HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH

Fidanacogene elaparvovec (BEQVEZ®) for the treatment of moderately severe to severe haemophilia B

HTA-Appendix

Appendix
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1 Medical condition and treatment options

Table 1-1: Recommendations and respective FVIII/FIX levels to achieve in different types of bleedings [1]

Type of bleeding	Target level (IU/dL)		Dosage interval (h)	Duration of therapy (days)	Comment
	Peak level (initial)	Trough level (maintenance)			
Joint	40-60	5-10	12-24	1-2 (longer if needed)	For large haemorrhages, higher trough levels should be aimed for
Muscle	40-60	5-10	12-24	2-3 (longer if needed)	Threatening muscle haemorrhages (e.g. impending compartment syndrome) should be treated in the same way as iliopsoas haemorrhage.
Iliopsoas	80-100	30-60	12	3-5 (longer if needed)	-
CNS-haemorrhage/ other life- or organ-threatening haemorrhages	>100	50-80	8-12	Day 1-7	Duration depends on expansion and resorption
		30-50	12-24	Day 8-21	
Gastrointestinal	80-100	30-60	12-24	3-14	-
Haematuria	50	15-30	24	3-5	-
Deep laceration or contusion	50	5-10	12-24	5-7	-
Large interventions	80-100 (preoperative)	60-80	8-12	Day 1-3	-
		40-60	12-24	Day 4-6	
		30-50	24	Day 7-14	
Small interventions	50-80 (preoperative)	30-80	12-24	1-5	Depending on the type of intervention

*Abbreviations: CNS: central nervous system, dL: decilitre, FVIII: factor VIII, FIX: factor IX, IU: International Unit, EHL: extended half-life, SHL: standard half-life; *The dosing intervals refer to SHL-FVIII/FIX concentrates. For EHLs, longer dosing intervals must be observed according to the respective half-life extension.*

2 Methods

2.1 Search strategy for BEQVEZ®

Cochrane (05.12.2024)

ID Search
#1 (BEQVEZ*) (Word variations have been searched)
#2 (fidanacogene*) (Word variations have been searched)
#3 (AAV8* NEAR hFIX19*) (Word variations have been searched)
#4 (AAV8?hFIX19*) (Word variations have been searched)
#5 (durveqtix*) (Word variations have been searched)
#6 (pf* NEAR (6838435* OR 06838435*)) (Word variations have been searched)
#7 (pf?06838435*) (Word variations have been searched)
#8 (pf?6838435*) (Word variations have been searched)
#9 (rAAV NEXT Spark100 NEXT hFIX39 NEXT Padua) (Word variations have been searched)
#10 (rAAV?Spark*) (Word variations have been searched)
#11 (spark NEXT 101) (Word variations have been searched)
#12 (spk NEXT 1001*) (Word variations have been searched)
#13 (spk1001*) (Word variations have been searched)
#14 (spk NEXT 101) (Word variations have been searched)
#15 (spk101*) (Word variations have been searched)
#16 (spk NEXT 9001*) (Word variations have been searched)
#17 (spk9001*) (Word variations have been searched)
#18 (spk NEXT fix NEXT padua*) (Word variations have been searched)
#19 (spkfix NEXT padua*) (Word variations have been searched)
#20 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
#21 English:la
#22 German:la
#23 #21 OR #22
#24 #20 AND #23

Embase (05.12.2024)

No. Query
#27. #26 AND ([english]/lim OR [german]/lim)
#26. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR
#20 OR #21 OR #22 OR #23 OR #24 OR #25
#25. 'spkfix padua*'
#24. 'spk fix padua*'
#23. spk9001*
#22. 'spk 9001*'
#21. spk101*
#20. 'spk 101*'
#19. spk1001*
#18. 'spk 1001*'
#17. 'spark 101*'
#16. raav*spark*
#15. 'raav spark100 hfix39 padua*'
#14. pf* NEAR/1 (6838435* OR 06838435*)
#12. 'pf 6838435*'
#11. pf*06838435*
#10. 'pf 06838435*'
#9. durveqtix*

#8. aav8*hfix19*
#7. aav8 NEAR/1 hfix19*
#6. 'aav8 hfix19*'
#5. BEQVEZ*
#4. aav8 NEAR/1 hfix19
#3. 'aav8 hfix19'
#2. fidanacogene*
#1. 'fidanacogene elaparvovec'/exp

Medline (05.12.2024)

1 BEQVEZ*.mp.
2 fidanacogene*.mp.
3 (AAV8* adj hFIX19*).mp.
4 AAV8?hFIX19*.mp.
5 durveqtix*.mp.
6 (pf* adj (6838435* or 06838435*)).mp.
7 pf?06838435*.mp.
8 pf?6838435*.mp.
9 rAAV-Spark100-hFIX39-Padua.mp.
10 rAAV?Spark*.mp.
11 spark 101*.mp.
12 spk 1001*.mp.
13 spk1001*.mp.
14 spk 101*.mp.
15 spk101*.mp.
16 spk 9001*.mp.
17 spk9001*.mp.
18 spk fix padua*.mp.
19 spkfix padua*.mp.
20 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21 limit 20 to (english or german)
22 remove duplicates from 21

International HTA database (05.12.2024)

5 ((durveqtix*) OR (fidanacogene*) OR (BEQVEZ*)) AND (English OR German)[Language],"1","2024-11-28T14:01:54.000000Z"
4 (durveqtix*) OR (fidanacogene*) OR (BEQVEZ*),"1","2024-11-28T14:01:33.000000Z"
3 durveqtix*,"0","2024-11-28T14:00:45.000000Z"
2 fidanacogene*,"1","2024-11-28T14:00:09.000000Z"
1 BEQVEZ*,"0","2024-11-28T13:59:44.000000Z"

2.2 Search strategy for HEMGENIX®

Cochrane (05.12.2024)

ID Search
#1 (hemgenix*) (Word variations have been searched)
#2 (etranacogene*) (Word variations have been searched)
#3 (amt NEXT 061*) (Word variations have been searched)
#4 (amt?061*) (Word variations have been searched)
#5 (csl NEXT 222*) (Word variations have been searched)
#6 (csl?222*) (Word variations have been searched)
#7 (etranadez*) (Word variations have been searched)
#8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#9 English:la
#10 German:la

#11 #9 OR #10
#12 #8 AND #11

Embase (05.12.2024)
No. Query
#10. #9 AND ([english]/lim OR [german]/lim)
#9. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#8. etranadez*
#7. csl222*
#6. 'csl 222*'
#5. amt061*
#4. 'amt 061*'
#3. hemgenix*
#2. etranacogene*
#1. 'etranacogene dezaparvovec'/exp

Medline (05.12.2024)
1 hemgenix*.mp.
2 etranacogene*.mp.
3 amt 061*.mp.
4 amt?061*.mp.
5 csl 222*.mp.
6 csl?222*.mp.
7 etranadez*.mp.
8 1 or 2 or 3 or 4 or 5 or 6 or 7
9 limit 8 to (english or german)
10 remove duplicates from 9

International HTA database (05.12.2024)
9 ((etranadez*) OR (csl222*) OR ("csl 222*") OR (amt061*) OR ("amt 061*") OR (etranacogene*) OR (hemgenix*)) AND (English OR German)[Lan guage],"6","2024-11-28T15:30:23.000000Z"
8 (etranadez*) OR (csl222*) OR ("csl 222*") OR (amt061*) OR ("amt 061*") OR (etranacogene*) OR (hemgenix*),"6","2024-11-28T15:29:50.000000Z"
7 etranadez*,"1","2024-11-28T15:29:34.000000Z"
6 csl222*,"0","2024-11-28T15:29:15.000000Z"
5 "csl 222*","0","2024-11-28T15:29:05.000000Z"
4 amt061*,"0","2024-11-28T15:28:41.000000Z"
3 "amt 061*","1","2024-11-28T15:28:30.000000Z"
2 etranacogene*,"6","2024-11-28T15:28:01.000000Z"
1 hemgenix*,"1","2024-11-28T15:27:40.000000Z"

2.3 Search strategies to identify trials on BEQVEZ® in Clinical Trials Registers

Date of search: 09.12.2024
ClinicalTrials.gov
Search string: PF-06838435 \(formerly SPK-9001\) OR PF-06838435/ fidanacogene elaparvovec OR 06838435 OR SPK-9001 OR fidanacogene OR BEQVEZ OR durveqtix OR pf 06838435 OR pf06838435 OR pf 6838435 OR pf6838435 OR rAAV-Spark100 OR spark 101 OR spk 1001 OR spk1001 OR spk 101 OR spk101 OR spk 9001 OR spk9001 OR spk fix padua OR spkfix padua in Intervention/treatment
6 studies identified

WHO ICTRP (Advanced search mode)
Search string: fidanacogene OR BEQVEZ OR durveqtix OR "pf 06838435" OR pf06838435 OR "pf 6838435" OR pf6838435 OR rAAV-Spark100 OR "spark 101" OR "spk 1001" OR spk1001 OR "spk 101" OR spk101 OR "spk 9001" OR spk9001 OR "spk fix padua" OR "spkfix padua" in Intervention
7 (4 further) studies identified

EU Clinical Trials (EUdraCT)
search string: fidanacogene OR BEQVEZ OR durveqtix OR "pf 06838435" OR pf06838435 OR "pf 6838435" OR pf6838435 OR rAAV-Spark100 OR "spark 101" OR "spk 1001" OR spk1001 OR "spk 101" OR spk101 OR "spk 9001" OR spk9001 OR "spk fix padua" OR "spkfix padua"
2 (0 further) studies identified

2.4 Search strategies to identify trials on HEMGENIX® in Clinical Trials Registers

Date of search: 09.12.2024

ClinicalTrials.gov
Search string: HEMGENIX OR CSL222 \(AAV5-hFIXco-Padua\) OR amt 061 OR amt061 OR csl 222 OR csl222 OR etranacogene OR etranadez in intervention/treatment
6 studies identified

WHO ICTRP (Advanced search mode)
Search string: "amt 061" OR amt061 OR "csl 222" OR csl222 OR etranacogene OR etranadez OR hemgenix in intervention
11 (6 further) studies identified

EU Clinical Trials (EUdraCT)
Search string: "amt 061" OR amt061 OR "csl 222" OR csl222 OR etranacogene OR etranadez OR hemgenix
1 (0 further) studies identified

2.5 Search strategies to identify public contributions

Table 2-1: Search terms used to identify public contributions

Database/ News outlet/ clinical trial registry/ funding website	Search terms used	Additional search terms	Relevant information found (Yes/no)	Search period	Type of information extracted
https://www.ema.europa.eu/en/medicines	BEQVEZ, fidanacogene elaparvovec	n.a.	Yes	Earliest mention – 12/2024	Active substance, medical specialty, pharmacotherapeutic group, therapeutic area, class, orphan designation, categorization, additional monitoring, conditional approval, accelerated assessment, PRIME: priority medicines, marketing authorization issued
https://adisinsight.springer.com/	BEQVEZ, Fidanacogene Elaparvovec		Yes		Alternative names
https://pubmed.ncbi.nlm.nih.gov/			Yes		Development history of the product
https://clinicaltrials.gov/			Yes		Clinical trials
https://euclinicaltrials.eu/			Yes		
https://eudract.ema.europa.eu/			Yes		
https://cordis.europa.eu/			Yes		

Database/ News outlet/ clinical trial registry/ funding website	Search terms used	Additional search terms	Relevant information found (Yes/no)	Search period	Type of information extracted
https://reporter.nih.gov/	BEQVEZ, Fidanacogene Elaparvovec , AAV8 factor IX gene therapy, AAV8 hFIX18, DURVEQTIX, haemophilia B gene therapy - Spark Therapeutics PF-06838434, rAAV-Spark100-hFIX-Padua, SPK 9000, SPK-FIX	Spark Therapeutics, Pfizer, Children's Hospital of Philadelphia, St. Jude Children's Research Hospital and Perelman School of Medicine	Yes		Basic research
https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm		n.a.	Yes		Patent information and associated references
https://trialsearch.who.int/			No		n.a.
https://competition-cases.ec.europa.eu/search			No		
https://www.ihi.europa.eu/			No		
https://eismea.ec.europa.eu/index_en			No		
https://eit.europa.eu/			No		
https://eic.ec.europa.eu/index_en			No		
https://www.eib.org/en/index			No		
https://research-and-innovation.ec.europa.eu/funding/funding-opportunities/funding-programmes-and-open-calls_en			No		
https://www.sbir.gov/		Spark Therapeutics, Pfizer	Yes		Project funding for companies involved in the development of the product.
https://www.nsf.gov/		n.a.	No		n.a.
https://www.ukri.org/			No		
https://foerderportal.bund.de/			No		
https://www.health-holland.com/			No		
https://www.bpifrance.com/			No		
https://www.inserm.fr/en/home/			No		
https://innovationsfonden.dk/da			No		
https://www.ucc.ie/en/apc/			No		
https://www.amractionfund.com/about			No		
https://reporter.nih.gov/			No		
https://www.gatesfoundation.org/			No		
https://www.google.com/			Yes		Patent deal information
https://www.forbes.com/			No		n.a.
https://www.reuters.com/			No		
https://www.science.org/			No		
https://www.cafepharma.com/			Yes		Collaborations, funding, financing, patent dispute, acquisitions
https://www.livescience.com/			Yes		
https://www.biospace.com/			Yes		
https://www.bioworld.com/			Yes		
https://www.biopharmadive.com/			Yes		
https://pharmaphorum.com/			Yes		
https://pharmatimes.com/			Yes		
https://pharmafile.com/			Yes		
https://www.fiercepharma.com/			Yes		
https://www.businesswire.com/			Yes		

Database/ News outlet/ clinical trial registry/ funding website	Search terms used	Additional search terms	Relevant information found (Yes/no)	Search period	Type of information extracted
https://www.businessinsider.com/		Spark Therapeutics, Pfizer, Children's Hospital of Philadelphia, St. Jude Children's Research Hospital and Perelman School of Medicine AND funding OR financing OR M&A OR patent deal OR collaboration OR grant	Yes		
https://www.statnews.com/			Yes		

2.6 Stakeholder involvement

Table 2-2: Questions asked to TED patients

Question 1	Rolle des Ausfüllenden (einzelne/ Patient/Angehörige/Andere)
Question 2	Hauptwohnsitz
Question 3	Mitglied einer Patient:innenorganisation Wenn ja, bitte nennen Sie die Patient:innenorganisation Wenn ja, welche Rolle haben Sie in der Patient:innenorganisation? Wenn ja, welche Erkrankung(en) wird/werden von der Organisation vertreten?
Question 4/1	Krankheitsstadium/ Schweregrad
Question 4/2	Krankheitsgeschichte Wie lange leben Sie schon mit der Krankheit/dem Leiden? Bitte beschreiben Sie Ihre Behandlungsgeschichte
Question 4/3	Zusätzliche Informationen, die Ihrer Meinung nach für die Ersteller des HTA-Berichtshilfreich wären
Question 5	Falls zutreffend, wo haben Sie Informationen über die Erfahrungen der Patient:innen eingeholt? Falls zutreffend, wie haben Sie Informationen über die Erfahrungen der Patient:innen gesammelt?
Question 6	Wie wirkt sich die mittelschwere bis schwere Hämophilie B auf Ihr tägliches Leben (eines Patienten/einer Patientin) aus?
Question 7	Wie wirkt sich die transfusionsabhängige Beta-Thalassämie auf Angehörige aus?
Question 8	Wie gut bewältigen Patient:innen mit mittelschwerer bis schwerer Hämophilie B ihre Erkrankung mit den derzeit verfügbaren Therapien?
Question 9	Was erwarten diejenigen Patient:innen, die keine Erfahrung mit Fidanacogene elaparvovec haben, von neuen Therapien im Allgemeinen?
Question 10	Für diejenigen, die Erfahrung mit Fidanacogene elaparvovec haben: Welche Auswirkungen hatte/hat es auf Ihr Leben?
Question 11	Bitte geben Sie alles an, was Ihrer Meinung nach für das für die gemeinsame Bewertung zuständige HTA-Team wissenswert sein könnte.
Question 12	Bitte fassen Sie Ihren Beitrag in maximal zehn Kernaussagen zusammen und listen Sie die wichtigsten Punkte auf.

Questions for clinical experts

Patient*innen und Patient*innenpopulation Österreich

- Wie hoch ist die jährliche Inzidenz der Hämophilie in Österreich?
- Wie hoch ist die geschätzte Prävalenz der Hämophilie B in der österreichischen Population?
- Inwieweit ist die Studienpopulation repräsentativ für die reale Patientenpopulation in Österreich, und welche Implikationen ergeben sich daraus für die Übertragbarkeit der Studienergebnisse?
- Welche definitiven Kontraindikationen bestehen für die Anwendung von Beqvez® im klinischen Alltag?
- Nach welchen klinischen und laborchemischen Parametern wird der Schweregrad der Hämophilie B klassifiziert?
- Welche klinische Relevanz hat die Hämophilie B bei weiblichen Patientinnen unter Berücksichtigung des meist milderen Krankheitsverlaufs?
- Evaluation der Patientenzahlen für Beqvez®-Therapie:
  a) Wie plausibel ist die Prognose von 38 geeigneten Patienten innerhalb eines dreijährigen Zeitraums?
  b) Welches Szenario ist für die Patientenrekrutierung in den nächsten drei Jahren am wahrscheinlichsten: eine gleichmäßige Verteilung von 13 Patienten pro Jahr oder eine initial höhere Aufnahmerate im ersten Jahr?

Intervention

- An welcher Stelle des therapeutischen Algorithmus ist die Intervention mit Beqvez® optimal zu platzieren?
- Welche diagnostischen Maßnahmen sind vor Initiierung der Beqvez®-Therapie erforderlich und welche ökonomischen Implikationen ergeben sich daraus?
- Welche spezifischen Neutralisationsantikörper-Tests (nAb) für AAVRh7evar und FIX-Inhibitoren sind notwendig und welche labordiagnostischen Voraussetzungen müssen dafür erfüllt sein?
- Welche hepatologische und infektiologische Diagnostik ist prätherapeutisch indiziert?
- Wie hoch ist die zu erwartende Rate an Therapieabbrüchen bei intravenöser Beqvez®-Applikation?
- Welche Parameter sind im Rahmen des kurzfristigen Therapiemonitorings zu erheben und in welchen Intervallen sollten diese kontrolliert werden?
- Inwieweit können FIX-Aktivität, Inhibitoren, ALT/AST und CPK in einem integrierten Analyseprofil erfasst werden?
- Welche Frequenz der Kontrollen ist für FIX-Aktivität und Inhibitoren über einen Zeitraum von drei Jahren erforderlich?
- Bei welchem Anteil der Patienten sind zusätzliche jährliche Alpha-Fetoprotein-Bestimmungen und hepatische Sonographien indiziert?
- Welche therapeutischen Interventionen sind bei schwerwiegenden oder häufigen unerwünschten Arzneimittelwirkungen erforderlich?
- Wie ist der durchschnittliche Transfusionsbedarf bei therapieassoziierter Anämie (4,4%) einzuschätzen?
- Welche Therapieoptionen bestehen bei erhöhten Transaminasen, verminderter FIX-Aktivität oder abnormer Leberfunktion (13,3%)?
- Welche Dauer der Nachbeobachtung ist nach Beqvez®-Administration erforderlich?

Komparator

- Wie gestaltet sich der aktuelle Behandlungsstandard (Standard of Care) in der prophylaktischen Therapie in Österreich?
- Welcher Prozentsatz der Patient*innen wird voraussichtlich eine FIX-Substitutionstherapie in den kommenden drei Jahren erhalten und mit welcher durchschnittlichen Verordnungsfrequenz pro Jahr ist zu rechnen?
- Welcher Anteil der Patient*innen wird voraussichtlich Faktor-unabhängige Therapien (Non-factor-therapies/Non-Replacement therapies) in den nächsten drei Jahren erhalten?
- Besteht die Möglichkeit einer Hemgenix-Therapie bei vorhandenen Antikörpern gegen Beqvez und wie hoch schätzen Sie den Anteil der Patient*innen in den nächsten drei Jahren?
- Welche schwerwiegenden und häufigen unerwünschten Ereignisse treten bei den verschiedenen Therapieoptionen (FIX-Substitutionstherapie, Faktor-unabhängige Therapien, Hemgenix-Behandlung) auf und welche Behandlungskosten entstehen durch deren Management?

- Wie viele Patient*innen benötigen durchschnittlich akute Therapien und wie lange beträgt die durchschnittliche Krankenhausverweildauer?
- Welche Produkte stehen in Österreich für die präoperative FIX-Substitution zur Verfügung und wie bewerten Sie die Kostenrelevanz hämostatischer Mittel?
- Welche therapeutischen Optionen stehen Patient*innen zur Verfügung, die keine prophylaktische Behandlung erhalten?

Outcomes

- Welche klinischen Endpunkte erachten Sie kurz- und langfristig als besonders relevant für die Bewertung des Therapieerfolgs?
- Wie bewerten Sie die Aussagekraft der Studienendpunkte im Zeitraum von Woche 12 bis Monat 15 im Hinblick auf die klinische Praxis?
- Wie objektiv und valide ist die jährliche Blutungsrate (Annual Bleeding Rate, ABR) als primärer Endpunkt einzuschätzen?
- Wie interpretieren Sie die jährliche Infusionsrate (Annualised Infusion Rate, AIR) von exogenem FIX im Zeitraum von Woche 12 bis Monat 15 im Vergleich zur Standard-FIX-Substitutionstherapie?
- Welche klinische Relevanz hat der nachgewiesene mittlere Vektor-abgeleitete FIX-C-Spiegel im Steady State von >5% (gemessen von Woche 12 bis Monat 15)?

Organisatorische Voraussetzungen

- Welche spezifischen organisatorischen Strukturen müssen für die Verabreichung von Beqvez® implementiert werden?
- Ist die Verabreichung von Beqvez® in allen zehn österreichischen Hämophilie-Zentren realisierbar oder sollte eine Konzentration auf spezialisierte Zentren erfolgen?
- Welche infrastrukturellen Anpassungen sind für eine sichere und effiziente Verabreichung von Beqvez® erforderlich?
- Welche technischen Anforderungen müssen Gentherapie-Zentren hinsichtlich Lagerung, Zubereitung, Verabreichung und Überwachung der Therapie erfüllen?

Langzeitüberwachung und Patient*innenmanagement

- Welche konkreten Anforderungen ergeben sich für die Langzeitüberwachung von Patient*innen nach Beqvez®-Therapie?
- Existiert bereits ein Register zur Dokumentation österreichischer Patient*innen oder ist die Implementierung eines solchen Systems geplant?
- Wie sollte die Nachsorge strukturiert werden, um mögliche Langzeit-Nebenwirkungen systematisch zu erfassen und adäquat zu behandeln?
- Steht den Patient*innen eine psychologische Betreuung zur Verfügung und wie ist diese in das Behandlungskonzept integriert?
- Welche klinischen, laborchemischen und bildgebenden Parameter sind für eine aussagekräftige Langzeitbeobachtung der Patient*innen essentiell?

3 Clinical effectiveness and safety assessment

3.1 Risk of Bias tables

Table 3-1: Risk of bias (non-randomised studies other than uncontrolled trials, cross-sectional studies and case series) report at study level (IHE checklist) [2]

Risk of bias - study level (case series) [2]									
1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
Was the hypothesis/ aim/ objective of the study clearly stated?	Was the study conducted prospectively?	Were the cases collected in more than one center?	Were patients recruited consecutively?	Were the characteristics of the patients included in the study described?	Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Did participants enter the study at a similar point in the disease?	Was the intervention clearly described?	Were additional interventions (co-interventions) clearly described?	Were relevant outcome measures established a priori?
yes	yes	yes	no1	no2	yes	unclear3	yes	no4	yes
11.	12.	13.	14.	15.	16.	17.	18.	19.	20.
Were outcome assessors blinded to the intervention that patients received?	Were the relevant outcomes measured using appropriate objective/ subjective methods?	Were the relevant outcomes measured before and after the intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was follow-up long enough for important events and outcomes to occur?	Was the loss to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were adverse events reported?	Were the conclusions of the study supported by the results?	Were both competing interests and sources of support for the study reported?

[1] Patients were recruited from BENEGENE-1 study at once.

[2] Important details like previous bleeding patterns, target joint severity scores and duration of the disease. Additionally, previous treatment patterns were not comprehensively described. Also, there is a difference between the severity of the disease as defined by the inclusion criteria of the study and the severity defined by the World Federation of Hemophilia.

[3] Important details like previous bleeding patterns, target joint severity scores, duration of the disease and distribution of patients based on the severity were not reported. Additionally, previous treatment patterns were not comprehensively described. Also, there is a difference between the severity of the disease as defined by the inclusion criteria of the study and the severity defined by the World Federation of Hemophilia.

[4] Patients were allowed FIX replacement therapy. The specific type and quantity of FIX therapy used was not described. There was also variability in the application and timing of corticosteroids.

Risk of bias – study level (case series) [2]									
no[5]	partial[6]	unclear[7]	partial[8]	partial[9]	yes	yes	yes	yes	yes
Overall risk of bias: moderate									

Abbreviations: EPAR: European public assessment report, FIX: factor IX.

[5] The study was open-label.

[6] Additionally, there are documented differences in the measurement of factor IX activity through one-stage and chromogenic assay [3]. This issue is described in the EPAR of BEQVEZ as well [4].

[7] Not clear if the ABR was measured in the same way as in BENEGENE-1 study, which provided the baseline values. Moreover, pre-intervention measurement period (6 months) in BENEGENE-1 study was relatively short for a chronic condition.

[8] While generally appropriate, the non-inferiority margin of 3.0 for annual bleeding rate seems large and its clinical justification is not well explained. Additionally, the primary endpoint changed throughout the study.

[9] While 15 months may be sufficient for initial efficacy assessment, it is inadequate for evaluating long-term safety and durability of effect for a one-time genetic intervention.

3.2 Applicability

Table 3-2: Summary table characterising the applicability the included study

Domain	Description of applicability of evidence
Population	The trial enrolled male patients aged 18-65 years (mean age 33.2) with haemophilia B (FIX level ≤2%) who had received FIX prophylaxis for at least 6 months. Of 316 screened patients, 59.5% were excluded due to AAV antibodies. The study population was predominantly White (73%), with underrepresentation of Black patients (2%). This selective population differs from the general haemophilia B population in terms of antibody status, severity definition (study used ≤2% vs. standard definitions of severe <1%, moderate 1-5%), and ethnic diversity, potentially affecting the generalisability of benefit-risk assessments.
Intervention	Fidanacogene elaparvovec was administered as a single intravenous infusion (5×10^{11} vector genome copies/kg) in specialised treatment centres. 62% of patients required glucocorticoid treatment for adverse events, with variable administration timing. The intervention required specific technical capabilities for storage, preparation, and administration not routinely available in all treatment settings. This complexity and the high rate of required supportive therapy may affect real-world effectiveness and safety outcomes.
Comparators	The study used an intra-individual comparison to prior FIX prophylaxis rather than a concurrent control group. Whilst FIX prophylaxis represents the current standard of care, the lack of a parallel control group and unblinded design may affect the reliability of the treatment effect size. The documentation of prophylaxis regimens was incomplete, making it difficult to assess whether the comparison reflects optimal standard therapy.
Outcomes	Primary outcomes focused on annualised bleeding rate (ABR) and factor IX activity levels over 15 months. Multiple protocol amendments changed the primary endpoint definition and analysis period. The 15-month follow-up is insufficient to assess long-term safety and durability, particularly relevant for a one-time gene therapy intervention. Key outcomes like quality of life and long-term complications were not fully captured within this timeframe.
Setting	The trial was conducted across 27 centres in 13 countries, all specialised haemophilia treatment centres with necessary technical capabilities for gene therapy. This setting differs from many routine care settings where haemophilia B patients are treated, particularly in terms of available expertise and infrastructure. The requirement for specialised centres may limit access and affect real-world implementation of the therapy.

3.3 Indirect treatment comparison

Indirect treatment comparison for fidanacogene elaparvovec and etranacogene dezaparvovec

Table 3-3: Critical Appraisal of ITC studies according to ISPOR Guideline 2011 [5], PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses [6]

Section	Merla et al. 2024 & Thakkar et. al. 2024 (Poster & Abstract)	Submission Dossier 2025	CADTH 2024	Klamroth et al. 2024
	ITC for fidanacogene elaparvovec	ITC for etranacogene dezaparvovec		
Introduction				
Are the rationale for the study and the study objectives stated clearly?	yes	yes	yes	yes
Methods				
Does the methods section include the following: description of eligibility criteria, information sources search strategy, study selection process, and data extraction (validity/quality assessment of individual studies)? Are the outcome measures described? Is there a description of methods for the analysis/ synthesis of evidence? Do the methods described include the following: description of analyses methods/models, handling of potential bias/inconsistency, analysis framework? Are sensitivity analyses presented?	no	Yes, however, while basic framework of outcomes measures are provided, sufficient details about definitions, measurement methods, and quality assurance processes are absent. Additionally, not all bias/inconsistency handling are discussed.	yes	yes
Results				
Do the results include a summary of the studies included in the network of evidence: individual study data, network of studies? Does the study describe an assessment of model fit? Are competing models being compared? Are the results of the evidence synthesis (ITC/MTC) presented clearly? Are the findings of sensitivity/scenario analysis described?	no	Yes, however, the model fit and competing models are not discussed.	yes	yes
Discussion				
Does the discussion include the following: description/summary of main findings, internal validity of analysis, and external validity? Implications of results for target audience	no	Partially. While some aspects of internal validity are addressed, the discussion could be more thorough, and the external validity discussion is notably limited.	yes	yes
Funding				
Are the sources of funding for the systematic review and other support (e.g., supply of data); and the role of funders for the systematic review reported?	yes	yes	yes	yes

Abbreviations: ITC: indirect treatment comparison.

4 Budget impact analysis

Unit costs for the budget impact analysis

Table 4-1: Unit cost data

	Average unit costs	Range	Reference
A: Fidanacogene elaparvovec, BEQVEZ®:			
A1: Drug acquisition (fidanacogene elaparvovec)	€3,400,000.00/patient	-	Assumption based on cost-utility analysis for CADTH
A2: Additonal treatments			
Inpatient stay for preparation, IV and monitoring of IV-reactions (assumption 1 night)	€2,670.00/stay	-	Payer
Eligibility assessment			
CE-marked in-vitro diagnostic (IVD): negative results for AAVRh74var nessecary	-	-	Assumption: organised by manufacturer in specialiesed laboratory
Other tests	Excluded due to low costs and low impact on overall costs	-	Information from clinical experts
Monitoring			
FIX-activity and FIX-inhibitors, liver health monitoring	Excluded due to low costs and low impact on overall costs	-	Information from clinical experts
Adverse event management			
Very common AE: increased alanine transaminase or decreased FIX levels, Rectodelt 100 mg Zäpf., Prednison (H02AB07): 6 St	€14,75/per event	-	EKO
Very common AE: nasopharyngitis, local treatment, anti-inflammatory drug	Excluded due to low costs and low impact on overall costs	-	Information from clinical experts
Very common AE: arthralgia, local treatment, NSAR, physio therapy	Excluded due to low costs and low impact on overall costs	-	Information from clinical experts
Prophylactic treatment (gene therapy scenario)			
On-demand FIX substitution (gene therapy scenario)			
Major surgeries after gene therapy	Excluded because very rare and not relevant	-	Information from clinical experts
Minor interventions: dental procedures after gene therapy and SoC-leftovers	€199,17	-	Costs per day per patient based on total FIX treatment outpatient costs from EKO
B: SoC for moderately severe and severe hemophilia B in Austria:			
ALPROLIX® annual costs per patient based on dosage (min/max) and kg (70/80)	Price per unit: €1.10	€200,713 - €229,386/pat/yr	Calculations based on EKO prices
IDELVION® annual costs per patient based on dosage (min/max) and kg (70/80)	Price per unit: €2.39	€304,427 - €497,024/pat/yr	Calculations based on EKO prices

	Average unit costs	Range	Reference
IMMUNINE® annual costs per patient based on dosage (min/max) and kg (70/80)	Price per unit: €0.65	€82,992 - €252,929/pat/yr	Calculations based on EKO prices
Management of very common adverse events	Excluded due to low costs and low impact on overall costs	-	Information from clinical experts
Monitoring			
FIX-activity and FIX-inhibitors, liver health monitoring	Excluded due to low costs		Information from clinical experts
C: non-factor-therapies (NFT)/Non-replacement therapies (NRT)	-	-	Not available in AT
D: gene therapy: etranacogene dezaparvovec (HEMGENIX®)	-	-	At the time of conducting the BIA, not available in AT

Abbreviations: AT: Austrian, BIA: budget impact analysis, CADTH: Canadian Agency for Drugs and Technologies in Health, EKO: Erstattungskodex, pat: patient, SoC: standard of care, yr: year

5 Summary of existing economic evaluations

Table 5-1: Economic evaluation of Fidanacogene elaparvovec

Author, year [reference]	Country	Intervention anc comparator	Target population (base case)	Economic evaluation	Model	Perspective and time horizon	Utility values	Severity modifier	Discount rate	Model assumptions and limitations
CADTH report [7]	CAN	Fidanacogene elaparvovec (single IV infusion of 5 × 10^{11} vg/kg of body weight) vs FIX prophylaxis treatments (EHL FIX prophylaxisa, SHL FIX prophylaxisb; SHL/EHL basket of FIX prophylaxis comprised of 25% SHL and 75% EHL)	Adult patients (aged 18 years and older) with moderately severe to severe hemophilia B	Cost-utility analysis	Markov model: 4 health states based on an annual number of bleeds (0 bleeds, > 0 to < 3 bleeds, ≥ 3 to < 5 bleeds, ≥ 5 bleeds) and death. cycle length: 1 year	Canadian publicly funded health care payer Lifetime (77 years)	QALYs, Lys Effectiveness of fidanacogene elaparvovec informed by the BENEGENE-2 trial; effectiveness of FIX prophylaxis treatments informed by the BENEGENE-1 study.	NR	1.5% p.a. for costs and effects	Submitted price:$4,773,595.20 (€3,390,018.69*) per administration (1 × 10^{13} vg/mL), regardeless of the number of vials required. Administration costs associated with fidanacogene elaparvovec were not included. Patients who received fidanacogene elaparvovec were assumed to experience an immediate treatment benefit and remain in their initial health state until year 25, after which patients were assumed to experience a one-time 15% effect loss at the beginning of year 26 and have a higher risk of transitioning to the next more-severe health state. Of those, 4% were assumed to initiate FIX (SHL or EHL) prophylaxis each year. Patients on FIX infusion at baseline were assumed to remain in their initial bleed-based health state until death. In each cycle, a proportion of patients in all health states were at risk of death.

Author, year [reference]	Country	Intervention anc comparator	Target population (base case)	Economic evaluation	Model	Perspective and time horizon	Utility values	Severity modifier	Discoun t rate	Model assumptions and limitations
										Serious AEs were reported in 16% of patients who received fidanacogene elaparvovec in BENEGENE-2; however, costs and consequences of AEs were not considered in the sponsor's model. The sponsor assumed that initiation of fidanacogene elaparvovec treatment was associated with a one-time utility decrement of 0.0164 lasting 1 year. nAb testing coverage status is uncertain. If costs associated with testing for the presence of nAbs are not covered by the sponsor, costs associated with fidanacogene elaparvovec will be higher than estimated in the sponsor's analysis.

Author, year [reference]	Country	Intervention anc comparator	Target population (base case)	Economic evaluation	Model	Perspective and time horizon	Utility values	Severity modifier	Discoun t rate	Model assumptions and limitations
										The sponsor assumed that the costs for FIX recombinant nonacog alfa is representative for all available SHL products, whereas the cost of EHL was assumed to be a weighted average between FIX recombinant Fc fusion protein and FIX recombinant pegylated nonacog beta pegol (11.8% and 88.2%, respectively). Administration costs associated with FIX prophylaxis were overestimated. The duration of benefit with fidanacogene elaparvovec is highly uncertain owing to a lack of long-term follow-up data. The long-term magnitude of benefit compared to FIX prophylaxis treatments is unknown owing to a lack of comparative data.

Abbreviations: AE: adverse event, CADTH - Canadian Agency for Drugs and Technologies in Health, CAN – Canada, NR – Not reported, EHL: extended half-life, FIX: factor IX, Ly: life-year, nAb: neutralising antibody, QALY: quality-adjusted life year, SHL: standard half-life

** Costs converted from $ (2023) to € (2024) with the CCEMG - EPPI-Centre Cost Converter (https://eppi.ioe.ac.uk/costconversion/default.aspx).*

Table 5-2: Main results of the included economic evaluations

Author, year [reference]	Country	Incremental costs (base-case)	Incremental effects (base-case)	ICER (base-case)	CE-threshold applied (base-case)	Sensitivity and scenario analyses	Reflection
CADTH report [7]	CAN	Fidanacogene elaparvovec, total costs: $7,744,097 (€5,499,551.93*) SHL FIX prophylaxis, total costs: $10,615,727 (€7,538,870.17*) EHL FIX prophylaxis, total costs: $13,320,535 (€9,459,718.02*) SHL/EHL FIX prophylaxis, total costs: $12,644,333 (€8,979,506.05*) Incremental costs: $2,871,630 (€2,039,318.24*) to $5,576,438 (€3,960,166.09*)	Fidanacogene elaparvovec, total QALYs: 19.503 SHL FIX prophylaxis, total QALYs: 18.421 EHL FIX prophylaxis, total QALYs: 18.420 SHL/EHL FIX prophylaxis, total QALYs: 18.420 Incremental QALYs: 1.08 vs. all comparators à approximately 93% of the predicted QALYs to be gained with fidanacogene elaparvovec accrued after the first 2 years of treatment (i.e., beyond the duration of the BeneGene-2 trial).	Fidanacogene elaparvovec was more effective and less costly (dominant) compared with SHL FIX prophylaxis, EHL FIX prophylaxis, and the basket of SHL and EHL FIX prophylaxis. Based on the sponsor's model, the acquisition cost of fidanacogene elaparvovec ($4,773,595 per administration) is predicted to be offset by such savings after approximately 12 years.	At a willingness-to-pay threshold of $50,000 per QALY gained, there was a 97% probability of fidanacogene elaparvovec being cost-effective.	Sensitivity analysis: Results were largely driven by the acquisition cost of fidanacogene elaparvovec (90% of the total costs associated with fidanacogene elaparvovec), as well as the predicted gain in QALYs and cost savings resulting from a reduction in bleeding events, FIX prophylaxis use, and health care resource use. Scenario analyses: Scenario analyses that included adopting alternative modelling assumptions (i.e., a discount rate and treatment-effectiveness waning) as well as alternate assumptions related to treatment adherence for FIX prophylaxis, treatment of bleeds, and utility values. In all scenarios, fidanacogene elaparvovec remained dominant over FIX prophylaxis. The outcome that triggers the outcome-based agreements is the addition of FIX prophylaxis infusions after fidanacogene elaparvovec: The first scenario considered annuity payments, in which the annual cost of fidanacogene elaparvovec is applied to each patient who has received fidanacogene elaparvovec but not initiated FIX prophylaxis infusion for 20 years.	Findings are highly uncertain as most of the incremental QALYs (93%) were accrued on the basis of extrapolation and any predicted cost savings would not be realised until approximately 12 years after fidanacogene elaparvovec infusion. If the magnitude of benefit between fidanacogene elaparvovec and FIX prophylaxis is less than estimated by the sponsor or if actual cost of FIX prophylaxis treatments is lower than incorporated in the sponsor's model, it will take longer for any potential savings to be realised in the health care system. The impact of AEs was not considered. The model structure does not appropriately capture the current treatment experience of patients with hemophilia B. FIX prophylaxis treatment is highly individualised and ABRs do not remain static over time as they depend on factors such as adherence to treatment and physical activity level. The assumption that patients will remain in their initial health state while on FIX prophylaxis or fidanacogene elaparvovec for the entirety of the time horizon is therefore likely not reflective of the treatment experience of hemophilia B patients in Canada. The patients who would benefit most from fidanacogene treatment would be those without pre-existing joint damage (e.g., to preserve joint function). The clinical efficacy of fidanacogene elaparvovec among those with or without joint damage is unknown.

Author, year [reference]	Country	Incremental costs (base-case)	Incremental effects (base-case)	ICER (base-case)	CE-threshold applied (base-case)	Sensitivity and scenario analyses	Reflection
			Fidanacogene elaparvovec was not associated with any life-year gains; however, the sponsor's model predicts an incremental gain of 9.13 years spent in the "no bleeds" health state.			The second scenario considered lump-sum payments, in which the upfront cost of fidanacogene elaparvovec is applied to all patients who receive fidanacogene elaparvovec but a refund is applied if a patient switches to FIX infusion during an eligibility period (assumed by the sponsor to be 18 years) following treatment administration (refund percentage varies depending on how many years after fidanacogene elaparvovec patients switch to FIX infusions). In both outcome-based agreement scenarios, fidanacogene elaparvovec remained dominant over FIX prophylaxis.	Etranacogene dezaparvovec is currently undergoing review by CADTH for the treatment of hemophilia B in adults. The cost-effectiveness of fidanacogene elaparvovec compared to etranacogene dezaparvovec is unknown. Given the limitations identified within the sponsor's economic analysis, including uncertainty related to the magnitude and duration of benefit for fidanacogene elaparvovec compared to FIX prophylaxis treatments, CADTH was unable to provide a more reliable estimate of the cost-effectiveness of fidanacogene elaparvovec.

Abbreviations: ABR: annualised bleeding rate, AE: adverse event, CADTH - Canadian Agency for Drugs and Technologies in Health, CAN – Canada, NR – Not reported, EHL: extended half-life, FIX: factor IX, QALY: quality-adjusted life year, SHL: standard half-life

** Costs converted from $ (2023) to € (2024) with the CCEMG - EPPI-Centre Cost Converter (https://eppi.ioe.ac.uk/costconversion/default.aspx).*

6 Drug development

Table 6-1: Clinical trials using fidanacogene elaparvovec for haemophilia B (as of 12/2024)

ClinicalTrials.gov ID	Primary investigator	Condition	Phase	Participants	Study Start (Actual)	Primary Completion (Estimated)	Collaborators	Type of sponsor	Link to clinicaltrials.gov
Hemophilia B gene therapy with AAV8 vector									
NCT01620801	Spark Therapeutics, Inc.	Haemophilia B	Phase 1	4	01.10.2012	01.03.2016	Children's Hospital of Philadelphia, USA University of Pittsburgh, USA Royal Prince Alfred Hospital, Sydney, Australia St. James's Hospital, Ireland	Industry and Public	https://clinicaltrials.gov/study/NCT01620801
A gene therapy study for hemophilia B									
NCT02484092	Pfizer	Haemophilia B	Phase 2	15	18.11.2015	08.04.2019	n.a.	Industry	https://clinicaltrials.gov/study/NCT02484092
Long-term safety and efficacy study and dose-escalation substudy of PF 06838435 in individuals with hemophilia B									
NCT03307980	Pfizer	Haemophilia B	Phase 2	21	22.06.2017	06.06.2029	n.a.	Industry	https://clinicaltrials.gov/study/NCT03307980
A study to Evaluate the efficacy and safety of factor IX gene therapy with PF-06838435 in adult males with moderately severe to severe hemophilia B (BENEGENE-2)									
NCT03861273	Pfizer	Haemophilia B	Phase 3	45	29.07.2019	09.01.2031	n.a.	Industry	https://clinicaltrials.gov/study/NCT03861273
Safety and effectiveness of giroctocogene fitelparvovec or fidanacogene elaparvovec in patients with hemophilia A or B respectively									
NCT05568719	Pfizer	Haemophilia A and B	Phase 3	263	28.12.2022	03.09.2039	n.a.	Industry	https://clinicaltrials.gov/study/NCT05568719

Table 6-2:Studies of fidanacogene elaparvovec for haemophilia B

Author(s)	Year	Main finding	Research institute/ Affiliations	Type of organization	Source
Gene Therapy with Fidanacogene Elaparvovec in Adults with Hemophilia B					
Cuker, A.	2024	The gene therapy significantly reduced bleeding in patients with hemophilia B, though many potential participants couldn't receive the treatment due to pre-existing antibodies.	Departments of Medicine and of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA	Academia (private)	https://www.nejm.org/doi/10.1056/NEJMoa2302982?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed
Kavakli, K.			Division of Hematology, Department of Pediatrics, Ege University Faculty of Medicine, Izmir, Turkey	Academia (public)	
Frenzel, L.			Department of Hematology, Hemophilia Care and Research, Necker Hospital, Institut Imagine, Paris	Hospital (public)	

Author(s)	Year	Main finding	Research institute/ Affiliations	Type of organization	Source
Wang, J.-D.			Center for Rare Disease and Hemophilia, Taichung Veterans General Hospital, Taichung, Taiwan	Hospital (public)	
Astermark, J.			Department of Translational Medicine, Lund University, Lund	Hospital (public)	
			Department of Hematology, Oncology and Radiation Physics, Skåne University Hospital, Malmö, Sweden		
Cerqueira, M.H.			Instituto de Hematologia do Estado do Rio de Janeiro, Rio de Janeiro, Brazil	Public	
Iorio, A. - Hamilton, ON, Canada			Departments of Health Research Methods, Evidence, and Impact and of Medicine, McMaster University	Academia (public)	
Katsarou-Fasouli, O.			Blood Transfusion Center, National Reference Center for Congenital Bleeding Disorders, Laiko General Hospital, Athens	Hospital (public)	
Klamroth, R.			Vivantes Hospital in Friedrichshain, Berlin, Germany	Hospital (public)	
Shapiro, A.D.			Indiana Hemophilia and Thrombosis Center, Indianapolis	Not-for-profit	
Hermans, C.			Hemostasis and Thrombosis Unit, Division of Hematology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels	Private (but mostly publicly funded)	
Ishiguro, A.			Division of Hematology, National Center for Child Health and Development, Tokyo	Public	
Leavitt, A.D.			Departments of Medicine and of Laboratory Medicine, University of California, San Francisco, San Francisco	Academia (public)	
Oldenburg, J.B.			Institute of Experimental Hematology and Transfusion Medicine, University Hospital Bonn, and	Hospial (public)	
			Center for Rare Diseases Bonn, University Clinic Bonn, Germany		
Ozelo, M.C.			Hemocentro UNICAMP, Department of Internal Medicine, School of Medical Sciences, University of Campinas, Campinas, Brazil	Academia (public)	
Teitel, J.			Division of Hematology, St. Michael's Hospital, University of Toronto, Toronto, Canada	Hospital (mixed-funding private and public)	
Biondo, F.			Pfizer, Rome	Industry	
Fang, A.			Pfizer, New York	Industry	
Field Study and Correlative Studies of FIX Variant FIX-R338L in Participants Treated with Fidanacogene Elaparvovec					
Pittman, D.D. [1]	2024		Rare Disease Research Unit, Pfizer Inc., Cambridge, Massachusetts, United States.	Industry	https://pubmed.ncbi.nlm.nih.gov/38863155/

Author(s)	Year	Main finding	Research institute/ Affiliations	Type of organization	Source
Carrieri, C. [2]		The different lab tests used to measure factor IX activity showed varying results, with one test showing higher readings than others for the gene therapy version of factor IX. While this could have been due to activated factor IX in the samples, this wasn't the case, and the gene therapy factor IX didn't interfere with regular factor IX treatment when both were present.	Pfizer Inc., New York, New York, United States.		
Soares, H. [2]			Pfizer Inc., New York, New York, United States.		
McKay, J. [3]			Pfizer Inc., Groton, Connecticut, United States.		
Tan, C.Y. [3]			Pfizer Inc., Groton, Connecticut, United States.		
Liang, J.Z. [2]			Pfizer Inc., New York, New York, United States.		
Rakhe, S. [1]			Rare Disease Research Unit, Pfizer Inc., Cambridge, Massachusetts, United States.		
Marshall, J-C. [3]			Pfizer Inc., Groton, Connecticut, United States.		
Murphy, J.E. [1]			Rare Disease Research Unit, Pfizer Inc., Cambridge, Massachusetts, United States.		
Gaitonde, P.			Pfizer Inc., Cambridge, Massachusetts, United States.		
Rupon, J. [5]			Pfizer Inc., Collegeville, Pennsylvania, United States.		
FIX assay discrepancies in the setting of liver gene therapy using a hyperfunctional variant FIX-Padua					
Robinson, M. M.[1]	2021	While FIX:C measurements showed strong correlation between local and central laboratories, there were consistent differences in absolute values and measurement methods. The central lab typically reported lower values, with variations observed across different assay types and reagents used for measuring factor IX activity after gene therapy.	Colorado Coagulation, Laboratory Corporation of America Holdings, Englewood, CO, USA	Industry	https://pubmed.ncbi.nlm.nih.gov/33636038/
George, L. A.[2]			Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA	Hospital (not-for-profit and receives public funding)	
Carr, M. E.[3]			Spark Therapeutics Inc, Philadelphia, PA, USA	Industry	
Samelson-Jones, B. J.[2]			Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA	Hospital (not-for-profit and receives public funding)	
Arruda, V. R.[2]			Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA	Hospital (not-for-profit and receives public funding)	
Murphy, J. E.[4]			Pfizer Inc, Cambridge, MA, USA	Industry	
Rybin, D.[4]			Pfizer Inc, Cambridge, MA, USA	Industry	
Rupon, J.[5]			Pfizer Inc, Collegeville, PA, USA	Industry	
High, K. A.[2],[3]			Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA	Hospital (not-for-profit and receives public funding)	
			Spark Therapeutics Inc, Philadelphia, PA, USA	Industry	
Tiefenbacher, S.[1]			Colorado Coagulation, Laboratory Corporation of America Holdings, Englewood, CO, USA	Industry	

Author(s)	Year	Main finding	Research institute/ Affiliations	Type of organization	Source
Hemophilia B Gene Therapy with a High-Specific-Activity FIX Variant					
George, L.A.	2017	A single infusion of gene therapy proved safe in 10 people with hemophilia, with no serious side effects. The treatment helped patients produce their own clotting factors, reducing yearly bleeding episodes from 11 to less than 1, and allowing 8 out of 10 patients to stop taking their regular medication completely. The therapy, funded by Spark Therapeutics and Pfizer, maintained its effectiveness throughout the study period of up to 78 weeks.	Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA	Hospital (not-for-profit and receives public funding)	https://pubmed.ncbi.nlm.nih.gov/29211678/
Sullivan, S.K.			Mississippi Center for Advanced Medicine, Department of Pediatrics	Medical facility (private)	
Giermasz, A.			University of California–Davis Medical School, Department of Medicine	Academia (public)	
Rasko, J.E.J.			University of Sydney (Department of Medicine, Sydney Medical School)	Academia (public)	
			Centenary Institute (Gene and Stem Cell Therapy Program), Royal Prince Alfred Hospital		
Samelson-Jones, B.J			Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA	Hospital (not-for-profit and receives public funding)	
Ducore, J.			University of California–Davis Medical School, Department of Pediatrics	Academia (public)	
Cuker, A.			Departments of Medicine and of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA	Academia (public)	
Sullivan, L.M.			University of Mississippi Medical School, Department of Pathology	Academia (public)	
Majumdar, S.					
Teitel, J.			University of Toronto Faculty of Medicine	Academia (public)	
			Division of Hematology, St. Michael's Hospital, University of Toronto, Toronto, Canada	Hospital (mixed-funding private and public)	
McGuinn, C.E.			Weill Cornell Medical College, Department of Pediatrics	Academia (private)	
Ragni, M.V.			University of Pittsburgh, Department of Medicine	Academia (public)	
Luk, A.Y.			Spark Therapeutics, Philadelphia	Industry	
Hui, D.					
Wright, J.F.					
Chen, Y.					
Liu, Y.					
Wachtel, K.					

Author(s)	Year	Main finding	Research institute/ Affiliations	Type of organization	Source
Winters, A.			Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA	Hospital (not-for-profit and receives public funding)	
Tiefenbacher, S.			Colorado Coagulation, Laboratory Corporation of America Holdings, Englewood	Industry	
Arruda, V.R.			Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA	Hospital (not-for-profit and receives public funding)	
			Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA	Academia (public)	
van der Loo, J.C.M.			Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA	Hospital (not-for-profit and receives public funding)	
Zelenaia, O.					
Successful transduction of liver in hemophilia by AAV-FIX and limitations imposed by the host immune response					
Manno, C. S.	2006	Following successful long-term expression of F.IX in hemophilic dogs using rAAV vectors, researchers conducted a phase 1/2 clinical trial in seven human subjects with severe hemophilia B. While the hepatic artery delivery of rAAV-2 vectors achieved therapeutic F.IX levels without significant toxicity, the expression lasted only 8 weeks due to an immune response against AAV capsid proteins, suggesting future trials may require immunomodulation for sustained therapeutic effect.	Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA	Hospital (not-for-profit and receives public funding)	https://pubmed.ncbi.nlm.nih.gov/16474400/
Pierce, G. F.			Avigen, Inc.	Industry	
Arruda, V. R.			Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA	Hospital (not-for-profit and receives public funding)	
Glader, B.			Stanford University	Academia (private)	
Ragni, M.			University of Pittsburgh Medical Center	Public-private partnership	
			Hemophilia Center of Western Pennsylvania	Medical center (Non-profit)	
Rasko, J. J. E.			Royal Prince Alfred Hospital	Hospital (public)	
			Centenary Institute	Academia (public)	
Ozelo, M. C.			University of Campinas, State University of Campinas	Academia (public)	
Hoots, K.			University of Texas Houston Health Science Center	Academia (public)	
Blatt, P.			Christiana Care, Christiana Hospital	Hospital (Private but operates as a non-profit)	
Konkle, B.			University of Pennsylvania School of Medicine Presbyterian Medical Center	(Public-private partnership)	
Dake, M.			Stanford University School of Medicine	Academia (private)	
Kaye, R.			Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA	Hospital (not-for-profit and receives public funding)	

Author(s)	Year	Main finding	Research institute/ Affiliations	Type of organization	Source
Razavi, M.			Stanford University School of Medicine	Academia (private)	
Zajko, A.			University of Pennsylvania School of Medicine Presbyterian Medical Center	Academia and Hospital (public-private partnership)	
Zehnder, J.			Stanford University School of Medicine	Academia (private)	
Rustagi, P.			Department of Hematology, Stanford University	Academia (private)	
Nakai, H.			Stanford University School of Medicine	Academia (private)	
Chew, A.			The Children's Hospital of Philadelphia	Hospital (not-for-profit and receives public funding)	
			Avigen, Inc.	Industry	
Leonard, D.			University of Pennsylvania School of Medicine	Academia (public-private partnership)	
			Weill Medical College of Cornell University	Academia (private)	
Wright, J. F.			Avigen, Inc.	Industry	
Lessard, R. R.			Avigen, Inc.	Industry	
Sommer, J. M.			Avigen, Inc.	Industry	
Tigges, M.			Avigen, Inc.	Industry	
Sabatino, D.			The Children's Hospital of Philadelphia	Hospital (not-for-profit and receives public funding)	
Luk, A.			Avigen, Inc.	Industry	
Jiang, H.			Avigen, Inc.	Industry	
Mingozzi, F.			The Children's Hospital of Philadelphia	Hospital (not-for-profit and receives public funding)	
Couto, L.			Avigen, Inc.	Industry Industry	
Ertl, H. C.			The Children's Hospital of Philadelphia	Hospital (not-for-profit and receives public funding)	
High, K. A.			Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA	Hospital (not-for-profit and receives public funding)	
			Howard Hughes Medical Institute	Medical center (private but not-for profit)	
Kay, M. A.			Stanford University School of Medicine	Academia (private)	
Long-Term Safety and Efficacy of FIX Gene Therapy in Hemophilia B					
Nathwani, A. C.	2015		Katharine Dormandy Haemophilia Centre and Thrombosis Unit, Royal Free NHS Trust	Medical center (public)	https://pmc.ncbi.nlm.nih.gov/articles/PMC4278802

Author(s)	Year	Main finding	Research institute/ Affiliations	Type of organization	Source
		A single intravenous infusion of AAV8 vector in 10 patients with severe hemophilia B produced sustained, dose-dependent factor IX expression (1-6% of normal levels) over a median 3.2-year period, with the high-dose group (6 patients) achieving mean levels of 5.1±1.7% that led to >90% reduction in bleeding episodes and prophylactic factor IX use. While four high-dose patients experienced temporary liver enzyme elevation that resolved with prednisolone treatment, no long-term toxic effects were observed during the follow-up period of <up to 3 years.	Department of Haematology, University College London Cancer Institute	Academia (public)	
			NHS Blood and Transplant, Watford	Medical center (public)	
Reiss, U. M.			Department of Hematology, St. Jude Children's Research Hospital	Hospital (not-for-profit and receives public funding)	
Tuddenham, E. G. D.			Katharine Dormandy Haemophilia Centre and Thrombosis Unit, Royal Free NHS Trust	Medical center (public)	
			Department of Haematology, University College London Cancer Institute	Academia (public)	
Rosales, C.			Department of Haematology, University College London Cancer Institute		
			NHS Blood and Transplant, Watford	Medical center (public)	
Chowdary, P.			Katharine Dormandy Haemophilia Centre and Thrombosis Unit, Royal Free NHS Trust		
McIntosh, J.			Katharine Dormandy Haemophilia Centre and Thrombosis Unit, Royal Free NHS Trust		
			Department of Haematology, University College London Cancer Institute	Academia (public)	
Della Peruta, M.			Department of Haematology, University College London Cancer Institute		
Lheriteau, E.			Department of Haematology, University College London Cancer Institute		
Patel, N.			Department of Haematology, University College London Cancer Institute		
Raj, D.			Department of Haematology, University College London Cancer Institute		
Riddell, A.			Department of Haematology, University College London Cancer Institute		
Pie, J.			Katharine Dormandy Haemophilia Centre and Thrombosis Unit, Royal Free NHS Trust	Medical center (public)	
Rangarajan, S.			St. Thomas' Hospital, London	Hospital (public)	
			Basingstoke and North Hampshire Foundation Trust		
Bevan, D.			St. Thomas' Hospital, London	Hospital (public)	
Recht, M.			Hemophilia Center, Oregon Health and Science University	Academia (public)	
Shen, Y-M.			Department of Internal Medicine, University of Texas Southwestern Medical Center		
Halka, K. G.			Scott and White Healthcare, Temple Clinic	Medical center (private but not-for-profit)	

Author(s)	Year	Main finding	Research institute/ Affiliations	Type of organization	Source
Basner-Tschakarjan, E.			Center for Cellular and Molecular Therapeutics, Children's Hospital of Philadelphia	Hospital (not-for-profit and receives public funding)	
Mingozzi, F.			Center for Cellular and Molecular Therapeutics, Children's Hospital of Philadelphia	Hospital (not-for-profit and receives public funding)	
High, K. A.			Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA		
Allay, J.			Poplar Healthcare, Memphis	Medical center (private)	
Kay, M. A.			Stanford University School of Medicine	Academia (private)	
Ng, C. Y. C.			Department of Surgery, St. Jude Children's Research Hospital	Hospital (not-for-profit and receives public funding)	
Zhou, J.			Department of Surgery, St. Jude Children's Research Hospital		
Cancio, M.			Department of Surgery, St. Jude Children's Research Hospital		
Morton, C. L.			Department of Surgery, St. Jude Children's Research Hospital		
Gray, J. T.			Department of Hematology, St. Jude Children's Research Hospital		
Srivastava, D.			Department of Biostatistics, St. Jude Children's Research Hospital		
Nienhuis, A. W.			Department of Hematology, St. Jude Children's Research Hospital		
Davidoff, A. M.			Department of Surgery, St. Jude Children's Research Hospital		
AAV liver expression of FIX-Padua prevents and eradicates FIX inhibitor without increasing thrombogenicity in hemophilia B dogs and mice					
Crudele, J. M.	2015		Department of Pediatrics, The Children's Hospital of Philadelphia	Hospital (not-for-profit and receives public funding)	https://pubmed.ncbi.nlm.nih.gov/25568350/
Finn, J. D.			Department of Pediatrics, The Children's Hospital of Philadelphia		
Siner, J. I.			Department of Pediatrics, The Children's Hospital of Philadelphia		
Martin, N. B.			Department of Pediatrics, The Children's Hospital of Philadelphia		
Niemeyer, G. P.			Department of Biochemistry, University of Alabama at Birmingham	Academia (public)	
Zhou, S.			Department of Pediatrics, The Children's Hospital of Philadelphia	Hospital (not-for-profit and receives public funding)	

Author(s)	**Year**	Main **finding**	Research institute/ Affiliations	Type of organization	**Source**
Mingozzi, F.		AAV-8 vectors encoding hyperfunctional FIX-Padua were tested in hemophilia B dogs, resulting in sustained expression with 8-12 fold increased activity (25-40%) in naïve dogs and successful immune tolerance in a dog with pre-existing inhibitors that achieved 200% activity. The study demonstrated phenotype correction without thrombotic complications, and mouse studies showed FIX-Padua had similar immunogenicity and thrombogenicity to wild-type FIX, supporting its potential use in human gene therapy.	Department of Pediatrics, The Children's Hospital of Philadelphia		
Lothrop Jr, C. D.			Department of Biochemistry, University of Alabama at Birmingham	Academia (public)	
Arruda, V. R.			Department of Pediatrics, The Children's Hospital of Philadelphia	Hospital (not-for-profit and receives public funding)	
			Perelman School of Medicine at the University of Pennsylvania	Academia (Public-private partnership)	

Table 6-3: Financing/patent deals/licensing/funding rounds of all companies involved in the development of fidanacogene elaparvovec (fidanacogene elaparvovec specific information in colour)

Type of financing	Details on collaboration, financing, public funding	Year	Amount (in USD)	Funders/investors/ acquiror	Source
Spark Therapeutics					
Licensing	Spark Therapeutics and CombiGene AB ('CombiGene') announced the signing of an exclusive collaboration and licensing agreement for CombiGene's CG01 project, an investigational gene therapy which aims to treat drug resistant focal epilepsy.	2021	n.a.	n.a.	https://www.biospace.com/spark-therapeutics-and-combigene-enter-into-exclusive-global-licensing-agreement-for-gene-therapy-candidate-cg01
Acquisition	Roche bought Spark for $4.3 billion, triggering its move into the gene therapy arena.	2019	$4.3 bn	Roche	https://www.fiercepharma.com/pharma/pfizer-scores-fda-nod-hemophilia-b-gene-therapy-will-charge-35m-dose
Licensing	Spark sells regulatory fast pass to Jazz for $110M Spark Therapeutics has sold a priority review voucher (PRV) to Jazz Pharmaceuticals for $110 million, according to a monday disclosure	2018	$110 mio	Spark Therapeutics/ Jazz	https://www.biopharmadive.com/news/spark-sells-regulatory-fast-pass-to-jazz-for-110m/522475/
Public offering	Spark Therapeutics announces pricing of $350 million public offering	2017	$350 mio	Funding by private investors/ organizations	https://www.biospace.com/spark-therapeutics-announces-pricing-of-350-0-million-public-offering
Acquisition	Trinity's gene medicine spin off genable technologies sold to Spark Therapeutics Shareholders in Genable Technologies received $6 million following the sale, along with 265,000 shares of Spark common stock. Additional financial terms were not disclosed.	2016	$6 mio	Spark Therapeutics	https://www.tcd.ie/news_events/articles/trinitys-gene-medicine-spin-off-genable-technologies-sold-to-spark-therapeutics/ https://www.fiercebiotech.com/biotech/spark-therapeutics-announces-acquisition-of-genable-technologies
Initial Public Offering (IPO)	Spark Therapeutics ($ONCE), at work on one-time treatments for rare diseases, pulled off a $161 million IPO, pricing above its range and keeping biotech's Wall Street hot streak rolling.	2015	$161 mio	Investment	https://www.fiercebiotech.com/r-d/spark-nails-a-161m-ipo-to-fund-its-breakthrough-gene-therapy

Type of financing	Details on collaboration, financing, public funding	Year	Amount (in USD)	Funders/investors/ acquiror	Source
Licensing	In 2014, Pfizer kicked off its gene therapy program, paying $20 million upfront and $260 million in potential milestones to Spark for the product, with an agreement that the Philadelphia gene therapy specialist would handle phase 1 and 2 development and Pfizer would take it from there.	2014	$20 mio + $260 mio	Spark Therapeutics/ Pfizer	https://www.fiercepharma.com/pharma/pfizer-scores-fda-nod-hemophilia-b-gene-therapy-will-charge-35m-dose
Series A financing	Spark Therapeutics launched with $50 million in financing to advance late- and mid-stage gene therapy programs with clinical proof of concept	2013	$50 mio	The Children's Hospital of Philadelphia (CHOP)	https://www.prnewswire.com/news-releases/spark-therapeutics-launched-with-50-million-in-financing-to-advance-late--and-mid-stage-gene-therapy-programs-with-clinical-proof-of-concept-228752221.html https://www.fiercebiotech.com/venture-capital/gene-therapy-upstart-launches-50m-and-long-term-commercial-goals
Series B financing	Spark Therapeutics raises $72.8 million in oversubscribed financing	2014	$72.8 mio	Sofinnova Ventures	https://www.prnewswire.com/news-releases/spark-therapeutics-raises-728-million-in-oversubscribed-financing-260806381.html
Children's *Hospital of Philadelphia*					
Project specific funding (all research projects that are for the treatment of hemophilia B using gene therapies)	Biochemistry of intrinsic xase	2022	732.776	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/10439608
	Biochemistry of intrinsic xase	2021	732.776	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/10175003
	Rational development of bioengineered factor IX variants for hemophilia B therapy	2021	159.408	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/10083221
	Biochemistry of intrinsic xase	2020	495.230	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/9846245
	Rational development of bioengineered factor IX variants for hemophilia B therapy	2020	159.408	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/9846245
	Novel factor VIII variants for improved efficacy in gene therapy for hemophilia A	2020	420.000	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/9844491
	Biochemistry of intrinsic xase	2019	426.871	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/9769860
	Rational development of bioengineered factor IX variants for hemophilia B therapy	2019	159.408	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/9846245
	Novel factor VIII variants for improved efficacy in gene therapy for hemophilia A	2019	420.000	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/9618256
	Rational development of bioengineered factor IX variants for hemophilia B therapy	2018	159.408	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/9637419
	Biochemistry of intrinsic xase	2018	430.000	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/9416300

Type of financing	Details on collaboration, financing, public funding	Year	Amount (in USD)	Funders/investors/ acquiror	Source
	Novel factor VIII variants for improved efficacy in gene therapy for hemophilia A	2018	420.000	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/9391192
	Novel factor VIII variants for improved efficacy in gene therapy for hemophilia A	2017	420.000	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/9198569
	Novel factor VIII variants for improved efficacy in gene therapy for hemophilia A	2016	420.000	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/9027334
	Gene therapy for hemophilia using muscle-expressed FVIIa	2015	450.208	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/8876764
	Novel therapy for hemophilia B using AAV-FIX variants	2015	511.160	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/8876763
	Gene therapy for hemophilia	2015	2.046.831	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/8876762
	Gene therapy for hemophilia using muscle-expressed FVIIa	2014	446.131	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/8691968
	Novel therapy for hemophilia B using AAV-FIX variants	2014	507.191	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/8691967
	Gene therapy for hemophilia	2014	2.026.513	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/8691966
	Gene therapy for hemophilia using muscle-expressed FVIIa	2013	430.683	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/8502301
	Novel therapy for hemophilia B using AAV-FIX variants	2013	493.617	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/8502298
	Gene therapy for hemophilia	2013	1.963.829	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/8502297
	Gene therapy for hemophilia using muscle-expressed FVIIa	2012	450.426	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/8379637
	Novel therapy for hemophilia B using AAV-FIX variants	2012	532.996	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/8379634
	Gene therapy for hemophilia	2012	2.069.413	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/8313853
	Animal core for gene therapy of hemophilia	2011	346.339	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/8185350
	Gene therapy for hemophilia using muscle-expressed FVIIa	2011	371.508	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/8185314
	Novel therapy for hemophilia B using AAV-FIX variants	2011	384.370	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/8185311
	Gene therapy for hemophilia	2011	1.951.418	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/8153509

Type of financing	Details on collaboration, financing, public funding	Year	Amount (in USD)	Funders/investors/ acquiror	Source
	CORE--canine	2009	179.397	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/7817146
	Safety & efficacy of intravas. del. of AAV-F.IX to skeletal muscle	2009	367.300	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/7817144
	Intravascular delivery of AAV to skeletal muscle	2009	558.266	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/7817143
	CORE--canine	2008	173.966	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/7617705
	Safety & efficacy of intravas. del. of AAV-F.IX to skeletal muscle	2008	349.395	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/7617703
	Molecular engineering of factor VIII gene for rAAV delivery	2009	74.025	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/7546648
	AAV2-F.IX hepatic gene transfer under immunomodulation	2008	371.214	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/7435223
	CORE--canine	2007	217.398	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/7417868
	Safety & efficacy of intravas. del. of AAV-F.IX to skeletal muscle	2007	345.664	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/7417866
	Molecular engineering of factor VIII gene for rAAV delivery	2008	364.302	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/7371308
	CORE--canine	2006	212.652	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/7312516
	AAV2-F.IX hepatic gene transfer under immunomodulation	2007	362.364	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/7246535
	AAV2-F.IX hepatic gene transfer under immunomodulation	2006	380.350	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/7078208
	Study in hem B using vector to deliver gene for human factor IX into liver	2004	6.029	NCRR	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/7041815
	CORE--canine	2005	225.281	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/6959252
	Immunology of factor IX gene transfer to liver	2005	82.809	NIAID	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/6861051
	AAV mediated muscle directed gene therapy for hemophilia B	2004	482.240	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/6832799
	Immunology of factor IX gene transfer to liver	2004	297.500	NIAID	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/6704238
	Gene therapy for hemophilia	2004	1.464.576	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/6700770

Type of financing	Details on collaboration, financing, public funding	Year	Amount (in USD)	Funders/investors/ acquiror	Source
	Gene therapy for hemophilia	2003	1.522.334	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/6640706
	Immunology of factor IX gene transfer to liver	2003	297.500	NIAID	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/6622916
	Gene therapy for hemophilia	2002	1.579.875	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/6556362
	Gene therapy for hemophilia	2001	82.212	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/6497029
	Immunology of factor IX gene transfer to liver	2002	291.200	NIAID	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/6459176
	Immune tolerance to factor IX in hemophilia B	2002	44.212	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/6446532
	Human application of AAV mediated muscle directed factor IX gene transfer	2001	380.508	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/6410597
	AAV mediated muscle directed gene therapy for hemophilia B	2001	380.508	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/6410594
	Inhibitor formation in gene therapy for hemophilia	2001	295.413	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/6390210
	Gene therapy for hemophilia	2001	1.863.373	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/6330198
	Human application of AAV mediated muscle directed factor IX gene transfer	2000	253.126	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/6313241
	AAV mediated muscle directed gene therapy for hemophilia B	2000	25.981	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/6313238
	Inhibitor formation in gene therapy for hemophilia	2000	295.413	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/6184564
	Gene therapy for hemophilia	2000	1.959.275	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/6041488
	Inhibitor formation in gene therapy for hemophilia	1999	303.325	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/6056585
	Novel strategies for gene therapy of hemophilia B	1998	427.583	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/2771392
	Inhibitor formation in gene therapy for hemophilia	1998	306.250	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/2762478
	Novel strategies for gene therapy of hemophilia B	1997	411.139	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/2519457
	Novel strategies for gene therapy of hemophilia B	1995	380.857	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/2231711

Type of financing	Details on collaboration, financing, public funding	Year	Amount (in USD)	Funders/investors/ acquiror	Source
	Novel strategies for gene therapy of hemophilia B	1994	336.492	NHLBI	https://reporter.nih.gov/search/Ho2n35ZqUU2GUSY9g4bTRQ/project-details/2231710
St. Jude Children's Research Hospital					
Project specific funding (all research projects that are for the treatment of hemophilia B using gene therapies)	AAV-mediated gene therapy for hemophilia	2015	533.454	NHLBI	https://reporter.nih.gov/search/rJStlJUSoUOm5kGOIH_KNA/project-details/8882512
	AAV-mediated gene therapy for hemophilia	2014	522.961	NHLBI	https://reporter.nih.gov/search/rJStlJUSoUOm5kGOIH_KNA/project-details/8677943
	AAV-mediated gene therapy for hemophilia	2013	508.019	NHLBI	https://reporter.nih.gov/search/rJStlJUSoUOm5kGOIH_KNA/project-details/8501629
	Clinical trial of self complementary AAV8-mediated gene transfer for hemophilia B	2013	607.042	NHLBI	https://reporter.nih.gov/search/rJStlJUSoUOm5kGOIH_KNA/project-details/8389602
	AAV-mediated gene therapy for hemophilia	2012	545.594	NHLBI	https://reporter.nih.gov/search/rJStlJUSoUOm5kGOIH_KNA/project-details/8287104
	Clinical trial of self complementary AAV8-mediated gene transfer for hemophilia B	2012	652.476	NHLBI	https://reporter.nih.gov/search/rJStlJUSoUOm5kGOIH_KNA/project-details/8231434
	AAV-mediated gene therapy for hemophilia	2011	548.387	NHLBI	https://reporter.nih.gov/search/rJStlJUSoUOm5kGOIH_KNA/project-details/8115643
	Clinical trial of self complementary AAV8-mediated gene transfer for hemophilia B	2011	782.602	NHLBI	https://reporter.nih.gov/search/rJStlJUSoUOm5kGOIH_KNA/project-details/7995962
	Clinical trial of self complementary AAV8-mediated gene transfer for hemophilia B	2010	780.538	NHLBI	https://reporter.nih.gov/search/rJStlJUSoUOm5kGOIH_KNA/project-details/7754692
	rAAV-mediated gene therapy for hemophillia B	2009	355.568	NHLBI	https://reporter.nih.gov/search/rJStlJUSoUOm5kGOIH_KNA/project-details/7616449
	Clinical trial of self complementary AAV8-mediated gene transfer for hemophilia B	2009	827.663	NHLBI	https://reporter.nih.gov/search/rJStlJUSoUOm5kGOIH_KNA/project-details/7565700
	rAAV-mediated gene therapy for hemophillia B	2008	355.568	NHLBI	https://reporter.nih.gov/search/rJStlJUSoUOm5kGOIH_KNA/project-details/7413581
	rAAV-mediated gene therapy for hemophillia B	2007	355.568	NHLBI	https://reporter.nih.gov/search/rJStlJUSoUOm5kGOIH_KNA/project-details/7228815
	rAAV-mediated gene therapy for hemophillia B	2006	366.188	NHLBI	https://reporter.nih.gov/search/rJStlJUSoUOm5kGOIH_KNA/project-details/7058847
	rAAV-mediated gene therapy for hemophillia B	2005	375.000	NHLBI	https://reporter.nih.gov/search/rJStlJUSoUOm5kGOIH_KNA/project-details/6869183

Abbreviation: NHLBI: National Heart Lung and Blood Institute, NCRR: National Center for Research Resources, NIAID: National Institute of Allergy and Infectious Diseases

Table 6-4: 10 biggest shareholders of Pfizer (information extracted from ORBIS)

Current shareholders					
Name of firm	**Country ID**	**Type**	**Ownership**		**Information as of Date**
			Direct %	**Total %**	
Vanguard Fiduciary Trust Co.	US	C	-	9.110 %	15/01/2025
BlackRock Advisors LLC	US	E		5.778 %	
State Street Corp.	US	E		5.125 %	
Wellington Trust Co., NA	US	E		2.889 %	
Charles Schwab Investment Management, Inc.	US	E		2.297 %	
Geode Capital Management LLC	US	F		2.076 %	
Ishares (DE) InvAG mit Teilgesellschaftsvermogen	DE	E		1.657 %	
Norges Bank (13F)	NO	B		1.482 %	
Eaton Vance Management	US	E		1.376 %	
Massachusetts Financial Services Co.	US	E		1.256 %	
Legend E = Mutual and pension fund, nominee, trust, trustee C = Corporate B = Banking company F = Financial company					

Table 6-5 Pfizer/Spark Therapeutics key financial information from 2014 to 2019

Spark Therapeutics Key financials & employees 2014-2019 (all available years) (in thousand $)						
Year of report (all published on the 31st of December)	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**
Source	10-K	10-K	10-K	10-K	10-K	10-K
Operating revenue (Turnover)	634	22,064	20,183	12,066	64,725	n.a.
P/L for period [=Net income]	-25,032	-47,761	-123,653	-253,482	-78,822	n.a.
Number of employees	50	113	213	315	368	n.a.
Pfizer Key financials & employees 2014-2019 (in million $)						
Year of report (all published on the 31st of December)	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**
Source	10-K	10-K	10-K	10-K	10-K	10-K
Operating revenue (Turnover)	49,605	48,851	52,824	52,546	40,825	41,172
P/L for period [=Net income]	9,134	6,959	7,213	21,308	11,151	16,272
Number of employees	78,300	97,900	96,500	90,200	92,400	88,300

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