DURVEQTIX® (FIDANACOGENE ELAPARVOVEC) RISK MANAGEMENT PLAN

RMP Version number: 1.0

Data lock point for this RMP: 30 August 2023 (C0371002 trial)

15 August 2023 (C0371003 trial)

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Rationale for submitting an updated RMP: Not applicable (for initial MAA submission)

Summary of significant changes in this RMP: Not applicable (for initial MAA submission)

Other RMP versions under evaluation: None

QPPV name: Barbara De Bernardi, MD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant´s QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS

AAV	adeno-associated virus
ABR	annualized bleeding rate
ADR	adverse drug reaction
AE	adverse event
AFP	alpha-fetoprotein
AIDS	acquired immunodeficiency syndrome
AJBR	annualized joint bleeding rate
ALP	alkaline phosphatase
ALT	alanine transaminase
aRMM	additional risk minimisation measure
AST	aspartate transaminase
ATHN	American Thrombosis and Hemostasis Network
BU	Bethesda unit
CI	confidence interval
CpG	cytosine-phosphate-guanine
CSR	clinical study report
DNA	deoxyribonucleic acid
EC	European Commission
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FIX	(coagulation) factor IX
FIX:C	factor IX activity in circulation
GTR	Gene Therapy Registry
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCP	healthcare provider
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
IS	integration site
IV	intravenous
kg	kilogram
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex
nAb	neutralizing antibody
PBMC	peripheral blood mononuclear cell
PL	package leaflet
PSUR	Periodic Safety Update Report

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PT	Preferred Term
RM	risk management
RMM	risk minimisation measure
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SMR	standardized mortality ratio
SOC	system organ class
UK	United Kingdom
UKHCDO	United Kingdom Haemophilia Centre Doctors' Organisation
ULN	upper limit of normal
US	United States
vg	vector genome
WFH	World Federation of Hemophilia

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TABLE OF CONTENTS

Medicinal product no longer authorised

Medicinal product no longer authorised

LIST OF TABLES

Medicinal product no longer authorised

PART I. PRODUCT(S) OVERVIEW

Active substance **(INN or common name)**	Fidanacogene elaparvovec
Pharmacotherapeutic group(s) (ATC Code)	Not yet assigned
Marketing Authorisation Applicant	Pfizer Europe MA EEIG
Medicinal products to which this RMP refers	1
Invented name in the European Economic Area (EEA)	DURVEQTIX
Marketing authorisation procedure	Centralised
Brief description of the product:	Chemical class Non-replicating recombinant Adeno-associated virus (AAV) vector that utilises AAVRh74var capsid to deliver a stable human factor IX transgene.
	Summary of mode of action Gene therapy designed to introduce a functional copy of the high activity Padua variant of the factor IX gene (FIX-R338L) in the transduced cells to address the monogenic root cause of haemophilia B.
	Important information about its composition Fidanacogene elaparvovec: - is a concentrate for solution for infusion - contains recombinant AAVRh74var capsid, containing the human coagulation factor IX transgene modified to be a high factor IX activity (Padua) variant known as FIX-R338L - contains the inactive ingredients: sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate heptahydrate, sodium chloride, poloxamer 188, and water for injection, with a pH of 6.8-7.8. This medicinal product contains 4.55 mg sodium per vial.
Hyperlink to the Product Information:	Please refer to Module 1.3.1.
Indication in the EEA	Current: Treatment of severe and moderately severe haemophilia B (congenital factor IX deficiency) in adult patients without a history of factor IX inhibitors and without detectable antibodies to variant AAV serotype Rh74.
Dosage in the EEA	Current: Single-dose of 5 x 10^{11} vector genomes per kg (vg/kg) of body weight administered as an intravenous infusion after dilution.

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Pharmaceutical form and strength	Current: Concentrate for solution for infusion (sterile concentrate), each mL of fidanacogene elaparvovec contains 0.79 - 1.21 x 10^{13} vector genomes (vg). Each vial contains an extractable volume of 1 mL.
Is/will the product be subject to additional monitoring in the EU?	Yes

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PART II. SAFETY SPECIFICATION

Module SI. Epidemiology of the Indication and Target Population

Haemophilia B

Fidanacogene Elaparvovec is an adeno-associated viral vector-based gene therapy 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 and without detectable antibodies to variant AAV serotype Rh74. Haemophilia B is an X-linked hereditary bleeding disorder in which the clotting factor, FIX, is deficient or inactive. The vast majority of cases are attributable to an inherited or sporadic mutation of the FIX gene located on the X-chromosome.[1]

Incidence:

Global

Haemophilia B occurs at a rate of approximately 3.33 to 5.0 per 100,000 male live births per year.[1,2]

Europe

In the European Economic Area (EEA), approximately 2.6 million male live births were reported in 2018.[3] Applying an incidence rate of 3.33 to 5.0 per 100,000 male live births[1,2], approximately 85 to 128 cases of haemophilia B were diagnosed in 2018 in the EEA.

Prevalence:

Global

The overall prevalence of haemophilia B among the male population of Western European countries, the United States (US), and Canada is estimated to be between 0.5 and 8.1 per 100,000 men.[4] The estimated prevalence of haemophilia B from registry data from six countries was 3.8/100,000 men,[2] corresponding to approximately 148,200 persons with haemophilia B globally.

The current worldwide population of patients with a diagnosis of haemophilia B, as determined by the World Federation of Hemophilia (WFH) 2021 survey (representing data reported from approximately 7.14 billion persons or roughly 92% of the world population), is estimated to be 37,998 individuals.[2] The reported number of patients with a diagnosis of haemophilia B in various countries is as follows: United Kingdom (UK), n = 1,607; [2] Austria, n = 148; [2] Russia, n = 1,274; [2] Germany, n = 755; [2] France, n = 1,841; [2] and the Netherlands, n = 198.[2]

Europe

Table 1 shows the estimated number of patients with haemophilia B (n=8499) in 28 countries in the EU-28 as reported by WFH Annual Global Surveys (2013 to 2021).[2,5,6,7,8,9]

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Table 1. Distribution of Patients with Haemophilia B in EU-28, 2007-2021

Country	Year of Data Collection	Total Patients with Haemophilia B (N)
Austria[2]	2021	148
Belgium[2]	2021	250
Bulgaria[6]	2018	68
Croatia	2021	69
Cyprus[8]	2013	56
Czech Republic[2]	2021	143
Denmark[6]	2018	102
Estonia[2]	2021	11
Finland[2]	2021	34
France[2]	2021	1841
Germany[2]	2021	755
Greece[5]	2020	185
Hungary[2]	2021	243
Ireland[2]	2021	223
Italy[5]	2020	882
Latvia[2]	2021	23
Lithuania[2]	2021	27
Luxembourg[2]	2021	4
Netherlands[2]	2021	198
Poland[2]	2021	477
Portugal[2]	2021	213
Romania[2]	2021	210
Slovakia[2]	2021	93
Slovenia[2]	2021	33
Spain[2]	2021	282
Sweden[2]	2021	216
United Kingdom[2]	2021	1607

Countries not included in WFH Survey: Malta*
*Included in WFH 2021 survey but did not report hemophilia B data
Source: World Federation of Hemophilia Annual Global Surveys[2,5,6,7,8,9]

US/Canada

The reported number of patients with a diagnosis of haemophilia B in North American countries according to the 2021 WFH survey is as follows: US, n = 4,300; Canada, n = 727.[2]

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Sex

Due to its sex-linked recessive pattern of inheritance, haemophilia B patients are predominantly male.[10] Among the 117 countries reporting data on haemophilia B to the WFH in 2021, 79% of cases were male, 6% were female, and 5% were of unknown sex.[2]

Age

The age distribution for haemophilia B patients registered at haemophilia centers in the US, Canada, and the UK in 2021 is shown in Table 2.[2]

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Table 2. Distribution of Haemophilia B Patients by Age Group in North America and the UK in 2021

	Proportion of Haemophilia B Patients		
	US	Canada	UK
0-4	10%	3%	5%
5-13 years	21%	10%	15%
14-18 years	12%	7%	6%
19-44 years	33%	40%	37%
45+ years	24%	40%	37%

Source: World Federation of Hemophilia, 2021.[2]

Race

In the published literature, the racial/ethnic distribution of haemophilia B patients in US-based studies was as follows: most patients were white (21.0 – 74.5%)[11,12,13,14,15] followed by African American (10.1 - 44.4%),[12,13,14,15] Hispanic (9.4 - 13.4%),[12,13,14,15] Asian (3.4%),[15] and other (5.5 - 10.9%)[13,14,15]. One study suggested that there is no difference in the incidence of haemophilia B between racial/ethnic groups.[4]

Risk factors

Since haemophilia B is a hereditary bleeding disorder caused by a lack of blood clotting FIX, risk factors are genetic predisposition and male sex.[16] Though rare, women can also have haemophilia if both of their X chromosomes are affected.[17,18,19]

The main existing treatment options:

Current treatment for haemophilia B is based on IV administration of plasma-derived or recombinant FIX protein to raise the circulating FIX activity level to the lowest effective level, to achieve either resolution of bleeding (on-demand or episodic treatment), or prevention of bleeding (prophylaxis treatment).[20, 21, 22] Prophylaxis, which is recommended by the WFH, has significantly reduced joint bleeding and improved joint health as compared to on-demand therapy.[23, 24] Prophylaxis treatment regimens are individualized as necessary based on age, venous access, bleeding phenotype, activity, the type and availability of clotting factors.[22] In a prophylaxis setting, the standard half-life factor products require infusion multiple times a week[25] whereas the extended half-life recombinant FIX products have reduced the frequency of infusions to once every 7-14 days.[26,27,28]

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Mortality

In developed countries, the age-adjusted mortality rate among patients with haemophilia A and B between 1973 to 1992 was approximately twice that of the general population, primarily due to the impact of Acquired Immunodeficiency Syndrome (AIDS)/Human Immunodeficiency Virus (HIV) and chronic liver disease.[29] In a cohort study in Sweden in 2013, the hazard ratios (HR) for all-cause mortality were 2.2 among patients with haemophilia A or B and 3.3 among patients with severe haemophilia A or B (excluding patients with HIV) compared with people without haemophilia.[30] Among patients registered

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in the UKHCDO nationwide database between 1977-1998, the annual age-specific death rate from all causes for patients with severe haemophilia A or B without HIV was nearly twice that for patients with moderate or mild haemophilia (death rate ratio: 1.82; 95% Confidence Interval [CI]: 1.54 - 2.16, after adjustment for calendar period, development of inhibitors and type of hemophilia).[31]

Since advances in the safety of replacement therapy due to the introduction of recombinant factor concentrates and viral inactivating procedures, the life expectancy of haemophilia patients has dramatically increased, at least in developed countries. A recent systematic review that demonstrated a reduction in an age and sex-matched standardized mortality ratio (SMR) before and after the year 2000, where the SMR decreased from 2.4 (95% CI 1.9-3.0) prior to 2000 to 1.2 (95% CI 1.0-1.4) after the year 2000.[32] In a prospective cohort study performed among all known patients with haemophilia in the Netherlands between 1992-2001, haemophilia B patients had a 2.3-times greater risk of death than the general population (standardized mortality ratio (SMR) = 2.3 [95% CI: 1.3 – 4.0]).[33] In a subsequent study on 1,066 haemophilia patients in the Netherlands between 2001 and 2018, age-standardized mortality in patients with haemophilia was 40% higher compared with the general male population (SMR 1.4, 95% confidence interval [CI] 1.2–1.7).[34]

Even though people with haemophilia are still at greater risk of death than the general population, the life expectancy of haemophilia patients is progressively approaching that of the general population. [32] Survival in people with haemophilia has improved over time, with a gain of 11 years from 1973 to 2018, and with adequate treatment, the life expectancy among people with haemophilia A or B is approximately 6 years less than among those without haemophilia.[34]

Across 13 recent studies from 2000, haemorrhage (31.7%) was the most common cause of death in persons with haemophilia[32], followed by liver disease (14.3%), HIV (13.9%), and cancer (12.8%).

Morbidity

In 21 studies reporting on the severity of haemophilia B cases, 21.0-63.9% were severe, 10.7 – 47.6% were moderate, and 8.7-61.9% were mild.[11,12,13,15,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51]

Complications from bleeding events in persons with hemophilia B include neurologic sequelae of intracranial hemorrhage and hemophilic arthropathy sequelae, including joint destruction, muscular atrophy and contraction, nerve damage, reduced bone mineral density, and chronic pain.[52,53]

Important co-morbidities:

Important comorbidities among patients with haemophilia B include infection (hepatitis C virus; HIV;[18,54,55] hepatitis A virus;[56] parvovirus B19[57]); variant Creutzfeldt-Jakob Disease;[58] chronic joint disease;[59] and chronic liver disease.[60] Due to the increase in life expectancy for people with haemophilia, the prevalence of age-related comorbidities, such as cancer/malignancies, cardiovascular and metabolic diseases, and chronic renal disease have increased in adults with haemophilia.[61,22]

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In the pivotal monkey single dose general toxicity study, the no observed adverse effect level was considered to be the highest dose of vector administered (5E12 vg/kg, which is 10x the human dose of 5E11 vg/kg). While deaths were observed in the 12-month mouse study, they were attributed to tissue/vascular injury related to the repeated submandibular blood collection procedure, with exacerbation by enhanced coagulation, and not primarily due to administration of fidanacogene elaparvovec. The vascular injury was not observed in the other toxicity studies.

The risk of germline transmission in males by AAV vectors when administered intravenously is considered to be low. The germline transmission of AAV-AAVRh74var-hFIX16-WT and AAV-AAVRh74var-hFIX19-Padua was evaluated in a rabbit model, and the results show that vector was no longer detected in semen at 5 months post dose.

Vector integration data from dogs and monkeys indicate the integration profile is benign and risk of hepatocellular carcinoma related to vector integration is low[66]. In the 2-year monkey study, there is no indication that integration sites that are within a predefined distance of 100 kb of a cancer associated gene resulted in altered liver function. There was no histologic evidence of increased cell proliferation in hepatocytes on Day 92 or in monkeys euthanized 2 years after vector administration. In the juvenile dog hemophilia B efficacy studies, there were no signs of clonal dominance, no preferred integration site (IS) locus and no single clones with elevated frequencies in proximity to cancer-associated genes have been observed. Additionally, the integration profile had minimal similarity to integration profiles published for other gene therapy vectors which is consistent with the random integration of AAV vectors.

Table 3. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
Toxicity: • No Noteworthy Findings In General Toxicity Studies in mice and monkeys	No risks relevant to the proposed patient population were identified.

• Reproductive/developmental toxicity
  ○ Vector was cleared after 5 months from rabbit semen
  ○ Female reproductive toxicity studies are not applicable
	Indicates that vector will be cleared from semen, and semen clearance was confirmed by clinical trial data.
	
	Germline transmission is considered an important potential risk for fidanacogene elaparvovec.

• Genotoxicity: Not applicable	No studies conducted

• Carcinogenicity
  ○ No evidence of hepatocellular proliferation in monkeys after 2 years or mice after 1 year
  ○ Vector integration profile did not indicate risk for hepatocellular carcinoma
	Indicates low risk for hepatocellular carcinoma
	
	As the clinical relevance of vector integration in humans is not known, risk of malignancy in relation to vector integration in the DNA of body cells is considered an important potential risk for fidanacogene elaparvovec.

• Safety pharmacology: Not applicable	No studies conducted

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Module SIII. Clinical Trial Exposure

Clinical trial exposure and safety data are being provided for ongoing studies as of 30 August 2023 for study C0371002 to provide updated 2-year data and as of 15 August 2023 for study C0371003.

Population for analysis of clinical trials data in this Risk Management Plan includes the following 3 studies:

- C0371002: Ongoing Phase 3, open label, single arm study to evaluate the efficacy and safety of FIX gene transfer with fidanacogene elaparvovec in adult male participants with moderately severe to severe hemophilia B (FIX:C≤2%)

- C0371005: Completed Phase 1/2a, gene therapy, open-label, dose-escalation study of SPK-9001[a] (adeno-associated viral vector with human Factor IX gene) in subjects with hemophilia B

- C0371003: Ongoing Phase 2a, A Factor IX (FIX) gene transfer, multi-center evaluation of the long-term safety and efficacy study of PF-06838435[a] and a dose-escalation substudy in individuals with hemophilia B

As of the cut-off dates, a total of 67 participants have received fidanacogene elaparvovec in completed and ongoing clinical trials.

- 60 participants received the proposed dose of fidanacogene elaparvovec 5 x 10^{11} vector genomes per kg (vg/kg)

- [redacted]

Studies C0371002 and C0371005/C0371003 were pooled to aggregate exposure and safety data as they enrolled comparable participant populations, with similar inclusion/exclusion criteria. Due to limited data available at time of submission, exposure and safety data from the dose-escalation substudy of C0371003 is not pooled and is provided separately where applicable. Thus, pooled exposure and safety data is provided for all participants with exposure to fidanacogene elaparvovec at the proposed dose of fidanacogene elaparvovec 5 x 10^{11} vg/kg.

All 60 participants received one dose of fidanacogene elaparvovec for the treatment of hemophilia B, were male, and were between the ages of 18 and 62 years of age at the time of administration of fidanacogene elaparvovec. Thus, separate tables by duration of exposure,

[a] Fidanacogene elaparvovec is also known as PF-06838435 or SPK-9001.

Medicinal Product no longer authorised

indication, gender, and age group are not provided. Exposure by race/ethnic origin is provided in Table 4 below.

Table 4. Exposure to Fidanacogene Elaparvovec by Race/Ethnic Origin (n=60)

Race	**Patients**
White	45
Black or African American	2
Asian	7
American Indian or Alaska Native	0
Native Hawaiian or Other Pacific Islander	1
Not reported	4
Multiracial	1
Ethnic Origin	
Hispanic or Latino	2
Not Hispanic or Latino	50
Not reported	8

Duration of follow-up is provided in Table 5.

Table 5. Numbers of Participants within Follow-up Interval by Study - All Dosed Population (Protocol C037)

Study	**3M to <6 M**	**6M to <9 M**	**9M to <12 M**	**12M to <15 M**	**15M to <18 M**	**18M to <21 M**	**21 M to <2Y**	**2Y to <2.5 Y**	**2.5 Y to <3Y**	**3Y to <3.5 Y**	**3.5 Y to <4Y**	**4Y to <4.5 Y**	**4.5 Y to <5Y**	**5Y to <5.5 Y**	**5.5 Y to <6Y**	**>=6 Y**
C0371005/C0371003 (N=15)	15	15	15	15	14	14	14	14	14	14	13	13	13	12	10	3
C0371002 (N=45)	45	45	45	45	44	43	43	40	31	15	11	1	0	0	0	0
Overall (N=60)	60	60	60	60	58	57	57	54	45	29	24	14	13	12	10	3

Follow-up interval is defined per month derived as (Study Day / 30.4375). >=3 months for '3M to <6M', >=6 months for '6M to <9M', >=9 months for '9M to <12M',
>=12 months for '12M to <15M', >=15 months for '15M to <18M', >=18 months for '18M to <21M', >=21 months for '21M to <2Y', >=24 months for '2Y to <2.5Y',
>=30 months for '2.5Y to <3Y', >=36 months for '3Y to <3.5Y', >=42 months for '3.5Y to <4Y', >=48 months for '4Y to <4.5Y', >=54 months for '4.5Y to <5Y',
>=60 months for '5Y to <5.5Y', >=66 months for '5.5Y to <6Y', '>=72 months for '>=6Y'.
M = Months, Y=Years.
[redacted] Source Data: adsl Table Generation: 11NOV2023 (16:14)
Study C0371005 (Snapshot date: 20JUN2019); Study C0371003 (Cutoff date: 15AUG2023; Snapshot date: 19SEP2023); Study C0371002 (Cutoff date: 30AUG2023; Snapshot date: 11OCT2023).
Output File: ./iAP/iAP_Safety_YEAR2l/adds_t001

Table 14.4.2.3.7 Fidanacogene Elaparvovec is for Pfizer internal use.

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Module SIV. Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

The participants enrolled were 18 years of age and older. Key exclusion criteria in the Phase 3 study C0371002 were:

- **Anti-AAVRh74var nAb titer ≥1:1 (ie, positive for nAb), performed by a central laboratory during screening.**

  Reason for exclusion: To avoid confounding the study results and to keep the study population homogeneous, as this may have an impact on efficacy and safety.

  Is it considered to be included as missing information: No

  Rationale: Only patients with negative results for the presence of AAVRh74var neutralizing antibodies are to be treated with fidanacogene elaparvovec.

- **Prior history of inhibitor to FIX or positive inhibitor testing as measured by the central laboratory ≥0.6 BU during screening. Clinical signs or symptoms of decreased response to FIX.**

  Reason for exclusion: To lower the risk of inhibitor development.

  Is it considered to be included as missing information: No

  Rationale: Patients with prior history of inhibitor to FIX or positive inhibitor testing are not recommended to be treated with fidanacogene elaparvovec as there is a risk of inhibitor recurrence for patients with prior history of inhibitor to FIX and a safety and efficacy impact for patients with inhibitors. Also the risk to develop an inhibitor is higher within the first 50 exposure days to exogenous FIX replacement products.

- **Known hypersensitivity to FIX replacement product or IV immunoglobulin administration.**

  Reason for exclusion: Previous hypersensitivity or history of hypersensitivity reactions may trigger a subsequent hypersensitivity reaction and may also lead to inhibitor development.

  Is it considered to be included as missing information: No

  Rationale: Patients with prior history of hypersensitivity to FIX replacement products are not recommended to be treated with fidanacogene elaparvovec as there is a risk of hypersensitivity recurrence.

Medicinal product no longer authorised

- **History of chronic infection or other chronic disease that investigator deems as an unacceptable risk.**

  Reason for exclusion: To avoid confounding the study results and to keep the study population homogenous.

  Is it considered to be included as missing information: No

  Rationale: Fidanacogene elaparvovec is not expected to have any additional safety concerns in this population. Use in patients with controlled HCV, HBV, or HIV infection is acceptable based on prescriber's discretion. Therefore, the Applicant does not consider information on this patient population as missing information for fidanacogene elaparvovec.

- **Any concurrent clinically significant major disease or condition that the investigator deems unsuitable for participation or other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior (including alcoholism) or laboratory abnormality that may increase the risk associated with study participation or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into the study.**

  Reason for exclusion: To avoid confounding the study results and to keep the study population homogenous.

  Is it considered to be included as missing information: No

  Rationale: Prescribers will be able to assess specific patient condition and whether treatment with fidanacogene elaparvovec administration is appropriate, without inclusion of this general exclusion criteria as missing information.

- **Exclusion criteria with respect to hepatic impairment and elevated hepatic enzymes:**

  - **ALT, AST, ALP >2xULN, based on central laboratory results.**
  - **Bilirubin >1.5xULN (isolated bilirubin >1.5xULN was acceptable if bilirubin was fractionated and direct bilirubin <35%), based on central laboratory results.**
  - **Current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, hepatic encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice, or cirrhosis. NOTE: Stable chronic liver disease (including Gilbert's syndrome, asymptomatic gallstones) was acceptable if the participant otherwise met entry criteria.**

Medicinal product no longer authorised

- **Significant liver disease, as defined by pre-existing diagnosis of portal hypertension, splenomegaly, or hepatic encephalopathy**

- **Active hepatitis B or C; HBsAg, HBV-DNA positivity, or HCV-RNA positivity**

Reason for exclusion: To protect participant safety while the effects of fidanacogene elaparvovec on hepatic parameters were further explored and understood.

Is it considered to be included as missing information: No

Rationale: In patients with significant hepatic impairment, efficacy of fidanacogene elaparvovec may be reduced and the risk of serious hepatic reactions may increase. Fidanacogene elaparvovec is contraindicated in patients with advanced hepatic fibrosis or advanced hepatic cirrhosis (pre-treatment evaluation of hepatobiliary condition should confirm the absence of clinically significant hepatobiliary disease).

- **Previously dosed in a gene therapy research trial at any time or in an interventional clinical study within the last 12 weeks, excluding participation in study C0371004.**

Reason for exclusion: May complicate interpretation of study data as other study intervention may have an impact on efficacy and safety, including the likelihood that it will significantly impact the efficiency of transduction.

Is it considered to be included as missing information: No

Rationale: Prescribers will be able to assess specific patient condition and whether treatment with fidanacogene elaparvovec administration is appropriate, without inclusion of this exclusion criteria as missing information.

- **Serological evidence of HIV-1 or HIV-2 infection with either CD4+cell count ≤200 mm^3 or viral load >20 copies/mL.**

Reason for exclusion: To avoid confounding the study results, to keep the study population homogenous, and to protect participant safety as participants treated with fidanacogene elaparvovec may require corticosteroid therapy.

Is it considered to be included as missing information: No

Rationale: As per the SmPC, within 8 weeks prior to infusion of fidanacogene elaparvovec, it is to be confirmed that patients with serological evidence of HIV1 or HIV2 infection have either CD4+ cell count > 200 mm^3 or viral load ≤20 copies/mL.

- **Sensitivity to heparin or heparin induced thrombocytopenia.**

Reason for exclusion: To protect clinical trial participants who may have required treatment with heparin in the setting of high FIX levels.

Medicinal product no longer authorised

Is it considered to be included as missing information: No

Rationale: Fidanacogene elaparvovec is not expected to have any additional safety concerns in this population as maintained circulating FIX activity levels >150% of normal have not been reported in the clinical program at the current proposed dose evaluating fidanacogene elaparvovec.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as common, uncommon or rare adverse reactions and adverse reactions with a long latency.

Hemophilia B is a rare disease which inherently limits the size of patient populations.

Participants are planned to be followed for up to 15 years. Long-term follow-up of patients administered gene therapy medicinal products is of importance due to limited data availability on long-term safety and effectiveness of gene therapy.

SIV.3. Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table 6. Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	Not included in the clinical development program.
Patients with relevant comorbidities:	
• Patients with hepatic impairment	Not included in the clinical development program.
• Patients with renal impairment	Not included in the clinical development program.
• Patients with HIV infection	3[b] patients exposed to fidanacogene elaparvovec were HIV positive.
• Immunocompromised patients	Not included in the clinical development program.
• Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program.

[b] Please note that 2 patients that had positive antibody results for HIV at screening, had undetectable viral load and no HIV history, and are not included in the number of patients with HIV infection.

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Table 6. Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Population with relevant different ethnic origin	See Table 4 for exposure information for fidanacogene elaparvovec by ethnic origin from the clinical trial development program.
Subpopulations carrying relevant genetic polymorphisms	All participants included in the clinical trials had an X-linked recessive disorder (haemophilia B). Genetic abnormalities in the factor IX gene are reported in the clinical study reports.
Paediatric patients	Not included in the clinical development program.
Elderly (≥65 years old) patients	Not included in the clinical development program.

Module SV. Post-Authorisation Experience

Fidanacogene elaparvovec was not marketed in any country as of the data lock point.

SV.1. Post-Authorisation Exposure

Not applicable.

SV.1.1. Method Used to Calculate Exposure

Not applicable.

SV.1.2. Exposure

Not applicable.

Module SVI. Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

Fidanacogene elaparvovec does not have characteristics that would make it attractive for use for illegal purposes; therefore, the potential for misuse of fidanacogene elaparvovec for illegal purposes is highly unlikely.

Module SVII. Identified and Potential Risks

Pooled safety data is presented for total follow up period from studies C0371005/C0371003 and C0371002 and includes all follow up available at the cutoff date. The median duration of follow-up across the pooled studies was 2.97 years, with a maximum follow-up of 6.0 years.

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

The safety concerns of fidanacogene elaparvovec in the initial RMP are listed in Table 7.

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Table 7. Summary of Safety Concerns

Important Identified Risks	Hepatotoxicity
Important Potential Risks	Development of FIX inhibitors Thromboembolic events Risk of malignancy in relation to vector integration in the DNA of body cells Transmission to third parties (horizontal transmission) Germline transmission
Missing Information	Long-term safety

SVII.1.1. Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated) and potential risks for infusions, which are well known to healthcare professionals, are not included in the list of safety concerns:

- Hypersensitivity/infusion reactions

Treatment with fidanacogene elaparvovec should be initiated and administered in clinical centers and supervised by a physician experienced in the treatment of hemophilia. It is recommended that this medicinal product is administered in a setting where personnel and equipment are available to treat possible infusion-related reactions. The risk of hypersensitivity/infusion reactions with infusions are well known to healthcare professionals. Product labeling states to minimize the risk of acute hypersensitivity reactions, closely monitor patients for clinical signs and symptoms of infusion reactions and acute or delayed hypersensitivity reactions. Patients should be informed of the early symptoms and signs of hypersensitivity reactions and advise them to contact their physician and/or seek immediate emergency care if they experience an infusion related reaction.

None of the 60 clinical trial participants that received fidanacogene elaparvovec at the proposed dose of 5×10^{11} vg/kg experienced a hypersensitivity event that was considered related to administration of fidanacogene elaparvovec.

To identify possible signs or symptoms associated with hypersensitivity/infusion reactions, a search was conducted using the following SMQs (narrow and broad scope): Hypersensitivity, Anaphylactic reaction, and Angioedema. Eleven (18.3%) of 60 participants that received fidanacogene elaparvovec experienced a treatment-emergent adverse event included in one of these SMQs. Events reported were as follows: 3 participants experienced an event coded to the MedDRA PT Cough and 2 participants experienced an event coded to the MedDRA PT Seasonal allergy (remaining events experienced by 1 participant each were: Chest discomfort, Conjunctivitis allergic, Dermatitis contact, Face oedema, Rash, Rash macular, and Rhinitis allergic). None of these events were serious adverse events, all were resolved/resolving, all were mild or moderate in severity, and none were considered

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related to fidanacogene elaparvovec as they had alternate etiologies and did not occur within 48 hours of infusion.

Based on the lack of hypersensitivity/infusion reactions reported with fidanacogene elaparvovec at the proposed dose and that no impact to public health is anticipated, this potential risk is not considered important for inclusion as a safety concern.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which routine risk minimisation measures are sufficient:

- Abdominal pain: Four adverse drug reactions (ADRs) were reported in the pooled safety data from studies C0371005/C0371003 and C0371002. All 4 ADRs were nonserious and either mild (n=3) or moderate (n=1). Abdominal pain is listed in the fidanacogene elaparvovec summary of product characteristics (SmPC). Routine pharmacovigilance is sufficient to monitor this risk.

- Headache: One ADR was reported in the pooled safety data from studies C0371005/C0371003 and C0371002. This ADR was nonserious and mild. Headache is listed in the fidanacogene elaparvovec SmPC. Routine pharmacovigilance is sufficient to monitor this risk.

- Nausea: One ADR was reported in the pooled safety data from studies C0371005/C0371003 and C0371002. This ADR was nonserious and mild. Nausea is listed in the fidanacogene elaparvovec SmPC. Routine pharmacovigilance is sufficient to monitor this risk.

- Pyrexia: Two ADRs were reported in the pooled safety data from studies C0371005/C0371003 and C0371002. Both ADRs were nonserious and either mild (n=1) or moderate (n=1). Pyrexia is listed in the fidanacogene elaparvovec SmPC. Routine pharmacovigilance is sufficient to monitor this risk.

- Asthenia: One ADR was reported in the pooled safety data from studies C0371005/C0371003 and C0371002. This ADR was nonserious and severe. Asthenia is listed in the fidanacogene elaparvovec SmPC. Routine pharmacovigilance is sufficient to monitor this risk.

Medicinal product no longer authorised

- Blood lactate dehydrogenase increased: Two ADRs were reported in the pooled safety data from studies C0371005/C0371003 and C0371002. Both ADRs were nonserious and mild (n=2). Blood lactate dehydrogenase is listed in the fidanacogene elaparvovec SmPC. Routine pharmacovigilance is sufficient to monitor this risk.

- Dizziness: No ADRs were reported in the pooled safety data from studies C0371005/C0371003 and C0371002. Dizziness is listed in the fidanacogene elaparvovec SmPC. Routine pharmacovigilance is sufficient to monitor this risk.

- Blood creatinine increased: No ADRs were reported in the pooled safety data from studies C0371005/C0371003 and C0371002. Blood creatinine increased is listed in the fidanacogene elaparvovec SmPC. Routine pharmacovigilance is sufficient to monitor this risk.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risk: Hepatotoxicity

Transaminases increased, which were generally mild and resolved, is a known adverse reaction for fidanacogene elaparvovec.

Risk-benefit impact: Monitoring of liver enzymes and Factor IX levels and treatment with corticosteroids in the event of liver enzyme increases or factor IX activity decreases, as recommended in the product SmPC minimizes the risk of hepatotoxicity and may also reduce the risk of loss of FIX expression, thus contributing to the favorable risk-benefit profile of fidanacogene elaparvovec.

Important Potential Risk: Development of FIX Inhibitors

No patients developed factor IX inhibitors during the clinical studies using fidanacogene elaparvovec. Further characterisation of the potential risk of development of FIX inhibitors may help to determine if there is a causal association with fidanacogene elaparvovec and the associated clinical outcomes.

Risk-benefit impact: Currently, the impact to the overall risk-benefit balance has not been characterised, but, if development of FIX inhibitors is established as related to fidanacogene elaparvovec, it may have the potential to affect the risk-benefit profile.

Important Potential Risk: Thromboembolic Events

No AEs suggestive of thromboembolic events were reported with fidanacogene elaparvovec treatment. Administration of fidanacogene elaparvovec did not result in Factor IX levels that were maintained above the threshold (>150% of normal) considered a risk factor for an increase in thromboembolic events. Further characterisation of the potential risk of thromboembolic events may help to determine if there is a causal association with fidanacogene elaparvovec.

Medicinal product no longer authorised

Risk-benefit impact: Currently, the impact to the overall risk-benefit balance has not been characterised, but, if thromboembolic events is established as related to fidanacogene elaparvovec, it may have the potential to affect the risk-benefit profile.

Important Potential Risk: Risk of Malignancy in Relation to Vector Integration in the DNA of Body Cells

No AEs suggestive of malignancy in relation to vector integration in the DNA of body cells were reported with fidanacogene elaparvovec treatment. Further characterisation of the potential risk of malignancy in relation to vector integration in the DNA of body cells may help to determine if there is a causal association with fidanacogene elaparvovec.

Risk-benefit impact: Currently, the impact to the overall risk-benefit balance has not been characterised, but, if risk of malignancy in relation to vector integration in the DNA of body cells is established as related to fidanacogene elaparvovec, it may have the potential to affect the risk-benefit profile.

Important Potential Risk: Transmission to Third Parties (Horizontal Transmission)

Vector DNA shedding occurs in patient's urine, blood, and saliva. Vector DNA fully cleared in plasma, serum, saliva, and semen within a mean of 1-4 months after infusion and PBMC was slowest fluid to full clearance within a mean of 12 months. In urine, the peak vector DNA concentration was very low and declined to full clearance within a mean of 4 weeks after infusion.

Risk-benefit impact: Guidance in the product SmPC for patients not to donate blood, organs, tissues, or cells for transplantation, and instruction of patients regarding proper hand hygiene when coming into direct contact with patient secretions or excretions minimizes the risk of transmission to third parties (horizontal transmission) and will contribute to the favourable risk-benefit profile of fidanacogene elaparvovec.

Important Potential Risk: Germline Transmission

Vector DNA shedding occurs in semen. In semen, the maximum observed time for vector DNA full clearance was 154 days.

Risk-benefit impact: Guidance in the product SmPC advising male patients to not donate semen and that patients of reproductive potential and their female partners of childbearing potential must prevent or postpone pregnancy using barrier contraception for 6 months after administration of fidanacogene elaparvovec minimizes the risk of germline transmission and will contribute to the favourable risk-benefit profile of fidanacogene elaparvovec.

Missing information: Long-Term Safety

Risk-benefit impact

The long-term safety of fidanacogene elaparvovec is unknown at present, however further safety data are being collected in ongoing studies, which include long-term follow-up of patients for up to 15 years after fidanacogene elaparvovec administration.

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SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable for the initial RMP.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

SVII.3.1.1. Important Identified Risks

SVII.3.1.1.1. Important Identified Risk: Hepatotoxicity

Potential mechanisms:

The cause of transaminase elevations has not been established with certainty. One hypothesis is that a cellular immune response is directed against capsid-derived peptides presented on MHC Class 1 molecules on the transduced hepatocytes, and that this leads to destruction of the transduced hepatocytes by primed cytotoxic lymphocytes, release of transaminases into the circulation, and declines in levels of FIX.[62,63] Another potential cause of immune-mediated destruction of the vector-transduced cells is the presence of CpG dinucleotides in the vector's expression cassette. Data suggest that these elements can heighten the innate immune response leading to a stronger adaptive immune response.[64,65] The expression cassette in fidanacogene elaparvovec has been modified to reduce the number of CpG dinucleotides.

Evidence source and strength of evidence:

Fidanacogene elaparvovec clinical trial data. The clinical trial data supports a causal association between fidanacogene elaparvovec and elevated transaminases.

Characterisation of the risk:

All-causality AEs possibly indicative of hepatotoxicity occurred with an incidence of 48.3% (29/60) in clinical trial participants that received fidanacogene elaparvovec. One (1.7%) participant experienced a serious adverse event of Drug-induced liver injury, which was assessed as not related to fidanacogene elaparvovec but assessed as related to concomitant medication (azithromycin). All AEs possibly indicative of hepatotoxicity resolved or were resolving, except for 2 AEs of Hepatic steatosis, which were assessed as not related to fidanacogene elaparvovec. A majority of the participants experienced events that were mild in severity.

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Seriousness/Outcomes

Table 8. Seriousness and Outcomes of Treatment-Emergent Hepatotoxicity Across the Total Follow-up Period by SOC and PT for Overall Studies (All Causalities)-Safety Analysis Set

Number (%) of Participants Evaluable for AEs	**C0371002 & C0371005/C0371003 (N=60)**			
	Serious	**Resolved**	**Resolving**	**Not resolved**
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
With any Relevant adverse event	1 (1.7)	29 (48.3)	1 (1.7)	2 (3.3)
HEPATOBILIARY DISORDERS	1 (1.7)	11 (18.3)	1 (1.7)	2 (3.3)
Drug-induced liver injury	1 (1.7)	1 (1.7)	0	0
Hepatic function abnormal	0	6 (10.0)	0	0
Hepatic steatosis	0	1 (1.7)	0	2 (3.3)
Hepatitis	0	1 (1.7)	0	0
Hepatotoxicity	0	1 (1.7)	0	0
Hypertransaminasaemia	0	2 (3.3)	0	0
Liver disorder	0	0	1 (1.7)	0
INVESTIGATIONS	0	20 (33.3)	0	0
Alanine aminotransferase increased	0	12 (20.0)	0	0
Aspartate aminotransferase increased	0	3 (5.0)	0	0
Hepatic enzyme increased	0	3 (5.0)	0	0
Liver function test abnormal	0	1 (1.7)	0	0
Transaminases increased	0	4 (6.7)	0	0

MedDRA v 26.0 coding dictionary applied.
[redacted] Source Data: adae Table Generation: 10NOV2023 (15:48)
Study C0371005 (Snapshot date: 20JUN2019); Study C0371004 (Cutoff date: 20MAR2023; Snapshot date: 11APR2023); Study C0371002 (Cutoff date: 30AUG2023; Snapshot date: 11OCT2023).
Output File: ./iAP/iAP_Safety_YEAR2/adae_serious_out_Hepatotoxicity
Hospitalization has not been included in the table; the 1 serious event resulted in hospitalization.
Outcomes of Resolved with sequelae and Fatal have not been included in table as no AEs met this criteria.

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Severity

Table 9. Incidence and Severity of Treatment-Emergent Hepatotoxicity Across the Total Follow-up Period by SOC and PT for Overall Studies (All Causalities)-Safety Analysis Set

Number of Participants Evaluable for AEs	**C0371002 & C0371005/C0371003 (N=60)**			
Severity[a]	**Mild**	**Moderate**	**Severe**	**Total**
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
With any Relevant event	19 (31.7)	9 (15.0)	1 (1.7)	29 (48.3) 95% CI (35.2, 61.6)
HEPATOBILIARY DISORDERS	9 (15.0)	2 (3.3)	1 (1.7)	12 (20.0)
Drug-induced liver injury	0	0	1 (1.7)	1 (1.7)
Hepatic function abnormal	6 (10.0)	0	0	6 (10.0)
Hepatic steatosis	2 (3.3)	1 (1.7)	0	3 (5.0)
Hepatitis	1 (1.7)	0	0	1 (1.7)
Hepatotoxicity	0	0	1 (1.7)	1 (1.7)
Hypertransaminasaemia	1 (1.7)	1 (1.7)	0	2 (3.3)
Liver disorder	1 (1.7)	0	0	1 (1.7)
INVESTIGATIONS	13 (21.7)	7 (11.7)	0	20 (33.3)
Alanine aminotransferase increased	9 (15.0)	3 (5.0)	0	12 (20.0)
Aspartate aminotransferase increased	3 (5.0)	0	0	3 (5.0)
Hepatic enzyme increased	1 (1.7)	2 (3.3)	0	3 (5.0)
Liver function test abnormal	1 (1.7)	0	0	1 (1.7)
Transaminases increased	2 (3.3)	2 (3.3)	0	4 (6.7)
Total preferred term events	27	9	2	38

N = Number of participants dosed with Fidanacogene Elaparvovec in C0371002 & C0371005 combined.
All adverse events (AE) were collected during the first 12 months after vector infusion; thereafter, any non-serious AE assessed as unrelated to fidanacogene elaparvovec was not collected.
Participants are counted only once per SOC per Preferred Term. For the AE severity imputation algorithm any missing severities have been imputed as severe unless the participants experienced another occurrence of the same event for which severity was recorded. In this case, the reported severity is summarized.
Maximum severity at any dictionary level is calculated after the report subset criteria is applied.
a If the same participant had more than one occurrence in the same preferred term event category, only the most severe occurrence is counted.
MedDRA v 26.0 coding dictionary applied.
[redacted] Source Data: adae Table Generation: 21NOV2023 (10:42)
Study C0371005 (Snapshot date: 20JUN2019); Study C0371003 (Cutoff date: 15AUG2023; Snapshot date: 19SEP2023); Study C0371002 (Cutoff date: 30AUG2023; Snapshot date: 11OCT2023).
Output File: ./iAP/iAP_Safety_YEAR2l/adae_s041_e_Hepatotoxicity

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Risk factors and risk groups:

Patients with uncontrolled chronic hepatic infections, known significant hepatic fibrosis or cirrhosis, or other hepatic disorders or on concomitant hepatotoxic medications including herbal supplements and alcohol may be considered potentially at risk for developing hepatocellular toxicity associated with AAV liver-directed gene therapies.

Preventability:

As per the SmPC, monitoring of transaminases and FIX levels after fidanacogene elaparvovec administration and corticosteroid treatment in response to transaminase elevations has been shown to mitigate the seriousness of hepatic reactions. Care should be exercised when administering potential hepatotoxic medicinal substances, herbal supplements, and alcohol to patients treated with fidanacogene elaparvovec. See Section V.2 for the proposed additional risk minimisation measures for hepatotoxicity.

Impact on the risk-benefit balance of the biologic product:

Monitoring of liver enzymes and Factor IX levels and treatment with corticosteroids in the event of liver enzyme increases or factor IX activity decreases, as recommended in the product SmPC minimizes the risk of hepatotoxicity and may also reduce the risk of loss of FIX expression, thus contributing to the favorable risk-benefit profile of fidanacogene elaparvovec.

Public health impact:

Considering that in clinical studies with fidanacogene elaparvovec, most participants had asymptomatic, and predominantly mild elevations in transaminase levels, and the small patient population, the public health impact of hepatotoxicity is expected to be minimal.

SVII.3.1.2. Important Potential Risks

SVII.3.1.2.1. Important Potential Risk: Development of FIX Inhibitors

Potential mechanisms:

Humoral immunity to a foreign protein.

Evidence source and strength of evidence:

No clinical trial participants developed Factor IX inhibitors as of the cutoff date.

Characterisation of the risk:

As of the data cutoff date, there were no relevant AEs suggestive of development of FIX inhibitors.

Medicinal product no longer authorised

Risk factors and risk groups:

Patients with <50 prior exposure days to recombinant and/or plasma-derived FIX protein products and patients with a previous history of FIX inhibitor.

Preventability:

Limiting therapy to patients who have been previously exposed to FIX infused protein (ie, those who have had greater than 50 previous exposure days to FIX concentrates) and by not treating patients with a previous history of FIX inhibitor may minimize the risk. See Section V.2 for the proposed additional risk minimisation measures for development of FIX inhibitors.

Impact on the risk-benefit balance of the biologic product:

Currently, the impact to the overall risk-benefit balance has not been characterised, but, if development of FIX inhibitors is established as related to fidanacogene elaparvovec, it may have the potential to affect the risk-benefit profile.

Public health impact:

Considering the lack of development of FIX inhibitors events reported in fidanacogene elaparvovec clinical trials to date and the small patient population, the public health impact of development of FIX inhibitors is expected to be minimal.

SVII.3.1.2.2. Important Potential Risk: Thromboembolic Events

Potential mechanisms:

FIX levels above the upper limit of normal may result in thromboembolic events. The FIX variant encoded in fidanacogene elaparvovec produces FIX-R338L, a FIX variant that has approximately 8-fold increased specific activity compared to wild-type FIX.

Evidence source and strength of evidence:

No clinical trial participants that received fidanacogene elaparvovec had experienced thromboembolic events as of the cutoff date. Administration of fidanacogene elaparvovec did not result in Factor IX levels that were maintained above the threshold (>150% of normal) considered a risk factor for an increase in thromboembolic events.

Characterisation of the risk:

As of the data cutoff date, there were no relevant AEs suggestive of thromboembolic events.

Risk factors and risk groups:

Elevated FIX levels.

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General risk factors for thromboembolic events include a history of thromboembolic events, increased age, tobacco smoking, diabetes mellitus, hypertension, hypercholesterolemia, coagulation defects (eg, anti-thrombin, protein C and protein S deficiencies), gene mutations (eg, Factor V Leiden and prothrombin gene mutations), anti-phospholipid antibody syndrome, major and minor trauma, immobilization, surgery, cancer, and pregnancy.

Preventability:

Monitoring of FIX levels after fidanacogene elaparvovec administration for detection of elevated FIX levels.

Identifying general risk factors and monitoring patients when they have risk factors for thromboembolic events could potentially allow early detection resulting in proactive and timely anti-coagulation intervention thereby decreasing the potential for worsening severity and subsequent complications. Identifying patients at risk and providing prophylactic treatment as applicable may reduce the frequency of thromboembolic events. See Section V.2 for the proposed additional risk minimisation measures for thromboembolic events.

Impact on the risk-benefit balance of the biologic product:

Currently, the impact to the overall risk-benefit balance has not been characterised, but, if thromboembolic events is established as related to fidanacogene elaparvovec, it may have the potential to affect the risk-benefit profile.

Public health impact:

Considering the lack of thromboembolic events reported in fidanacogene elaparvovec clinical trials to date and the small patient population, the public health impact of thromboembolic events is expected to be minimal.

SVII.3.1.2.3. Important Potential Risk: Risk of Malignancy in Relation to Vector Integration in the DNA of Body Cells

Potential mechanisms:

Vector integration into the host cell DNA.

Evidence source and strength of evidence:

In a small portion of AAV transduced cells, the transgene will integrate into the cell's genome. It is assumed that the greatest potential for integration would be into cells within the liver, but given the results of tissue distribution studies, the potential for integration into cells of other tissues also exists.

The genotoxicity and carcinogenicity risk of delivering adeno-associated virus vectors to the liver is low, although a few nonclinical studies have shown hepatocellular carcinoma related to AAV administration in neonatal mice. A recent review has comprehensively discussed the evidence of rAAV-related host genome integration in animal models and possible risks of

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insertional mutagenesis in patients.[66] In a 2-year vector integration study in cynomolgus monkeys administered fidanacogene elaparvovec $5x10^{12}$ vg/kg, there is no indication that integration of vector DNA into host cell DNA resulted in hepatocellular hyperplasia and carcinoma. The integration profile was considered benign as the integrations were generally random with a low frequency that was below published spontaneous mutation rate estimates for the liver and due to the absence of significant clonal expansion. Similar integration site results were found using liver samples from juvenile dogs administered fidanacogene elaparvovec.

An asymptomatic case of HCC was identified in an older subject with previously documented HBV infection who was enrolled in a clinical trial of etranacogene dezaparvovec, an AAV5 carrying a gene cassette with the Padua variant of Factor IX. The occurrence of HCC was considered unlikely related to treatment with etranacogene dezaparvovec based upon the results of genetic analysis and pre-existing risk factors[67].

No clinical trial participants that received fidanacogene elaparvovec had experienced malignancy events as of the cutoff date.

Characterisation of the risk:

As of the data cutoff date, there were no relevant AEs suggestive of cancer.

Risk factors and risk groups:

No risk factors for this risk have been identified.

General risk factors for hepatocellular carcinoma include hepatitis C virus, hepatitis B virus, cirrhosis, high alcohol consumption, non-alcoholic fatty liver disease/non-alcoholic steatohepatitis[68].

Preventability:

Patients with pre-existing risk factors for hepatocellular carcinoma (such as hepatic fibrosis, hepatitis B, hepatitis C, non-alcoholic fatty liver disease/non-alcoholic steatohepatitis) are recommended to undergo regular liver ultrasound screenings and regularly monitored for alpha-fetoprotein elevations, which could potentially allow for early detection. See Section V.2 for the proposed additional risk minimisation measures for risk of malignancy in relation to vector integration in the DNA of body cells.

Impact on the risk-benefit balance of the biologic product:

Currently, the impact to the overall risk-benefit balance has not been characterised, but, if risk of malignancy in relation to vector integration in the DNA of body cells is established as related to fidanacogene elaparvovec, it may have the potential to affect the risk-benefit profile.

Medicinal product no longer authorised

Public health impact:

Considering the lack of cancers reported in fidanacogene elaparvovec clinical trials to date and the small patient population, the public health impact of risk of malignancy in relation to vector integration in the DNA of body cells is expected to be minimal.

SVII.3.1.2.4. Important Potential Risk: Transmission to Third Parties (Horizontal Transmission)

Potential mechanisms:

Vector shedding in patient's urine, blood, semen and saliva.

Evidence source and strength of evidence:

Vector DNA shedding after infusion with fidanacogene elaparvovec was assessed in clinical trials C0371005/C10371003 and C0371002. Vector DNA was shed in peripheral blood mononuclear cells (PBMC), saliva, urine, semen, and serum/plasma. In general, peak levels of vector occurred within the first two weeks after infusion. Highest peak vector DNA concentrations were found in serum/plasma compared to the other liquid matrices (saliva, urine, semen). Full clearance of vector DNA was defined as having 3 consecutive negative results (i.e. below quantification limit). Vector DNA fully cleared in plasma, serum, saliva, and semen within a mean of 1-4 months after infusion and PBMC was slowest fluid to full clearance within a mean of 12 months. In urine, the peak vector DNA concentration was very low and declined to full clearance within a mean of 4 weeks after infusion.

AAV is a defective virus that can replicate only in the presence of a helper virus. Because the viral genes have been removed to generate fidanacogene elaparvovec, the vector would require the presence of both wild-type AAV and a helper virus to replicate. If replication did occur, the only expected by-product would be the generation of more fidanacogene elaparvovec. The likelihood of such an occurrence is extremely low.

Characterisation of the risk:

No events of transmission to third parties (horizontal transmission) have been reported.

Risk factors and risk groups:

Patient caregivers, close contacts, and partners.

Preventability:

Patients should not donate blood, organs, tissues, or cells for transplantation. Use of a male condom for 6 months after receiving fidanacogene elaparvovec.

Proper handling of any raw materials that have come in contact with patient bodily waste or fluids and proper hand hygiene when coming into direct contact with patient secretions or excretions. See Section V.2 for the proposed additional risk minimisation measures for transmission to third parties (horizontal transmission).

Medicinal product no longer authorised

Impact on the risk-benefit balance of the biologic product:

Guidance in the product SmPC for patients not to donate blood, organs, tissues, or cells for transplantation minimizes the risk of transmission to third parties (horizontal transmission) and will contribute to the favourable risk-benefit profile of fidanacogene elaparvovec.

Public health impact:

Considering that the likelihood of vector replication is extremely low, the public health impact of transmission to third parties (horizontal transmission) is expected to be minimal.

SVII.3.1.2.5. Important Potential Risk: Germline Transmission

Potential mechanisms:

Vector shedding in patient's semen.

Evidence source and strength of evidence:

Vector DNA shedding after infusion with fidanacogene elaparvovec was assessed in clinical trials C0371005/C10371003 and C0371002. Vector DNA was shed in semen. In general, peak levels of vector occurred within the first two weeks after infusion. Higher peak vector DNA concentrations were found in plasma/serum compared to other liquid matrices (semen). Full clearance of vector DNA was defined as having 3 consecutive negative results (i.e. below quantification limit). In semen, the maximum observed time for vector DNA full clearance was 154 days.

Characterisation of the risk:

Cases of maternal exposure via partner during pregnancy have been reported in the clinical trials; however, no evidence of vector transmission is available at this time.

Risk factors and risk groups:

Male patients engaged in sexual intercourse with a woman of childbearing potential within 6 months of fidanacogene elaparvovec administration.

Preventability:

Male patients treated with fidanacogene elaparvovec should not donate semen. For patients of reproductive potential and their female partners of childbearing potential, prevent or postpone pregnancy using barrier contraception for 6 months after administration of fidanacogene elaparvovec. See Section V.2 for the proposed additional risk minimisation measures for germline transmission.

Impact on the risk-benefit balance of the biologic product:

Guidance in the product SmPC advising male patients to not donate semen and that patients of reproductive potential and their female partners of childbearing potential must prevent or

Medicinal product no longer authorised

postpone pregnancy using barrier contraception for 6 months after administration of fidanacogene elaparvovec minimizes the risk of germline transmission and will contribute to the favourable risk-benefit profile of fidanacogene elaparvovec.

Public health impact:

Considering the small patient population, the public health impact of germline transmission is expected to be minimal.

SVII.3.2. Presentation of the Missing Information

Table 10. Missing Information: Long-Term Safety

Evidence source: As of data cutoff, 58 clinical trial participants have data available 15 months after administration of fidanacogene elaparvovec. The median duration of follow-up across the pooled studies was 2.97 years (range from 1.0 years to 6.0 years). Long-term safety is unknown. Population in need of further characterisation: Additional long-term safety data, which will be obtained from long-term follow-up of participants in ongoing and planned clinical studies. The long-term follow-up studies will characterize the long-term safety of fidanacogene elaparvovec.

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Module SVIII. Summary of the Safety Concerns

Table 11. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Hepatotoxicity
Important potential risks	Development of FIX inhibitors Thromboembolic events Risk of malignancy in relation to vector integration in the DNA of body cells Transmission to third parties (horizontal transmission) Germline transmission
Missing information	Long-term safety

Medicinal product no longer authorised

PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond ADRs reporting and signal detection:

- **Specific adverse reaction follow-up questionnaires for safety concerns:**

The following questionnaires (which can be found in Annex 4) are utilized for fidanacogene elaparvovec to gather follow up information:

  - Malignancy Questionnaire
  - Hepatic Events Questionnaire
  - Thromboembolic event Questionnaire
  - Pregnancy Questionnaire

- **Other forms of routine pharmacovigilance activities for safety concerns:**

None proposed.

III.2. Additional Pharmacovigilance Activities

Post authorisation efficacy studies, which are detailed in Section PART IV, will also address safety concerns for fidanacogene elaparvovec. Please see Section PART IV for further details on which safety concerns each post authorisation efficacy study will address. There are no additional pharmacovigilance activities planned or ongoing for fidanacogene elaparvovec beyond the studies classified as post authorisation efficacy studies in PART IV.

III.3. Summary Table of Additional Pharmacovigilance Activities

III.3.1. On-Going and Planned Additional Pharmacovigilance Activities

Table 12. On-going and planned additional pharmacovigilance activities

Study	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities (by the competent authority)				
None				

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PART IV. PLANS FOR POST AUTHORISATION EFFICACY STUDIES

Table 13. Planned and On-going Post-Authorisation Efficacy Studies that are Conditions of the Marketing Authorisation or that are Specific Obligations

Study Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorisation				
C0371017 A Phase 3, Non-Investigational Product, Multi Country Cohort Study to Describe the Long-Term Safety and Effectiveness of a Prior Single-Dose Treatment with Investigative Giroctocogene Fitelparvovec[a] or Fidanacogene Elaparvovec in Participants with Hemophilia A or Hemophilia B, Respectively Ongoing An approximate number of participants is (up to 142).	<u>Primary objective:</u> To describe durability of transgene expression of fidanacogene elaparvovec. To characterize the long-term safety of participants who have received prior treatment with fidanacogene elaparvovec. <u>Secondary objectives:</u> To assess the effect of fidanacogene elaparvovec on clinical outcomes. To further evaluate the long-term safety profile of fidanacogene elaparvovec in participants. To evaluate the effect of fidanacogene elaparvovec on the participant's quality of life.	Long term effect Safety concerns also addressed: - Hepatotoxicity - Development of FIX inhibitors - Thromboembolic events - Risk of malignancy in relation to vector integration in the DNA of body cells - Long-term safety	Interim CSRs	Every 3 years
			Final CSR	31 March 2040
C0371007 A Multi-Country, Non-Interventional, Observational, Cohort Study to Describe Long-Term Effectiveness of Fidanacogene Elaparvovec for	<u>Primary objectives:</u> To evaluate FIX activity level, annualized bleeding rate and annualized joint bleeding rate in patients with hemophilia B treated with approved fidanacogene elaparvovec and in patients with hemophilia B not exposed to gene therapy. <u>Secondary objectives:</u>	Long term effect Safety concerns also addressed: - Hepatotoxicity - Development of FIX inhibitors - Thromboembolic events - Risk of malignancy in relation to vector	Protocol submission	Within 3 months after EC Decision
			Progress Report	1.5 years after start of data collection

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Table 13. Planned and On-going Post-Authorisation Efficacy Studies that are Conditions of the Marketing Authorisation or that are Specific Obligations

Study Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Date
the Treatment of Hemophilia B in a Real-World Setting Planned Study will aim to enroll approximately 220 patients in the Real-World Fidanacogene Elaparvovec Cohort.	To estimate the incidence of hepatotoxicity, thromboembolic events, development of FIX inhibitors and hepatic malignancy in patients with hemophilia B treated with approved fidanacogene elaparvovec and in patients with hemophilia B not exposed to gene therapy. To describe durability of effectiveness in patients with hemophilia B treated with approved fidanacogene elaparvovec. To assess exogenous FIX utilization/treatment in patients with hemophilia B treated with approved fidanacogene elaparvovec and in patients with hemophilia B not exposed to gene therapy. To estimate the incidence of auto-immune disorders, liver abnormalities, non-hepatic malignancy, hypersensitivity reactions (including infusion-related reactions), and other serious adverse events and all-cause mortality in patients with hemophilia B treated with approved fidanacogene elaparvovec and in patients not exposed to gene therapy.	integration in the DNA of body cells - Long-term safety	Interim Reports (including study progress)	Every 3 years, first report prepared 3 years after start of data collection
			Final CSR	At earliest 2045 (within 12 months after study end [6 months after study end if any paediatric patients are enrolled in the study]; study anticipated to end in 2044).

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Table 13. Planned and On-going Post-Authorisation Efficacy Studies that are Conditions of the Marketing Authorisation or that are Specific Obligations

Study Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Date
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
C0371002 Phase 3, Open Label, Single Arm Study to Evaluate Efficacy and Safety of FIX Gene Transfer with PF-06838435 (rAAV-Spark100-hFIX-R338L) in Adult Male Participants with Moderately Severe to Severe Hemophilia B (FIX:C≤2%) (BeneGene-2) Ongoing Approximately 50 participants will be screened to achieve at least 40 evaluable participants at the time of primary completion date.	<u>Primary objective:</u> To demonstrate the efficacy of a single infusion of PF-06838435 in male participants ≥18 years of age with moderately severe to severe hemophilia B (FIX:C ≤2%). <u>Secondary objectives:</u> To demonstrate the efficacy of PF-06838435 in terms of the use of exogenous FIX, the treated bleeds, and FIX:C. To compare additional efficacy parameters post-PF-06838435 infusion to baseline in order to further characterize PF-06838435 treatment, including use of exogenous FIX, information on bleeding events, and patient reported outcomes addressing health related quality of life, activities of daily living and general health status. Safety and tolerability of PF-06838435, including immunogenicity, for the study duration of 6 years after PF-06838435 infusion. Assess durability of efficacy up to 6 years.	Long term effect Safety concerns also addressed: - Hepatotoxicity - Development of FIX inhibitors - Thromboembolic events - Risk of malignancy in relation to vector integration in the DNA of body cells - Transmission to third parties (horizontal transmission) - Germline transmission - Long-term safety	Interim CSR (4-year follow-up data from subjects with dose calculated using actual batch concentration [cutoff date August 2025])	28 February 2026
			Interim CSR (final 6-year data from subjects with dose calculated using actual batch concentration [cutoff date June 2028])[b]	31 December 2028
C0371003 A Factor IX (FIX) Gene Transfer, Multi-Center Evaluation of the Long-Term Safety and Efficacy Study	<u>Primary objective:</u> Evaluate the long-term safety in participants who previously received a single administration of PF-06838435 in the C0371005 clinical study and the short-and long-term safety in participants who enter from the dose-escalation	Long term effect Safety concerns also addressed: - Hepatotoxicity - Development of FIX inhibitors - Thromboembolic events	Interim CSR (final 5-year data[d] from all subjects dosed with 5 x 10^{11} vector genomes per kg (vg/kg) of body weight; will also include higher	31 January 2025

Medicinal product no longer authorised

Table 13. Planned and On-going Post-Authorisation Efficacy Studies that are Conditions of the Marketing Authorisation or that are Specific Obligations

Study Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Date
of PF-06838435 and a Dose-Escalation Substudy in Individuals with Hemophilia B Ongoing Fifteen participants who received a single administration of PF-06838435 from the now completed C0371005 study were eligible to enroll in this long-term follow-up study	substudy of this study, C0371003. <u>Secondary objectives:</u> To evaluate the safety and tolerability of a single IV infusion of PF-06838435 in participants in the dose-escalation substudy. Determine the durability of transgene expression of PF-06838435. To characterize the kinetics of PF-06838435 during first year after vector infusion in participants in the dose-escalation substudy. Assess the effect of PF-06838435 on clinical outcomes.	- Risk of malignancy in relation to vector integration in the DNA of body cells - Transmission to third parties (horizontal transmission) - Germline transmission - Long-term safety	dose data to 15 months)[c]	

a. Study includes a separate cohort of haemophilia A participants related to a separate clinical development program (giroctocogene fitelparvovec), which is not in scope for this RMP and thus will not be discussed (further mentions of study C0371017 omit the giroctocogene fitelparvovec cohort information).
b.Please note that one further report will be available (6-year follow-up for additional subjects receiving nominal batch concentration; these participants are not within the scope of the current indication) in January 2031. This report is not part of the Specific Obligations and is mentioned here for transparency.
c.Please note that one further report will be available (6-year follow-up for higher dose subjects; these participants are not within the scope of the current indication) in November 2029. This report is not part of the Specific Obligations and is mentioned here for transparency.
d. 5 years follow-up for all subjects dosed with 5 x 10^{11} vg/kg of body weight in study C0371003, amounting to a total of 6 year follow-up post-infusion [ie, across studies C0371005 and C0371003].

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PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

RISK MINIMISATION PLAN

V.1. Routine Risk Minimisation Measures

Table 14. Description of routine risk minimisation measures by safety concern

Safety Concern	Routine risk minimisation activities
Important Identified Risks	
Hepatotoxicity	Routine risk communication: SmPC Section 4.4, Special warnings and precautions for use SmPC Section 4.5, Interaction with other medicinal products and other forms of interaction SmPC Section 4.8, Undesirable effects Package Leaflet (PL) Sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.4 states that ALT/AST and factor IX activity levels should be monitored following the administration of fidanacogene elaparvovec, once or twice weekly from weeks 1-12, weekly from weeks 13-18, at weeks 24, 32, 42 and 52 from weeks 19 to 52 (end of year 1), quarterly from Year 2 to end of year 3[a], twice yearly from Year 4 to end of year 6, and annually after year 6. Corticosteroid treatment should be instituted in response to aminotransferase elevations to control hepatic reactions and prevent or mitigate a potential reduction in transgene expression. PL Section 2 states that during the first year, liver enzyme testing and factor IX testing will be repeated once or twice weekly for the first 12 weeks, weekly from weeks 13 to 18, and at weeks 24, 32, 42, and 52. Then, from year 2 to end of year 3 testing will be performed quarterly, moving to twice yearly from year 4 to end of year 6, and annually after year 6. Other routine risk minimisation measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription. Treatment should be administered in a qualified treatment centre by a physician experienced in the treatment of haemophilia.

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Table 14. Description of routine risk minimisation measures by safety concern

Safety Concern	Routine risk minimisation activities
Important Potential Risks	
Development of FIX inhibitors	Routine risk communication: SmPC Section 4.2, Posology and method of administration SmPC Section 4.4, Special warnings and precautions for use PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.2 states that eligibility for treatment should be confirmed within 8 weeks prior to infusion by: negative for factor IX inhibitors by history and test <0.6 Bethesda Units (BU). SmPC Section 4.4 states to monitor patients through appropriate clinical observations and laboratory tests for the development of inhibitors to factor IX after fidanacogene elaparvovec administration. Perform an assay that detects factor IX inhibitors if bleeding is not controlled, or plasma factor IX activity levels decrease. PL Section 2 states that after fidanacogene elaparvovec administration, there is a risk of developing neutralising antibodies against factor IX, which may prevent factor IX from working properly. Blood tests may be checked for these antibodies, if bleeding episodes cannot be controlled. Other routine risk minimisation measures beyond the Product Information: Legal status: Medicinal product subject to restricted medical prescription. Treatment should be administered in a qualified treatment centre by a physician experienced in the treatment of haemophilia.
Thromboembolic events	Routine risk communication: SmPC Section 4.4, Special warnings and precautions for use PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.4 states to monitor factor IX activity levels at baseline, once or twice weekly from weeks 1-12, weekly from weeks 13-18, at weeks 24, 32, 42 and 52 from weeks 19 to 52 (end of year 1), quarterly from Year 2 to end of year 3[a], twice yearly from Year 4 to end of year 6, and annually after year 6, following the administration of fidanacogene elaparvovec. SmPC Section 4.4 states that patients should be evaluated before and after administration of fidanacogene elaparvovec for risk factors for thrombosis and general cardiovascular risk factors. Based on factor IX activity levels achieved, patients should be advised according to their individual condition.

Medicinal product no longer authorised

Table 14. Description of routine risk minimisation measures by safety concern

Safety Concern	Routine risk minimisation activities
	PL Section 2 states that during the first year, factor IX testing will be repeated once or twice weekly for the first 12 weeks, weekly from weeks 13 to 18, and at weeks 24, 32, 42, and 52. Then, from year 2 to end of year 3 testing will be performed quarterly, moving to twice yearly from year 4 to end of year 6, and annually after year 6. <u>Other routine risk minimisation measures beyond the Product Information:</u> Legal status: Medicinal product subject to restricted medical prescription. Treatment should be administered in a qualified treatment centre by a physician experienced in the treatment of haemophilia.
Risk of malignancy in relation to vector integration in the DNA of body cells	<u>Routine risk communication:</u> SmPC Section 4.4, Special warnings and precautions for use PL Section 2 <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> SmPC Section 4.4 states that it is recommended that patients with preexisting risk factors for hepatocellular carcinoma (such as hepatic fibrosis, hepatitis C or B disease, non-alcoholic fatty liver disease) undergo regular liver ultrasound screenings and are regularly monitored for alpha-fetoprotein (AFP) elevations on a yearly basis for at least 5 years after fidanacogene elaparvovec administration. In the event that a malignancy occurs, the marketing authorisation holder should be contacted by the treating healthcare professional to obtain instructions on collecting patient samples for potential vector integration examination and integration site analysis. <u>Other routine risk minimisation measures beyond the Product Information:</u> Legal status: Medicinal product subject to restricted medical prescription. Treatment should be administered in a qualified treatment centre by a physician experienced in the treatment of haemophilia.
Transmission to third parties (horizontal transmission)	<u>Routine risk communication:</u> SmPC Section 4.4, Special warnings and precautions for use SmPC Section 4.6, Fertility, pregnancy and lactation SmPC Section 5.2, Pharmacokinetic properties SmPC Section 6.6, Special precautions for disposal and other handling PL Section 2 <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u>

Medicinal product no longer authorised

Table 14. Description of routine risk minimisation measures by safety concern

Safety Concern	Routine risk minimisation activities
	SmPC Section 4.4 states that patients treated with this medicinal product should not donate blood, organs, tissue and cells for transplantation. SmPC Section 4.4 states to minimise the risk of transmission to other persons, patients should be instructed regarding proper hand hygiene when coming into direct contact with patient secretions or excretions. SmPC Section 4.6 states that for 6 months after administration of fidanacogene elaparvovec, treated patients of reproductive potential and their female partners of childbearing potential must prevent or postpone pregnancy using barrier contraception and avoid contact with semen. <u>Other routine risk minimisation measures beyond the Product Information:</u> Legal status: Medicinal product subject to restricted medical prescription. Treatment should be administered in a qualified treatment centre by a physician experienced in the treatment of haemophilia.
Germline transmission	<u>Routine risk communication:</u> SmPC Section 4.4, Special warnings and precautions for use SmPC Section 4.6, Fertility, pregnancy and lactation SmPC Section 5.2, Pharmacokinetic properties PL Section 2 <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> SmPC Section 4.6 states that for 6 months after administration of fidanacogene elaparvovec treated patients of reproductive potential and their female partners of childbearing potential must prevent or postpone pregnancy using barrier contraception. Males treated with fidanacogene elaparvovec must not donate semen to minimise the potential risk of paternal germline transmission. <u>Other routine risk minimisation measures beyond the Product Information:</u> Legal status: Medicinal product subject to restricted medical prescription. Treatment should be administered in a qualified treatment centre by a physician experienced in the treatment of haemophilia.
Missing Information	
Long-term safety	<u>Routine risk communication:</u> SmPC Section 4.4, Special warnings and precautions for use PL Section 2 <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u>

Medicinal product no longer authorised

Table 14. Description of routine risk minimisation measures by safety concern

Safety Concern	Routine risk minimisation activities
	SmPC Section 4.4 states that patients are expected to be enrolled in a registry to follow haemophilia patients for 15 years after infusion, to better understand the long-term safety and efficacy of this gene therapy. PL Section 2 states that after receiving this treatment, patients will be expected to enroll in a follow-up study to help study the long-term effect of the treatment for 15 years, how well it continues to work and any side effects that may be linked to the treatment. <u>Other routine risk minimisation measures beyond the Product Information:</u> Legal status: Medicinal product subject to restricted medical prescription. Treatment should be administered in a qualified treatment centre by a physician experienced in the treatment of haemophilia.

a. Starting at week 65.

V.2. Additional Risk Minimisation Measures

Guide for Healthcare Professionals

<u>Objectives:</u>

The objective of the proposed aRMM is to provide an appropriate tool designed to enhance the awareness and knowledge of prescribers and patients about the following safety concerns and to ensure the optimal use of fidanacogene elaparvovec.

To accomplish the objective, the Guide for Healthcare Professionals was developed to inform prescribers about the risks and provide recommendations on how to mitigate the risk through appropriate monitoring and management.

- Hepatotoxicity
- Development of FIX inhibitors
- Thromboembolic events
- Risk of malignancy in relation to vector integration in the DNA of body cells
- Transmission to third parties (horizontal transmission)
- Germline transmission

Medicinal product no longer authorised

- Long-term safety[c]

Rationale for the additional risk minimisation activity:

Additional awareness and knowledge of physicians about the risks help to mitigate these risks.

Target audience and planned distribution path:

The intended audience includes HCPs and patients (via HCPs and patient organizations)

- Haemophilia Treatment Centres that plan to participate in the gene therapy administration patient journey, either as administration, referral, or follow-up centre, depending on the care delivery model determined by health authorities in EU member states.

- Potential Haemophilia B patients entering the gene therapy journey – via Hemophilia main patient organizations in EU member states, as well as European Hemophilia Consortium, which serves as the European umbrella patient organization.

Planned communication plan:

The communication plan will be tailored to meet the local and regulatory requirements.

- Pfizer's Medical Affairs teams will provide Haemophilia Treatment Centres with training on RMP/RMM/aRMM, during the onboarding process for gene therapy.

- HCP and patient guides and patient cards will be distributed to Haemophilia Treatment centres that intend to participate in the gene therapy patient journey.

- Patient training materials and patient cards will be disseminated to Haemophilia main patient organizations in EU member states, as well as European Haemophilia Consortium.

- HCP and patient training materials and patient cards will be disseminated through Pfizer's DURVEQTIX appropriate websites in EU / member states

Plans to evaluate the effectiveness of the interventions and criteria for success:

Pfizer proposes to evaluate the effectiveness of the aRMMs via routine pharmacovigilance.

Patient Guide

[c] Missing information, not an important risk.

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Objectives:

The objective of the proposed additional measure is to provide an appropriate tool designed to enhance the awareness and knowledge of patients about the following safety concerns and to ensure the optimal use of fidanacogene elaparvovec.

- Hepatotoxicity
- Development of FIX inhibitors
- Thromboembolic events
- Risk of malignancy in relation to vector integration in the DNA of body cells
- Transmission to third parties (horizontal transmission)
- Germline transmission
- Long-term safety[c]

Rationale for the additional risk minimisation activity:

Additional awareness and knowledge of patients about the risks will help to mitigate these risks.

Target audience and planned distribution path:

The intended audience includes HCPs and patients (via HCPs and patient organizations)

- Haemophilia Treatment Centres that plan to participate in the gene therapy administration patient journey, either as administration, referral, or follow-up centre, depending on the care delivery model determined by health authorities in EU member states.
- Potential Haemophilia B patients entering the gene therapy journey – via Hemophilia main patient organizations in EU member states, as well as European Hemophilia Consortium, which serves as the European umbrella patient organization.

Planned communication plan:

The communication plan will be tailored to meet the local and regulatory requirements.

- Pfizer's Medical Affairs teams will provide Haemophilia Treatment Centres with training on RMP/RMM/aRMM, during the onboarding process for gene therapy.
- HCP and patient guides and patient cards will be distributed to Haemophilia Treatment centres that intend to participate in the gene therapy patient journey.

Medicinal product no longer authorised

- Patient training materials and patient cards will be disseminated to Haemophilia main patient organizations in EU member states, as well as European Haemophilia Consortium.

- HCP and patient training materials and patient cards will be disseminated through Pfizer's DURVEQTIX appropriate websites in EU / member states

Plans to evaluate the effectiveness of the interventions and criteria for success:

Pfizer proposes to evaluate the effectiveness of the aRMMs via routine pharmacovigilance.

Patient Card

Objectives:

The objective of the proposed additional measure is to inform healthcare professionals that the patient has received fidanacogene elaparvovec and to provide information for the patients regarding regular blood tests and examinations as directed by their doctor. The Patient Card will include information about the following risks:

- Hepatotoxicity
- Development of FIX inhibitors
- Thromboembolic events
- Risk of malignancy in relation to vector integration in the DNA of body cells
- Transmission to third parties (horizontal transmission)
- Germline transmission

Rationale for the additional risk minimisation activity:

Important information regarding treatment with fidanacogene elaparvovec can be held by the patient at all times.

Target audience and planned distribution path:

The intended audience includes HCPs and patients (via HCPs and patient organizations)

- Haemophilia Treatment Centres that plan to participate in the gene therapy administration patient journey, either as administration, referral, or follow-up centre, depending on the care delivery model determined by health authorities in EU member states.

- Potential Haemophilia B patients entering the gene therapy journey – via Hemophilia main patient organizations in EU member states, as well as European Hemophilia Consortium, which serves as the European umbrella patient organization.

Medicinal product no longer authorised

Planned communication plan:

The communication plan will be tailored to meet the local and regulatory requirements.

- Pfizer's Medical Affairs teams will provide Haemophilia Treatment Centres with training on RMP/RMM/aRMM, during the onboarding process for gene therapy.
- HCP and patient guides and patient cards will be distributed to Haemophilia Treatment centres that intend to participate in the gene therapy patient journey.
- Patient training materials and patient cards will be disseminated to Haemophilia main patient organizations in EU member states, as well as European Haemophilia Consortium.
- HCP and patient training materials and patient cards will be disseminated through Pfizer's DURVEQTIX appropriate websites in EU / member states

Plans to evaluate the effectiveness of the interventions and criteria for success:

Pfizer proposes to evaluate the effectiveness of the aRMMs via routine pharmacovigilance.

V.3. Summary of Risk Minimisation Measures

Table 15. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risk		
Hepatotoxicity	Routine risk minimisation measures: SmPC Section 4.4, Special warnings and precautions for use SmPC Section 4.5, Interaction with other medicinal products and other forms of interaction SmPC Section 4.8, Undesirable effects PL Sections 2 and 4 Legal status: Medicinal product subject to restricted medical prescription. Treatment should be administered in a qualified treatment centre by a physician experienced in the treatment of haemophilia. Additional risk minimisation measures: Guide for Healthcare Professionals Patient Guide Patient Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Hepatic Events Questionnaire Additional pharmacovigilance activities: None
Important Potential Risks		

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Table 15. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Development of FIX inhibitors	Routine risk minimisation measures: SmPC Section 4.2, Posology and method of administration SmPC Section 4.4, Special warnings and precautions for use PL Section 2 Legal status: Medicinal product subject to restricted medical prescription. Treatment should be administered in a qualified treatment centre by a physician experienced in the treatment of haemophilia. Additional risk minimisation measures: Guide for Healthcare Professionals Patient Guide Patient Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Thromboembolic events	Routine risk minimisation measures: SmPC Section 4.4, Special warnings and precautions for use PL Section 2 Legal status: Medicinal product subject to restricted medical prescription. Treatment should be administered in a qualified treatment centre by a physician experienced in the treatment of haemophilia. Additional risk minimisation measures: Guide for Healthcare Professionals Patient Guide Patient Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Thromboembolic Events Questionnaire Additional pharmacovigilance activities: None
Risk of malignancy in relation to vector integration in the DNA of body cells	Routine risk minimisation measures: SmPC Section 4.4, Special warnings and precautions for use PL Section 2 Legal status: Medicinal product subject to restricted medical prescription. Treatment should be administered in a qualified treatment centre by a physician experienced in the treatment of haemophilia. Additional risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Malignancy Questionnaire Additional pharmacovigilance activities: None

Medicinal product no longer authorised

Table 15. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Guide for Healthcare Professionals Patient Guide Patient Card	
Transmission to third parties (horizontal transmission)	Routine risk minimisation measures: SmPC Section 4.4, Special warnings and precautions for use SmPC Section 4.6, Fertility, pregnancy and lactation SmPC Section 5.2, Pharmacokinetic properties SmPC Section 6.6, Special precautions for disposal and other handling PL Section 2 Legal status: Medicinal product subject to restricted medical prescription. Treatment should be administered in a qualified treatment centre by a physician experienced in the treatment of haemophilia. Additional risk minimisation measures: Guide for Healthcare Professionals Patient Guide Patient Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Germline transmission	Routine risk minimisation measures: SmPC Section 4.4, Special warnings and precautions for use SmPC Section 4.6, Fertility, pregnancy and lactation SmPC Section 5.2, Pharmacokinetic properties PL Section 2 Legal status: Medicinal product subject to restricted medical prescription. Treatment should be administered in a qualified treatment centre by a physician experienced in the treatment of haemophilia. Additional risk minimisation measures: Guide for Healthcare Professionals Patient Guide Patient Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Pregnancy Questionnaire Additional pharmacovigilance activities: None

Medicinal product no longer authorised

Table 15. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Missing Information		
Long-term safety	Routine risk minimisation measures: SmPC Section 4.4, Special warnings and precautions for use PL Section 2 Legal status: Medicinal product subject to restricted medical prescription. Treatment should be administered in a qualified treatment centre by a physician experienced in the treatment of haemophilia. Additional risk minimisation measures: Guide for Healthcare Professionals Patient Guide	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

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PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for DURVEQTIX (fidanacogene elaparvovec)

This is a summary of the risk management plan (RMP) for DURVEQTIX. The RMP details important risks of DURVEQTIX, how these risks can be minimised, and how more information will be obtained about DURVEQTIX's risks and uncertainties (missing information).

DURVEQTIX's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how DURVEQTIX should be used.

This summary of the RMP for DURVEQTIX should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of DURVEQTIX's RMP.

I. The Medicine and What It Is Used For

DURVEQTIX is authorised for the treatment of severe and moderately severe haemophilia B (congenital factor IX deficiency) in adult patients without a history of factor IX inhibitors and without detectable antibodies to variant AAV serotype Rh74 (see SmPC for the full indication). It contains fidanacogene elaparvovec, as the active substance and it is given by intravenous infusion.

Further information about the evaluation of DURVEQTIX's benefits can be found in DURVEQTIX's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of DURVEQTIX, together with measures to minimise such risks and the proposed studies for learning more about DURVEQTIX's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

Medicinal product no longer authorised

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of DURVEQTIX, these measures are supplemented with *additional risk minimisation* measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of DURVEQTIXis not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of DURVEQTIX are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of DURVEQTIX. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Table 16. List of important risks and missing information

Important identified risks	Hepatotoxicity
Important potential risks	Development of FIX inhibitors Thromboembolic events Risk of malignancy in relation to vector integration in the DNA of body cells Transmission to third parties (horizontal transmission) Germline transmission
Missing information	Long-term safety

II.B Summary of Important Risks

Table 17. Important Identified Risk: Hepatotoxicity

Evidence for linking the risk to the medicine	Fidanacogene elaparvovec clinical trial data. The clinical trial data supports a causal association between fidanacogene elaparvovec and elevated transaminases.
Risk factors and risk groups	Patients with uncontrolled chronic hepatic infections, known significant hepatic fibrosis or cirrhosis, or other hepatic disorders or on concomitant hepatotoxic medications including herbal supplements and alcohol may be considered potentially at risk for developing hepatocellular toxicity associated with AAV liver-directed gene therapies.

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Table 17. Important Identified Risk: Hepatotoxicity

Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4, Special warnings and precautions for use SmPC Section 4.5, Interaction with other medicinal products and other forms of interaction SmPC Section 4.8, Undesirable effects PL Sections 2 and 4 Legal status: Medicinal product subject to restricted medical prescription. Treatment should be administered in a qualified treatment centre by a physician experienced in the treatment of haemophilia. Additional risk minimisation measures: Guide for Healthcare Professionals Patient Guide Patient Card

Table 18. Important Potential Risk: Development of FIX Inhibitors

Evidence for linking the risk to the medicine	No clinical trial participants had experienced an event of FIX inhibitor development as of the cutoff date.
Risk factors and risk groups	Patients with <50 prior exposure days to recombinant and/or plasma-derived FIX protein products and patients with a previous history of FIX inhibitor.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2, Posology and method of administration SmPC Section 4.4, Special warnings and precautions for use PL Section 2 Legal status: Medicinal product subject to restricted medical prescription. Treatment should be administered in a qualified treatment centre by a physician experienced in the treatment of haemophilia. Additional risk minimisation measures: Guide for Healthcare Professionals Patient Guide Patient Card

Table 19. Important Potential Risk: Thromboembolic Events

Evidence for linking the risk to the medicine	No clinical trial participants that received fidanacogene elaparvovec had experienced thromboembolic events as of the cutoff date.
Risk factors and risk groups	Elevated FIX levels. General risk factors for thromboembolic events include a history of thromboembolic events, increased age, tobacco smoking, diabetes mellitus, hypertension, hypercholesterolemia, coagulation defects (eg, anti-thrombin, protein C and protein S deficiencies), gene mutations (eg, Factor V Leiden and prothrombin gene mutations), anti-phospholipid antibody syndrome, major and minor trauma, immobilization, surgery, cancer, and pregnancy.

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Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC Section 4.4, Special warnings and precautions for use PL Section 2 Legal status: Medicinal product subject to restricted medical prescription. Treatment should be administered in a qualified treatment centre by a physician experienced in the treatment of haemophilia. <u>Additional risk minimisation measures:</u> Guide for Healthcare Professionals Patient Guide Patient Card

Table 20. Important Potential Risk: Risk of Malignancy in Relation to Vector Integration in the DNA of Body Cells

Evidence for linking the risk to the medicine	In a small portion of AAV transduced cells, the transgene will integrate into the cell's genome. It is assumed that the greatest potential for integration would be into cells within the liver, but given the results of tissue distribution studies, the potential for integration into cells of other tissues also exists. The genotoxicity and carcinogenicity risk of delivering adeno-associated virus vectors to the liver is low, although a few nonclinical studies have shown hepatocellular carcinoma related to AAV administration in neonatal mice. A recent review has comprehensively discussed the evidence of rAAV-related host genome integration in animal models and possible risks of insertional mutagenesis in patients. In a 2-year vector integration study in cynomolgus monkeys administered fidanacogene elaparvovec $5x10^{12}$ vg/kg, there is no indication that integration of vector DNA into host cell DNA resulted in hepatocellular hyperplasia and carcinoma. The integration profile was considered benign as the integrations were generally random with a low frequency that was below published spontaneous mutation rate estimates for the liver and due to the absence of significant clonal expansion. Similar integration site results were found using liver samples from juvenile dogs administered fidanacogene elaparvovec. An asymptomatic case of HCC was identified in an older subject with previously documented HBV infection who was enrolled in a clinical trial of etranacogene dezaparvovec, an AAV5 carrying a gene cassette with the Padua variant of Factor IX. The occurrence of HCC was considered unlikely related to treatment with etranacogene dezaparvovec based upon the results of genetic analysis and pre-existing risk factors. No clinical trial participants that received fidanacogene elaparvovec had experienced malignancy events as of the cutoff date.
Risk factors and risk groups	No risk factors for this risk have been identified. General risk factors for hepatocellular carcinoma include hepatitis C virus, Hepatitis B virus, cirrhosis, high alcohol consumption, non-alcoholic fatty liver disease/non-alcoholic steatohepatitis.

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Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4, Special warnings and precautions for use PL Section 2 Legal status: Medicinal product subject to restricted medical prescription. Treatment should be administered in a qualified treatment centre by a physician experienced in the treatment of haemophilia. Additional risk minimisation measures: Guide for Healthcare Professionals Patient Guide Patient Card

Table 21. Important Potential Risk: Transmission to Third Parties (Horizontal Transmission)

Evidence for linking the risk to the medicine	Vector DNA shedding after infusion with fidanacogene elaparvovec was assessed in clinical trials C0371005/C10371003 and C0371002. Vector DNA was shed in peripheral blood mononuclear cells (PBMC), saliva, urine, semen, and serum/plasma. In general, peak levels of vector occurred within the first two weeks after infusion. Highest peak vector DNA concentrations were found in plasma/serum compared to the other liquid matrices (saliva, serum, urine). Full clearance of vector DNA was defined as having 3 consecutive negative results (i.e. below quantification limit). Vector DNA fully cleared in plasma, serum, saliva, and semen within a mean of 1-4 months after infusion and PBMC was slowest fluid to full clearance within a mean of 12 months. In urine, the peak vector DNA concentration was very low and declined to full clearance within a mean of 4 weeks after infusion. AAV is a defective virus that can replicate only in the presence of a helper virus. Because the viral genes have been removed to generate fidanacogene elaparvovec, the vector would require the presence of both wild-type AAV and a helper virus to replicate. If replication did occur, the only expected by-product would be the generation of more fidanacogene elaparvovec. The likelihood of such an occurrence is extremely low.
Risk factors and risk groups	Patient caregivers, close contact, and partners.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4, Special warnings and precautions for use SmPC Section 4.6, Fertility, pregnancy and lactation SmPC Section 5.2, Pharmacokinetic properties SmPC Section 6.6, Special precautions for disposal and other handling PL Section 2 Legal status: Medicinal product subject to restricted medical prescription. Treatment should be administered in a qualified treatment centre by a physician experienced in the treatment of haemophilia. Additional risk minimisation measures: Guide for Healthcare Professionals Patient Guide Patient Card

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Table 22. Important Potential Risk: Germline Transmission

Evidence for linking the risk to the medicine	Vector DNA shedding after infusion with fidanacogene elaparvovec was assessed in clinical trials C0371005/C10371003 and C0371002. Vector DNA was shed in semen. In general, peak levels of vector occurred within the first two weeks after infusion. Higher peak vector DNA concentrations were found in plasma/serum compared to other liquid matrices (semen). Full clearance of vector DNA was defined as having 3 consecutive negative results (i.e. below quantification limit). In semen, the maximum observed time for vector DNA full clearance was 154 days.
Risk factors and risk groups	Male patients engaged in sexual intercourse with a woman of childbearing potential within 6 months of fidanacogene elaparvovec administration.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4, Special warnings and precautions for use SmPC Section 4.6, Fertility, pregnancy and lactation SmPC Section 5.2, Pharmacokinetic properties PL Section 2 Legal status: Medicinal product subject to restricted medical prescription. Treatment should be administered in a qualified treatment centre by a physician experienced in the treatment of haemophilia. Additional risk minimisation measures: Guide for Healthcare Professionals Patient Guide Patient Card

Table 23. Missing Information: Long-Term Safety

Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4, Special warnings and precautions for use PL Section 2 Legal status: Medicinal product subject to restricted medical prescription. Treatment should be administered in a qualified treatment centre by a physician experienced in the treatment of haemophilia. Additional risk minimisation measures: Guide for Healthcare Professionals Patient Guide

II.C Post-Authorisation Development Plan

II.C.1 Studies which are Conditions of the Marketing Authorisation

The following studies are conditions of the marketing authorisation:

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C0371017: A Phase 3, Non-Investigational Product, Multi Country Cohort Study to Describe the Long-Term Safety and Effectiveness of a Prior Single-Dose Treatment with Investigative Giroctocogene Fitelparvovec[a] or Fidanacogene Elaparvovec in Participants with Hemophilia A or Hemophilia B, Respectively

Purpose of the study: The primary objectives are to describe durability of transgene expression of fidanacogene elaparvovec and to characterize the long-term safety of participants who have received prior treatment with fidanacogene elaparvovec.

Secondary objectives include to assess the effect of fidanacogene elaparvovec on clinical outcomes, to further evaluate the long-term safety profile of fidanacogene elaparvovec in participants, and to evaluate the effect of fidanacogene elaparvovec on the participant's quality of life. This study will address the efficacy uncertainty of long-term effect and safety concerns of hepatotoxicity, development of FIX inhibitors, thromboembolic events, risk of malignancy in relation to vector integration in the DNA of body cells, and long-term safety.

C0371007: A Multi-Country, Non-Interventional, Observational, Cohort Study to Describe Long-Term Effectiveness of Fidanacogene Elaparvovec for the Treatment of Hemophilia B in a Real-World Setting

Purpose of the study: The goals of this study are to characterise the long-term effectiveness of fidanacogene elaparvovec in patients with haemophilia B in a real-world setting. The primary objectives are to evaluate FIX activity level, annualized bleeding rate and annualized joint bleeding rate in patients with haemophilia B treated with approved fidanacogene elaparvovec and in patients with haemophilia B not exposed to gene therapy.

Secondary objectives include to estimate the incidence of hepatotoxicity, thromboembolic events, development of FIX inhibitors, and hepatic malignancy in patients with haemophilia B treated with approved fidanacogene elaparvovec and in patients with haemophilia B not exposed to gene therapy, and, to estimate the incidence of auto-immune disorders, liver abnormalities, non-hepatic malignancy, hypersensitivity reactions (including infusion-related reactions), other serious adverse events and all-cause mortality in patients with haemophilia B treated with approved fidanacogene elaparvovec and in patients with haemophilia B not exposed to gene therapy, to describe the durability of effectiveness in patients with haemophilia B treated with approved fidanacogene elaparvovec, to assess exogenous FIX utilization/treatment in patients with haemophilia B treated with approved fidanacogene elaparvovec and in patients with haemophilia B not exposed to gene therapy, to assess Health Related Quality of Life in patients with haemophilia B treated with approved fidanacogene elaparvovec in routine care settings, and to assess ABR and AJBR in patients treated with fidanacogene elaparvovec comparatively with patients not treated with gene therapy. This study will address the efficacy uncertainty of long-term effect and safety concerns of hepatotoxicity, development of FIX inhibitors, thromboembolic events, risk of malignancy in relation to vector integration in the DNA of body cells, and long-term safety.

C0371002: Phase 3, Open Label, Single Arm Study to Evaluate Efficacy and Safety of FIX Gene Transfer with PF-06838435 (rAAV-Spark100-hFIX-R338L) in Adult Male

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Participants with Moderately Severe to Severe Hemophilia B (FIX:C≤2%) (BeneGene-2)

Purpose of the study: The primary objective is to demonstrate the efficacy of a single infusion of fidanacogene elaparvovec in male patients ≥18 years of age with moderately severe to severe hemophilia B (FIX:C ≤2%).

Secondary objectives include the safety and tolerability of fidanacogene elaparvovec, including immunogenicity, for the study duration of 6 years after fidanacogene elaparvovec infusion, and to assess durability of efficacy up to 6 years. This study will address the efficacy uncertainty of long-term effect and safety concerns of hepatotoxicity, development of FIX inhibitors, thromboembolic events, risk of malignancy in relation to vector integration in the DNA of body cells, transmission to third parties (horizontal transmission), germline transmission, and long-term safety.

C0371003: A Factor IX (FIX) Gene Transfer, Multi-Center Evaluation of the Long-Term Safety and Efficacy Study of PF-06838435 and a Dose-Escalation Substudy in Individuals with Hemophilia B

Purpose of the study: The primary objective is to evaluate the long-term safety in participants who previously received a single administration of fidanacogene elaparvovec in the C0371005 clinical study and in participants who enter from the dose-escalation substudy of this study, C0371003.

Secondary objectives include determining the durability of transgene expression of fidanacogene elaparvovec and to assess the effect of fidanacogene elaparvovec on clinical outcomes. This study will address the efficacy uncertainty of long-term effect and safety concerns of hepatotoxicity, development of FIX inhibitors, thromboembolic events, risk of malignancy in relation to vector integration in the DNA of body cells, transmission to third parties (horizontal transmission), germline transmission, and long-term safety.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for DURVEQTIX.

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PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN

Annex 2 – Tabulated summary of planned, on-going, and completed pharmacovigilance study programme

Annex 3 - Protocols for proposed, on-going, and completed studies in the pharmacovigilance plan

Annex 4 - Specific Adverse Drug Reaction Follow-Up Forms

Annex 5 - Protocols for proposed and on-going studies in RMP Part IV

Annex 6 - Details of Proposed Additional Risk Minimisation Activities

Annex 7 - Other Supporting Data (Including Referenced Material)

Annex 8 – Summary of Changes to the Risk Management Plan over Time

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ANNEX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Table of contents

Follow-up forms

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Fidanacogene elaparvovec (BEQVEZ/DURVEQTIX) malignancy Follow-up questions

Instructions for use:
Select questions as needed to obtain any DCA-defined information described below that was not included in the initial report.

AER/Manufacturer Report #: _____

Suspect product: _____

Reported event term prompting special follow-up activities: _____

PATIENT / EVENT INFORMATION (Please provide as much data as possible)

Name / Patient Identifier number:		
Age (years)	**Gender:**	**Weight (kg):**
Height (cm):	**BMI:**	**Race:**
Date of BEQVEZ/DURVEQTIX infusion (DD/MM/YYYY):		**Time to onset / diagnosis of malignancy:**
Dose of BEQVEZ/DURVEQTIX administered: **vg/kg**		
Event seriousness: Serious: **Non-Serious:**		**Reporter:**
Causality assessment (please check): Related:		**Not-related:**
Outcome (Please check): Not recovered: **Recovered:**		**Fatal:**
Recovered with treatment (specify below)		**Recovered with sequelae (specify below)**

Malignancy Follow-up Questions

In the event that a new malignancy is identified, testing of samples is important for further understanding of underlying mechanisms. Contact Pfizer Inc to obtain instructions on the collection of patient samples for testing.

Please provide additional details on a separate page if needed, and reference the question number.

1. Please mark whether the patient presented with any of the following:

- ☐ Liver malignancy
- ☐ Other *(please specify)*

2. Method of diagnosis

- ☐ Imaging
- ☐ Biopsy
- ☐ Biochemical / biomarkers (Please specify)

3. Additional test results:

4. Please mark whether the patient had any of the following known risk factors:

- ☐ Cancer chemotherapy agents within past 10 years *(please specify)*
- ☐ Hepatitis B,C background ☐ Current ☐ Past ☐ Liver Fibrosis ☐ Liver Cirrhosis
  Please provide date of diagnosis: _____
- ☐ Alcohol use: → ☐ Current ☐ Past
  Please estimate use/duration: _____
- ☐ Occupational exposures to carcinogens (solvents, DDT, Vinyl Chloride, Arsenic, Cadmium, nitrosamines, etc) *(please specify)*
- ☐ Family history *(please continue on question 4)*
- ☐ Environmental exposures *(please specify)*
- ☐ Smoking
- ☐ Immune suppression
- ☐ Auto-Immune disease
- ☐ Other *(please specify)*

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Fidanacogene elaparvovec (BEQVEZ/DURVEQTIX) malignancy Follow-up questions

5. Is there a family history of cancer?

☐ Unknown ☐ No ☐ Yes

If yes, please mark any of the following that apply:

☐ Maternal *(please specify type)*
☐ Paternal *(please specify type)*
☐ Sibling *(please specify type)*
☐ Other *(please specify type)*

6. Please specify whether the patient received any of the following treatments:

Chemotherapy	☐ Yes	☐ No	☐ Unknown
Radiation	☐ Yes	☐ No	☐ Unknown
Transplant	☐ Yes	☐ No	☐ Unknown

Other *(please specify)*

7. Please provide patient's present / prior history of cancer in order of occurrence (use additional pages if necessary):

Date of Diagnosis (DD-MMM-YYYY)	**Type of Cancer / Stage**	**Biopsy** Please attach copy of biopsy reports if possible	**Histology results** Please include FAB subtype, cellularity, myeloperoxidase positivity, presence of Auer rods, and cytogenetics; or attach copy of the report(s)	**Current status**
		☐ Yes ☐ No ☐ Unknown		
		☐ Yes ☐ No ☐ Unknown		
		☐ Yes ☐ No ☐ Unknown		
Date of Diagnosis (DD-MMM-YYYY)	**Type of Cancer / Stage**	**Laboratory /Imaging test**	**Laboratory / Imaging test results**	**Current status**
Date of Diagnosis (DD-MMM-YYYY)		☐ Yes ☐ No ☐ Unknown		

Medicinal product no longer authorised

Version History

Version	Version Date	Summary of Revisions
1.0	03-Oct-2022	Existing DCA converted to latest DCA format.

Fidanacogene elaparvovec (BEQVEZ/DURVEQTIX) Hepatic Events
Follow-up questions

Instructions for use:

Select questions as needed to obtain any DCA-defined information described below that was not included in the initial report.

AER/Manufacturer Report #: _____

Suspect product: _____

Reported event term prompting special follow-up activities: _____

Date of AE report: _____

PATIENT / EVENT INFORMATION (Please provide as much data as possible)

Name / Patient Identifier number:		
Age (years)	**Gender:**	**Weight (kg):**
Height (cm):	**BMI:**	**Race:**
Date of BEQVEZ/DURVEQTIX infusion (DD/MM/YYYY):		**Time to hepatic event onset:**
Dose of BEQVEZ/DURVEQTIX administered: **vg/kg**		
Event seriousness: Serious: **Non-Serious:**		**Reporter:**
Causality assessment (please check): Related:		**Not-related:**
Outcome (Please check): Not recovered: **Recovered:**		**Fatal:**
Recovered with treatment (specify below)		**Recovered with sequelae (specify below)**

Hepatic Events Follow-up Questions

Please provide additional details on a separate page if needed, and reference the question number.

1. Is the reported hepatic adverse event a:

☐ New event

☐ Recurrence (Repeat of a previously resolved event) *(Please specify details of the prior events)*

☐ Worsening of existing condition *(please provide details)*

Details:

2. Please provide: name, e-mail address, postal address, and telephone number of any specialist to whom the patient was referred for further evaluation of the reported adverse event(s) *(if applicable based on local privacy regulations)*

3. Was hepatic function test monitoring (e.g., AST, ALT, Bilirubin) done at the following times?

- **Routine LFTs prior to start of drug:**
  ☐ Unknown ☐ No ☐ Yes

  If Yes, please provide details of monitoring below and record relevant results in the laboratory data section.

  Details:

- **Baseline at start of therapy** ☐ Unknown ☐ No ☐ Yes

  If Yes, please provide details of monitoring below and record relevant results in the laboratory data section.

  Details:

- **During therapy:** ☐ Unknown ☐ No ☐ Yes

  If Yes, please provide details of monitoring below and record relevant results in the laboratory data section:

  Details:

- **After therapy:** ☐ Unknown ☐ No ☐ Yes

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Fidanacogene elaparvovec (BEQVEZ/DURVEQTIX) Hepatic Events
Follow-up questions

4. Please mark whether the patient experienced any of the following signs / symptoms:

- ☐ Rash
- ☐ Pruritus
- ☐ Purpura
- ☐ Fever
- ☐ Joint Pain
- ☐ Abdominal distension
- ☐ Abdominal Pain
- ☐ Nausea
- ☐ Vomiting
- ☐ Coma
- ☐ Ascites
- ☐ Asthenia
- ☐ Asterixis / "Flapping"
- ☐ Jaundice
- ☐ Hepatomegaly
- ☐ Splenomegaly
- ☐ Weight gain *(please specify)*_____
- ☐ Hepatic encephalopathy
- ☐ Sepsis *(if yes, describe time to onset and course of the event [e.g., progression and outcome])*_____
- ☐ Multi-organ failure *(if yes, include time to onset and the course [e.g., progression and outcome])*_____
- ☐ Other signs / symptoms *(including those related to infections, please specify)* _____

If Yes, please provide details of monitoring below and record relevant results in the laboratory data secti

5. Has the patient received corticosteroids for the management of increased transaminases after the administration of BEQVEZ/DURVEQTIX?

☐ Unknown ☐ No ☐ Yes

If yes, please provide: name of corticosteroid, therapeutic regime, date and time of administration and treatment duration.

6. Please mark whether the patient was taking any of the following medications / substances at the time of the adverse event or within two weeks prior to the onset of the adverse event: *(Please provide details - specify the products generic names, dates off administration, and dosage)*

- ☐ Antibiotics
- ☐ Diuretics
- ☐ Oral contraceptives
- ☐ Anti-arrhythmic drugs
- ☐ Beta blockers
- ☐ Dietary supplements
- ☐ ACE inhibitors
- ☐ Angiotensin II receptor antagonists
- ☐ Over-the-counter drugs
- ☐ Potassium supplements
- ☐ Potassium-sparing diuretics
- ☐ Herbal preparations
- ☐ Protease inhibitors
- ☐ PDE5 inhibitors
- ☐ Recreational drugs (e.g., cocaine, crack cocaine, heroin, methamphetamines)
- ☐ Retroviral agents
- ☐ Vitamin K antagonists
- ☐ Cytotoxic chemotherapy
- ☐ Anticoagulants
- ☐ Cyclosporin A
- ☐ Disease modifying drugs (e.g. DMARD medications for the treatment of rheumatoid arthritis)
- ☐ Other heart or blood pressure medications
- ☐ Products for the treatment of pulmonary arterial hypertension
- ☐ Other *(please specify)* _____
- ☐ None

Details:

7. Please mark whether the patient had prior to start of therapy any of the following: *(Please provide details and indicate whether ongoing condition or whether occurred in the past)*

- ☐ Hepatic dysfunction
- ☐ Hepatobiliary disease or dysfunction
- ☐ Elevated liver function tests
- ☐ Elevated bilirubin
- ☐ Jaundice
- ☐ Cirrhosis
- ☐ Fatty liver
- ☐ Pancreatitis
- ☐ Gallstones
- ☐ Gall bladder disease
- ☐ Bile duct obstruction
- ☐ Viral hepatitis
- ☐ Congenital heart disease
- ☐ Parasitic diseases
- ☐ Mycobacterium Avium Complex infection
- ☐ Other non-viral suspected liver infections
- ☐ Cytomegalovirus infection
- ☐ Ischemic hepatitis
- ☐ Cystic fibrosis
- ☐ Granulomatosis
- ☐ Sickle cell anemia
- ☐ Connective tissue disease
- ☐ Lactic acidosis syndrome
- ☐ Blood product transfusions
- ☐ Renal impairment
- ☐ Gilbert's disease
- ☐ Metabolic disease
- ☐ Diabetes mellitus (Type I or II)
- ☐ Heart failure
- ☐ Hypertension
- ☐ Hypertriglyceridemia
- ☐ Portal hypertension
- ☐ Veno-occlusive disease
- ☐ Atherosclerotic / vascular disease
- ☐ Transplant
- ☐ Valvular heart disease
- ☐ Primary malignancy
- ☐ Liver metastases
- ☐ Hepatoma
- ☐ Auto-immune disorder
- ☐ Immune reconstitution disease
- ☐ HIV infection
- ☐ Sepsis
- ☐ Drug toxicity *(please specify)* _____
- ☐ Vitamin deficiency *(please specify)* _____

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Fidanacogene elaparvovec (BEQVEZ/DURVEQTIX) Hepatic Events
Follow-up questions

8. (cont) Please mark whether the patient had prior to start of therapy any of the following: *(Please provide details and indicate whether ongoing condition or whether occurred in the past)*

- ☐ Drug-induced liver toxicity *(please specify drug)* _____
- ☐ Recent travel to other countries *(please specify)*
- ☐ Other *(please specify)* _____
- ☐ Alcohol use *(If checked, complete question 8)*

Details:

- ☐ Contact with jaundiced patient
- ☐ Epstein–Barr virus infection
- ☐ Substance abuse/Drug abuse (e.g., recreational/illicit drug use)
- ☐ Alternative medication use (e.g., herbal supplements and vitamins)
- ☐ None

9. Did the patient have a family history of liver disease? *(i.e., genetic conditions)*

☐ Unknown ☐ No ☐ Yes *(please provide details)*

Details:

10. If "Alcohol use" checked above, please answer the following:

How often does the patient drink beverages containing alcohol? _____ *(e.g., monthly, 2-4 times a week, more than 5 times a week, etc)*

How many drinks on a typical day when patient is drinking?: _____ *(e.g., less than 1 drink, 2 or 3 drinks, more than 3 drinks, etc)*

Please specify the type/brand of alcohol patient typically drinks: _____ *(e.g., beer)*

If this drinking history is more than one year, please specify duration: _____

11. Were any of the following laboratory tests / procedures performed? Please specify results with date(s) of test, results with units, and reference ranges. If a test was administered multiple times, please enter the date(s) of test, units, and reference ranges for each test in chronological order.

Laboratory Test / Procedure	Date Performed (DD-MMM-YYYY)	Results with units if applicable	Reference Ranges if applicable
☐ AST			
☐ ALT			
☐ GGT			
☐ Total bilirubin			
☐ Conjugated bilirubin			
☐ Total protein			
☐ Albumin			
☐ Prothrombin time (PT)			
☐ Partial thromboplastin time (PTT)			
☐ International normalized ratio (INR)			
☐ Clotting time			
☐ Alkaline phosphatase			
☐ Hepatitis A serology			
☐ Hepatitis B serology			
☐ Hepatitis C serology			
☐ Cytomegalovirus (CMV) serology			
☐ Epstein Barr serology			
☐ Other serology			
☐ Eosinophil count			
☐ Amylase			
☐ Lipase			
☐ Other pancreatic enzymes tests			

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☐ Serum or plasma concentrations for any concomitant drugs			
11. (cont) Were any of the following laboratory tests / procedures performed? Please specify results with date(s) of test, results with units, and reference ranges. If a test was administered multiple times, please enter the date(s) of test, units, and reference ranges for each test in chronological order.			
☐ Liver ultrasound			
☐ Liver biopsy			
☐ Abdominal X-ray			
☐ Abdominal CT			
☐ Abdominal endoscopic retrograde cholangiopancreatography (ERCP)			
☐ Serum ceruloplasmin			
☐ Serum copper			
☐ Serum alpha 1-antitrypsin			
☐ Serum alpha-fetoprotein			
☐ Serum ammonia			
☐ Other relevant lab data *(please specify)*			

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Fidanacogene elaparvovec (BEQVEZ/DURVEQTIX) Hepatic Events
Follow-up questions

Version History

Version	Version Date	Summary of Revisions
1.0	03-Oct-2022	Existing DCA converted to latest DCA format.

Medicinal product no longer authorised

Fidanacogene elaparvovec (BEQVEZ/DURVEQTIX) Thromboembolic event Follow-up Questions

Instructions for use:

Select questions as needed to obtain any DCA-defined information described below that was not included in the initial report.

AER/Manufacturer Report #: _____

Suspect product: _____

Reported event term prompting special follow-up activities: _____

PATIENT / EVENT INFORMATION (Please provide as much data as possible)

Name / Patient Identifier number:		
Age (years)	**Gender:**	**Weight (kg):**
Height (cm):	**BMI:**	**Race:**
Date of BEQVEZ/DURVEQTIX infusion (DD/MM/YYYY):		**Time to thromboembolic event onset:**
Dose of BEQVEZ/DURVEQTIX administered: **vg/kg**		
Event seriousness: Serious: **Non-Serious:**		**Reporter:**
Causality assessment (please check): Related:		**Not-related:**
Outcome (Please check): Not recovered: **Recovered:**		**Fatal:**
Recovered with treatment (specify below)		**Recovered with sequelae (specify below)**

Thromboembolic event Follow-up Questions

Please provide additional details on a separate page if needed, and reference the question number.

EVENT DESCRIPTION

1. Describe the thromboembolic event:

How was the event diagnosed?

Signs/Symptoms:

Treatment:

Outcome:

Resolution Date *(dd-mmm-yyyy)*: _____

2. Has the patient previously experienced thromboembolic events?

☐ No

☐ Yes *(please specify dates and circumstances of previous events)*

3. Were there alternative etiologies or explanations for the reported event?

☐ Unknown

☐ No

☐ Yes (**If yes, please specify:**

4. Did the patient have concomitant illnesses at the time of the event?

☐ Unknown

☐ No

☐ Yes *(Details)*

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Fidanacogene elaparvovec (BEQVEZ/DURVEQTIX) Thromboembolic event Follow-up Questions

5. Please input available laboratory data

Prothrombin time (PT): _____

Partial Thromboplastin Time (PTT):_____

INR:_____

Platelet count:

Factor IX activity (%): _____

D-Dimer: _____

Troponin T:_____

Other (specify): _____

6. Was the patient on concomitant medications at the time of the event?

☐ Unknown

☐ No

☐ Yes *(Details)*

7. Was the patient receiving Factor IX prophylaxis at the time of the event. ☐ **Yes** ☐ No ☐ Unknown **If yes, please specify FIX prophylactic medication name:**

☐ Prophylaxis: IU/kg: _____ Frequency: _____

→ If on prophylaxis, please specify whether :

☐ Primary ☐ Secondary ☐ Continual ☐ Intermittent

☐ On Demand: IU/kg: _____ Frequency: _____

☐ Continuous Infusion: Dose regimen: _____

☐ Surgery

8. For surgical patients experiencing thrombogenesis:

Thrombogenesis occurred: ☐ During surgery ☐ After surgery Type of surgery: _____

Estimated blood loss (EBL): _____ mL

Did the patient receive pre-surgical prophylaxis? ☐ No ☐ Yes

If yes, please specify product and dose:_____

Was EBL higher than expected for this type of surgery? ☐ No ☐ Yes

Did the patient require transfusion of RBCs? ☐ No ☐ Yes → If Yes, how many units? _____

Were additional (unplanned) factor infusion(s) given during or after surgery?

☐ No ☐ Yes ☐ Unknown

Patient's clinical status immediately post-operative? _____

9. Please mark whether the patient had <u>relevant personal history</u> of:

☐ Baseline Deficiency of Factor IX:

☐ Severe (<1%)

☐ Moderate (1-5%)

☐ Mild (>5%)

Factor Gene mutation: _____

☐ Unknown

☐ Known risk factors for thrombosis *(please specify)*

☐ Other relevant medical history *(please specify)*

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10. Please mark whether the patient had relevant family history of:

- ☐ Hemophilia
- ☐ Inhibitors
- ☐ Allergic reactions to Factor replacement products
- ☐ Thrombosis
- ☐ Other *(please specify)*

Details:

11. Please describe therapies instituted for the thromboembolic event

Version History

Version	Version Date	Summary of Revisions
1.0	03-Oct-2022	Existing DCA converted to latest DCA format.

Medicinal product no longer authorised

BEQVEZ/DURVEQTIX Pregnancy Assessment and Follow-up Questionnaire

Manufacturer Reference Number (case number)

Complete all questions and boxes to the best of your ability and knowledge. If more space is needed, please attach additional pages. Forward additional relevant information as it becomes available.

As you or your partner has received therapy with BEQVEZ/DURVEQTIX, there is a risk for your child to be exposed to this drug. The assessment and follow-up of your pregnancy and the development of your child is important to determine the extent of this exposure (if any) and any untoward effects deriving from it. It will also help determine if, you or your child can be eligible for AAV-based gene therapies in the future or if viral DNA has been passed on to your child.

Information previously provided does not need to be repeated on this form.

*****Privacy notice to be provided to reporters in applicable countries (e.g., China, United Kingdom, European Economic Area countries): Adverse event information, your contact details and the personal information that you provided shall be processed by Pfizer in accordance with Pfizer Pharmacovigilance Privacy Policy, which is available on https://privacycenter.pfizer.com/safety***

☐ **Check if you grant permission for us to contact your healthcare professional (HCP) for additional information. If agreed, please provide contact information.**

General Information

Source of Information: ○ HCP ○ Patient ○ Other, please specify

Name, address, and contact details of the source/ reporter:

Name and contact information of gynaecologist/obstetrician:

Mother's Information - Demographics

Date of Birth (dd-Mmm-yyyy) **OR Age (years) or age group (e.g., adult):**	**Height:** ○ **cm** ○ **ft & in.**	**Weight:** ○ kgs ○ lbs

Occupation:

Mother's Information - Pregnancy

First day of last menstrual period Date (dd-Mmm-yyyy):	**Number of foetuses:**	**Estimated delivery date** (dd-Mmm-yyyy):

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Gestational period at time of initial exposure: _____ Months _____Trimester

Manufacturer Reference Number (case number)

Mother Information – Exposure to Products – Pfizer Drug Details

Please complete the drug details below.

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Product	Indication	Start date (dd-Mmm-yyyy)	Stop date (dd-Mmm-yyyy) + Reason for Stopping	Formulation	Dose/Frequency

Were any other drugs taken during pregnancy (e.g., prescription, over-the-counter)? ○ No ○ Yes, please complete the drug details below.

Product	Indication	Start date (dd-Mmm-yyyy)	Stop date (dd-Mmm-yyyy) + Reason for Stopping	Formulation	Dose/Frequency

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Manufacturer Reference Number (case number)

Mother's Information - Recreational Drug Use During Pregnancy

Did the mother smoke during this pregnancy? ○ No ○ Yes: Number per day? _____

Did the mother drink alcohol during this pregnancy? ○ No ○ Yes: Frequency? _____

Did the mother use illicit drugs during this pregnancy ○ No ○ Yes: Frequency? _____

Mother's Information - Obstetrical History

(Check the box if not applicable) ☐ Not Applicable: No previous pregnancy

Number of previous pregnancies:	**Number of other children:**

Outcome of previous pregnancies (*live birth, miscarriage, elective termination with specification of gestational length and context, late fetal death, ectopic pregnancy, molar pregnancy*). Previous maternal pregnancy complications. Previous fetal/neonatal abnormalities and type. History of sub-fertility:

Mother's Information – Relevant History

Maternal medical history – risk factors for adverse pregnancy outcomes including environmental or occupational exposures, medical disorder (e.g., hypertension, diabetes, seizure disorder, thyroid disorder, asthma, allergic disease, heart disease, psychiatric or mental health disorders, sexual transmitted disorders, hepatitis, AIDS, and other predisposing factors for neurodevelopmental disorders). Family history of congenital abnormality/ genetic diseases, consanguinity (or any family relation or lineage) between parents (specify degree):

Treatment for infertility (*specify*):

Results of serology tests, (e.g., *rubella, toxoplasmosis, etc*):

Ante-natal check-up (specify dates and results) (e.g., fetal ultrasound, serum markers, etc):

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Medicinal product no longer auth

Manufacturer Reference Number (case number)

Mother's Information - Delivery

Any problems before delivery? ○ No ○ Yes: please specify:

Any problems during delivery? (*including delivery complications, foetal distress, amniotic fluid abnormal, abnormal placenta*): ○ No ○ Yes: please specify:

Any problems after delivery? ○ No ○ Yes: please specify:

Mode of delivery e.g., natural birth (i.e., vaginal delivery without medication or anesthesia), cesarean section:

Outcome of Pregnancy

○ Full term live birth ○ Premature live birth ○ Stillbirth ○ Late foetal death ○ Ectopic pregnancy ○ Molar pregnancy ○ Spontaneous abortion/miscarriage

○ Induced/elective abortion ○ Unknown

Date of Outcome of Pregnancy (dd-Mmm-yyyy):	**Gestational age at birth in weeks, (if known):** _____ Weeks

Neonatal Information - Outcome of Infant

○ Normal Newborn Apgar Score: 1 min _____ 5 min_____

○ Congenital malformation/Anomaly (specify) :

○ Other neonatal problem/abnormality (include dysmaturity, neonatal illness, hospitalization, drug therapies) (specify)*:

○ Unknown

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Manufacturer Reference Number (case number)

Neonatal Information – Infant Details

Gender (sex):	Weight at birth:	Length at birth:	Head circumference at birth:
○ Male ○ Female	○ Grams ○ lbs ozs	○ cm ○ in	○ cm ○ in

Follow-up of Infant

(Check the box if not applicable) ☐ Not Applicable

Malformation/anomalies diagnosed:

Developmental assessment:

Infant illnesses, hospitalizations, drug therapies, breastfeeding:

Fetal Information

(Check the box if not applicable) ☐ Not Applicable

(In the event of an elective termination, spontaneous abortion, late fetal death – provide details if available)

Reason for termination:

Gestational age at termination:

Results of physical examination (gender, external anomalies) and pathology:

BEQVEZ/DURVEQTIX antibody and vector integration testing

Have any BEQVEZ/DURVEQTIX -specific tests been conducted in either maternal, foetal or newborn tissue/blood samples. Yes / No **Mother:** **Child:** **Both:**

Tests performed (please *specify*):

Test results (antibody / biopsy / serum / other)

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Manufacturer Reference Number (case number)

Paternal Information (Check the box if not applicable) ☐ Not applicable

Age (years):	**Date of Birth** (dd-Mmm-yyyy):	**Occupation:**

Relevant History:
Risk factors including environmental or occupational exposures, e.g., AIDS, toxins. Family history of congenital abnormality/ genetic diseases, consanguinity (or any family relation or lineage) between parents (*specify degree*):

Paternal Information - Exposure to Products

BEQVEZ//DURVEQTIX Exposure information (if applicable)

Date of BEQVEZ/DURVEQTIX infusion (dd-Mmm-yyyy):

Dose of BEQVEZ/DURVEQTIX administered (vg/kg):

Were any drugs (e.g., over-the-counter, medical prescription) taken by the father during or six months before the mother's pregnancy? ○ No ○ Yes: please specify

Product	**Indication**	**Start date** (dd-Mmm-yyyy)	**Stop date** (dd-Mmm-yyyy) + Reason for Stopping	**Formulation**	**Dose/Frequency**

Paternal Information – Exposure to Products – Recreational Drug Use

Did the father smoke during the mother's pregnancy?	○ No	○ Yes: Number per day? _____
Did the father drink alcohol during the mother's pregnancy?	○ No	○ Yes, Frequency? _____
Did the father use illicit drugs during the mother's pregnancy	○ No	○ Yes, Frequency? _____

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Medicinal product no longer auth

For Internal Pfizer Use – Completion by the DSU			
AER Number	**Telephone Number**		
Person Contacted		**Pfizer Receipt Date**	**Safety Receipt Date (Date of Contact)***
Privacy notice provided ** ○ **Yes** ○ **No** ○ **Not applicable**			
Transcription Certification *I hereby certify that the data transcribed into this form accurately and completely reflect the information provided. Where required by local regulations, the reporter has been made aware that their personal information will be shared with Pfizer's related parties.*			
Signature		**Date**	
Preparer of the Report			

* Date of filling in the form = Safety Receipt Date (Date of Contact).

ANNEX 6. DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

Draft key messages of the additional risk minimisation measures

Prior to the launch of DURVEQTIX in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at providing information on the safe use of DURVEQTIX and to inform about important risks associated with DURVEQTIX.

The MAH shall ensure that in each Member State where DURVEQTIX is marketed, all healthcare professionals and patients/carers who are expected to prescribe, use or oversee the administration of DURVEQTIX have access to/are provided with the following educational package. These documents will be translated in the local language to ensure understanding of proposed mitigation measures by physicians and patients:

- Physician Educational Material
- Patient Information Pack

The Physician Educational Material consists of:

- The Summary of Product Characteristics
- The Guide for Healthcare Professionals
- The Patient Guide
- The Patient Card

The Guide for Healthcare Professionals:

- Patients should be selected for treatment with DURVEQTIX based on the absence of pre-existing antibodies to AAVrh74var using a validated assay and status of liver health based on laboratory and imaging data.
- To inform of the important identified risk of hepatotoxicity and the important potential risks of development of Factor IX inhibitors, thromboembolic events, risk of malignancy in relation to vector integration in the DNA of body cells, transmission to third parties (horizontal transmission), and germline transmission, and missing information of long-term safety and details on how these risks can be minimised.
- Before a treatment decision is made, the healthcare professional should discuss the risks, benefits, and uncertainties of DURVEQTIX with the patient when presenting DURVEQTIX as a treatment option, including:

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- That no predictive factors for no or low responders have been identified. Patients who do not respond are still exposed to long-term risks.
- That the long-term treatment effects cannot be predicted.
- That there would be no plans to re-administer the medicinal product for patients who do not respond or have lost the response.
- Reminding patients about the importance to enroll in a registry for follow-up of long-term effects.
- That DURVEQTIX use will require in some cases co-administration of corticosteroids to manage the liver damage that this medicinal product might induce. This requires adequate monitoring of patients and careful consideration of other co-medications, herbal supplements, and/or alcohol to minimise the risk of hepatoxicity and a potential reduced therapeutic effect of DURVEQTIX.
- That the patient should be routinely tested for Factor IX inhibitors development after DURVEQTIX treatment.
- That the patient will be provided the patient guide and the patient card by the healthcare professional.

The Patient Information Pack consists of

- The Patient Information Leaflet
- The Patient Guide
- The Patient Card

The Patient Guide:

- Importance of fully understanding the benefits and risks of DURVEQTIX treatment, what is known and not yet known about the long-term effects, related to safety and efficacy.
- Therefore, before a decision is made about starting on the therapy the doctor will discuss with the patient the following:
  - That DURVEQTIX will, in some cases, require co-treatment with corticosteroids to overcome the liver damage that this medicine may produce, and that the doctor will ensure that patients are available for regular blood tests to check responses to DURVEQTIX and assess liver health. Patients should inform the healthcare professional about current use of corticosteroids or other immunosuppressants. If the patient cannot take corticosteroids, the doctor may recommend alternative medicines to manage problems with the liver.

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- That not all patients may benefit from treatment with DURVEQTIX and the reasons for this have not been established. Patients not responding to treatment will still be exposed to long-term risks of DURVEQTIX.
- Details how the important potential risks of development of Factor IX inhibitors, thromboembolic events, risk of malignancy in relation to vector integration in the DNA of body cells, transmission to third parties (horizontal transmission) and germline transmission can be recognised and minimised by regular monitoring as recommended by doctors.
    - The patient should seek immediate medical advice for any symptoms suggestive of a thromboembolic event.
    - Male patients or their female partners should use barrier contraception for six months after administration of DURVEQTIX.
    - That DURVEQTIX has a viral vector component, and it may be associated with an increased risk of malignant tumour. Regular liver monitoring for at least 5 years after DURVEQTIX treatment is needed in patients with preexisting risk factors for hepatocellular carcinoma.
    - Patients should not donate blood, semen, or organs, tissues, and cells for transplantation

- That the Patient Card should be carried by the patient at any time and shared with any doctor or nurse whenever the patient has a medical appointment.
- The importance to participate in the patients' registry for long-term surveillance of 15 years.

The Patient Card:

- This card is to inform healthcare professionals that the patient has received DURVEQTIX for haemophilia B.
- The patient should show the patient card to a doctor or a nurse whenever they have an appointment.
- The patient should seek medical advice for any symptoms suggestive of a thromboembolic event.
- That the patient should have regular blood tests and examinations as directed by their doctor.
- The card should warn healthcare professionals that the patient may undergo treatment with corticosteroids for minimising the risk of hepatotoxicity with DURVEQTIX.
- The patient should not donate blood, semen, organs, tissues and cells for transplantation.
- Male patients should ensure that they use a barrier method of contraception for 6 months after receiving DURVEQTIX.

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