Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Australian Public Assessment Report for **Hemgenix**

Active ingredient: **etranacogene dezaparvovec**

Sponsor: **CSL Behring (Australia) Pty Ltd**

June 2024

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
AAV5	Adenovirus-associated viral vector serotype 5
ABR	Annualised bleeding rate
ACM	Advisory Committee on Medicines
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
APTT	Activated Partial Thromboplastin Clotting Time
ARTG	Australian Register of Therapeutic Goods
ASA	Australia-specific annex
AST	Aspartate aminotransferase
cf	Confer/conferatur (Compare; latin)
CI	Confidence interval
CMI	Consumer Medicine Information
DNIR	Dealings Not Involving Intentional Release
EMA	European Medicines Agency
EQ-5D-5L	EuroQol-5 dimension-5 levels
EU	European Union
FAS	Full analysis set
FDA	United States Federal Drugs Administration
FIX	Factor IX
FIX-Padua	Human coagulation factor IX variant R338L
gc	Genome copies
HB	Haemophilia B
HCC	Hepatocellular carcinoma
iPAQ	International physical activity questionnaire
IV	Intravenous

Abbreviation	Meaning
kg	Kilogram
LP1	Liver-specific promoter
NCE	New chemical entity
NSAIDS	Non-steroidal anti-inflammatories
OGTR	Office of Gene Technology Regulator
PI	Product Information
PSUR	Periodic safety update report
RMP	Risk Management Plan
QoL	Quality of life
SAE	Serious adverse event
TEAE	Treatment-emergent adverse event
TGA	Therapeutic Goods Administration
TRAE	Treatment-related adverse event
UK	United Kingdom
USA	United States of America
VAS	Visual analogue scale

Product submission

Submission details

Type of submission:	New Chemical Entity
Product name:	Hemgenix
Active ingredient:	Etranacogene dezaparvovec
Decision:	Approved for provisional registration
Date of decision:	15 March 2024
Date of entry onto ARTG:	19 March 2024
ARTG number:	405360
▼*Black Triangle Scheme*	Yes
Sponsor's name and address:	CSL Behring Australia Pty Ltd 189-209 Camp Road, Broadmeadows, VIC, 3047 Australia
Dose form:	Injection, intravenous infusion
Strength:	1 x 10^{13} genome copies (gc)/mL
Container:	Vial, Glass Type I Clear
Pack size:	12 × 10 mL multi-vial finished pack 24 × 10 mL multi-vial finished pack 36 × 10 mL multi-vial finished pack 48 × 10 mL multi-vial finished pack 10 mL vial
Approved therapeutic use for the current submission:	Hemgenix is an adeno-associated virus vector-based gene therapy indicated for the treatment of haemophilia B (congenital factor IX deficiency) in adults without a history of factor IX inhibitors, who: • currently use factor IX prophylaxis therapy, or • have current or historical life-threatening haemorrhage, or repeated, serious spontaneous bleeding episodes. The decision to approve this indication has been made on the basis of short-term efficacy and safety data from the clinical trial program. Continued approval of this indication depends on confirmation of longer-term benefit from ongoing clinical trials.
Route of administration:	Intravenous infusion
Dosage:	A single dose of 2 × 10^{13} gc per kilogram (kg) of body weight, corresponding to 2.0 mL/kg body weight. This is administered as an intravenous infusion after dilution with 0.9% sodium chloride solution (normal saline). The dose should be calculated as follows: Hemgenix dose (mL) = patient body weight (in kilograms) × 2

	For further information regarding dosage, such as dosage modifications to manage adverse reactions, refer to the Product Information.
Pregnancy category:	B2:
	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
	Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.
	The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Product background

This AusPAR describes the submission by CSL Behring Australia Pty Ltd (the Sponsor) to register Hemgenix (etranacogene dezaparvovec) for the following proposed indication:[1]

- Hemgenix is an adeno-associated virus vector-based gene therapy indicated for treatment of adults with haemophilia B (congenital factor IX deficiency) and with a pre-existing neutralising anti-AAV5 antibody titre below 1:700 to reduce the frequency of bleeding episodes and the need for factor IX replacement therapy who:
  - currently use factor IX prophylaxis therapy, or
  - have current or historical life-threatening haemorrhage, or repeated, serious spontaneous bleeding episodes.

The disease/condition

Haemophilia is an inherited bleeding disorder where the blood does not clot properly, leading to spontaneous bleeding. Haemophilia B (HB) is an inherited deficiency of Factor IX (FIX). The condition is an X-linked recessive disorder that predominantly affects males. Severity is classified as mild, moderate or severe depending on the residual or baseline factor activity level. Severe haemophilia is defined as <1% factor activity, moderate haemophilia is defined as a factor activity level ≥1% of normal and ≤5% of normal and mild haemophilia is defined as a factor activity level >5% of normal and <40% of normal.

The incidence of HB is approximately 1 in 15,000 to 1 in 30,000 live male births. Approximately one-third to half have severe disease (FIX activity <1% of normal).

[1] This is the original indication proposed by the Sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered in the Australian Register of Therapeutic Goods.

Current treatment options

There are currently no curative therapeutic options for HB and treatment is designed to prevent or treat severe bleeding and reduce mortality / morbidity. In Australia, haemophilia is managed in highly specialised centres and treatment aims to both manage and prevent bleeding episodes.

Treatment with FIX is currently the preferred therapy in HB. Patients with moderate deficiency with factor levels ≥ 1 IU/dl rarely experience spontaneous bleeding and have better preservation of joint function. To achieve clinical effect, factor levels do not need to remain ≥ 1 IU/dl at all times. The decision to commence prophylaxis is complex and individualised and the strategy may change over a patient's lifetime.

One major complication and limitation to treatment is the development of immunoglobulin G antibodies that deactivate the factor concentrate referred to as inhibitors. Inhibitors develop in <5% of individuals with HB. Regular monitoring for inhibitors dependent on amount of FIX concentrate exposure should occur, along with in patients with new lack of response to concentrate or prior to haemostatic challenge.

Prophylactic factor replacement can be used to prevent bleeding, this includes specific replacement prior to procedures. Prophylaxis can be short term (intermittent or on demand) or long term to convert a severe phenotype, to levels more consistent with a moderate or mild phenotype. Patients may switch from short- or long-term strategies or even cease at various time points depending on the clinical situation. Preventing bleeding can help avoid joint destruction.

Conservative measures to prevent or minimise bleeding include prolonged pressure post venepuncture, avoidance of aspirin and non-steroidal anti-inflammatories (NSAIDs), good oral hygiene, physical activity to promote bone health, use of central access venous devices and avoiding trauma prone activities. Home therapy is encouraged if available and preferred by patients. Other management priorities include prevention of complications (e.g. joint damage, FIX inhibitor development and blood product transmitted viral infections) which can also help improve quality of life (QoL).

Clinical rationale

Etranacogene dezaparvovec (Hemgenix) is a non-replicating adeno-associated viral vector-based gene therapy (serotype 5; AAV5). It is designed to deliver a codon-optimised coding sequence of the Padua variant of human FIX (hFIXco-Padua) under the control of a liver-specific promotor (LP1) (Figure 1). The hFIXco-Padua variant is a naturally occurring variant that differs from wild-type human FIX protein by a single amino acid which increases FIX activity 6- to 8-fold.

Etranacogene dezaparvovec preferentially targets liver cells where it resides, mostly in episomal form, directing expression of hFIX-Padua protein. The clinical rationale is to increase circulating FIX activity in patients with severe HB thereby reducing the frequency of bleeding episodes and the need for FIX replacement therapies.

Figure 1. Etranacogene dezaparvovec vector genome structure

Regulatory status

Australian regulatory status

Etranacogene dezaparvovec is not currently registered in Australia. Etranacogene dezaparvovec was granted Orphan Drug Designation on 30 August 2022 and extended on 22 February 2023. Etranacogene dezaparvovec was granted Provisional Designation on 20 December 2022.

The Office of Gene Technology Regulator (OGTR) evaluates the environmental issues associated with genetic products such as transport and disposal. A licence application for Dealings Not Involving Intentional Release (DNIR) was submitted to the OGTR on 28 November 2022 (DNIR-659).

International regulatory status

Etranacogene dezaparvovec was approved by the FDA on 22 November 2022. Etranacogene dezaparvovec received Orphan Drug Designation and Breakthrough Therapy Designation on 17 April 2019 and 25 January 2017 respectively.

Etranacogene dezaparvovec was granted conditional approval by the EMA on 20 February 2023 and the MHRA on 22 March 2023. Etranacogene dezaparvovec was designated an orphan medicine by the EMA on 21 March 2018 and approved for accelerated assessment on 12 November 2021, however the timetable was switched to standard during assessment.

Etranacogene dezaparvovec was approved by Health Canada on 23 October 2023.

Table 1. Hemgenix indication by region

Country/ Region	Indication
USA	Hemgenix is an adeno-associated virus vector-based gene therapy indicated for the treatment of adults with Hemophilia B (congenital Factor IX deficiency) who: • Currently use Factor IX prophylaxis therapy, or • Have current or historical life-threatening hemorrhage, or • Have repeated, serious spontaneous bleeding episodes.
EU and UK	Hemgenix is indicated for the treatment of severe and moderately severe Haemophilia B (congenital Factor IX deficiency) in adult patients without a history of Factor IX inhibitors.
Canada	Hemgenix (etranacogene dezaparvovec) is indicated for treatment of adults (aged 18 years of age or older) with Hemophilia B (congenital Factor IX deficiency) who require routine prophylaxis to prevent or reduce the frequency of bleeding episodes. There is no clinical experience of Hemgenix use in patients with mild or moderate Hemophilia B (FIX activity > 2%).

Registration timeline

This submission was evaluated under the provisional registration process.

Table 2 captures the key steps and dates for this submission.

Table 2: Hemgenix evaluation (submission PM-2023-00668-1-6) – key dates

Description	Date
Designation (Orphan)	30 August 2022
Determination (Provisional)	20 December 2022
Submission dossier accepted and first round evaluation commenced	31 March 2023
First round evaluation completed	30 August 2023
Sponsor provides responses on questions raised in first round evaluation	4 October 2023
Second round evaluation completed	15 November 2023
Delegate's[2] Overall benefit-risk assessment and request for Advisory Committee advice	8 January 2024
Sponsor's pre-Advisory Committee response	22 January 2024
Advisory Committee meeting	February 2024
Registration decision (Outcome)	15 March 2024
Administrative activities and registration in the ARTG completed	9 April 2024
Number of working days from submission dossier acceptance to registration decision*	258 days

*Statutory timeframe for standard submissions is 255 working days

Submission overview and risk/benefit assessment

Quality evaluation summary

The quality Evaluator raised no objections to the provisional approval of Hemgenix (etranacogene dezaparvovec). The Sponsor has committed to providing additional data as part of a minor variation before the product is launched in the Australian market. The PI, CMI and labels were satisfactory from a quality perspective.

Etranacogene dezaparvovec is a non-replicating recombinant adeno-associated viral vector serotype 5 (AAV5) containing the cDNA for human coagulation factor IX variant R338L (FIX-Padua) under the control of a liver-specific promoter. Hemgenix is produced by co-infection of *Spodoptera frugiperda* Sf9 insect cells, with recombinant baculoviruses. The AAV5 is then purified and concentrated.

[2] In this report the 'Delegate' is the Delegate of the Secretary of the Department of Health and Aged Care who decided the submission under section 25 of the Act.

The drug product (DP) is formulated at 1 x 10^{13} vector genome copies (gc)/mL. The finished drug product is provided as a preservative-free, concentrate for solution for intravenous (IV) infusion, with a nominal concentration of 1 × 10^{13} gc/mL in a single-use 10 mL glass vial.

The recommended dose for a single-dose IV infusion is 2 x 10^{13} vector gc/kg of body weight (following dilution with 0.9% saline). Following IV infusion, etranacogene dezaparvovec preferentially transduces liver cells, leading to LP1 promoter-directed long-term expression of FIX-Padua.

The quality of the product is considered acceptable when used in accordance with the conditions defined in the PI, labels, CMI and the ARTG. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. From a quality perspective, compliance with Therapeutic Goods Legislation (TG Act/Regs) and relevant Therapeutic Goods Orders as well as consistency with relevant guidelines and the Australian Regulatory Guidelines for Prescription Medicines has been demonstrated.

Nonclinical (toxicology) evaluation summary

The nonclinical Evaluator raised no objections to the registration of Hemgenix for the proposed indication.

Most of the submitted nonclinical studies were performed with AMT-060, a predecessor of etranacogene dezaparvovec designed to express wild-type human FIX (hFIX). AMT-060 and etranacogene dezaparvovec differ only by two nucleotides that encode the hFIX-R338L substitution of the Padua variant. Findings for AMT-060 are considered applicable to etranacogene dezaparvovec.

Primary pharmacology studies were performed in wild-type mice and monkeys, and in a mouse model of HB. Supporting the utility of etranacogene dezaparvovec for the proposed indication, dose-dependent delivery of vector DNA to the liver, hepatic transgene expression, circulating hFIX protein and increased plasma FIX activity were demonstrated after single IV administration in animals.

ECG was unaffected in monkeys treated with either etranacogene dezaparvovec or AMT-060. There were no clinical signs observed in the general toxicity studies in mice and monkeys to indicate effects on CNS or respiratory function.

The highest levels of vector DNA following IV administration of etranacogene dezaparvovec were detected in liver in both mice and monkeys. Transgene expression analysis of various tissues in monkeys revealed hFIX mRNA expression was highest in liver.

Shedding of AMT-060 vector DNA into urine and saliva was shown in monkeys. Shedding into faeces was not examined in animals.

General toxicity studies were performed with etranacogene dezaparvovec or AMT-060 in male mice and monkeys. Treatment was well tolerated, with notable findings limited to a low incidence of pulmonary thrombosis in mice (occurring in the context of supraphysiological plasma FIX activity) and a transient increase in serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in monkeys.

Integration of AMT-060 vector DNA into liver genomic DNA in mice and monkeys occurred at low levels. Integration was not preferentially next to or within genes implicated in malignant transformation and there was no sign of resultant clonal expansion. The integration profile does not raise particular concerns for carcinogenicity. Further allaying carcinogenic concern, no proliferative lesions were observed in treated animals.

Fertility was shown to be unaffected in male mice treated with AMT-060. Vector DNA was detected in sperm and male reproductive tissues. Paternal germline transmission was not observed.

No embryofetal development studies have been performed, justified by the almost exclusively male patient population, and warranting assignment of the product to Pregnancy Category B2.

Clinical evaluation summary

Summary of clinical studies

The clinical Evaluator recommended provisional approval of Hemgenix although recommended changes to the wording of the indication relating to the presence of FIX inhibitors.

The clinical dossier included interim reports from one pivotal Phase 3 study (CT-AMT-061-02, also referred to as HOPE B or CSL222_3001) and a supportive Phase 2b study (CT-AMT-061-01, also referred to as CSL222_2001), both using AMT-061, and a final report from a supportive Phase 1/2 study (CT-AMT-060-01, also referred to as CSL220_1001) using the earlier formulation AMT-060. All studies were conducted in male adult subjects with severe or moderately severe HB (Table 3).

Table 3. Summary of clinical studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report
Phase 1/2	CT-AMT-060-01	Module 5.3.5.2 CT-AMT-060-01 5-year CSR	To investigate an AAV vector containing a codon-optimized human FIX gene (AAV5-hFIXco; AMT-060) administered to adult subjects with severe or moderately severe hemophilia B	Open-label, uncontrolled, single-dose, dose-ascending	AMT-060 Cohort 1: 5 subjects received 5×10^{12} gc/kg Cohort 2: 5 subjects received 2×10^{13} gc/kg Single IV dose	10	Adult subjects with severe or moderately severe hemophilia B	Single dose with follow-up for 5 years postdose: 1 year Post-treatment Follow-up Period and 4 year Long-term Follow-up Period	Completed Final CSR (5 years): 06 January 2022
Phase 2b	CT-AMT-061-01	Module 5.3.5.2 CT-AMT-061-01 3-year CSR	To confirm the FIX activity level of etranacogene dezaparvovec (AAV5-hFIXco-Padua, AMT-061) administered to adult subjects with severe or moderately severe hemophilia B	Open-label, uncontrolled, single-dose, single-arm	Etranacogene dezaparvovec 3 subjects received 2×10^{13} gc/kg Single IV dose	3	Adult subjects with severe or moderately severe hemophilia B	Single dose with follow-up for 5 years postdose: 1 year Post-treatment Follow-up Period and 4 year Long-term Follow-up Period	Ongoing Interim CSR (3 years): 11 May 2022 Final CSR expected: December 2023
Phase 3	CT-AMT-061-02	Module 5.3.5.2 CT-AMT-061-02 2-year CSR	To demonstrate noninferiority of etranacogene dezaparvovec (AAV5-hFIXco-Padua, AMT-061) during the 52 weeks of stable FIX expression (Months 6 to 18) after administration to adult subjects with severe or moderately severe hemophilia B, compared with standard of care continuous routine FIX prophylaxis during the Lead-in Phase, as measured by ABR	Open-label, uncontrolled, single-dose	Etranacogene dezaparvovec 53 subjects received 2×10^{13} gc/kg 1 subject received approximately 10% of the 2×10^{13} gc/kg dose Single IV dose	54	Adult subjects with severe or moderately severe hemophilia B	≥ 6-month Lead-in Period with standard of care FIX prophylaxis Single dose of AMT-061 with follow-up for 5 years postdose: 1 year Post-treatment Follow-up Period and 4 year Long-term Follow-up Period	Ongoing Interim CSR (2 years): 20 June 2022 Final CSR expected: July 2025

AAV = adeno-associated virus; AAV5 = adeno-associated virus serotype 5; AAV5-hFIXco = Recombinant adeno-associated viral vector containing a codon-optimized human coagulation factor IX cDNA; AAV5-hFIXco-Padua = recombinant adeno-associated viral vector containing a codon-optimized Padua derivative of human coagulation factor IX cDNA (etranacogene dezaparvovec); ABR = annualized bleeding rate; AMT-060 = AAV5-hFIXco (predecessor of etranacogene dezaparvovec); cDNA = complementary DNA; CSR = Clinical Study Report; FIX = factor IX; IV = intravenous; gc/kg = genome copies per kilogram; hFIX = human factor IX.

Pharmacology

Pharmacokinetics

Conventional pharmacokinetic (PK) studies are not required for viral vector-based gene therapies. Biodistribution, vector shedding, and the kinetics of FIX activity and FIX protein levels were characterised in two clinical studies: Phase 2b Study CT-AMT-061-01 and Phase 3 Study CT-AMT-061-02.

As etranacogene dezaparvovec is administered IV, there is no absorption data. Gene therapy derived FIX protein is produced in the liver and is expected to undergo similar distribution and metabolism to the native protein. No radiolabel studies have been performed to assess elimination.

Vector shedding

Vector shedding occurs in saliva, nasal secretions, urine and faeces. In CT-AMT-061-01 and CTAMT-061-02 a status of no longer shedding was attained once vector DNA was negative for > 3 consecutive time points. In CT-AMT-061-01, 2 of the 3 subjects attained the status of no longer

shedding vector DNA. The time to first negative shedding in blood occurred at a mean of 54.71 weeks (range 31.1-78.3) and in semen at a mean of 26.21 weeks (range 26.1-26.3).

In CT-AMT-061-02, clearance of vector DNA from semen was achieved in 32/54 (59.3%) subjects at a median of 47.3 weeks. At month 24, 59.4% of subjects reached absence of shedding from semen. At most recent testing (month 24), 51/54 subjects had a negative test result. Clearance of vector DNA was achieved in blood by 30/54 (55.6%) subjects at a median of 52.3 weeks. A total of 56% (30/54) of subjects reached absence of vector DNA from blood by month 24. At most recent testing (month 24), 53/54 subjects had a negative test result.

FIX activity

Study CT-AMT-060-01 included 10 subjects, cohort 1 (5 subjects) were dosed with AMT-060 at $5x10^{12}$ gc/kg and cohort 2 (5 subjects) were dosed at $2x10^{13}$ gc/kg. All subjects were able to maintain an endogenous FIX activity of > 2%. Mean endogenous FIX activity in cohort 1 were 2.8-8.2% and in cohort 2 was 4-10.7%. In cohort 1, 3/5 subjects achieved a FIX activity of > 5% (i.e. converted from severe or moderately-severe to mild deficiency). In cohort 2, 4/5 subjects achieved FIX activity of > 5% with the remaining subject having FIX activity levels of 4%. At the final visit, the mean FIX activity (aPTT) was 8.3% (range 6.3-11.8) in cohort 1 and 6.6% (range 3.8-8.3) in cohort 2. FIX protein concentration for cohort 1 varied from 6.4-33.89% during visit 13 to 35. In cohort 2 the variation was 7.57-10.54% from visit 13-16 and 21.64-32.40% from visit 17-35.

Study CT-AMT-061-01 included three subjects who received a dose of 2 x 10^{13} gc/kg AMT-061 (etranacogene dezaparvovec). FIX activity at 6 weeks post dosing was 37.8%, 30.0%, and 23.9% for each patient (mean 30.57%). FIX activity at 52 weeks were 50.2%, 40.8% and 31.3% for the 3 patients (mean 40.77%). Mean FIX activity of > 5% were achieved by week 3 and maintained through to month 36. The uncontaminated FIX protein concentration ranged between 3.91-5.69%, 3.7-5.57% and 2.16-5.29% in the 3 subjects, respectively.

Study CT-AMT-061-02 included 54 subjects who received a dose of 2 x 10^{13} gc/kg etranacogene dezaparvovec. A statistically significant increase from baseline FIX activity was observed at 6 months [36% (31.47-40.54) p<0.0001], 12 months [38.81% (34.01-43.60) p<0.0001] and 18 months [34.31% (29.52-39.31) p<0.0001]. FIX protein levels were also increased by week 3 to month 24 but at a lower level compared to FIX activity.

Special populations

Patients with significant hepatic dysfunction or fibrosis were excluded from the studies. Lower levels of FIX activity were observed in patients with a controlled attenuation parameter (CAP) score of > S2.

Etranacogene dezaparvovec has not been studied in subjects with severe renal impairment. Subjects with mild renal impairment had higher FIX activity levels than those with normal renal function. A subject with moderate renal impairment, also achieved FIX activity levels similar to the baseline population with some readings higher than in those with normal renal function.

Etranacogene dezaparvovec has not been evaluated in the paediatric population.

Analyses of CT-AMT-061-02 of patients ≥ 60 years old found that they generally had higher FIX activity levels than those aged 40-60 years or <40 years. However, interpretation was limited by small numbers of patients.

All subjects enrolled in the clinical development program were male.

Pharmacodynamics

The pharmacodynamic (PD) properties of etranacogene dezaparvovec were characterised in phase 2b Study CT-AMT-061-01 and phase 3 Study CT-AMT-061-02. The primary PD effects of FIX protein concentration and protein levels are discussed above as is the secondary PD effect of viral vector shedding.

In the phase 3 study, 11.1% of subjects had an AAV5 capsid-specific T cell response at baseline. In response to etranacogene dezaparvovec, this increased to a maximum at week 6 of 39.5% of patients and 72.2% had at least one visit documenting an AAV5 capsid-specific T cell response.

Information regarding the relationship between drug concentration and pharmacodynamic effects is limited.

Dose selection

Selection of the proposed dose was based on the dose-ranging study CT-AMT-060-01 which evaluated the earlier formulation of proposed drug product. The Phase 2 study (CT-AMT-061-01) and pivotal Phase 3 study (CT-AMT-061-02) only evaluated a single dose (proposed dose 2 x 10^{13} gc/kg). Whilst this dose appears to achieve the aim, it is unclear whether a lower dose would be adequate given that compared to AMT-060, AMT-061 has a 6- to 9-fold increase in function with the same protein expression.

Efficacy

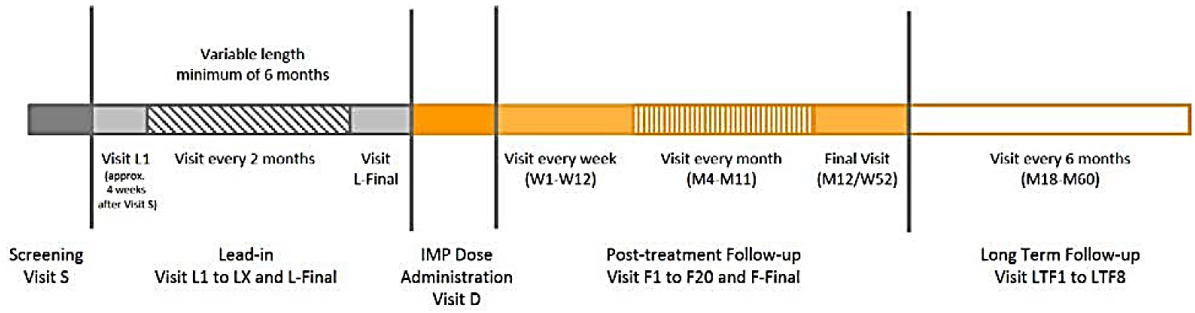
Study CT-AMT-061-02

A two-year interim analysis was submitted for ongoing pivotal study CT-AMT-061-02 (HOPE B study), a Phase III, open-label, single-dose, multi-centre multinational trial of AMT-061 (etranacogene dezaparvovec). The primary objective was to demonstrate non-inferiority of AMT-061 (2 x 10^{13} gc/kg) during the 52 weeks following establishment of stable FIX expression (months 6-18) post-treatment (AMT-061) follow-up compared to standard of care continuous routine FIX prophylaxis during the lead-in phase, as measured by the annualised bleeding rate (ABR). The main secondary objectives were to investigate effects of AMT-061 at 2 x 10^{13} gc/kg on:

- Endogenous FIX activity at 6, 12 and 18 months after AMT-061 and trough FIX activity
- Annualised consumption and infusion rate of FIX replacement therapy
- Discontinuation of routine prophylaxis
- Prevention of bleedings (superiority comparison), spontaneous bleeding and joint bleeding including occurrence and resolution of target joints and proportion of patients with zero bleeding episodes during the 52 weeks following stable FIX levels
- Estimated ABR during 52 weeks following stable FIX expression
- Comparison of pre and post treatment anti-AAV5 antibody titres
- Quality of life metrics (international physical activity questionnaire (iPAQ) and EuroQol-5 dimensions-5 levels (EQ-5D-5L) Visual Analogue Scale (VAS).

The study consisted of a screening period, a lead-in period where the subject received usual recombinant FIX (minimum 26-weeks), treatment with AMT-061, post treatment follow-up (1 year) and long-term follow-up (4 years) (Figure 2).

Figure 2. CT-AMT-061-02 Study Design



D = dosing; F = Post-treatment Follow-up; IMP = investigational medicinal product; L = Lead-in; LTF = Long-term Follow-up; M = month; S = Screening; W = week

The study included adult males with severe or moderately severe FIX deficiency (<2% FIX activity) for which they received continuous FIX prophylaxis. Patients with a history of FIX inhibitors or a positive inhibitor screening test were excluded. During the study, continuous routine FIX prophylaxis was prohibited if FIX activity was >5%. Re-initiation of FIX prophylaxis was considered if FIX levels were 2-5% and mandated if FIX levels were <2%. On demand or intermittent prophylaxis was at the discretion of the investigator. Infusions were not recommended if FIX levels were >40%.

All subjects received a single IV dose of AMT-061 at 2 x 10^{13} gc/kg after a minimum of 26 weeks of lead-in therapy. Within subject comparison was done with each patient acting as their own control during lead-in prior to intervention.

A non-inferiority margin of 1.8 was selected for the rate ratio of ABR between AMT-061 (post-treatment) and FIX prophylaxis (lead-in). An ABR of 2.4 between FIX prophylaxis and placebo treatment was assumed.

Overall, 75 subjects were screened, 67 entered the lead-in period (89.3%) and 54 received AMT-061 (60.6%) and constituted the full analysis set (FAS). Fifty-three subjects completed treatment and were included in the per protocol (PP) population. One patient received a partial dose due to an infusion reaction. Two patients withdrew from the study (3.7%), one due to an adverse event (AE) and the other withdrew consent.

The average age of patients in the full analysis set (FAS) was 41.5 years and the majority (74.1%) were white, and all subjects were male. 94.4% were negative for HIV, 16.7% had prior resolved hepatitis B and 57.4% had prior or ongoing hepatitis C.

Baseline pre-dose anti-AAV5 titre was < 1:3000 in 53/54 patients. Most patients had severe HB at diagnosis (81.5%) and the remainder had moderately severe disease (18.5%). In the year prior, 81.5% of patients experienced a bleeding episode (55.6% experienced joint bleeding, 55.6% spontaneous bleeding, 37% traumatic bleeding and 20.4% unknown bleeding episodes). Only 18.5% of patients had not experienced any bleeding episodes in the last year with 16.7% experiencing one, 18.5% experiencing two and 14.8% experiencing three bleeds.

Prophylactic FIX replacement was used in 100% of patients with only 7.4% having on demand therapy. FIX replacement was generally extended half-life products (57.4%). Corticosteroids were used in the lead-in period in 7.4% including local and IV use. This increased in the post treatment period to 37% receiving systemic corticosteroids with mean number of days of usage being 41.6 days. Post treatment, 16.7% received oral corticosteroids for transaminase elevations with mean number of days for this indication being 79.8 days. IV steroids for infusion reactions

were used in 5.6% at baseline. 21/54 patients had pre-existing neutralising AAV5 antibody titres.

The primary endpoint was met, demonstrating the non-inferiority of etranacogene dezaparvovec, with a reduction in the ABR for all bleeding episodes from the lead-in period of 4.19 (95% CI: 3.22-5.45) to 1.51 (95% CI: 0.81-2.82) in months 7-18 (64% reduction, CI 36-80% p=0.0002). This translated into an adjusted ABR ratio of lead-in period to months 7-18 post treatment of 0.36 (95% Wald CI: 0.2-0.64) (Table 3).

Results for the secondary endpoints are outlined in Table 4. Changes in FIX activity are discussed in the PK section above. There was a significant reduction in the mean annualised consumption of FIX replacement -3056.8 IU/kg/year [(95% CI -3642.8, -2470.8) p<0.0001]. After AMT-061 treatment, 52/54 (96.3%) of patients ceased FIX prophylaxis and remained free of routine prophylaxis from months 7-24. The subjects who did require FIX prophylaxis either did not receive the full AMT-061 dose or had an elevated baseline anti-AAV5 NAb titre (1:3213.3).

In the lead-in period, 43/54 (79.6%) of patients had FIX trough levels <12%. This improved to 4/51 (7.8%) at 3 months, 3/50 (6%) at month 18, and 5/50 (10%) at month 24. The OR of having FIX levels <12% for months 7-18 following AMT-061 treatment was 0.027 [(95% CI: 0.009-0.080) p<0.0001].

Superiority was met for adjusted ABR months 7-18 compared to lead-in (ABR ratio 0.36 (0.2-0.64) p=0.0002).

The adjusted ABR lead-in compared to months 7-18 for spontaneous bleeding episodes was 0.29 (95% CI: 0.12-0.71) p=0.0034. This translated from a spontaneous bleeding episode ABR in lead-in of 1.52 (95% CI: 1.01-2.30) and in months 7-18 of 0.44 (95% CI: 0.17-1.12).

The adjusted ABR ratio of lead-in compared to months 7-18 for joint bleeding was 0.22 (95% CI: 0.10-0.46) p<0.0001. This translated from a lead-in ABR for joint bleeding of 2.35 (95% CI: 1.74-3.16) compared to 0.51 (95% CI 0.23-1.12) in months 7-18. Statistical significance was not achieved for the quality-of-life measures iPAQ and EQ-5D-5L VAS.

Table 4. CT-AMT-061-02: Summary of Type I Error-Controlled Primary and Secondary Endpoints After 18 Months Post-treatment (Full Analysis Set)

Endpoint	Point Estimate	95% CI	One-sided p-value	Statistical Significance[1]
Primary Efficacy				
Adjusted ABR Ratio (Month 7 to 18 Post-treatment: Lead-in Period) for Non-inferiority[2]	0.36	0.20, 0.64	NA	Yes
Secondary Efficacy				
Change From Baseline One-stage (aPTT-based) FIX Activity (%) at 6 Months Post-treatment	36.00	31.47, 40.54	<0.0001	Yes
Change From Baseline One-stage (aPTT-based) FIX (%) Activity at Year 1 Post-treatment	38.82	34.04, 43.60	<0.0001	Yes
Change From Baseline One-stage (aPTT-based) FIX (%) Activity at Month 18 Post-treatment	34.31	29.52, 39.11	<0.0001	Yes
Mean Difference in Annualized Consumption of FIX Replacement Therapy Use (IU/kg/yr; Month 7 to 18 Post-treatment – Lead-in Period)	-3056.8	-3642.8, -2470.8	<0.0001	Yes
Adjusted Ratio for Annualized Infusion Rate of FIX Replacement Therapy (Month 7 to 18 Post-treatment: Lead-in Period)	0.03	0.01, 0.10	<0.0001	Yes
Odds Ratio One-stage (aPTT-based) FIX Activity <12% of Normal (Month 6 to 18 Post-treatment: Lead-in Period)	0.036	0.014, 0.093	<0.0001	Yes
Adjusted ABR Ratio (Month 7 to 18 Post-treatment: Lead-in Period) for Superiority	0.36	0.20, 0.64	0.0002	Yes
Adjusted ABR Ratio (Month 7 to 18 Post-treatment: Lead-in Period), Spontaneous Bleeding Episodes	0.29	0.12, 0.71	0.0034	Yes
Adjusted ABR Ratio (Month 7 to 18 Post-treatment: Lead-in Period), Joint Bleeding Episodes	0.22	0.10, 0.46	<0.0001	Yes

Endpoint	Point Estimate	95% CI	One-sided p-value	Statistical Significance[1]
LS Mean Difference in iPAQ Total Physical Activity Score (Post-treatment Period 1st Year – Lead-in Period)	-721.2	-1770.6, 328.3	0.9121	No
LS Mean Difference in EQ-5D-5L VAS (Post-treatment Period 1st Year – Lead-in Period)	0.1	-3.5, 3.8	0.4753	No

Abbreviations: ABR = annualized bleeding rate; aPTT = activated partial thromboplastin time; CI = confidence interval; EQ-5D-5L = EuroQol-5 Dimensions-5 Levels; FIX = Factor IX; iPAQ = International Physical Activity Questionnaire; LS = least squares; NA = not applicable; VAS = visual analog scale.
The lead-in period was ≥6 months.

1. Statistical significance was determined by sequential testing and was not assessed for the endpoints listed after the first non-significant result.
2. The upper limit of the CI of the rate ratio was compared to the non-inferiority margin of 1.8. If the upper limit was <1.8, then non-inferiority was declared.

Anti-AAV5 neutralising antibody titre

For subjects with an anti-AAV5 NAb titre < 1:3000, 75.5% (40/53) experienced bleeding episodes in lead-in compared to 35.8% (19/53) in months 7-18 and 49.1% in months 7-24

(26/53). The adjusted ABR ratio for lead-in compared to months 7-18 was 0.28 (Wald 95% CI: 0.17-0.43; p<0.0001). This is based on adjusted ABR in lead-in of 3.89 (95% CI: 2.95-5.16) compared to 1.017 (95% CI: 0.63-1.82) at months 7-18. This result excludes one patient with an anti-AAV5 NAb titre of 1:3212.3 from the FAS who did not respond to AMT-061. The adjusted ABR in months 7-18 for patients with positive baseline anti-AAV5 NAbs was 8.77 (95% CI: 1.97-39.06) compared to 0.93 (95% CI: 0.44-1.98) for those who were negative. In the lead-in the adjusted ABR for patients with positive anti-AAV5 NAbs was 4.97 (95% CI: 3.66-6.75). Following treatment with AMT-061, the adjusted ABR ratio for patients with positive anti-AAV5 NAbs was 1.77 (0.41-7.62, p=0.2232). This was not considered significant; however, the result was significant for patients with a titre < 1:3000. FIX activity was generally higher for those without anti AAV5 NAbs (n=33) compared to those with NAbs (n=21).

FIX levels for patients with pre-existing anti-AAV5 NAb titres were generally less than those without pre-existing antibodies. No significant correlation was observed between month 24 FIX activity levels and pre-treatment anti-AAV5 NAb titre; analysis done following both inclusion and exclusion of the subject with titres > 1:3000 showed similar results.

Study CT-AMT-060-01

Phase I/II study CT-AMT-060-01 was an open-label, uncontrolled, single-dose, dose-ascending, multi-centre trial of AMT-060 in patients with severe or moderately severe HB. AMT-060 was the predecessor of etranacogene dezaparvovec, designed to express wild-type hFIX. All patients were male and lacked FIX inhibitors or AAV NAbs. Cohort 1 (5 subjects) was dosed with AMT-060 at 5 x 10^{12} gc/kg and cohort 2 (5 subjects) was dosed at 2 x 10^{13} gc/kg.

The primary objective was to investigate the safety of systemic administration of AMT-060.

The secondary efficacy endpoints investigated the effect of AMT-060 on the following:

- FIX activity level
- Use of FIX replacement therapy
- On bleeding episodes
- On QoL parameters

In cohort 1 100% of patients were white, compared with 80% in cohort 2. The mean age of cohort 1 was 60.2 years, whereas cohort 2 was younger (38.2 years). Mean weight was similar between cohorts (83.6kg and 83.2kg, respectively). A total of 4/5 patients in cohort 1 and 2/5 in cohort 2 had a history of hepatitis C infection. One subject in cohort 1 had anti-viral controlled HIV with an undetectable viral load.

FIX activity level is discussed above in the PK section. FIX replacement usage was reduced in both cohorts although baseline mean ABR was higher in cohort 1. The total mean ABR in the year prior to screening was 14.40 and 4.00 in cohorts 1 and 2, respectively. This reduced to 5.39 and 0.71, respectively, in the post-tapering period. The mean spontaneous ABR also reduced from 9.80 in the year prior to screening to 3.00 in cohort 1 and from 3.38 to 0.21 in cohort 2. QoL measures remained similar over the course of the study.

Study CT-AMT-061-01

CT-AMT-061-01 was a phase IIb, open-label, uncontrolled, single-dose, dose-ascending, multi-centre study of AMT-061 in patients with severe or moderately severe HB. All three subjects received a single dose of AMT-061 at 2 x 10^{13} gc/kg. The study consisted of a maximum of 6 weeks screening period, dosing (separated by at least 14 calendar days) and then post-treatment follow up for 5 years.

The primary objective of this study was: to confirm that a single dose of 2 x 10^{13} gc/kg AMT-061 resulted in FIX activity levels of > 5% at 6 weeks after dosing.

Secondary endpoints were to assess the effect of 2 x 10^{13} gc/kg of AMT-061 on:

- endogenous FIX level at 52 weeks
- Discontinuation of previous continuous prophylaxis
- On total usage of FIX replacement therapy
- On ABR
- On specific types of bleeding events (e.g., spontaneous, joint and traumatic bleeds)

FIX activity level is discussed above in the PK section. Endogenous FIX levels increased at week 3 and remained elevated compared to baseline at week 52.

All subjects discontinued routine prophylaxis. Two subjects did not receive further FIX replacement after AMT-061 administration. The mean annualised FIX usage per year at screening was 299330.7 IU/year. Following administration of AMT-061, this reduced to 1157.2 IU/year. Post continuous prophylaxis mean usage was 714.6 IU/year overall, 583.3 IU/year in year 1 and 1133.3 IU/year in year 2.

The ABR after continuous prophylaxis discontinuation was 0.22 over 3 years of follow up. Two subjects did not experience bleeding post AMT-061. The remaining subject experienced 2 bleeding episodes occurring in the first 18 months post dosing (1 traumatic and 1 spontaneous). The ABR for spontaneous and traumatic bleeds post-continuous prophylaxis were both 0.11.

Safety

A total of 57 patients were exposed to AMT-061 over 2 studies and 10 patients were exposed to the precursor AMT-060. Three patients from CT-AMT-061-01 have been followed for 3 years, the remaining 54 patients in CT-AMT-061-02, have been followed for 2 years. No integrated safety analysis was submitted.

In all 3 studies, 100% of subjects experienced at least 1 treatment emergent adverse event (TEAE). In the phase 3 study, there were 54 patients who received AMT-061 and 67 controls in the lead-in period. In the lead in period, 62.7% of patients experienced 103 events compared with post-treatment where 100% of patients experienced 557 events. In the post treatment period, 100% of patients experienced mild TEAEs (424/557), 68.5% moderate (115/557) and 20.4% severe (18/557). In the post-treatment period, 22.2% experienced an adverse event of special interest (AESI; 19/557 events), 25.9% a serious adverse event (SAE; 17/557 events) and there was one death (1.9%).

In the phase 3 study, 70.4% of patients experienced treatment related adverse events (TRAEs). These were most commonly ALT increased, headache, influenza-like illness, AST increased, fatigue, CPK increased, dizziness, nausea, infusion related reaction and arthralgia. Infusion related reactions occurred in 3/21 (14.3%, 3 events) in the AAV5 positive population compared to 3/54 (5.6%) in the overall population. The one patient with TRAE drug ineffective and hypersensitivity occurred in this subpopulation (1/21, 4.8%). Skin and subcutaneous tissue disorder was overall increased compared to the general trial population (3/21 14.3% cf 3/54 5.6%) which included the TRAEs of night sweats, psoriasis and urticaria.

In the Phase 3 study, there was 1 fatality 15 months post treatment. The patient experienced cardiogenic shock preceded by bacterial urinary tract infection with features of systemic infection (AE of urinary sepsis was not considered an SAE) and a previous SAE of atrial

fibrillation. The subject had a history of atrial fibrillation, biatrial enlargement and hypertension. The event was judged as not related.

There was also a death reported after the completion of study CT-AMT-060-01. The patient was in cohort 1 and the death was an unexpected and unwitnessed and cause of death was unable to be determined. The investigator determined the death to be unlikely to be treatment-related. This is of concern, as this study has the longest safety follow up in the dossier (5 years). Related SAEs in this study were related to transaminitis and pyrexia. Unrelated SAEs were renal colic/calculus and myelopathy. A plausible alternate mechanism for myelopathy exists. It is noted that only a small number of patients have received treatment with etranacogene dezaparvovec and renal calculi was also observed as an SAE in CT-AMT-061-02 (in subject with PMHx).

In the Phase III study, 25.9% of subjects experienced SAEs in the post-treatment period, most commonly related to infections. There were 2 episodes of blood loss anaemia with documented causes. Hepatocellular carcinoma (HCC) occurred in 1 subject (1.9%). This subject had a history of cleared hepatitis, A, B and C and did not have significant fibrosis/cirrhosis on baseline abdominal US. Causality as not related was determined by genetic analysis of the tumour compared to control excluding vector integration with expansion. The tumour also showed mutations consistent with increased risk of HCC in chronic hepatitis C patients. It is important to exercise caution and monitoring for risk of HCC considering the mechanism of action and novel nature of the IP.

Six subjects (11%) experienced malignancies (basal cell carcinoma, gastrointestinal lymphoma, hepatocellular carcinoma, pancreatic neuroendocrine tumour and prostate cancer), three of which were classified as adverse events of special interest (AESI).

AESI were similar across the studies, mainly relating to product administration, reactions including allergy, lack of efficacy, transaminitis and new/recurrent cancers. In the Phase 3 study 22.2% experienced AESI post-treatment with 73.7% of events being treatment related. AESI's related to IMP administration in 11.1% of subjects and hypersensitivity accounted for one further AESI. Five of 7 subjects were positive for anti-AAV5 antibodies. Three of 54 experienced AESI related to new or recurrent cancers (HCC, prostate cancer and basal cell carcinoma) which were determined as not treatment related. An AESI of drug ineffective was recorded in the subject with an AAV-5 antibody titre > 1:3000. AESIs during CT-AMT-061-01, were related to transaminitis, drug ineffectiveness (cohort 1) and anxiety.

An analysis by anti-AAV5 NAb status found rates of AEs were generally similar with exception of 'neoplasms, benign, malignant and benign breast neoplasm' which was higher in the anti-AAV5 NAb positive group (4/21 19% cf 2/33 6.1%). In the anti-AAV5 positive subgroup, 8/21 (38.1%) experienced 11 SAEs (including an event of hepatocellular carcinoma). The SAE of cardiogenic shock occurred in the anti-AAV5 positive subgroup. In the anti-AAV5 negative group, 6/33 (18.2%) experienced 6 SAEs.

None of the studies formally evaluated cardiac toxicity with no ECG monitoring in the schedule of activities.

Across 3 studies, there was only one TRAE/AESI of hypersensitivity that led to treatment discontinuation. The TRAE/AESI resulted in discontinuation of treatment and a partial dose of 10% of IP being delivered.

Transaminase elevations were reported frequently across all three studies but usually mild to moderate in nature and transient. These were assessed as not related. In CT-AMT-061-01, 2/3 (66.6%) of subjects experienced AST and/or ALT rises which were not managed with glucocorticoids. No permanent liver dysfunction has been recorded. Related transaminase elevations treated with steroids have not led to ongoing liver dysfunction. There did not seem to

be significant difference in the rates of liver dysfunction between the anti-AAV5 positive and negative subgroups. Significant alpha-fetoprotein rises have not occurred. Caution in interpreting causality of new hepatic steatosis and HCC should be exercised.

No significant changes in renal function were seen. The most common other biochemical abnormalities were CRP (7.4%) and CPK rises (14.8%). CPK rise is included in the PI, however CRP is not. CRP rises would be a questionable clinical significance and so this decision seems reasonable.

Overall, 7.4% (4/54) of subjects experienced anaemia (in 4 events) and iron deficiency anaemia in 3/54 (5.6%, 3 events). However, overall mean haematological values remained in reference ranges. Anaemia is not mentioned in the PI, however, in this population with frequent bleeding episodes, some degree of anaemia would seem expected. Hypertension was noted in 1/3 (33.3%) in CT-AMT-061-01 and 6/54 (11.1%) in the post treatment period compared to 1/67 (1.5%) in the lead-in period of CT-AMT-061-02. This has been classified and not related and not mentioned in the PI. However, given the change in rates it would be prudent to use caution when reporting this (although increase in vital signs measurement in trial circumstances may account for it given population prevalence). Vital sign abnormalities in CT-AMT-061-02, apart from hypertension were mostly related to infusion type reaction events (pyrexia, chills, hot flush, flushing, feeling hot) which occurred in 10/54 (18.5%) overall.

IL-2 levels showed a transient increase post dosing in 11.2% following week 1 and returned to normal by month 4. IFNγ also showed an increase, with all subjects having elevated levels at week 1 and then remaining elevated in the majority of subjects until month 12. However, the mean baseline and month 12 values were not significantly different (in fact month 12 was lower). This is of unclear clinical significance.

Overall, the data supports that etranacogene dezaparvovec is safe in HB. Most TRAEs were mild or moderate in nature with notable TRAEs being infusion reactions and transaminitis, which was transient and glucocorticoid responsive. Some TRAEs, mainly infusion related reactions and SAEs were more common in the anti-AAV5 subgroup. There was also development of HCC in the anti-AAV5 subgroup, along with increased rates of neoplasms (benign, malignant and benign breast) compared to the anti-AAV5 negative subgroup.

Companion diagnostic tests

The *in vitro* diagnostics Evaluator has indicated that sufficient evidence has been provided to demonstrate the safety and efficacy of the companion testing plan for the provisional registration of Hemgenix (etranacogene dezaparvovec).

The cut-off set for the companion test, neutralising anti-AAV5 antibody assay, is a titre below 1:700 based on the lack of response from one patient with a titre of 1:3212 with responses observed for all other patients with a titre below 1:678. The stated cut-off of 1:700 for the assay is conservative and may lead to the exclusion of patients that could potentially benefit from treatment with Hemgenix. Further patient enrolment in clinical studies is recommended (and is planned by the Sponsor) to provide clarity around the appropriateness of the cut-off titre.

The clinical efficacy endpoints for the clinical studies were met, demonstrating the superiority of Hemgenix over stand of care routine FIX prophylaxis in treatment of HB. The analytical validation provided for the neutralising anti-AAV5 antibody assay is acceptable. The companion testing plan is acceptable.

The Evaluator recommended the following condition be imposed:

Further clinical studies should be provided to validate the cut-off titre of the neutralising anti-AAV5 antibody assay at the conclusion of the provisional period for Hemgenix (etranacogene dezaparvovec).

Risk management plan evaluation summary

The Sponsor has submitted EU-RMP version 1.0 (date 14 December 2022; DLP 18 October 2021) and ASA version 1.0 (date 2 February 2023). At rounds 2 and 3 the Sponsor submitted ASA version 2.0 (date 30 September 2023) and ASA version 3.0 (date 15 November 2023), respectively.

The summary of safety concerns is acceptable from an RMP perspective (Table 5). The Sponsor has proposed routine pharmacovigilance for all safety concerns. Routine pharmacovigilance activities include specific adverse reaction follow-up questionnaires (questionnaire on liver toxicity, Hemgenix Liver malignancy and thromboembolic events).

The Sponsor also proposes additional pharmacovigilance activities as per the EU RMP for all safety concerns except missing information 'Use in patients with severe hepatic impairment' and 'Use in female patients'.

The Sponsor has proposed routine risk minimisation for all safety concerns except 'thromboembolic events' and 'Long-term effect'. Additional risk minimisation activities include a patient guide, patient alert card and prescriber guide to address several safety concerns, aligning with the EU RMP.

A clinical study plan has been provided in support of the provisional registration of Hemgenix (Table 6). The plan includes the final analyses for studies CT-AMT-061-01 and CT-AMT-061-02 and one-year follow-up data from CSL222_4001, an observational study that will follow HB patients for 15 years, to substantiate the long-term safety and efficacy of Hemgenix. Study CSL222_4001 may include Australian patients.

Table 5. RMP summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Hepatotoxicity	✓*	✓†‡	✓	✓§‖¶
	Infusion reactions (including hypersensitivity)	✓	✓†‡	✓	–
Important potential risks	Risk of malignancy in relation to vector integration in the DNA of body cells	✓*	✓†‡	✓	✓§‖¶
	Bleeding as a result of lack of efficacy due to immune-mediated neutralization of the AAV-5 vector capsid	✓	✓†‡	✓	–
	Thromboembolic events	✓*	✓†‡	–	✓§‖¶
	Germline transmission	✓	✓†‡	✓	✓§‖¶
	Transmission to third parties (horizontal transmission)	✓	✓†‡	✓	✓§‖¶
	Development of FIX inhibitors	✓	✓†‡	✓	✓§‖¶
Missing information	Use in patients with severe hepatic impairment	✓*	✓†	✓	–
	Long-term effect	✓	✓†‡	–	✓‖¶
	Use in female patients	✓	✓†	✓	–

* Specific follow-up questionnaire
† Post authorisation safety studies (PASS)
‡ Clinical trials
§ Patient alert card
‖ Patient guide
¶ Healthcare professional guide

Table 6. Etranacogene dezaparvovec clinical study plan

Study Description	Data proposed to convert from provisional to full approval	Expected availability*
CSL222_2001 Phase 2b; 3 subjects	Completion of study; 5-years	June 2024
CSL222_3001 (HOPE-B) Phase 3; 54 subjects	Completion of study; 5-years	October 2025
CSL222_4001 Observational Phase 4; Expected 250 subjects Enrolling	1-year follow-up data in 50 subjects	Anticipated prior to 2029

RMP = Risk Management Plan.
*Refer to RMP for milestones.

The Evaluator noted several inconsistencies between the EU SmPC and the proposed PI. Of note, the EU SmPC lists active infections and advanced hepatic fibrosis or cirrhosis as contraindications for use. Section 4.4 also includes sections on the risk of thromboembolic events, immunocompromised patients, HIV positive patients, as well as repeat treatment and the impact on other AAV-mediated therapies. The EU-SmPC also includes additional details around FIX activity monitoring, recommending specific frequencies for up to and more than 2 years after treatment. Recommendations to avoid concomitant use of hepatotoxic medication or potential hepatotoxic agents is only stated in the SmPC.

The EU SmPC also contains information regarding the expectation of patients to be enrolled in a long-term follow-up. The Sponsor has indicated study CSL222_4001 may include Australian patients but the proposed PI does not include this information.

RMP Evaluator recommendations regarding conditions of registration

The suggested wording is:

- The Hemgenix EU-Risk Management Plan (RMP) (version 1.0, dated 14 December 2022, data lock point 18 October 2021), with Australian Specific Annex (version 3.0, dated 15 November 2023), included with submission PM-2023-00668-1-6, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter, or the entire period of provisional registration, whichever is longer.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

Hemgenix (etranacogene dezaparvovec) is to be included in the Black Triangle Scheme. The PI and CMI for Hemgenix must include the black triangle symbol and mandatory accompanying text for five years, or the product's entire period of provisional registration, whichever is longer.

Specifically, the Sponsor must conduct studies as described in the clinical study plan in version 3.0 (date 15 November 2023) of the Australia-Specific Annex. The following study reports should be submitted to TGA:

- CSL222_2001, by June 2024
- CSL222_3001, HOPE-B, by October 2025
- CSL222_4001, prior to 2029

Discussion

The Sponsor is requesting provisional approval of etranacogene dezaparvovec. Preliminary data from the clinical development program have demonstrated the efficacy of etranacogene dezaparvovec over the short-term. In the pivotal Phase 3 study, treatment led to a statistically significant reduction in ABR for all bleeding episodes at months 7-18 compared to the study lead-in period. Significant improvements were also demonstrated for FIX activity levels, FIX replacement consumption and FIX trough levels as well as spontaneous bleeding and joint bleeding episodes. The durability of effect has been only demonstrated up to 24 months. The final analyses will determine whether these effects are maintained beyond two years.

Study limitations include the low number of patients enrolled in the pivotal study, the lack of a control arm (patients acted as controls during the study lead-in period) and the lack of data to support safety and durability of effect beyond 24 months.

Overall, the available safety data were supportive. Notable TRAEs included infusion reactions and transaminitis, which was transient and glucocorticoid responsive. There remain concerns regarding the potential risk of malignancy due to vector integration particularly given the limited number of patients included in the studies and the short duration of follow-up data available at this time.

There is no data available in female patients, paediatric patients, patients with severe hepatic or renal impairment, or immunocompromised patients. There is limited data available in several patient subgroups such as the elderly and patients with HIV. The Delegate notes that unlike the EU SmPC, the draft PI does not include statements in section 4.4 of the PI regarding the lack of or limited data in HIV positive patients, immunocompromised patients and has requested this information be included in the Australian PI.

The impact of pre-existing anti-AAV NAbs on efficacy and safety is yet to be elucidated. There was one non-responder in the pivotal study who had a NAb titre > 1:3000 at baseline and whilst rates of AEs were generally similar by NAbs status, there was a higher rate of 'neoplasms, benign, malignant and benign breast neoplasm' in the anti-AAV NAb positive group. Further studies are planned to investigate the efficacy and safety of Hemgenix in patients with pre-existing anti-AAV NAbs.

Proposed indication

The proposed indication for Hemgenix is:

> *Hemgenix® is an adeno-associated virus vector-based gene therapy indicated for treatment of adults with haemophilia B (congenital factor IX deficiency) and with a pre-existing neutralising anti-AAV5 antibody titre below 1:900 to reduce the frequency of bleeding episodes and the need for factor IX replacement therapy who:*
>
> - currently use factor IX prophylaxis therapy, or
> - have current or historical life-threatening haemorrhage, or repeated, serious spontaneous bleeding episodes.
>
> *The decision to approve this indication has been made on the basis of the efficacy and safety demonstrated in the clinical trial program. Continued approval of this indication depends on confirmation of longer-term benefit from ongoing clinical trials.*

The Hemgenix clinical trial program included patients with severe or moderately severe FIX deficiency and a severe bleeding type (on FIX prophylaxis for a history of bleeding or receiving on-demand FIX replacement with current or a history of frequent bleeding). The clinical Evaluator agreed that the proposed indication wording aligns with the clinical trial patient population. The EU has opted for a simpler definition of 'severe and moderately severe Haemophilia B (congenital FIX deficiency)', but the clinical Evaluator has indicated this definition covers a much broader patient population. The proposed wording indirectly defines the severity of HB based on FIX prophylaxis requirements or clinical history whereas the clinical trial inclusion criteria also defined severity by FIX activity level. The Delegate seeks the committee's advice on whether the proposed wording accurately reflects the clinical trial population.

The Sponsor proposes to exclude patients with a neutralising antibody (NAb) titre above 1:900 in the indication. This NAb titre cut-off was revised during the evaluation period from <1:700 to <1:900 due to the change from the clinical trial 7-point NAb assay to the 9- point assay intended for use in the post-market setting. Clarification has been sought whether supporting information for both assays have been submitted to the TGA for evaluation. The assay used in the clinical trials was unvalidated and patients with detectable pre-treatment anti-AAV5 NAbs were not

excluded from the pivotal phase 3 study. The initial cut-off set for the unvalidated companion test neutralising anti-AAV5 antibody assay, was a titre below 1:700 based on the lack of response from one patient with a titre of 1:3212 with responses observed for all other patients with a titre below 1:678. The Evaluator has indicated that this cut-off is conservative and may lead to the exclusion of patients that could potentially benefit from treatment with Hemgenix.

More information has been requested from the Sponsor about the 9-point assay and planned clinical studies. Study CSL222_3005 will assess the relationship of pre-treatment AAV5 NAbs with the efficacy of Hemgenix to determine if there is an appropriate pre-treatment AAV5 NAb threshold associated with lack of efficacy. The expected completion date is December 2028. As a condition of provisional registration, the Sponsor will be required to submit studies to validate the cut-off titre of the neutralising anti-AAV5 antibody assay at the conclusion of the provisional period.

The Delegate is of the opinion that anti-AAV antibody titre should not be included in the indication wording as there is limited information about the correlation between anti-AAV antibody titre and efficacy. The Delegate is of the view that including available information about anti-AAV antibody titre in the patient assessment and special warnings and precautions for use sections of the PI is sufficient at this stage of development. It is noted that neither the EMA nor FDA have included this information in the product indication. In addition, the FDA does not include anti-AAV antibody testing as part of the baseline patient assessment.

The safety and efficacy of Hemgenix in patients with FIX inhibitors has not been established as these patients were excluded from the clinical trial program. The clinical Evaluator has recommended amending the indication to exclude this subset of patients. International PI documents and the proposed draft PI all advise that patients with FIX inhibitors not receive Hemgenix but the EU is the only jurisdiction to exclude these patients in the indication. The Delegate is of the opinion that as patients with FIX inhibitors were excluded from the clinical trials and there is no data in this patient population that the wording of the indication should exclude patients with a history of FIX inhibitors. In addition, the Delegate requests a precaution be added to section 4.4 to indicate the lack of clinical experience in these patients and to recommend monitoring for the development of FIX inhibitors.

Pivotal Phase 3 study CT-AMT-061-02 has produced promising 2-year results but the study is ongoing and long-term benefit is yet to be demonstrated. The Delegate is of the view that the statement regarding outstanding information should be edited to reflect this.

Clinical setting and administration

The Sponsor has proposed limiting the prescription and administration of Hemgenix to clinical treatment centres under the supervision of healthcare professionals with experience in treating HB. The Delegate agrees that treatment should be restricted to clinical treatment centres as HB is a rare disease and treatment centres would have adequate staffing and clinical experience to manage both administration of Hemgenix and associated infusion reactions, hepatotoxicity and AEs. However, the Delegate is of the opinion that the term 'healthcare professional' is too broad and that Hemgenix should be prescribing and administered under the supervision of a haematologist or physician experienced in the diagnosis and management of patients with HB. This is consistent with the approach taken for previously registered gene therapies Zolgensma and Luxturna.

Acute infection or uncontrolled chronic infections

The clinical trial program for Hemgenix did not include patients with acute or uncontrolled chronic infections. In the EU, Hemgenix is contraindicated in these patients and a statement in section 4.4 recommends deferral until the infection is resolved or controlled. There is the

potential risk that an active infection could reduce the efficacy of treatment or result in AEs. Patients with past or controlled HIV and hepatitis infections were not excluded from the Phase 3 study but those with active HIV or hepatitis were.

Two gene therapies have previously been approved in Australia, Zolgensma (onasemnogene abeparvovec) and Luxturna (voretigene neparvovec). Neither list active or uncontrolled infections as a contraindication although the Luxturna PI lists ocular or periocular infection and active ocular inflammation as contraindications. However, the PIs for both products contain statements advising treatment deferral during periods of active infection (sections 4.2 and 4.4 of the Zolgensma PI and section 4.2 of the Luxturna PI in section 4.2). Given this risk is likely to be common to AAV vector-based gene therapies and there is no clinical experience in this patient population, the Delegate is of the view that a statement recommending deferral should be included in section 4.2 of the PI and a precautionary statement should be included in section 4.4. The Delegate seeks the committee's advice as to whether this is sufficient to manage this safety concern or whether a contraindication is warranted.

Hepatotoxicity and advanced hepatic fibrosis or cirrhosis

In Phase 3 study CT-AMT-061-02, a sub-analysis comparing the degree of hepatic steatosis with the Controlled Attenuation Parameter (CAP) score of ≥S2 (n=12) vs <S2 (n=28) found no clinically relevant difference in FIX activity levels following Hemgenix administration. Patients with advanced liver impairment and advanced fibrosis were not included in the Hemgenix clinical trial program. In the EU, Hemgenix is contraindicated in these patients.

Hepatotoxicity is listed as an important identified risk in the RMP and there is no available information on the use of Hemgenix in patients with severe hepatic impairment. The draft PI recognises the risk of hepatotoxicity and hepatocellular carcinogenicity with Hemgenix treatment in section 4.4 but recommends additional monitoring for these patients. This approach is similar to that taken in the US and Canada. The Delegate seeks the committee's advice as to whether a contraindication is warranted for this patient population.

Chromosomal integration, carcinogenicity and germline transmission

The Delegate seeks the committee's advice as to whether the risks of carcinogenicity and germline transmission are adequately communicated in the PI. Etranacogene dezaparvovec is intended to reside in cells in its episomal form although chromosomal integration was noted to occur at low levels in animal studies. The observed integration profile did not raise particular concern for carcinogenicity and no proliferative lesions were observed in treated animals.

In the clinical studies, six subjects experienced malignancies including one case of hepatocellular carcinoma, although genetic analysis of the tumour did not identify vector integration with expansion. The 'risk of malignancy in relation to vector integration in the DNA of body cells' has been identified as an important potential risk in the RMP. The proposed PI includes a precaution on hepatocellular carcinogenicity whereas the EU SmPC discusses the risk of malignancy due to vector integration more broadly. In the event of a malignancy post-treatment, both the EU SmPC and PI advise healthcare professionals contact the Sponsor to obtain instructions on collecting patient samples for potential vector integration examination and integration site analysis.

Vector shedding has been demonstrated in saliva, nasal secretions, urine and faeces. In the Phase 3 study, 56% (30/54) of subjects reached absence of vector DNA from blood by month 24 and vector clearance was achieved in blood at a median of 52.3 weeks. At month 24, 59.4% reached absence of shedding from semen and vector clearance from semen was achieved at a median of 47.3 weeks. Paternal germline transmission was not observed in animal studies. Male patients of reproductive potential and their female partners of childbearing potential are advised to prevent

or postpone pregnancy using barrier contraception for 12 months after treatment with Hemgenix.

Use in female patients

As haemophilia B is a rare, recessive x-linked condition no female patients were included in the clinical development program. As a result, there is no data available for this patient population and 'use in female patients' is listed as missing information in the RMP summary of safety concerns. There is no scientific rationale why Hemgenix would not also be effective in female patients. However, no data are available regarding use in pregnant or breast-feeding women and no animal embryofetal development studies have been performed. There is no data available to recommend a specific duration of contraceptive measures in women of childbearing potential. As a result, Hemgenix is not recommended in women of childbearing potential.

Risk of thromboembolic events

Compared to the general population, those with HB are at a lower risk of thromboembolic events due to the nature of the FIX deficiency. There is a risk that restoring FIX activity may increase a patient's risk of thromboembolism, although no thromboembolic events have been reported in clinical studies with Hemgenix. The Padua variant of FIX is associated with thrombophilia and in animal studies, a low incidence of pulmonary thrombosis was observed in mice in the context of supraphysiological plasma FIX activity. No supraphysiologic levels of FIX activity were observed during the Hemgenix clinical study program. However, thromboembolic events are listed as an important potential risk for Hemgenix in the RMP. The risk of thromboembolic events is listed as a precaution in both the EU SmPC and the Health Canada Product Monograph (HCPM). The Delegate is of the view that a precautionary statement in section 4.4 of the PI is warranted.

Dosage, administration and patient assessment and monitoring

Baseline assessment of pre-existing anti-AAV antibody titre, FIX inhibitors and liver health is required to determine eligibility for Hemgenix treatment. Regular monitoring of FIX activity and liver health and FIX inhibitors is also required post-administration. In the draft PI this information is split across sections 4.2 and 4.4. It is noted that the EU SmPC includes additional information recommendations regarding the frequency of FIX activity monitoring beyond three months following Hemgenix administration. The reasons for the differing advice are not clear.

As Hemgenix can only be administered once, it is especially important that the PI dosing instructions are clear in order to minimise the risk of drug administration errors. The draft Hemgenix PI includes a dosing guide for a limited range of patient body weights. A similar table was included in section 4.2 of the Zolgensma PI but the dose calculation for this product was more complicated and based on patient weight ranges. The proposed Hemgenix dosing guide is missing information for the weight ranges 55-85 kg, 91-113 kg, 119-149 kg and >155 kg and the Delegate is concerned that the dosing recommendations could be misinterpreted leading to dosing error. The Delegate notes that there is a lot of variability in the presentation of this information across the international PI documents.

Section 4.2 of the PI advises prescriber that Hemgenix can only be administered once but unlike the EU SmPC does not discuss the potential for cross-reacting antibodies with AAV vectors used by other gene therapies. The draft PI does state that exposure to Hemgenix results in an immune response to the AAV5 capsid proteins but does not indicate that this may decrease the efficacy of additional treatments with Hemgenix or other AAV vector-based gene therapies.

Interactions with other medicines and other forms of interactions

No drug interaction studies have been performed with Hemgenix. However, the EU SmPC includes additional advice relating to anticipated interactions with hepatotoxic products, agents that may reduce or increase plasma concentrations of corticosteroids. Physicians are warned that hepatotoxic agents may reduce efficacy and increase the risk of serious hepatic reactions. Similarly, agents that interact with corticosteroids may decrease the efficacy of the corticosteroid therapies and increase AEs. There is no data available regarding concomitant use of hepatotoxic agents but the Delegate is of the view that it is reasonable to anticipate an interaction and that this information should also be included in section 4.5 of the Hemgenix PI.

The EU SmPC also contains advice regarding vaccinations that is not included in the draft PI. It is also recommended that healthcare professionals ensure the patient's vaccinations are up to date prior to treatment and that the vaccine schedule be adjusted if required. The EU SmPC states that live vaccines should not be administered to patients on immunomodulatory therapy. The Zolgensma PI includes advice regarding vaccination administration, including live vaccines. Whilst Zolgensma is a gene therapy that is also administered as an IV infusion, it is intended for a much younger patient population where the vaccine schedule is more pertinent.

Long-term data

The clinical efficacy of Hemgenix in terms of reduction in ABRs and durability of FIX activity has not been established beyond 24 months. The longest follow-up was 5 years for the predecessor drug (AMT-060) in a slightly different formulation. Long-term durability of gene expression following administration of Hemgenix may be affected by the presence of pre-existing antibody-mediated or cellular-mediated immune responses that recognize the AAV vector or by the anticipated normal slow turnover of end-differentiated hepatocytes. Demonstration of maintenance of efficacy over the long-term will be required to support the transition to full registration.

Recommendation following the clinical evaluation

Subject to advice from ACM, the preliminary view tends towards a favourable benefit-risk profile for etranacogene dezaparvovec for the treatment of severe and moderately severe HB based on the interim results of the submitted clinical studies.

Advisory Committee on Medicines considerations

The Advisory Committee on Medicines (ACM) considered the evaluations and the Delegate's overview, as well as the Sponsor's response to these documents, advised the following in response to the Delegate's specific request for advice:

1. ***What is the committee's advice regarding the wording of the indication? In providing this advice, please comment specifically on whether:***
    - ***The definition of haemophilia B severity adequately reflects the clinical trial population.***
    - ***The indication should be restricted to those without FIX neutralising antibodies.***
    - ***The indication should be restricted to those with a neutralising antibody titre below 1:900.***

The ACM advised that the phenotypic definition of HB severity adequately reflects the clinical trial population however noted that the eligibility criteria for the HOPE-B study was FIX activity

<2%. The ACM advised that clinical efficacy is only seen in those with a bleeding type. Although there is a strong correlation with FIX levels and bleeding, there are exceptions and variability therefore, on balance the ACM supported a phenotypic definition within the indication.

The ACM was of the view that the indication should be restricted to those without FIX neutralising antibodies as the efficacy outside this space is unknown.

The ACM discussed the utility of including the neutralising antibody (NAb) titre in the indication. The ACM agreed the NAb titre should not be included in the indication as there is currently limited information to determine an appropriate pretreatment AAV5 NAb threshold, with the ACM noting that if the cut off is too high treatment is unlikely to be effective and if too low patients that may benefit from treatment will be excluded. The ACM also noted the potential for challenges accessing the scientifically validated companion diagnostic test. The ACM supported NAb titre information being included in other relevant sections of the PI. The ACM also noted the collection of ongoing clinical data to clinically validate NAb thresholds.

2. ***The Delegate proposes to limit to haematologists or physicians with experience in the diagnosis and management of patients with haemophilia B. Is this a reasonable request in the context of likely use in Australian clinical practice?***

The ACM agreed that it is reasonable to limit care to haematologists or physicians with experience in the diagnosis and management of patients with haemophilia B.

Th ACM noted that currently within Australia haemophilia treatment is largely restricted to designated haemophilia treatment centres. For Hemgenix it will be important that candidates are appropriately screened and monitored and these specialised centres are best placed to undertake these activities.

The ACM also noted that this approach aligns with the Clinical Implementation Plan – A roadmap for the implementation of gene therapy for haemophilia in Australia (November 2022).

3. ***Are the safety concerns for patients with active infections (acute or uncontrolled chronic infections) adequately addressed in the draft PI? Is a contraindication warranted for these conditions?***

The ACM was of the view that patients should be optimised for success prior to treatment and as such active infections (acute or uncontrolled chronic infections) should be a contraindication. The ACM advised that it is currently unknown whether the effect of an active infection will impact long term efficacy and to what extent adding a viral vector driven therapy might exacerbate infection related complications, including liver injury.

The ACM noted that chronic controlled infections were included in the study population and advised that this population should not be specifically excluded.

4. ***Are the safety concerns for patients with advanced hepatic fibrosis or cirrhosis adequately addressed in the draft PI? Is a contraindication warranted for this condition?***

The ACM was of the view that concerns need to be clearly outlined within the PI and that a contraindication within the PI for advanced hepatic fibrosis or cirrhosis was warranted.

The ACM discussed safety (and efficacy) concerns for patients with advanced hepatic fibrosis or cirrhosis and noted that FIX production is decreased by liver damage, there is a risk of transient exacerbation due to an inflammatory response to the vector and there is an increased risk of hepatocellular carcinoma.

5. ***What is the committee's opinion regarding the potential risks of chromosomal integration, carcinogenicity and germ line transmission?***

The ACM noted that AAV vectors do integrate at a rate of approximately 0.1 to 1.0%.[3] However the degree of integration and the impact of this in relation to Hemgenix is currently unknown. The ACM also advised carcinogenesis was biologically plausible and highlighted the importance of post market monitoring.

In the HOPE-B trial (published in the NEJM) only one cancer was described; a hepatocellular carcinoma in a patient with treated hepatitis B infection and other risk factors. The ACM noted that no vector genome was identified in the tumour and the hepatocellular carcinoma was deemed unrelated to gene therapy.

The ACM reiterated long term, ongoing post market data is vital to monitor for integration and carcinogenesis. The ACM highlighted the importance of the testing for integration should a malignancy occur. The ACM also supported the establishment of a register of cancer cases in gene therapy patients.

The ACM discussed germ-line transmission and indicated that the risk is currently unknown. The ACM noted that paternal germ line transmission was not observed in animal studies. Vector shedding in semen was demonstrated in the clinical trial and the ACM noted that the draft PI states 69% of subjects reached absence of vector DNA from semen by month 24. Considering this, the ACM supported statements on the need for contraceptive measures while shedding continues within the PI in addition to discussions with patients.

6. ***There is no clinical experience with Hemgenix in female patients and use is not recommended in women of childbearing potential. What is the committee's view on the management of this risk in the PI?***

The ACM noted that there is no clinical experience with Hemgenix in female patients and agreed that this should be highlighted in the PI. In regard to a contraindication the ACM noted that the term 'Women of childbearing potential' is quite broad and advised a case-by-case approach would be practicable noting that screening and treatment is managed in specialised centres.

7. ***What is the committee's view on the risk of thromboembolism and the management of this risk in the PI?***

The ACM advised that there does not appear to be an elevated risk of thromboembolism from FIX activity associated with the therapeutic dosage of Hemgenix and as such a general warning is not required within the PI. The ACM did note that a cautionary statement in the PI regarding supratherapeutic levels could be considered.

8. ***Is the presentation of the dosage and administration information acceptable? In particular:***

   - ***Are the sections on laboratory testing and monitoring adequate?***
   - ***Is Table 1 in section 4.2 of the PI useful for preventing dose administration errors?***
   - ***Is more information required on the risks of repeat administration or exposure to other AAV-vector based gene therapies?***

The ACM advised that the PI sections on laboratory testing and monitoring are adequate.

The ACM was of the view that Table 1 in section 4.2 may cause confusion and lead to dosing errors. The ACM preferred the inclusion of the formula to calculate the weight-based dosing.

Based on current knowledge the information on risks of repeat administration or exposure to other AAV-vector based gene therapies within the PI is adequate. The ACM supported the inclusion of 'Hemgenix can be administered only once' and noted that more data on immune responses and efficacy would be needed to provide more specific advice. The ACM indicated a

[3] Wang et al, Nat Rev Drug Discov, 2019

statement on the potential for antibody cross-reaction with the use of AAV-vector based gene therapies could be considered.

9. ***What is the committee's view on the risk of interactions with hepatotoxic medicinal products or substances and agents that may increase or decrease plasma concentrations of corticosteroids?***

The ACM noted that it would be best practice to avoid concurrent hepatoxic therapies given the potential transient hepatic effects.

The ACM was supportive of more guidance on avoiding alcohol, hepatotoxic therapies as well as complementary and alternative medicines.

10. ***The committee is requested to provide advice on any other issues that it thinks may be relevant to the decision whether or not to grant provisional approval for Hemgenix.***

The ACM noted that the HOPE-B interim data appears promising and warranted consideration of provisional approval. However, the ACM also noted the current lack of long-term data and the unknowns associated with this novel therapy.

The ACM reiterated the importance of restricting treatment to designated haemophilia treatment centres and ongoing data collection.

ACM conclusion

The ACM considered this product to have a provisional positive benefit-risk profile.

The ACM agreed on the following wording for the indication:

> *This medicine has provisional approval in Australia.*
>
> *Hemgenix is an adeno-associated virus vector-based gene therapy indicated for treatment of adults with haemophilia B (congenital factor IX deficiency), without a history of factor IX inhibitors, who:*
>
> - *currently use factor IX prophylaxis therapy, or*
> - *have current or historical life-threatening haemorrhage, or repeated, serious spontaneous bleeding episodes.*
>
> *The decision to approve this indication has been made on the basis of short-term efficacy and safety data in the clinical trial program. Continued approval of this indication depends on confirmation of longer-term benefit from ongoing clinical trials.*

Outcome

Based on a review of quality, safety, and efficacy data, the TGA decided to register Hemgenix for the indication as agreed by the ACM, as stated above.

Product Information

The Product Information (PI) approved with this submission for Hemgenix which is referred to in this AusPAR (and can be accessed on this AusPAR's webpage) may have been superseded. For the most recent PI and Consumer Medicines Information (CMI), please refer to the TGA PI/CMI search facility.

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Reference/Publication #