohort from Study CT-AMT-060-01. *Secondary efficacy analysis* Endogenous FIX activity and FIX replacement therapy will be summarized individually and overall. Annualized bleeding rates will be summarized individually and overall. Quality of life and HJHS will be described at each time point and overall change from Baseline in Study CT-AMT-060-01. Summaries will be done by each dosing cohort from Study CT-AMT-060-01
CT-AMT-061-01 (Phase 2b) with OLE	Given the small sample size (N = 3), no formal, inferential statistical analyses will be performed, and no analysis populations will be defined. Data will be presented descriptively in plots and tabular displays to visualize individual effects for selected efficacy and safety measures and/or in subject data listings. If applicable, continuous variables will be summarized with descriptive statistics including: the number of non-missing values, mean, SD, median, minimum, and maximum. In some cases, the standard error of the mean and/or confidence intervals were optionally to be provided. Categorical variables will be summarized by number, percent of subjects and, if applicable, the number of events.
CT-AMT-061-02 (HOPE-B, Phase 3) with OLE	**CT-AMT-061-02 (HOPE-B, Phase 3)** *Selection of subjects to be included in the analyses* The FAS (Full Analysis Set) will include all subjects who are enrolled, entered the lead-in phase, were dosed with AMT-061, and provide at least one efficacy endpoint. The FAS population will be the primary population considered in the primary analysis. The PP population (PP) will include all subjects from the FAS population, for whom efficacy data are available until and including Week 52, and who adhere to a stable and adequate prophylaxis use during the lead-in phase. The PP population will be the primary population considered in the ABR analysis. The safety population will consist of all subjects who receive AMT-061, irrespective of any protocol deviations

	Subject disposition Subjects in each analysis set, as well as subjects who complete the trial, and subjects who prematurely discontinue from the trial will be summarized using descriptive statistics. In addition, for subjects who prematurely discontinue from the trial, the reasons for discontinuation will be summarized *Demographic and baseline characteristics* Descriptive summaries of demographic and baseline characteristics will be presented for the FAS, PP, and safety populations. Descriptive statistics will be number of observations, mean, standard deviation, median, minimum, and maximum for quantitative data. For qualitative data, frequency counts and percentage will be determined. A full description of demographic variables will be included in the SAP. Individual subject demographics and baseline information will be provided in data listings. *Efficacy analyses* All efficacy analyses will be performed for the FAS and PP populations. Statistical analysis will be performed and plots and tabular displays will be created, visualizing individual effects for the selected efficacy measures as specified in the following sections. The primary efficacy analysis will be completed using the FAS population. The analysis using the PP population is considered to be a sensitivity analysis. Subjects in the FAS population that have not been treated with AMT-061 will be included using a missing imputation method The primary aim of the trial is to demonstrate the effect of AMT-061 on endogenous FIX activity 6 months after a single AMT-061 treatment (reported already: Pipe SW, et al. Gene Therapy with Etranacogene Dezaparvovec for Hemophilia B. N Engl J Med. 2023 Feb 23;388(8):706-718. doi: 10.1056/NEJMoa2211644. PMID: 36812434) The non-inferiority of a single AMT-061 treatment as compared to FIX prophylaxis treatment, with respect to ABR will be assessed as a secondary endpoint. Other secondary endpoints of the trial will focus on investigating the effect of 2 x 10^{13} gc/kg AMT 061 on assessment of trough FIX activity, discontinuation of previous continuous routine prophylaxis, total consumption of FIX replacement therapy, bleeding events, occurrence and resolution of target joints, correlation of FIX activity levels and observed anti-AAV5 antibody titers using the luciferase based NAB assay after AMT-061 dosing, endogenous FIX activity after AMT-061 dosing, and safety **OLE** Statistical analyses plan will be finalised at entry to study

Ownership of the data

- For all clinical trial data listed above, CSL Behring will be the owner.

Publication

- Publications regarding the implementation or managed access process are permitted as long as no data collected in clinical practice is included (e.g. patient leaflets, NICE presentations about operational aspects of MAAs).
- Any draft abstracts or manuscripts related to this DCA must be shared with the MAOG prior to submission to conferences, journals or any other publicly available site.
- The contribution of all relevant individuals must be acknowledged in any publications related to this DCA. Authors will need to contact the NICE Managed Access Team for the full list of relevant individuals.

Patient Safety

- The company, and clinical MAOG members if applicable, have a responsibility to report any suspected unexpected serious adverse reactions (SUSARs) to the MAOG. The MAOG will assess any SUSARs and if there are safety concerns will take steps, as appropriate, to mitigate the risk including but not limited to updating the eligibility criteria or recommending that the managed access be halted.

Data protection

- Patient data collected as part of this Data Collection Arrangement will be managed in accordance with all applicable data protection legislation, including but not limited to the Data Protection Act 2018 and the UK General Data Protection Regulation.

- The terms of the Managed Access Agreement relating to data protection, as apply between NHSE and the company, shall also apply between the parties to this Data Collection Arrangement in relation to the performance of their obligations under this Data Collection Arrangement.

Equality considerations

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

☐ Yes ☐ No

- Due to the male-only clinical trial populations for this product, data collected within the managed access agreement will not obtain any data for female patients. However, given that there are no female patients with severe haemophilia B in the UK, we perceive this to have minimal impact. Moreover, real-world data will also be collected via the Phase IV, observational post-authorisation long-term follow-up study. Data pertaining to any female patients receiving etranacogene dezaparvovec will be collected within this.

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.