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

Health Technology Assessment

Final report

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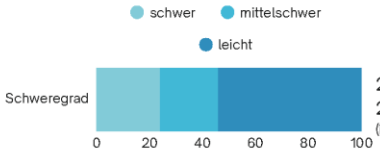
Ergebnisse auf einen Blick

KRANKHEITSBESCHREIBUNG

Hämophilie B: X-chromosomal vererbte Blutgerinnungsstörung, durch Mangel an Gerinnungsfaktor IX (FIX) verursacht

Hauptsymptome: Blutungen in Gelenken, Muskeln und anderen Körperregionen

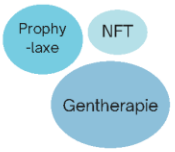


22,3 % mittelschwere & 24,6% schwere Hämophilie B (in Österreich)

Standardbehandlung (SoC): Prophylaxe (Substitutionstherapie)

- regelmäßige Substitution des fehlenden oder verminderten Blutgerinnungsfaktors (Faktorkonzentrate) oder Nicht-Faktor-Therapien (NFT)
- Komplikationen: Infektionsrisiko & Entwicklung von Inhibitoren (blockieren Wirkung von Gerinnungsfaktor)

ÜBERBLICK ARZNEIMITTEL



Fidanacogene elaparvovec (BEQVEZ®) 2. in Europa zugelassene Gentherapie für Hämophilie

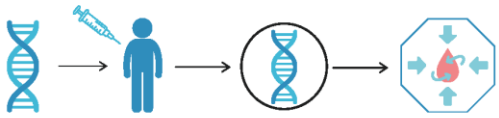
Bedingte Marktzulassung: Juli 2024 durch Europäische Kommission - unter Auflagen & zusätzlicher Überwachung

ab 18 zugelassen ohne Vorgeschichte mit FIX-Inhibitoren & Antikörpern gegen AAVRh74var

1x intravenöse Infusion

130 gemeldete Patient*innen (p.a) in Ö mit Hämophilie B, davon 9 für BEQVEZ® geeignet

MECHANISMUS



BEQVEZ® schleust mithilfe eines speziellen Virus-Trägers (AAVRh74var) das funktionierende FIX-Gen in Leberzellen ein → Gen verbleibt dort → produziert kontinuierlich fehlenden FIX → verbessert Blutgerinnung

KLINISCHE ASPEKTE

BENEGENE-2 STUDIE (2019-2031)

einarmige Phase-3-Studie

männliche Population (n=45, 18-62 Jahren)

mit Hämophilie B (FIX-Spiegel 2%)

WIRKSAMKEIT GEGENÜBER PROPHYLAXE

Primärer Endpunkt: jährliche Blutungsrate (ABR)

Unterschied von -3,15 (p=0,008)

71%ige Reduktion der ABR

Verbesserung der gesundheitsbezogenen Lebensqualität
(Information vom Hersteller nachgereicht)

SICHERHEIT

84% der Patienten haben Nebenwirkungen, davon sind 16% schwerwiegend

15 Monate Nachbeobachtungszeit, keine Garantie der langzeitigen Wirkung und Sicherheit gewährleistet

EINSCHRÄNKUNGEN

- Kurze Nachbeobachtungszeit
- Offenes Studiendesign
- Kleine Stichprobengröße
- Unvollständige Baseline-Charakteristika
- Endpunkt-Modifikation & Subjektivität des Endpunkts

INDIREKTER VERGLEICH (ITC)

Durch Matching-Adjusted Indirect Comparison (MAIC)
(Vergleich mit anderen Therapien für Hämophilie B)

STATISTISCH SIGNIFIKANTER UNTERSCHIED GEGENÜBER PROPHYLAXE

Reduktion ABR:

- BEQVEZ® vs. BeneFIX®

Reduktion Blutungsereignisse & Reduktion FIX-Verbrauch:

- BEQVEZ® vs. BeneFIX®
- BEQVEZ® vs. ALPROLIX®

KEIN STATISTISCH SIGNIFIKANTER UNTERSCHIED GEGENÜBER GENTHERAPIE HEMGENIX®

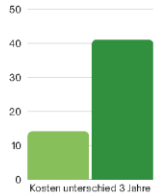
EINSCHRÄNKUNGEN

- Inkonsistente Ergebnisdarstellung
- Unzureichende Berücksichtigung systematischer Verzerrungen
- Eingeschränkte interne/externe Validität

ÖKONOMISCHE ASPEKTE

Geschätzter Preis (basierend auf kanadischem Preis):
- € 3,4 Millionen pro Verabreichung

Gesamtkosten (inkl. Verabreichungskosten, Einsparungen der Standardbehandlung, etc.):
- € 41 Millionen (über 3 Jahre)



3-fache Kostensteigerung im Vergleich zu SoC (innerhalb der ersten 3 Jahre)
- CADTH-Studie: Behandlungskosten könnten sich nach 12 Jahren durch den Wegfall der Prophylaxe amortisieren - vorausgesetzt Therapieeffekte sind dauerhaft

Auswirkungen auf Sektoren bei anhaltender Wirkung:
- Kosteneinsparungen im niedergelassenen Sektor
- Kostenerhöhung im stationären Sektor

Kosten-Nutzen-Analyse von Sponsor für Kanada:
- ermittelte Kosten-Wirksamkeits-Ergebnisse (dominante Therapie) sehr unsicher
- Übertragbarkeit auf Ö stark eingeschränkt

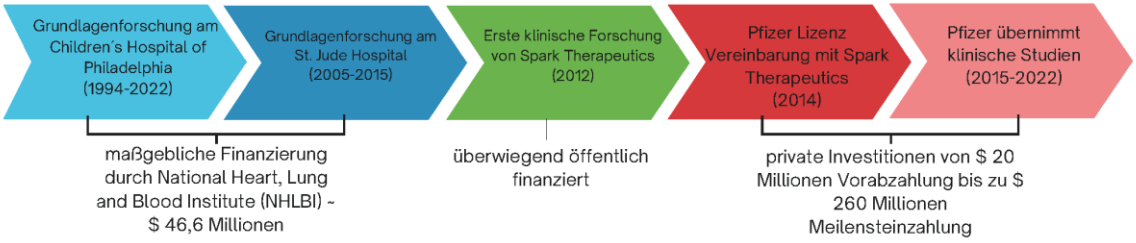
SOZIALE, ORGANISATORISCHE UND ETHISCHE ASPEKTE

HUB-and-SPOKE-Modell vorgeschlagen:
- spezialisierte Behandlungszentren
- lokale Nachsorge

Patient*innen äußern sich:
- optimistisch über reduzierte Behandlungslast & verbesserte Lebensqualität, durch Therapieform und Behandlungsfreiheit
- unsicher bzgl. langfristiger Wirksamkeit und möglicher Nebenwirkungen

Regelmäßige Überwachung und Dokumentation in Registern empfohlen

WESENTLICHE FORSCHUNGSEINRICHTUNGEN UND INVESTITIONEN



FAZIT VON FIDANACOGENE ELAPARVOVEC (BEQVEZ®)

wirkungsvollere Therapie, Unsicherheit über langfristige Wirkung	Sicherheit nicht gewährleistet, v.a. langfristige Sicherheit	Hinweise für verbesserte Lebensqualität durch geringere Einschränkungen im Alltag	Schätzung einer langfristigen Kosteneinsparung bei langfristiger Wirkung, keine sichere Analyse für Ö	Entwicklung von HUB- & SPOKE Einrichtungen mit hohem organisatorischen Aufwand

ABKÜRZUNGEN

AAVRh74var: Adeno-assoziierte Viren-Serotyp-Variante Rh74; *ABR:* Annual bleeding rate (jährliche Blutungsrate); *CADTH:* Canadian Agency for Drugs and Technologies in Health; *FIX:* Faktor-IX; *ITC:* indirect treatment of comparison (indirekter Behandlungsvergleich); *MAIC:* Matching-Adjusted Indirect Comparison; *NFT:* Nicht- Faktor-Therapie; *NHLBI:* National Heart, Lung and Blood Institute; *Ö:* Österreich; *p.a:* per annum (pro Jahr); *SoC:* Standard of care (Standardtherapie)

Zusammenfassung

Krankheitsbeschreibung und Behandlungsoptionen

Hämophilie B

Die Hämophilie B ist eine X-chromosomal rezessiv vererbte Blutgerinnungsstörung, die durch einen Mangel an Gerinnungsfaktor IX verursacht wird. Der Schweregrad von Hämophilie B wird nach Faktoraktivität eingestuft und in leicht (FIX-Aktivität 5-40 %), mittelschwer (FIX-Aktivität 1-5 %) und schwer (FIX-Aktivität <1 %) unterteilt. Die Erkrankung ist primär erblich, jedoch treten auch sporadische Fälle häufig auf. Studien zeigten, dass sporadische Ursachen bis zu 43 % der Fälle von schwerer Hämophilie B ausmachen. Schwere Hämophilie tritt fast ausschließlich bei Männern auf, obwohl in seltenen Fällen auch Frauen betroffen sein können.

Das auffälligste klinische Merkmal sind Blutungen in verschiedenen Bereichen des Körpers, die auf einen gestörten Gerinnungsmechanismus zurückzuführen sind. Häufige Blutungsstellen bei Kindern und Erwachsenen umfassen die Gelenke, Muskeln, das zentrale Nervensystem sowie den Verdauungstrakt. Die schwere Hämophilie ist insbesondere durch spontane und schwere Blutungen zu einem frühen Zeitpunkt im Leben der Patient:innen charakterisiert. Bei einer mittelschweren Hämophilie ist das Auftreten von Blutungen seltener als bei der schweren Form – typischerweise vier bis sechs Mal im Jahr. Aufgrund der Blutungen sind Spätfolgen möglich, die üblicherweise Gelenkstörungen und Muskelatrophie umfassen. Allgemein wird beobachtet, dass Patient:innen mit Hämophilie ein höheres Risiko für Bluthochdruck als die Allgemeinbevölkerung (Gesamtprävalenz 49 % gegenüber 32 %) aufweisen und Bluthochdruck in einem jüngeren Alter entwickeln. Eine auffällige Spätfolge bei schwerer Hämophilie ist die Hämophile Arthropathie, eine chronische Gelenkerkrankung, die bei bis zu 50 % der Patient:innen auftritt und zu einer verminderten körperlichen Funktionalität und Behinderungen führt.

Wenn die Hämophilie B unbehandelt bleibt, verläuft die Erkrankung schwer. Bei der schweren Form der Hämophilie B ist ohne Behandlung die Lebenserwartung deutlich eingeschränkt. Unzureichende oder falsche Behandlung von wiederkehrenden Gelenkblutungen und Hämatomen führen zu körperlichen Beeinträchtigungen mit schwerer Behinderung, die mit Steifheit, Gelenkdeformationen und körperlicher Einschränkung verbunden sind. Mit den aktuellen Therapiemöglichkeiten haben Hämophilie-Patient:innen eine normale Lebenserwartung, die jener der gesunden Bevölkerung entspricht. Eine Ausnahme bilden Patient:innen mit nicht behandelten bzw. unkontrollierten Infektion (Hepatitis B, Hepatitis C, HIV).

Inzidenz, Prävalenz und geschätzte Zahl der Patient:innen

Mit einer Inzidenzrate von 1:30.000 ist Hämophilie B eine seltene Erkrankung. Die Prävalenz der mittelschweren und schweren Hämophilie B liegt weltweit bei ein bis neun pro 100.000. Schätzungsweise sind 30 % der Patient:innen von der mittelschweren Form betroffen, während 40 % unter der schweren Verlaufsform leiden. In Österreich wurden im Jahr 2024 130 Patient:innen von der Österreichischen Hämophilie Gesellschaft (ÖHR) gemeldet. Davon waren 22,3 % von der mittelschweren und 24,6 % von der schweren Hämophilie betroffen. Hämophilie B betrifft Patient:innen aller Altersgruppen.

Behandlungsstandard (Standard of Care, SoC) und damit verbundene Komplikationen

Laut der österreichischen Leitlinie „Hämophilie-Behandlung in Österreich“ ist die Prophylaxe der Goldstandard und die erste Wahl für alle Patient:innen mit schwerer Hämophilie A und B sowie für Patient:innen mit mittelschwerer Hämophilie aber schwerem klinischen Phänotyp. Die Prophylaxe bei Hämophilie ist definiert als die regelmäßige Substitution des fehlenden oder verminderten Blutgerinnungsfaktors (Faktorkonzentrate) oder Nicht-Faktor-Therapien (NFT, derzeit in Österreich nicht verfügbar) zur Vorbeugung von Blutungen. Dabei wird die Wirksamkeit der Prophylaxe regelmäßig geprüft und gegebenenfalls angepasst. Ein wichtiges Ziel der Behandlung ist, die Therapie als regelmäßige Prophylaxe mit einem Faktor IX Konzentrat (intravenöse Applikation) überwiegend selbständig als Heimselbst-

therapie durchführen zu können. Durch den unmittelbaren Zugang zu Faktor IX Konzentraten können Blutungen, die zu Gelenkschäden und Funktionseinschränkungen führen, minimiert und die Anzahl der Krankenhausaufenthalte deutlich reduziert werden.

Bei der Prophylaxe mit Faktorkonzentraten, die intravenös appliziert werden müssen, können jedoch zwei wesentliche Komplikationen auftreten. Bei der ersten möglichen Komplikation handelt es sich um das potenzielle Infektionsrisiko durch Plasma-Produkte, das durch moderne Herstellungsverfahren inzwischen als sehr gering einzustufen ist, da das Übertragungsrisiko von Viren auf ein Minimum reduziert wurde. Die zweite und schwerwiegendere Komplikation ist die Entwicklung von Inhibitoren, auch Hemmkörper genannt. Diese Antikörper blockieren die Wirkung des zugeführten Gerinnungsfaktors und treten bei etwa 5-15 % der Patient:innen mit schwerer Hämophilie B auf. Bei Patient:innen mit leichter oder mittelschwerer Hämophilie ist diese Komplikation seltener zu beobachten. Die Entwicklung von Inhibitoren hat weitreichende Folgen für die Betroffenen: Die Wirksamkeit der Faktorgaben nimmt ab, und die Behandlung von Blutungen wird erheblich erschwert. Zudem können allergische Reaktionen auftreten.

Weitere Behandlungsoptionen

Zu den zusätzlichen Behandlungsmöglichkeiten gehören Antifibrinolytika als Supportivtherapie und eine weitere Gentherapie, Etranacogene dezaparvovec (HEMGENIX®). Ein Antifibrinolytikum (Tranexamsäure) kann bei Patient:innen mit Hämophilie begleitend zur Behandlung von Blutungen und Eingriffen an den Schleimhäuten eingesetzt werden, ersetzen jedoch nicht die Faktor-basierte Therapie. Antifibrinolytika hemmen die Aktivierung von Plasminogen zu Plasmin und sind besonders wirksam bei Schleimhautblutungen wie Nasenbluten oder starken Menstruationsblutungen. Auf Gelenkblutungen hat der Wirkstoff Tranexamsäure allein allerdings keine vorbeugende Wirkung.

Die Gentherapien als neue Behandlungsmöglichkeiten für schwere Hämophilie A und B zielen darauf ab, durch eine einmalige Infusion die Produktion des fehlenden oder unzureichend produzierten Gerinnungsfaktors wiederherzustellen. In Europa ist die Gentherapie sowohl für Hämophilie A als auch für die Hämophilie B zugelassen. Basierend auf der HOPE-B-Studie wurde im Februar 2023 die AAV5-basierte Gentherapie für die Behandlung der mittelschweren und schweren Hämophilie B bei erwachsenen Patient:innen ohne FIX-Inhibitoren in der Vorgeschichte zugelassen (Etranacogene dezaparvovec, HEMGENIX®). Für diese Behandlung liegt in Österreich derzeit noch keine Erfahrung vor.

Überblick über das neue Arzneimittel

Fidanacogene elaparvovec (BEQVEZ®) erhielt am 24. Juli 2024 von der Europäischen Kommission (European Commission, EC) eine bedingte Marktzulassung für die Behandlung von schwerer und mittelschwerer Hämophilie B (angeborener Faktor-IX [FIX]-Mangel). Fidanacogene elaparvovec ist die zweite in Europa zugelassene Gentherapie für Hämophilie B, und wird als Advanced Therapy Medicinal Product (ATMP) klassifiziert. Das Produkt ist im Priority-Medicines-Programm (PRIME) der Europäischen Arzneimittel-Agentur (European Medicines Agency, EMA) enthalten.

Die zugelassene Indikation ist die Behandlung von Patient:innen ab 18 Jahren ohne Vorgeschichte von FIX-Inhibitoren und nachweisbaren Antikörpern gegen die Adeno-assoziierte Viren-Serotyp-Variante Rh74 (AAVRh74var). Fidanacogene elaparvovec wird als einmalige intravenöse Infusion über etwa 60 Minuten in einem angemessenen Infusionsvolumen verabreicht. Die empfohlene Dosis beträgt eine Einmaldosis von 5×10^{11} Vektorgenomen pro kg (vg/kg) Körpergewicht. Fidanacogene elaparvovec schleust mithilfe eines speziellen Virus-Trägers (AAVRh74var) das funktionierende Gerinnungsfaktor-IX-Gen gezielt in die Leberzellen ein. Dort verbleibt das Gen und produziert kontinuierlich den fehlenden Gerinnungsfaktor IX, was zu einer verbesserten Blutgerinnung führt.

Relative klinische Wirksamkeit und Sicherheit

Ergebnisse der BENEGENE-2 Studie

Fidanacogene elaparvovec zeigte in einer einarmigen Phase-3-Studie (BENEGENE-2) bei einer erwachsenen männlichen Population (n=45, Altersbereich 18-62 Jahre) mit Hämophilie B (FIX-Spiegel ≤2 %) eine Reduktion der jährlichen Blutungsrate (annualised bleeding rate, ABR) im Vergleich zur vorherigen Behandlung dieser Population mit FIX-Prophylaxe-Therapie. Dies ergab einen Behandlungsunterschied von -3,15 (p=0,008), eine 71 %ige Reduktion, die zu erfolgreichen Nichtunterlegenheits- und Überlegenheitstests führte. Zusätzlich gab es eine klinisch bedeutsame Verbesserung der gesundheitsbezogenen Lebensqualität, und die ABR blieb bis zu 36 Monate (n=40) und 48 Monate (n=15) stabil. Unerwünschte Ereignisse traten bei 84 % der Patienten auf, darunter schwerwiegende unerwünschte Ereignisse bei sieben Patienten (16 %). Das häufigste unerwünschte Ereignis unabhängig vom Schweregrad war ein erhöhter Aminotransferase-Spiegel, der bei 53 % der Patienten auftrat. Die Erhebung von Sicherheits- und Wirksamkeitsdaten wird fortgesetzt, bis jeder Teilnehmer eine Nachbeobachtungszeit von sechs Jahren erreicht hat. Der Abschluss der Studie ist für das Jahr 2031 vorgesehen.

Einschränkungen der BENEGENE-2 Studie

Die klinische Studie wies mehrere Einschränkungen auf. Zum einen liegen bisher nur Daten aus einer 15-monatigen Nachbeobachtungszeit vor, obwohl für Gentherapien eine deutlich längere Nachbeobachtung erforderlich ist (mindestens fünf Jahre). Die langfristige Dauer der Wirkung von Fidanacogene elaparvovec ist derzeit unbekannt, und auch Langzeit-Sicherheitsdaten liegen nicht vor. Außerdem basiert die unverblindete, nicht-randomisierte Studie ausschließlich auf intra-individuellen Vergleichsdaten der Patienten mit ihrer vorherigen Standardtherapie. Das Fehlen einer randomisierten Kontrollgruppe und direkter Vergleichsdaten zur aktuellen Standardtherapie unter kontrollierten Bedingungen bedingt ein methodisches Verzerrungspotenzial.

Zusätzlich wurde die Definition des primären Endpunkts im Studienverlauf geändert. Ursprünglich war ein co-primärer Endpunkt vorgesehen (jährliche Blutungsrate und FIX-Aktivität). Dieser wurde auf die jährliche Gesamtblutungsrate reduziert. Zudem wurde keine wissenschaftliche Rationale für die gewählte Nichtunterlegenheitsgrenze von 3,0 Blutungsepisoden pro Jahr angegeben. Details zu den Patienten, wie bisherige Blutungsmuster und die Krankheitsdauer, fehlen. Zudem weicht die Definition des Schweregrades der Erkrankung in der Studie (mittelschwer bis schwer bei FIX-Aktivität ≤2 %) von den Standards der World Federation of Hemophilia ab (schwer: <1 %, mittelschwer: 1-5 % FIX-Aktivität). Diese Abweichung von den international etablierten Kriterien erschwert die Übertragbarkeit der Studienergebnisse auf die Gesamtpopulation der Hämophilie B-Patienten. Insbesondere lässt sich nicht klar ableiten, für welche Schweregrade der Erkrankung die Therapie einen relevanten Nutzen zeigt. Diese Einschränkungen in der Charakterisierung der Studienpopulation werden durch Unsicherheiten bei der Erfassung des primären Endpunkts verstärkt: Die jährliche Blutungsrate ist anfällig für subjektive Einflüsse. Es bleibt unklar, ob eine konsistente Datenerhebung zwischen der BENEGENE-2- und der BENEGENE-1-Studie (welche die Baseline-Daten lieferte) gewährleistet war.

Indirekter Behandlungsvergleich von Fidanacogene elaparvovec

Der indirekte Behandlungsvergleich (indirect treatment comparison, ITC) von Fidanacogene elaparvovec, der vom vertriebsberechtigten Unternehmen in Auftrag gegeben wurde, zeigte im Vergleich zu Nonacog alfa eine statistisch signifikant niedrigere ABR (RR: 0.29, 95 % CI: 0.13–0.63) und einen höheren Anteil von Patienten ohne Blutungsereignisse (OR: 3.55, 95 % CI: 1.17–10.79). Auch im Vergleich zu Eftrenonacog alfa war der Anteil der Patienten ohne Blutungsereignisse signifikant höher (OR: 3.92, 95 % CI: 1.48–10.39). Gegenüber beiden Produkten zeigte sich zudem ein reduzierter FIX-Verbrauch. Im Vergleich zu Etranacogen dezaparvovec ergaben sich keine statistisch signifikanten Unterschiede.

Diese Ergebnisse sollten jedoch mit Vorsicht interpretiert werden, da der ITC methodische Einschränkungen aufwies. Es wurde nicht detailliert beschrieben, wie die Endpunkte gemessen worden sind. Aufgrund fehlender detaillierterer Informationen zur Methodik des indirekten Vergleichs ist die jährliche Blutungsrate ein subjektiver Endpunkt, dessen Messung je nach Studie variieren kann. Zusätzlich fehlen

detaillierte, individuelle Angaben zu Studiendaten und Patient:innen-Charakteristika und eine Interpretation der Validität der Ergebnisse. Wie auch bei Fidanacogene elaparvovec, bestehen große Unsicherheiten hinsichtlich der Langzeitwirkung von Etranacogen dezaparvovec aufgrund der kurzen Nachbeobachtungszeit von 36 Monaten.

Ökonomische Aspekte

Derzeit ist in Europa noch kein Preis für Fidanacogene elaparvovec verfügbar. Daher basiert die Berechnung der Budgetfolgenanalyse (Budget-Impact-Analyse, BIA) auf einem vorläufigen Preis von 3,4 Millionen Euro pro Verabreichung. Unter der Annahme, dass neun Patient:innen die Therapie mit einer steigenden Aufnahme über drei Jahre erhalten (Jahr 1: 20 %, Jahr 2: 30 %, Jahr 3: 50 %), würde sich die gesamte dreijährige Budgetauswirkung auf etwa 41 Millionen Euro belaufen. Dabei werden die Kosten der Gentherapie, zusätzliche Kosten für deren Verabreichung, mögliche Kosteneinsparungen in der aktuellen Standardbehandlung und die Behandlung der verbleibenden Patient:innen wie üblich berücksichtigt. Dies entspricht einer 3-fachen Steigerung im Vergleich zu den Kosten, die bei der derzeitigen Behandlung in den nächsten drei Jahren entstehen würden (ca. 14 Millionen Euro). Halten die Behandlungseffekte langfristig an, könnten nach internationalen Schätzungen nach 12 Jahren die Behandlungskosten durch Wegfall der Prophylaxe ausgeglichen werden. Unsicherheiten bestehen hinsichtlich der Kostendeckung für Tests auf neutralisierende Antikörper, der Kosten der Standardbehandlung und des noch unbekannten endgültigen Verhandlungspreises von Fidanacogene elaparvovec. Die BIA schätzt, dass die Kostenauswirkungen von Fidanacogene elaparvovec zu Kosteneinsparungen im ambulanten Bereich führen, aber zu erhöhten Kosten im stationären Sektor.

Eine Kosten-Nutzwert-Analyse des vertriebsberechtigten Unternehmens, die der Canadian Health Technology Assessment Agency zur Verfügung gestellt wurde, zeigt unsichere Kosteneffektivitätsergebnisse, insbesondere im Hinblick auf das Ausmaß und die Dauer des Nutzens von Fidanacogene elaparvovec im Vergleich zu FIX-Prophylaxe-Behandlungen. Dies ist auf das offene, einarmige Studiendesign, die Selbstberichterstattung von Blutungsereignissen und die unsichere Langzeitwirkung zurückzuführen. Fidanacogene elaparvovec erwies sich im Vergleich zur Prophylaxe-Therapie als wirksamer und kostengünstiger (dominant). Die Übertragbarkeit dieser Ergebnisse auf Österreich ist jedoch stark eingeschränkt.

Soziale, organisatorische, ethische und rechtliche Aspekte

Klinische Expert:innen schlugen ein HUB-and-SPOKE-Modell vor, das auf der Koordinierung spezialisierter Verabreichungszentren und lokaler Nachsorgeeinrichtungen für die Gentherapie bei Hämophilie B beruht. Nach diesem Modell würden geeignete Patient:innen eine einmalige Infusion in ausgewiesenen HUB-Zentren erhalten, gefolgt von einer engmaschigeren Erstüberwachung in SPOKE-Zentren mit zweimal wöchentlich stattfindenden Laboruntersuchungen, deren Häufigkeit schrittweise abnimmt. Dieses Modell würde erhebliche Investitionen in die Ausbildung des Personals und die Entwicklung der Infrastruktur erfordern, um die komplexen Überwachungsanforderungen für Gentherapien und mögliche Komplikationen, sowie Maßnahmen den Datenschutz der Patient:innen betreffend, zu bewältigen.

Im AIHTA Fragebogen äußerten sich Patient:innen hinsichtlich der potenziell neuen gentherapeutischen Behandlungsoption optimistisch über die reduzierte Behandlungslast und die verbesserte Lebensqualität, die sich aus einer vereinfachten Therapieform und Behandlungsfreiheit ergibt. Gleichzeitig sind die Patient:innen besorgt über die Ungewissheit hinsichtlich der langfristigen Wirksamkeit und möglicher Nebenwirkungen dieser neuen Therapie. Eine niederländische Studie führte Interviews mit Stakeholdern durch und identifizierte drei Hauptthemen, die die Akzeptanz beeinflussen: „Freiheit/Unabhängigkeit“, „Vertrauen/Altruismus“ und „schrittweise Verbesserungen“.

Für die Umsetzung in Österreich wird eine verpflichtende klinische Nachbeobachtung aller behandelten Patient:innen dringend empfohlen.

Öffentliche Investition

Die ersten Schritte in der Grundlagenforschung begannen Anfang der 2000er Jahre in öffentlichen Einrichtungen, insbesondere am Children's Hospital of Philadelphia (CHOP), am St. Jude Children's Research Hospital und anderen akademischen Zentren, die die AAV-basierte Gentherapie entwickelten. Die Entwicklung der Gentherapie für Hämophilie B wurde maßgeblich durch öffentliche Gelder unterstützt, besonders durch das staatlich finanzierte US-amerikanische National Heart, Lung and Blood Institute (NHLBI).

Die erste klinische Studie wurde 2012 von Spark Therapeutics in Zusammenarbeit mit überwiegend öffentlich finanzierten Institutionen durchgeführt. Das industrielle Interesse stieg deutlich an, als Spark Therapeutics im Jahr 2014 Fidanacogene elaparvovec exklusiv an Pfizer lizenzierte. Dabei führte Spark Therapeutics die Phase 1- und 2-Studien durch, während Pfizer die weitere Entwicklung übernahm. Pfizer übernahm anschließend die späteren klinischen Studien (von 2015 bis 2022) und erweiterte das Forschungsnetzwerk auf internationale Zentren.

Schlussfolgerung/Fazit

Zusammenfassend zeigt Fidanacogene elaparvovec vielversprechendes kurativ Potenzial. Allerdings bestehen wesentliche Unsicherheiten bezüglich der Langzeitwirksamkeit und -sicherheit, der vergleichenden Effektivität gegenüber etablierten Therapieoptionen sowie der Generalisierbarkeit der Studienergebnisse auf die breite Patient:innenpopulation. Auch die ökonomische Nachhaltigkeit angesichts substanzieller Therapiekosten bleibt zu klären. Regelmäßige Überwachung und Dokumentation in Registern wird wesentlich sein, vorzugsweise in Kombination mit Risikoverteilungsmodellen, um diese Unsicherheiten zu klären.

Executive Summary

Overview of the New Medicinal Product

Fidanacogene elaparvovec (BEQVEZ®) received conditional marketing authorisation from the European Commission (EC) on 24 July 2024 for the treatment of severe and moderately severe haemophilia B (congenital factor IX [FIX] deficiency) in adult patients without a history of FIX inhibitors and detectable antibodies to variant AAV serotype Rh74. It is the second gene therapy approved for haemophilia B after etranacogene dezaparvovec (HEMGENIX®). It is included in the EMA Priority Medicines (PRIME) scheme.

Disease Description and Standard of Care (SoC)

Haemophilia B is an X-linked bleeding disorder, with a recessive inheritance pattern, caused by a deficiency of the coagulation FIX. The disease is primarily hereditary; however, sporadic cases are also common. The prominent clinical characteristic is bleeding at various locations due to the impaired coagulation mechanism. The prevalence of moderately severe and severe haemophilia B is one to nine per 100,000 worldwide. In Austria, 130 patients were reported in 2024.

The current SoC in Austria is the substitution/replacement of the blood coagulation factor. According to the Austrian Guideline, non-factor therapies provide another therapeutical option; Recently, ALHEMO® and HYMPAVZI® have been authorised for the treatment of (severe) haemophilia A and B, with HYMPAVZI® for patients without inhibitors and ALHEMO® for those with inhibitors. However, these treatment options are not yet available in Austria. Additional treatments include antifibrinolytics and another gene therapy, etranacogene dezaparvovec (HEMGENIX®), for which experience in Austria is currently absent.

Clinical Effectiveness and Safety

Fidanacogene elaparvovec demonstrated a reduction of annualised bleeding rate (ABR) in a single-arm phase 3 study (BENEGENE-2) in an adult male population (n=45) with haemophilia B (FIX level, ≤2%) in comparison to the prior treatment of this population with FIX prophylaxis therapy. This constituted a treatment difference of -3.15 (p=0.008), a 71% reduction resulting in a successful non-inferiority and superiority test. Additionally, there was a clinically meaningful improvement in health-related quality of life (HRQoL). Furthermore, ABR remained stable up to month 36 (n=40) and month 48 (n=15). Adverse events occurred in 84% of patients, including seven patients (16%) with serious adverse events. The most common adverse event of any grade was an increased level of aminotransferase (53%).

The clinical study had several methodological limitations, including open-label design, a small number of patients, incomplete baseline characteristics, differences in the definition of haemophilia B severity, the subjectivity of the ABR endpoint, an unjustified non-inferiority margin and several protocol amendments, resulting in a moderate risk of bias.

The long-term durability of the effect of fidanacogene elaparvovec in the treatment of haemophilia B is currently unknown, and long-term safety data are not available.

The indirect treatment comparison (ITC) of fidanacogene elaparvovec, commissioned by the marketing authorisation holder, demonstrated statistically significant advantages compared to FIX-prophylaxis only in a lower ABR versus nonacog alfa, a higher proportion of patients with zero bleeding events compared to nonacog alfa and eftrenonacog alfa, and a reduced FIX consumption compared to both these products. Of note, there was no statistically significant difference in comparison to HEMGENIX®. However, these results should be taken with caution, since the ITC faced methodological limitations.

Economic Aspects

Fidanacogene elaparvovec currently has no set price in Europe. Hence, the budget impact analysis (BIA) calculation was based on a placeholder price of €3.4 million per administration. The expected net budget impact per year is around € 28 million over three years. However, the results are limited due to the uncertain cost of SoC treatments and the unknown price of fidanacogene elaparvovec and its market uptake (year 1: 20%, year 2: 30%, year 3: 50%), as well as the uncertain coverage of testing for neutralising antibodies.

One cost-utility analysis conducted by the sponsor for the Canadian Health Technology Assessment Agency was identified, resulting in fidanacogene elaparvovec being more effective and less costly than prophylaxis therapy. However, these cost-effectiveness results are highly uncertain when considering the lack of long-term data on the magnitude and duration of the benefit of fidanacogene elaparvovec compared to FIX prophylaxis. Consequently, the results of this analysis are not transferable to other contexts.

Social, Organisational, Ethical and Legal Aspects

Clinical experts proposed a HUB-and-SPOKE model based on coordinating specialised administration centres and local follow-up facilities for gene therapy for haemophilia B. This model would demand significant investment in staff training and infrastructure development to manage the complex monitoring requirements for gene therapies and potential complications, including patient privacy concerns.

While patients express optimism about reduced treatment burden and improved quality of life, they are also concerned about uncertainty regarding long-term efficacy and potential side effects of this new therapy.

For the Austrian context, mandatory clinical follow-up of all treated patients is strongly recommended.

Public Investment Aspect

The development of AAV-based gene therapy for haemophilia B originated in public institutions, primarily at the Children's Hospital of Philadelphia (CHOP), St. Jude Children's Research Hospital, and other academic centres, with substantial funding from the National Heart, Lung and Blood Institute (NHLBI). Spark Therapeutics initiated the first clinical trial in 2012 in collaboration with publicly funded institutions, conducting phase 1 and 2 trials. 2014 industrial involvement increased significantly when Spark exclusively licensed fidanacogene elaparvovec to Pfizer. Following the licensing agreement, Pfizer took over subsequent development, expanding the research network internationally through clinical trials from 2015 to 2022.

Conclusion

In conclusion, fidanacogene elaparvovec represents a potentially curative treatment, however, there are uncertainties regarding the long-term effectiveness and safety, comparative effectiveness versus other therapies, transferability to real-world populations and economic sustainability due to the high cost. Regular monitoring and documentation in registries, preferably in combination with risk-sharing models, will be essential to address these uncertainties.

1 Medical condition and treatment options

1.1 Disease

Definitions and overview

Hämophilie B: X-chromosomal vererbte Blutgerinnungsstörung

Haemophilia B ("Christmas disease") is an X-linked bleeding disorder, with a recessive inheritance pattern, caused by a deficiency of the coagulation factor IX (FIX). Most commonly, haemophilia is inherited; however, sporadic disease without a positive family history (presumed due to a de novo mutation) is also common. Studies showed that sporadic "causes account for as much as 43% of cases of severe haemophilia B. On the contrary, in moderate and mild haemophilia A and B, approximately 30% are sporadic cases [1].

geschätzte 43 % der weltweit Betroffenen leben in Indien, Bangladesch, Indonesien und China

Haemophilia is a disease occurring throughout the world. However, according to the World Federation of Haemophilia (WFH), an estimated 43% of the world's haemophilia population lives in India, Bangladesh, Indonesia, and China, of which only 12% have been diagnosed. Epidemiologic estimates may be biased in other regions by reduced diagnostic capabilities [1].

Schweregrade nach Faktoraktivität: leicht, mittelschwer, schwer

The severity of haemophilia is characterised as mild, moderate, or severe, based on the residual or baseline factor activity level (also referred to as „factor level"). It is expressed as a percent of normal or international units per millilitre (IU/mL). Typically, factor levels correlate with the degree of bleeding symptoms:

- Severe haemophilia is defined as <1% factor activity, corresponding to <0.01 IU/mL.
- Moderate haemophilia is defined as a factor activity level ≥1% and ≤5% of normal, corresponding to ≥0.01 and ≤0.05 IU/mL, respectively.
- Mild haemophilia is defined as a factor activity level >5% and <40% of normal, corresponding to ≥0.05 and <0.40 IU/mL, respectively. Individuals may also be classified as having mild haemophilia despite having a factor level of ≥40% if they share a genetic variant in the relevant factor gene F8 or F9 with a family member who is affected by haemophilia [1].

Schweregrad nicht ausschließlich durch Faktoraktivität definierbar

However, FIX activity alone may not reflect clinical disease severity [2]. In clinical practice, disease severity is defined by patient phenotype and bleeding tendency rather than FIX activity level alone [3].

fast ausschließlich Männer von schwerer Hämophilie betroffen

Severe haemophilia almost exclusively occurs in males, although females can be affected in rare cases. Causes of severe haemophilia in females include the inheritance of disease-causing variants from both parents (an affected male and a female carrier), extreme degrees of X chromosome inactivation (lyonisation), loss of part or all of the X chromosome that contains the normal factor VIII (FVIII) or FIX allele (as in Turner syndrome) [1].

Clinical manifestations

klinische Manifestationen: Blutungen und deren Folgen

The clinical manifestations of haemophilia are related to bleeding and are caused by impaired haemostasis, sequelae from bleeding, or complications arising from coagulation factor infusion [1].

Blutungen können zu verschiedenen Zeitpunkten erstmals auftreten

The range of ages at which bleeding first occurs is broad. Most infants with severe haemophilia present within the first year to one and a half years of life, exhibiting easy bruising, haemarthrosis, bleeding due to oral injury, or bleeding following an invasive procedure [1].

Blutungen können überall im Körper auftreten: ZNS, Gelenke, Muskeln, Verdauungstrakt

Bleeding may occur anywhere in the body; the initial bleeding site depends on differences in disease severity and haemostatic challenges throughout life. Common sites of bleeding in newborns include the central nervous system (CNS), extracranial sites such as cephalohaematoma, and sites of medical interventions, including circumcision, heel sticks, and venipunctures. Approximately 3-5% of infants with severe haemophilia develop subgaleal or intracerebral haemorrhage in the perinatal period, and approximately one-half of the infants have excessive bleeding with circumcision. Once children become mobile, bruising, joint haemorrhages, and bleeding at other musculoskeletal sites occur more frequently. Forehead haematomas ('goose-eggs') have been reported as a common presenting finding. Common bleeding sites in older children and adults include the joints, muscles, CNS, and the oral or gastrointestinal tract [1].

schwere Hämophilie: spontane und schwere Blutungen, frühes Auftreten

Patients with more severe haemophilia are more likely to experience spontaneous and severe bleeding. In addition, they are younger when the first bleeding episode occurs, which can begin as early as birth. After experiencing trauma, immediate and delayed bleeding is common and can be massive or may persist as continuous oozing for days or weeks. [1].

mittelschwere Hämophilie: Blutungen seltener als bei schwerer Form, 4-6 Mal pro Jahr

Patients with moderate haemophilia often bleed due to intercurrent injury and invasive procedures. Bleeding occurs less frequently than in severe haemophilia and typically four to six times per year. However, haemorrhage may occur more frequently, if a target joint (defined as a joint with three or more recurrent bleeding episodes in six months) develops. Some patients with moderate haemophilia may express a more severe phenotype requiring prophylactic treatment [1].

heterozygote Trägerinnen: Blutungen möglich

While patients with moderate haemophilia may exhibit a more severe phenotype requiring prophylactic treatment, heterozygous female carriers present a distinct challenge due to variable factor activity levels and their implications for clinical management. Females with a factor activity level above 50% of normal are not expected to experience excessive bleeding. In these cases, the carrier status is primarily important for the potential reproductive implications regarding the risk to male children. Some female carriers may have factor activity levels below 50% of normal and experience more significant bleeding than unaffected relatives or matched controls. Obtaining an accurate baseline factor activity level may be challenging, as factors such as the stress response, hormonal regulation for birth control or menstruation, or pregnancy can elevate factor VIII levels. Clinical observation and close attention to management are required [1].

Bleedings can occur in different sites:

- **Intracranial haemorrhage (ICH)**

ICH is relatively rare compared with other sites of bleeding; however, it is one of the most dangerous and life-threatening events in patients with haemophilia. It can occur in haemophilia patients of all ages, spontaneously or after trauma. The overall incidence of ICH in people with haemophilia is approximately 3-4% at birth [1]. ICH risks include trauma, severe factor deficiency (activity <1%), presence of an inhibitor, age over 50 years, hypertension, and, in some cases, human immunodeficiency virus (HIV) infection. Prophylaxis is associated with a reduction in the risk of ICH. Risk factors for ICH during birth include lack of awareness of the haemophilia diagnosis, severity of factor deficiency, nulliparity, a prolonged second stage of labour, and the use of forceps or vacuum devices for assisted delivery. ICH related to birth may present at the time of delivery or up to one month later [1].

verschiedene Blutungsstellen
intrakranielle Blutungen: spontan oder posttraumatisch, lebensbedrohlich
…

…
ICH-Risikofaktoren: Trauma, schwerer Faktormangel, Inhibitoren, Alter >50 Jahre, erhöhter Blutdruck

Spontaneous ICH can occur in infants as well as in adults. Risk factors for spontaneous ICH include disease severity and the presence of an inhibitor; in adults, additional risk factors such as hypertension may play a role. Presenting symptoms are headache, vomiting, lethargy and seizures; however, some ICH are silent and can only be detected by imaging [1]. ICH can also occur post-traumatic, immediately after trauma, or as a delayed complication up to three to four weeks after trauma. Thus, immediate factor replacement for all head and neck injuries (except for those that are insignificant) is required. [1].

spontane intrakranielle Blutungen: bei Kindern und Erwachsenen möglich

intrakranielle Blutungen bis zu 4 Wochen nach Trauma möglich

Persistent neurologic sequelae of ICH are common; psychomotor impairment and cerebral palsy were reported. Hence, all children who have experienced an ICH should have neuropsychiatric testing to detect subtle sequelae. In cases of suspected ICH, neuroimaging is appropriate; however, factor infusion should occur immediately if ICH is suspected and should not be delayed while awaiting neuroimaging [1].

bleibende neurologische Folgeerscheinungen häufig

- **Joints and muscle**

Haemarthrosis is the most common site of bleeding in ambulatory patients, representing up to 80% of haemorrhages. Spontaneous haemorrhages into a joint are characteristic of severe disease; multiple bleeding sites are not uncommon. Bleeding episodes occur most commonly in the index joints (elbows, ankles, and knees). [1]. As distension of the synovial space and associated muscle spasm lead to markedly increased intrasynovial pressure, haemarthrosis is painful and can be physically debilitating. In infants, early signs of bleeding include irritability and decreased use of the affected limb; whereas in older children and adults, haemarthrosis is manifested by prodromal stiffness and, sometimes, a characteristic warm sensation followed by acute pain and swelling. If joint damage and inflammation occur, the joint can become more susceptible to further bleeding and may become a target joint; chronic synovitis and permanent disability may develop subsequently. Prevention, an early diagnosis, and immediate treatment of haemarthroses may preserve the joints or delay the progression of haemophilic arthropathy. Bleeding into muscles, including haematoma formation, is common. Most frequently affected are large muscle groups, (in the leg, hip and arm). Muscle bleeding may be extensive, compromise neurovascular structures, and lead to compartment syndrome, especially in the lower leg and forearm. If haemorrhage remains untreated or inadequately treated, a pseudotumor with haematoma surrounded by a fibrous membrane can develop. Pseudotumors can occur with bleeding of any severity, may increase the bleeding risk, and may

Hämarthrose: 80 % aller Blutungen

Schmerzen und Bewegungseinschränkung

Muskelblutungen: häufig

Entstehung von Pseudotumoren möglich

make bleeding more challenging to treat. As a result, recurrent haemorrhage is common. [1].

- **Epistaxis, oral, gastrointestinal bleeding**

  Bleeding can develop from different oropharyngeal sites such as the nose, oral mucosa, gingiva, and frenulum; sometimes following minor trauma or dental procedures. Additionally, coughing or vomiting can produce bleeding into the posterior pharynx or floor of the mouth. Bleeding can be dissected into the neck, leading to airway compromise or obstruction. A variety of lesions in the gastrointestinal tract, such as oesophagitis, gastritis, polyps, diverticuli, and swallowed blood from epistaxis, can present with blood in the stool or lead to haematemesis. Bleeding into the abdominal wall and the retroperitoneal space can also occur [1].

Nasenbluten, Blutungen der Mundschleimhaut und gastrointestinale Blutungen

- **Genitourinary tract**

  Haematuria is a frequent clinical manifestation of severe haemophilia. Usually, it is benign and not associated with progressive loss of renal function. The haemorrhage can arise from the kidneys or bladder and may persist for days or weeks. When clots form within the ureter, an obstruction with colic may occur [1].

häufiges Symptom: Hämaturie

Late complications

Complications due to the disease

In general, late complications of bleeding in haemophilia patients include neurologic sequelae of intracranial haemorrhage and sequelae from repetitive haemarthrosis, including joint destruction, muscular atrophy and contraction, nerve damage from compartment syndrome, and bone mineral density loss with an increased risk of fracture. In rare cases, the development of a pseudotumor may occur [1].

Spätfolgen: neurologische Komplikationen, Gelenkzerstörung, Muskelatrophie, Nervenschädigung durch Kompartment-Syndrom

- **Haemophilic arthropathy (haemophilic arthritis)**

  Haemophilic arthropathy, a persistent joint disease, occurs in up to 50% of patients with severe haemophilia. Sequelae can include muscular atrophy and contraction, nerve damage and loss of function from compartment syndrome, loss of bone mineral density with increased risk of fracture, chronic pain and decreased quality of life (QoL), as well as a need for joint replacement [1].

hämophile Arthropathie: in bis zu 50 % der Pat.

- **Cardiovascular disease (CVD)**

  Patients with haemophilia have a higher risk of hypertension than the general population (overall prevalence, 49% vs. 32%) and develop hypertension at a younger age [4].

erhöhtes Risiko für Hypertonie

Complications due to FIX prophylaxis

FIX products are used to treat FIX deficiency in patients with haemophilia B [5]. For further information on factor concentrates, please see Chapter 1.6. Complications from factor infusion include infections transmitted from plasma-derived factor products (typically viral). In addition, the development of antibodies to factors called “inhibitors” can occur; inhibitors typically develop following factor infusions in patients with severe disease [1].

Komplikationen der Faktorsubstitution: Infektionen, Inhibitoren

- **Infection from plasma-derived products**

Infektion durch Faktorpräparate: Risiko gering

Available clotting factor products derived from human plasma undergo several procedures to reduce the risk of transmission of infectious organisms. These procedures and recombinant factor products produced in cell culture have generated products with an extremely low risk of viral transmission [1].

- **Development of inhibitors**

Entwicklung von Inhibitoren stellt schwere Komplikation dar

The development of inhibitors (alloantibodies) in patients with severe haemophilia is an important complication since the inhibitors block the activity of the relevant factor. Inhibitors can also develop in patients with moderate and mild haemophilia. The inhibitory antibodies develop in response to exogenous factors and are observed in approximately 5-15% of patients with severe haemophilia B. Inhibitors are much less common in patients with mild or moderate disease. This is presumed because the infused factor is less likely to be recognised as a foreign protein in these individuals. Due to decreasing responsiveness to factor infusions, inhibitors complicate bleeding episodes. Inhibitors may be associated with complications such as maturational delays (delayed bone age and Tanner stage transition, lower maximum growth velocity, and lower serum testosterone levels) [1].

1.2 Diagnosis

Initialdiagnostik beginnt mit (Familien-)Anamnese

The initial diagnostic evaluation of people with suspected haemophilia and a history of bleeding tendencies begins with an assessment of the patient's family and personal history, with particular emphasis on coagulation disorders in the family. Diagnostics are carried out if a familial predisposition is suspected, even if the bleeding tendency is not observed, to rule out or confirm haemophilia [6]. Table 1-1 shows the most important laboratory tests for initial and follow-up diagnostics.

Table 1-1: Laboratory tests for initial and follow-up diagnostics [6]

Initial diagnostics	Follow-up diagnostics
Global coagulation tests: prothrombin time (PT), activated partial thromboplastin time (factor-sensitive, aPTT), thrombin time (TT), fibrinogen (Clauss)	Global coagulation test
Coagulation factor single analysis (esp. FVIII/FIX, coagulometric, possibly chromogenic in addition) Von Willebrand disease diagnostic (esp. to exclude type 2N)	FVIII/IX trough level (coagulometric and/or chromogenic); possibly recovery examination (factor analysis 30-60 minutes after factor substitution); FVII/IX-time course determination (pharmacokinetics) to optimise prophylactic factor therapy
Exclusion of inhibitors against FVIII and FIX, resp.; lupus anticoagulans; anticoagulant effect	Inhibitors against FVIII and FIX, resp. (Bethesda-method)
CBC; liver and kidney function parameters; c-reactive protein (CRP)	CBC; liver and kidney function parameters
Infection status (serology hepatitis A, B, C, HIV)	Infection status (serology hepatitis A, B, C, HIV)
Blood group determination	
Mutation diagnostics (confirmation of diagnosis, estimation of risk for inhibitor, conductor status)	

Abbreviations: aPTT … activated partial thromboplastin time, CBC … complete blood count, CRP … c-reactive protein, HIV … human immunodeficiency virus, PT … prothrombin time, TT … thrombin time

nach Diagnosestellung unverzügliche Anbindung an Hämophilie-Zentrum empfohlen

Once the diagnosis has been made, the affected patient should be connected to a haemophilia centre without delay. Ideally, this should be a "Haemophilia Comprehensive Care Centre" (HCCC), where multidisciplinary care is possible, or at least a Haemophilia Treatment Centre (HTC) [6]. The Austrian treatment centres are listed in Table 1-2 [7].

Table 1-2: Treatment centres in Austria [7]

Treatment centre
Universitätsklinikum AKH Wien*. Währinger Gürtel 18-20, 1090 Wien
Universitätsklinikum St. Pölten. Dunant-Platz 1, 3100 Sankt Pölten
Linz Kepler Universitätsklinikum. Krankenhausstr. 26-30, 4021 Linz
Landesklinikum Amstetten. Krankenhausstraße 21, 3300 Amstetten
LKH Salzburg. Müllner Hauptstraße 48, 5020 Salzburg
Univ.-Klinik Innsbruck, Tirol Kliniken. Anichstraße 35, 6020 Innsbruck
LKH Bregenz. Carl-Pedenz-Straße 2, 6900 Bregenz
LKH Feldkirch. Carinagasse 47, 6807 Feldkirch
LKH-Univ. Klinikum Graz. Auenbruggerplatz 38, 8036 Graz
Klinikum Klagenfurt am Wörthersee. Feschnigstraße 11, 9020 Klagenfurt

* *Certification as Comprehensive Care Hemophilia Center (CCHC) since 2014.*

Verlaufsdiagnostik

The follow-up diagnosis consists of the following examinations:

- Physical examination, including the clinical joint status: Standardised physical scores are recommended to assess the musculoskeletal system and follow-up.
- Laboratory diagnostics are displayed in Table 1-1.
- If necessary, imaging examinations of joints (ultrasound, native X-ray, magnetic resonance imaging).
- The follow-up examinations at the haemophilia centre should be used to adjust the treatment plan (dose, frequency) [6].

Kontrolluntersuchungen in der Anfangsphase der Behandlung

In case of severe and moderate haemophilia, check-ups in children in the initial phase of treatment (up to the 50th day of exposure) should be conducted initially every five to ten factor exposure days and then at least every six months [6].

Spiegelmessungen: enger Kontakt zwischen Therapeut:innen und Labor erforderlich

Level measurements for different extended half-life (EHL)-FIX concentrates require specific tests (chromogenic or coagulometric), which should be locally available and evaluated. Therefore, close contact should exist between the requesting therapists and the laboratory performing the test to select the test suitable for the product used. Manufacturers should provide the laboratories with specific control materials for the new therapeutic agents to check the test strategies and recovery [6].

Differentialdiagnosen

The differential diagnosis should include haemophilia A, von Willebrand disease, and other coagulation defects leading to prolonged blood coagulation times [8].

1.3 Prognosis

ohne Behandlung: schwerer/fataler Verlauf

If haemophilia B is left untreated, the disease course is severe, with progression of joint damage, functional limitations, reduced quality of life and life expectancy. Inadequate prophylaxis and treatment of recurrent haemarthroses and haematomas lead to physical impairment with severe disability, which is associated with stiffness, joint deformation and physical disability. However, current treatment approaches (early prophylaxis) prevent these complications, and the prognosis of haemophilia is favourable. The leading causes of death in patients with haemophilia include haemorrhage, HIV and hepatitis C virus (HCV) infections, and hepatic disease [8].

Lebenserwartung mit der gesunden Bevölkerung vergleichbar

Due to the improved medical care, the life expectancy of patients with haemophilia B in high-resource countries is nowadays comparable to that of the general male population [9].

Inhibitoren: in 5-10 % bei schwerer Hämophilie B

Inhibitors are among the most serious complications in the treatment of haemophilia. They are immunoglobulin G (IgG) antibodies directed against therapeutically administered FVIII or FIX. Inhibitors develop in 5-10% of people with severe haemophilia B, with about 80% of cases occurring within the first 20 exposures to factor concentrate and the remaining 20% within the first 75 exposures [6].

1.4 Epidemiology

Hämophilie B: seltene Erkrankung, Inzidenz 1:30.000

With an incidence rate of 1:30,000, haemophilia B is an orphan disease [6]. Worldwide, the prevalence rate for moderately severe and severe haemophilia B is one to nine per 100,000. Approximately 30% of patients with haemophilia B are affected by the moderately severe form, whereas 40% are affected by severe disease [10, 11].

ÖHR: 130 Pat. in AT (2024), alle Altersgruppen betroffen

According to the Austrian Haemophilia Registry (ÖHR), 130 patients were reported in Austria in 2024. Of these, 32 patients (24.6%) were affected by severe disease, and 29 patients (22.3%) had moderate disease. Haemophilia B affected patients across all age groups [12]; for detailed age distribution, see Figure 1-1.

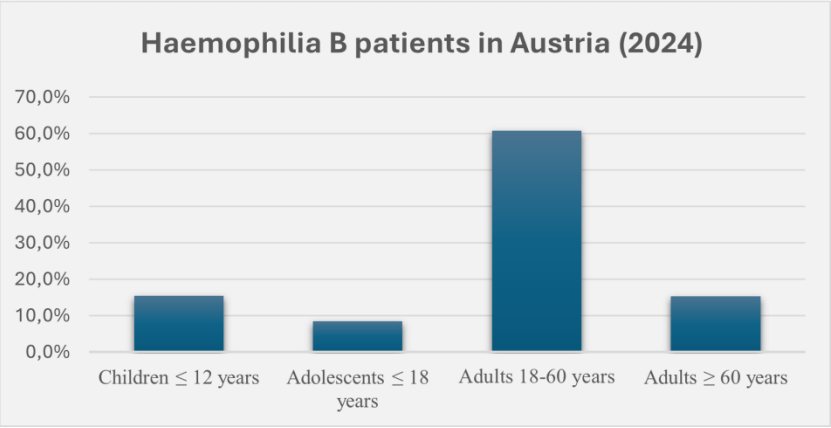


Figure 1-1: Age distribution of patients with haemophilia B in Austria

1.5 National and international treatment guidelines

Leitlinie (2024) "Hämophilie-Behandlung in Österreich"

In Austria, the guideline "Hämophilie-Behandlung in Österreich (2024)" [6], published in the "Wiener Klinische Wochenschrift" is available to provide practical guidance for the diagnosis and treatment of haemophilia in Austria.

internationale Leitlinien

Internationally, among others, the following guidelines are available for the treatment of haemophilia:

- WFH Guidelines for the management of haemophilia [13].
- International Society on Thrombosis and Haemostasis clinical practice guideline for treating congenital haemophilia A and B based on the Grading of Recommendations Assessment [14].
- International consensus recommendations on the management of people with haemophilia B [15].
- Nordic Hemophilia Council Hemophilia Guidelines (updated version 2024) [16].

1.6 Treatment guidelines

Available treatments are divided into prophylaxis and on-demand treatments, potentially curative treatments, further treatment options for acute bleeding or planned interventions, and concomitant therapy options.

Prophylaxis and on-demand treatments

Prophylaxe:

Prophylaxis in haemophilia is defined as the regular substitution of the missing or reduced blood coagulation factor (factor concentrates) or non-factor therapies (NFT, currently not available in Austria) to prevent bleeding. Prophylaxis is the gold standard and the first choice for all patients with severe haemophilia A and B and for patients with moderate haemophilia but severe clinical phenotype. In Austria, prophylaxis is recommended at any age (primary, secondary or tertiary[1]) and at any time. To optimise prophylaxis, it should be adjusted individually, considering age and weight, bleeding frequency, lifestyle, physical activity, existing synovitis or arthropathy, individual pharmacokinetics and half-life of the factor product (standard half-life [SHL] or EHL) [6].

regelmäßige Substitution des fehlenden oder verminderten Blutgerinnungsfaktors oder NFT um Blutungen zu verhindern

idealerweise sollten Talspiegel von ≥3-5 % angestrebt werden

Traditionally, for prophylaxis, factor trough levels ≥1%, which significantly reduce the occurrence of spontaneous haemorrhage and less bleeding in joints and muscles than with trough levels below 1%, were aimed for. Ideally, higher levels (≥3-5%) should be achieved, as this results in an even lower risk of haemorrhage and long-term damage to the joints can be better avoided. In clinical practice, however, these higher target levels will not be achievable in all situations [6].

[1] "Primary" means before the 2nd clinical joint haemorrhage, before the age of three years and before documented joint damage. "Secondary" means after two or more joint haemorrhages, but before joint damage occurs (usually after the age of three years). "Tertiary" means after the occurrence of joint damage (typically only in adulthood).

The effectiveness of the prophylaxis should be checked regularly based on the frequency of bleeding. If bleeding continues despite prophylaxis, the prophylaxis regimen should be escalated in dose and/or frequency [6].

regelmäßige Überprüfung der Wirksamkeit der Prophylaxe – ggfs. Anpassungen

On-demand treatment is defined as the substitution of factor concentrates in the event of acute bleeding. In Austria, only people with mild haemophilia or a mild phenotype receive on-demand therapy. For people with severe haemophilia, on-demand therapy should only be administered for the treatment of breakthrough haemorrhages under prophylaxis. On-demand therapy should be administered as quickly as possible, starting as soon as the first signs or suspicion of bleeding occur and should then be continued every eight to twelve or 24 hours. A relevant joint haemorrhage with proven effusion should be treated consistently over several days. On-demand therapy is possible with all factor concentrates; the administration intervals can be adjusted based on the product's half-life [6].

Bedarfsbehandlung ("on-demand"):

Substitution von Faktorkonzentraten

im Fall akuter Blutungen

In the medium term, the aim for haemophilia-patients and their carers must be to be able to carry out prophylaxis and on-demand therapy independently. Home therapy gives people with haemophilia immediate access to factor concentrates, coagulation therapies, and haemostatic agents (e.g., antifibrinolytics), enabling optimal early treatment. This results in less pain, dysfunction, and long-term disability and significantly reduced hospitalisation rates for haemophilic bleeding complications. The practical organisation and implementation of home therapy should be adapted to the individual circumstances of the patients and their social environment (parents, family, carers). This can initially be achieved by using mobile nurses and subsequently by informing and training the parents and later the affected children, adolescents and adults. General practitioners, paediatricians and peripheral paediatric departments can also be involved in administration and training [6, 17].

Heimtherapie: selbständige Durchführung von Prophylaxe und Bedarfsbehandlung

Factor concentrates

Factor concentrates are intravenously administered. In general, it can be distinguished between factor concentrates with SHL and EHL:

- **Factor concentrates with SHL** have a plasma half-life of approximately twelve to 20 hours for FIX, with large inter-individual variability. FIX concentrates are either plasma-derived or produced recombinantly [6].

  Faktorkonzentrate mit Standard-Halbwertszeit

- **Factor concentrates with EHL** are based on recombinantly modified FVIII or FIX molecules and achieve their half-life extension through covalent binding to polyethylene glycol (PEGylation), fusion with the Fc fragment of immunoglobulins or with albumin (FIX only). For FIX concentrates, an extension of the half-life by approximately three to five times can be achieved [6].

  Faktorkonzentrate mit verlängerter Halbwertszeit

- The advantages of factor concentrates with EHL are higher trough levels, reduced bleeding and the extension of injection interval for prophylaxis (FIX every seven to 14 days). The disadvantages are the potential accumulation of PEG, and the lack of final data for some EHL-factor concentrates regarding the incidence of inhibitors in treatment-naïve patients [6].

  höhere Talspiegel aber potenziell Akkumulation von PEG

- A unique combined EHL-FVIII-Von-Willebrand-Faktor product with highly EHL (efanesoctocog alfa[2], ALTUVOCT®) is on the verge of ap-

[2] Of note, Altuvoct® received marketing authorisation by the European Medicines Agency (EMA) on 17 June 2024.

proval in Europe. Outside registration studies, insufficient clinical data is available [6].

Faktorkonzentrate als Prophylaxe oder Bedarfsbehandlung bei akuten Blutungen

Factor concentrates can be used as a prophylactic treatment and on-demand, e.g., for acute bleeding. In severe bleeding, normal factor level should be achieved, and appropriate dosages of factor concentrates should be used. In haemophilia B, the lower recovery rate of FIX should be considered. In contrast to NFT (currently not available in Austria), due to their pharmacokinetic properties, only factor concentrates are suitable for treating acute haemorrhages and allow individualisation for single patients in case of prophylaxis [6]. An overview of recommendations for achieving FIX levels in different types of bleedings is given in Chapter 1 in the Appendix.

Non-factor therapies (NFT)

NFT: Antikörper gegen TFPI, Hemmstoff der Produktion von Antithrombin in der Leber oder des aktivierten Protein C

NFTs, or non-replacement-therapies (NRTs), represent a prophylactic treatment option. In general, NFTs include antibodies against tissue factor pathway inhibitor (TFPI) (concizumab, marstacimab), an inhibitor of antithrombin production in the liver (fitusiran) and an inhibitor of activated protein C (serpinPC). These agents are all administered subcutaneously, are intended for prophylaxis in haemophilia A and B without and with inhibitors and are only suitable for prophylaxis [6]. Recently, ALHEMO® and HYMPAVZI® have been authorised for the treatment of (severe) haemophilia A and B, with HYMPAVZI® for patients without inhibitors and ALHEMO® for those with inhibitors. However, these treatment options are not yet available in Austria. Fitusiran has been granted orphan designation on 29 July 2014; SerpinPC has not yet been approved by the European Medicines Agency (EMA) [18-20]. Since these therapies received approval just recently, they were not yet available for clinical practice in Austria [12].

A NFT already longer authorised in Austria and subscribed in the outpatient sector is emicizumab (B02BX06, HEMLIBRA®), a bispecific monoclonal FVIII-mimetic antibody indicated in patients with haemophilia A, and therefore not relevant for this assessment [2].

Further treatment options for acute bleeding or planned interventions

In addition, the prophylactic and on-demand treatment, other treatment options are indicated for acute bleeding or planned interventions, such as surgeries:

Antifibrinolytics (tranexamic acid)

Antifibrinolytika: adjuvant bei Blutungen und Eingriffen an den Schleimhäuten

- An antifibrinolytic (tranexamic acid) can be administered adjuvantly to treat bleeding and interventions on the mucous membranes in patients with very mild forms of haemophilia. It does not prevent bleeding in severe and moderate haemophilia. Antifibrinolytics inhibit plasminogen activation to plasmin and are particularly effective in cases of mucosal bleeding, such as epistaxis or menorrhagia. However, tranexamic acid alone has no preventive effect on joint haemorrhages. Tranexamic acid can be administered at a dose of 10-15 milligrams/kilogram (mg/kg) intravenously (IV) (3-4 × daily), orally (20-25 mg/kg, 3-4 × daily) or locally. Intravenous administration should be slow to prevent a drop in blood pressure and vertigo. A dose reduction is necessary if renal function is impaired. Tranexamic acid is beneficial as supportive therapy during dental procedures and can stop bleeding around teething [6].

- In case of bleeding in the oral mucosa, local application of the intravenous preparation in a quantity equivalent to the oral dose is possible. The solution can be used for mouth rinsing or gargling and can then be swallowed to achieve an additional systemic effect. The duration of therapy is between ten and 14 days. Tranexamic acid can be combined with factor concentrate or desmopressin and activated prothrombin complex concentrate or recombinant factor VIIa. Antifibrinolytics should be used cautiously in haematuria due to the risk of forming obstructive blood clots in the bladder [6].

auch lokale Anwendung der intravenösen Zubereitung in einer der oralen Dosis äquivalenten Menge möglich

Local therapeutics (haemostatic agents) and non-specific measures

- Compression and a pressure bandage should be applied as the first local measure for external bleeding. Local haemostatic agents can be a helpful addition to treating heavy bleeds. Wound dressings impregnated with kaolin, thrombin, or tranexamic acid lead to faster haemostasis than standard wound dressings. If necessary, surgical haemostasis with or without fibrin glue is indicated. Transfusion of erythrocyte concentrates may also be necessary in the event of severe blood loss; the indication for transfusion should be made individually for each patient based on the overall clinical picture and the current transfusion recommendations [6].

Lokaltherapeutika, z. B. Druckverbände oder auch chirurgische Blutstillung

bei schwerem Blutverlust auch Bluttransfusionen

Potentially curative treatments

Gene therapy

- Gene therapies as new therapeutic options for treating severe haemophilia A and B aim to use a single infusion to restore the production of the missing or insufficiently produced factor. The missing or defective gene segment in haemophilia is transferred as a transgene with a vector (i.e., capsid of the adeno-associated virus, AAV) into liver cells, where the endogenous production of FVIII or FIX begins [6].

Gentherapie: einmalige Infusion

- In Europe, gene therapy is approved for both haemophilia A and B. Based on the HOPE-B study, AAV5-based gene therapy was approved on 20 February 2023 for the treatment of moderately severe and severe haemophilia B in adults without a history of FIX inhibitors (etranacogene dezaparvovec, HEMGENIX®) [6].

Etranacogene dezaparvovec (HEMGENIX ®) bereits in Europa zugelassen

- There is currently no experience using gene therapy in routine clinical practice in Austria. National and international recommendations for implementing gene therapy have been published, describing the process from evaluating patient suitability to implementing the gene therapy infusion and close follow-up care. The establishment and implementation of gene therapy in Austria should be based on these recommendations and occur in a haemophilia centre with the appropriate infrastructure [6].

derzeit in AT noch keine Erfahrungen in der Anwendung der Gentherapie in der klinischen Routine

ITC of HEMGENIX® and standard therapy

Two ITC analyses [21, 22] are available in the literature for HEMGENIX®.

indirekter Vergleich von HEMGENIX® mit Standardtherapie:

2 Analysen verfügbar;

- The Canadian Agency for Drugs and Technologies in Health (CADTH) ITC [21] was based on an unanchored matching-adjusted indirect comparison (MAIC) (provided by the manufacturer) between etranacogene dezaparvovec and three comparators: eftrenonacog alfa (ALPROLIX®), albutrepenonacog alfa (IDELVION® for recombinant factor IX albu-

min fusion protein (rIX-FP) or recombinant factor IX-Fc fusion protein (rFIXFc), nonacog beta pegol (REFIXIA®). HEMGENIX® was favoured in terms of ABR compared to rIX-FP, rFIXFc and REFIXIA®. However, the authors reported that no conclusions could be drawn on relative efficacy due to several limitations of the ITC (see Chapter 5 in the Appendix). In addition, there was uncertainty regarding the long-term efficacy due to the relatively short duration of follow-up (i.e., 36 months) of the study with HEMGENIX®. The clinical experts consulted by CADTH noted that a longer follow-up of 20 to 25 years may be warranted.

keine Schlussfolgerung über die relative Wirksamkeit möglich

- The Klamroth ITC [22] was also based on an unanchored MAIC between HEMGENIX® and two comparators, IDELVION® and REFIXIA®. Results demonstrated that HEMGENIX® had statistically significantly lower ABR versus all comparators. The authors (with conflicts of interest with CSL-Behring) concluded that HEMGENIX® improves protection against bleeding and eliminates FIX consumption for patients with severe or moderately severe haemophilia B. However, the ITC was limited (see Chapter 5 in the Appendix), including potential differences in ABR definition, short follow-up, and difficulty matching the trials.

HEMGENIX® zeigte Verbesserungen gegenüber 2 Vergleichsprodukten

Concomitant therapy options

In addition to the abovementioned treatments, concomitant therapy options are available, including physical medicine, orthopaedics, and pain management.

begleitende Therapieoptionen

Physical medicine

In haemophilia patients who receive appropriate prophylaxis, regular physical activity is generally recommended to maintain or build up bone density, improve the basic motor skills of strength, coordination, endurance, function and flexibility, and maintain a healthy body weight. The appropriate activity should be chosen individually; contact sports should be avoided [6].

physikalische Medizin bei entsprechender Prophylaxe

Orthopaedics

Orthopaedic interventions include conservative treatment (puncture of joint haemorrhages, physical therapy, radiosynoviorthesis) as well as surgical treatment (arthroscopic synevectomy, arthrodesis, joint replacement) [6].

orthopädische Behandlungen (konservativ oder operativ)

Pain management

Acute and chronic pain is common in haemophilia. The most important pain prevention is consistent factor prophylaxis. Nevertheless, some patients require additional adequate pain therapy depending on the cause of the pain, intensity and extent of the arthropathy. For structured and individualised pain therapy, age-appropriate pain measurement is required [6].

Schmerztherapie

Current standard of care (SoC) in Austria

According to the Austrian Guideline "Hämophilie-Behandlung in Österreich", prophylaxis (defined as regular substitution of the missing or reduced blood coagulation factor) is the gold standard and the first choice for all patients with severe haemophilia A and B and patients with moderate haemophilia but severe clinical phenotype [6].

Goldstandard (AT) für mittelschwere/schwere Hämophilie B: Prophylaxe mit Faktorkonzentraten

Of patients with severe disease, 12.5% received primary prophylaxis, 53.1% received secondary prophylaxis, 15.6% received tertiary prophylaxis, and 18.8% of patients were on on-demand therapy in Austria in 2024 [12].

>50 % der Pat. mit schwerer Hämophilie B in AT erhielten sekundäre Prophylaxe

2 Medicinal product under review

2.1 Drug description

HTA-Bericht zu Fidanacogene elaparvovec (BEQVEZ®): Gentherapie, ATMP

The medicinal product under evaluation in this health technology assessment (HTA) report is fidanacogene elaparvovec (BEQVEZ®). Fidanacogene elaparvovec, a product named "BEQVEZ®" (previously "DURVEQTIX®"), is a gene therapy classified as an advanced therapy medicinal product (ATMP) by the European Medicines Agency (EMA). The Anatomical Therapeutic Chemical (ATC) of fidanacogene elaparvovec is B02BD17. The marketing authorisation holder of BEQVEZ® is Pfizer Europe MA EEIG [23]. Table 2-1 summarises the most important information of this product.

Table 2-1: Characteristics of the medicinal product [23, 24]

INN	Fidanacogene elaparvovec
Product name	BEQVEZ® (previously DURVEQTIX®)
Active substance(s)	Fidanacogene elaparvovec
ATC code	B02BD17
Pharmacologic class	Gene therapy: this medicine is classified as an ATMP by the EMA.
Manufacturer/marketing authorisation holder	The marketing authorisation holder of BEQVEZ® is Pfizer Europe MA EEIG.

Abbreviations: ATC … Anatomical Therapeutic Chemical, ATMP … advanced therapy medicinal product, DNA … deoxyribonucleic acid, EMA … European Medicines Agency, INN … International non-proprietary name

EMA-Zulassung: schwere und mittelschwere Hämophilie B ohne FIX-Inhibitoren & AAVRh74-Antikörper

Fidanacogene elaparvovec (BEQVEZ®) is indicated for the treatment of severe and moderately severe haemophilia B (congenital factor IX [FIX] deficiency) in adult patients without a history of FIX inhibitors and detectable antibodies to variant AAV serotype Rh74 [24]. Fidanacogene elaparvovec is a non-replicating recombinant adeno-associated virus (AAV) vector that utilises AAVRh74var capsid to deliver a stable human FIX transgene. AAVRh74var capsid can transduce hepatocytes, the natural site of FIX synthesis. The FIX gene present in fidanacogene elaparvovec is designed to reside predominately as episomal deoxyribonucleic acid (DNA) within transduced cells, and expression of the transgene is driven by a liver-specific promoter, which results in tissue-specific, continuous and sustained FIX protein expression. Fidanacogene elaparvovec therapy results in measurable vector-derived coagulation FIX activity [24].

2.2 Regulatory status

EC-Zulassung: Juli 2024 Änderung Handelsname zu BEQVEZ®

On 30 May 2024, the Committee for Human Medicinal Products (CHMP) recommended conditional marketing authorisation for fidanacogene elaparvovec (formerly "DURVEQTIX®"). On 24 July 2024, the European Commission (EC) issued a marketing authorisation to DURVEQTIX®. On 24 September 2024, the EC issued an opinion for a change in the name of the medicinal product from "DURVEQTIX®" to "BEQVEZ®" [23, 25, 26].

zusätzliche Überwachung & PRIME

Besides, the medicine is under additional monitoring and was granted the EMA Priority Medicines (PRIME) scheme on 23 February 2017 for treating severe haemophilia B [23, 26].

Fidanacogene elaparvovec (BEQVEZ®) vs. Etranacogene dezaparvovec (HEMGENIX®)

Regarding information related to orphan market exclusivity, 'similarity' was highlighted. The applicant (Pfizer Europe MA EEIG) submitted a critical report addressing the potential similarity with authorised orphan medicinal products. The Committee for Advanced Therapies (CAT) by consensus is of the opinion that DURVEQTIX® is not similar to ALPROLIX®, IDELVION® and HEMGENIX® within the meaning of Article 3 of Commission Regulation No. 847/2000. During the marketing authorisation application evaluation, a third-party intervention was received, claiming that fidanacogene elaparvovec should be considered similar to etranacogene dezaparvovec (HEMGENIX®). CAT/CHMP considered this intervention and concluded that the arguments put forward do not alter the conclusion that fidanacogene elaparvovec is not similar to etranacogene dezaparvovec. The CHMP endorsed the CAT conclusion on similarity as described in the assessment report. [25, 27]. Table 2-2 summarises the regulatory information of fidanacogene elaparvovec.

Table 2-2: Regulatory information on fidanacogene elaparvovec (BEQVEZ®) in the EU [23, 28]

Orphan medicinal product	No
Conditional marketing authorisation	Yes
Specific obligations of the conditional marketing authorisation	Further evidence is awaited
Additional monitoring	Yes
Accelerated approval	No
Exceptional circumstances	No
PRIME	Yes
First approved indication	Yes
Early Access Programme/Named Patient Programmed	Not applicable

Abbreviations: EU … European Union, PRIME … Priority Medicines
[a] According to the submission dossier.

2.3 Expected role of the new medicinal product within treatment pathway

Fidanacogene elaparvovec: potenzielle Heilung bei schwerer und mittelschwerer Hämophilie B

Within the established treatment pathway, the expected role of fidanacogene elaparvovec is to provide a potentially curative treatment option for adult patients with severe and moderately severe haemophilia B (congenital FIX deficiency) without a history of FIX inhibitors and detectable antibodies to variant AAV serotype Rh74.

According to manufacturer information, early access- or named patient programmes are not applicable [28].

2.4 Posology

autorisierte Zentren und erfahrene Ärzt:innen erforderlich

Fidanacogene elaparvovec treatment should be administered in a qualified treatment centre by a physician experienced in treating haemophilia. It is recommended that fidanacogene elaparvovec is administered in a setting where personnel and equipment are available to treat possible infusion-related reactions. A prophylactic FIX replacement dose should be given before the fidanacogene elaparvovec infusion [24].

intravenöse Infusion über ca. 60 Minuten

Fidanacogene elaparvovec is intended for intravenous use after dilution in sodium chloride nine milligrams/millilitre (mg/mL, 0.9%) solution for injection with 0.25% human serum albumin. It is administered as a single-dose intravenous infusion over approximately 60 minutes in an appropriate infusion volume. If an infusion reaction occurs during administration, the infusion rate should be slowed or stopped to ensure patient tolerability. If the infusion stops, it may be restarted slower when the reaction is resolved [24].

einmalige Anwendung: 5×10^{11} vg/kg

The recommended dose of fidanacogene elaparvovec is a single dose of 5×10^{11} vector genomes per kilogram (vg/kg) of body weight [24].

Identitätsprüfung und Bestätigung der Gesamtzahl der zu verabreichenden Durchstechflaschen

Before administering fidanacogene elaparvovec, it must be confirmed that the patient's identity matches the unique patient information (i.e., lot number) on the vials, inner cartons, outer cartons, and accompanying documentation. The total number of vials to be administered must also be confirmed with the patient-specific information on the Lot Information Sheet (LIS) [24].

Kontraindikationen: Überempfindlichkeit gegen Wirkstoff und Hilfsstoffe, akute/unkontrollierte chronische Infektionen, fortgeschrittene Leberfibrose/-zirrhose

Fidanacogene elaparvovec is contraindicated in case of hypersensitivity to the active substance or any of the excipients, including sodium dihydrogen phosphate monohydrate (E339), disodium hydrogen phosphate heptahydrate (E339), sodium chloride, poloxamer 188 and water for injection. There is no clinical experience administering fidanacogene elaparvovec in patients with acute or uncontrolled chronic infections. However, they could affect the response to fidanacogene elaparvovec, reduce its efficacy, and/or cause adverse reactions. In patients with such infections, fidanacogene elaparvovec treatment is contraindicated. Further contraindications include advanced hepatic fibrosis and advanced hepatic cirrhosis. Live vaccines should not be administered to patients on immunomodulatory therapy [24].

keine Daten zur Wirkung auf Fertilität, Barriere-Kontrazeption für sechs Monate erforderlich

No information is available on the effects of fidanacogene elaparvovec on female or male fertility. For six 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. Males treated with fidanacogene elaparvovec must not donate semen to minimise the potential risk of paternal germline transmission. Fidanacogene elaparvovec is not recommended in women of childbearing potential or during pregnancy and breast-feeding. Patients treated with this product should not donate blood, organs, tissue and cells for transplantation [24].

immunsupprimierte Personen: behandelnde/r Arzt/Ärztin entscheidet über Anwendung

The safety and efficacy of fidanacogene elaparvovec in immunocompromised patients have not been established. Use in these patients is based on healthcare professionals' judgement, considering the patient's general health and potential for corticosteroid use following fidanacogene elaparvovec treatment [24].

It is unknown whether or under what conditions fidanacogene elaparvovec therapy may be repeated and to what extent developed endogenous cross-reacting antibodies could interact with the capsids of AAV vectors used by other gene therapies, potentially impacting their treatment efficacy [24].

nicht bekannt, ob Therapie wiederholt werden kann

Patient selection

Given the contra-indications, eligibility for the treatment should be confirmed within eight weeks before fidanacogene elaparvovec infusion by the following test results (described in detail in chapter 2.6.1) [24]:

- Negativity for AAVRh74var pre-existing antibodies.
- Negativity for FIX inhibitors.
- Absence of clinically significant liver disease.
- Absence of acute infections, such as acute respiratory infections or acute hepatitis.
- Absence of uncontrolled chronic infections, such as active chronic hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) infection.

Auswahl der Pat.: keine Antikörper gegen AAVRh73var, keine FIX-Inhibitoren, keine klinisch signifikante Lebererkrankung, keine akute oder unkontrollierte chronische Infektion

Special populations

The safety and efficacy of fidanacogene elaparvovec in patients with severe hepatic impairment have not been studied. Fidanacogene elaparvovec is contraindicated in patients with advanced hepatic fibrosis or hepatic cirrhosis. The product is not recommended in patients with other significant hepatobiliary disorders [24].

keine Daten für Pat. zu Leberfunktionsstörung

No dose adjustment is needed in patients who are hepatitis C virus (HCV) positive, hepatitis B virus (HBV) positive and/or HIV positive. Limited data are available in patients with controlled HIV infections and a past medical history of active HCV and HBV [24].

HCV-, HBV-, HIV-positive Pat.: keine Dosisanpassung nötig

No dose adjustment is needed in patients with renal impairment. The safety and efficacy of fidanacogene elaparvovec have not been studied in patients with clinically relevant renal impairment (creatinine >2.0 mg/dL). The safety and efficacy of fidanacogene elaparvovec in patients ≥63 years old have not been established. No dose adjustment is needed in elderly patients [24].

Pat. mit Nierenfunktionsstörung & ältere Pat.: keine Dosisanpassung nötig

The safety and efficacy of fidanacogene elaparvovec in children and adolescents under 18 years of age have not yet been established. No data are available [24].

Kinder und Jugendliche: keine Daten vorhanden

Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed [24].

keine Studien zu Wechselwirkungen vorhanden

Experience with the use of fidanacogene elaparvovec in patients receiving hepatotoxic medicinal products or using hepatotoxic substances is limited. Care should be exercised when administering potential hepatotoxic medicinal substances, herbal supplements, and alcohol to patients treated with fidanacogene elaparvovec, as the efficacy of the product may be reduced, and the risk of severe hepatic reactions may increase following fidanacogene elaparvovec administration [24].

Medicinal products that may reduce or increase the plasma concentration of corticosteroids, including medicinal products that induce or inhibit cytochrome P450 3A4, can decrease the efficacy of the corticosteroid regimen or increase their side effects [24].

Einfluss auf Kortikosteroid-Behandlung

2.5 Requirements for companion diagnostics and monitoring

Requirements prior to the administration of fidanacogene elaparvovec

- **Assessment of immunity against AAVRh74var**

  Nachweis der Abwesenheit von Antikörpern gegen AAVRh74

  Before administering fidanacogene elaparvovec, the absence of antibodies to AAVRh74var must be demonstrated using an appropriately validated assay, using a CE-marked in vitro diagnostic (IVD) with the corresponding intended purpose. If the CE-marked IVD is unavailable, an alternative validated test should be used. Following antibody testing confirming the absence of anti-AAVRh74var antibodies, patients should be dosed as soon as possible (e.g., within eight weeks) [24].

- **Assessment of negativity for FIX inhibitors**

  Nachweis der Negativität für FIX-Inhibitoren

  Before the administration of fidanacogene elaparvovec, an assessment of negativity for FIX inhibitors should be conducted by history and test (<0.6 Bethesda Units, BU).

- **Evaluation of hepatobiliary condition**

  Untersuchungen auf hepatobiliäre Erkrankungen

  An evaluation of hepatobiliary condition before fidanacogene elaparvovec administration should confirm the absence of clinically significant hepatobiliary disease, as defined by any of the below [24]:

  - Alanine transaminase (ALT), aspartate transaminase (AST), or alkaline phosphatase (ALP) levels >2 × upper limit of normal (ULN); at least two readings may be required to interpret variability over time, at most within four weeks.
  - Bilirubin >1.5 × ULN (at most within 4 weeks).
  - Current liver-related coagulopathy, hypoalbuminemia, persistent jaundice, cirrhosis, active viral hepatitis.
  - History of portal hypertension, splenomegaly, or hepatic encephalopathy.
  - Negative fibrosis assessment, at most, three months before infusion.

- In case of radiological liver abnormalities and/or sustained liver enzyme elevations, a consultation with a hepatologist is recommended to assess eligibility for fidanacogene elaparvovec treatment [24].

- Before administering fidanacogene elaparvovec, the patient's existing concomitant hepatotoxic medicinal products or substances should be reviewed to determine whether they should be modified to prevent possible anticipated interactions [24].

  Einnahme hepatotoxischer Medikamente/Substanzen prüfen

- Within eight weeks before infusion of fidanacogene elaparvovec, the absence of active infections, either acute (such as acute respiratory infections or acute hepatitis) or uncontrolled chronic (such as active chronic hepatitis B, hepatitis C, or HIV), should be confirmed [24].

  Vorliegen von Infektionen prüfen

- Before fidanacogene elaparvovec infusion, the patient's vaccinations should be confirmed to be up to date, and the patient's vaccination schedule may need to be adjusted to accommodate concomitant immunomodulatory therapy [24].

  Impfschutz überprüfen

Requirements during or after the administration of fidanacogene elaparvovec

- **Monitoring for infusion-related reactions**

  Infusion reactions, including hypersensitivity reactions and anaphylaxis, can occur during or shortly after fidanacogene elaparvovec infusion. Patients should be closely monitored for infusion reactions throughout the infusion period and at least for three hours after the end of the infusion. The recommended infusion rate should be closely adhered to ensure patient tolerability.

  Monitoring auf Infusionsreaktionen: während und mind. 3 Stunden nach der Infusion

  Patients should be informed of the early symptoms and signs of hypersensitivity reactions; they should be advised to contact their physician and/or seek immediate emergency care if they experience an infusion-related reaction. If an infusion reaction is suspected, slowing or immediate stopping of the infusion is required. Based on clinical judgment, the management of infusion reactions should be conducted according to guidelines for managing allergic reactions, including the discontinuation and/or the administration of appropriate treatment [24].

  Aufklärung der Pat. über mögliche Unverträglichkeitsreaktionen wichtig

- **Discontinuation of FIX concentrates**

  Following the administration of fidanacogene elaparvovec, patients should discontinue prophylaxis once the endogenous FIX concentrate activity levels are sufficient to prevent spontaneous bleeding [24].

  Überwachung von ALT, AST, FIX-Aktivitätsspiegel und CPK

- **Monitoring of FIX activity and hepatic function**

  After administering fidanacogene elaparvovec, patients can develop transient and asymptomatic elevation of transaminases. Although the exact aetiology of elevations has not yet been established, immune-mediated elevations in liver function tests are believed to result from an AAV capsid-triggered response with subsequent hepatocyte lysis and inflammation. ALT/AST and FIX activity levels should be monitored following the administration of fidanacogene elaparvovec, and monitoring of creatine phosphokinase (CPK) is recommended to evaluate for alternative causes for ALT elevations (including potentially hepatotoxic medications or agents, alcohol consumption, or strenuous exercise) [24].

  bei Erhöhung von Aminotransferasen: Beginn einer Kortikosteroidbehandlung

- **Initiation and use of corticosteroids**

  As described above, corticosteroid treatment should be administered if aminotransferase elevations or a decrease in the activity of FIX are observed to maintain the transgene expression by transduced hepatocytes. Limited information is available regarding the benefit of starting a new course of corticosteroid treatment after the first six months of fidanacogene elaparvovec administration [24].

  Einleitung und Anwendung von Kortikosteroiden

  Oral corticosteroids, including prednisone/prednisolone, will be the first consideration for suppressing laboratory abnormalities in the liver. In the absence of alternative aetiology, corticosteroid treatment for vector-induced hepatitis would be highly recommended if any of the following criteria are met:

  erste Behandlungsoption: orale Kortikosteroide

  - Transaminase increase (ALT and AST):
  - Transaminase value 2 × ULN or single increase ≥ 1.5-fold since the last value obtained before infusion.
  - Consecutive increases.
  - FIX activity decrease: A significant decrease could trigger the risk of bleeding that is not associated with a recent infusion of an ex-

  Kriterien für Kortikosteroidbehandlung bei vektorinduzierter Hepatitis

ternal FIX product or FIX inhibitor. Consecutive decreases if occurring during the first 120 days post-infusion [24].

- If there is no evidence of resolution of transaminase elevation or in the decrease in activity of FIX after the first week of oral corticosteroid treatment, using a combination of intravenous methylprednisolone and oral corticosteroids should be considered, and a hepatologist should be consulted as required [24].

keine Besserung nach einer Woche: Methylprednisolon IV+ orale Kortikosteroide

- **Monitoring for FIX inhibitor development**

Überwachung auf die Entwicklung von FIX-Inhibitoren

Fidanacogene elaparvovec is not indicated for use in patients with a history of FIX inhibitors; no clinical data is available in patients with detectable FIX inhibitors treated with fidanacogene elaparvovec. Patients should be monitored through appropriate clinical observations and laboratory tests for the development of inhibitors to FIX after fidanacogene elaparvovec administration. An assay that detects FIX inhibitors if bleeding is not controlled or plasma FIX activity levels decrease should be performed [24].

- **Monitoring for liver disease**

theoretisches Risiko für maligne Transformation

As there is a theoretical risk of malignant transformation leading to cancer resulting from AAV-mediated integration into the host cell DNA, considerations should be given to regular long-term follow-up monitoring [24].

regelmäßige Ultraschalluntersuchungen bei Pat. mit Risikofaktoren

It is recommended that patients with pre-existing risk factors for hepatocellular carcinoma, including hepatic fibrosis, hepatitis C or B disease, and non-alcoholic fatty liver disease, undergo regular liver ultrasound screenings and are regularly monitored for alpha-fetoprotein (AFP) elevations every year for at least five years after administration of fidanacogene elaparvovec. If 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 [24].

- **Measures concerning transgene DNA shedding**

Wirkstoff kann durch Ausscheidungen und Sekrete auf andere Personen übertragen werden

Fidanacogene elaparvovec may be transmitted to persons other than the patient receiving the treatment through patient excretions and secretions. Temporary vector shedding of intravenously administered AAV-based gene therapies occurs primarily through urine, saliva, and mucus. Patients should be instructed on proper hand hygiene to reduce the risk of transmission to other persons. These precautions should be followed for six months after fidanacogene elaparvovec infusion, especially in the case of pregnancy or immunodeficiency of close contacts [24].

- **Risk of thromboembolic events**

Thromboserisiko kann bei vorbestehenden Risikofaktoren erhöht sein

In patients with haemophilia B with pre-existing risk factors for thromboembolic events, including a history of cardiovascular or cardiometabolic disease, arteriosclerosis, hypertension, diabetes, and advanced age, the potential risk of thrombogenicity may be higher after treatment. Patients should be evaluated before and after administration of fidanacogene elaparvovec for risk factors for thrombosis and general cardiovascular risk factors. Patients should be advised according to their condition based on FIX activity levels achieved. Patients should seek immediate medical attention if they observe signs or symptoms that may indicate a thrombotic event [24].

- **Use of FIX concentrates or haemostatic agents after treatment with fidanacogene elaparvovec**

  Following treatment with fidanacogene elaparvovec, FIX concentrates/haemostatic agents may be used in the management of the perioperative setting and in case of invasive procedures, surgery, trauma, or bleeds, following current treatment guidelines for the management of haemophilia and based on the patient's current FIX activity levels [24].

  If the FIX activity levels of the patient are consistently ≤2 IU/dL and the patient has experienced recurrent spontaneous bleeding episodes, physicians should consider the use of FIX concentrates to minimise such episodes (consistent with current treatment guidelines for the management of haemophilia). Target joints should be treated according to relevant treatment guidelines [24].

FIX-Konzentrate/ Hämostatika: bei operativen Eingriffen und bei invasiven Eingriffen, Blutungen, etc. basierend auf FIX-Konzentrat

- **Monitoring of concomitant treatments**

  After fidanacogene elaparvovec treatment, the patient's concomitant medications should be monitored, particularly during the first year, and the need to change concomitant medicinal products based on the patient's hepatic health status and risk should be evaluated. When a new medication is started, close monitoring of ALT and FIX activity levels (e.g., weekly to every two weeks for the first month) is recommended to evaluate potential effects on both levels [24].

Monitoring der Begleitmedikation (ALT & FIX-Konzentratlevel)

Long-term follow-up

Patients are expected to be enrolled in a registry that will follow them for 15 years after infusion to better understand this gene therapy's long-term safety and efficacy [24].

Pat.-Register zur Nachbeobachtung über 15 Jahre wichtig

3 Scope of assessment

3.1 Research question

The following research questions will be answered in the present report:

Fragestellungen

1. **Clinical domain:**

   In adult patients with severe and moderately severe haemophilia B (congenital Factor IX [FIX] deficiency) without a history of FIX inhibitors and detectable antibodies to variant adeno-associated virus (AAV) serotype Rh74 is fidanacogene elaparvovec, in comparison to factor-replacement products, non-factor-therapies, non-replacement therapies, gene therapy (etranacogene dezaparvovec, HEMGENIX®), antifibrinolytic agents, local therapies and non-specific interventions more effective and safe concerning change from baseline in annual bleeding rate (ABR) for total bleeds (treated and untreated), mean annualised infusion rate (AIR) of exogenous FIX, structured patient questionnaire responses , (severe) adverse events (S/AEs) and mortality?

   klinische Domäne: vergleichende Wirksamkeit von Fidanacogene elaparvovec vs. Standardtherapie bei Pat. mit schwerer oder mittelschwere Hämophilie B in Pat.- und systemrelevanten Endpunkten

2. **Non-clinical domains:**

   What are the economic, ethical, organisational and social consequences of implementing fidanacogene elaparvovec into the Austrian healthcare system?

   What were the key contributions of publicly funded research institutions and private companies in the discovery and development of fidanacogene elaparvovec as a gene therapy for haemophilia B, and how did the transfer of intellectual property rights impact the therapy's advancement through clinical trials to market authorisation?

   nicht-klinische Domänen: ökonomisch, ethisch, organisatorisch sozial & Entwicklungskosten

3.2 Inclusion criteria

Inclusion criteria for relevant studies are summarised in Table 3-1

Einschlusskriterien für relevante klinische Studien

Regarding the non-clinical domains, for the economic domain relevant literature was included with information about teprotumumab prices and drug costs, as well as health economic evaluations. For the ethical, social and domain on public investment relevant literature with information on public grants, funding and contributions were included.

Einschlusskriterien für Literatur zu nicht-klinischen Aspekten

Table 3-1: Assessment scope including the PICO questions for the clinical domain

Description of PICO elements	PICO
P	Adult patients with severe and moderately severe haemophilia B (congenital FIX deficiency) without a history of FIX inhibitors and detectable antibodies to variant AAV serotype Rh74.
I	Fidanacogene elaparvovec (BEQVEZ®) is a blood coagulation factor gene therapy administered as a single-dose intravenous infusion over approximately 60 minutes in an appropriate infusion volume. The recommended dose of BEQVEZ® is a single-dose of 5 × 1011 vector genomes per kg (vg/kg) of body weight.
C	*Factor replacement products:* Factor concentrates with standard half-life (SHL)[3] ■ Factor IX, nonacog alfa (BENEFIX®) ■ Factor IX (HAEMONINE®) ■ Factor IX (IMMUNINE®) ■ Factor IX (OCTANINE®) ■ Factor IX (RIXUBIS®) Factor concentrates with extended half-life (EHL)[4] ■ eftrenonacog alfa (ALPROLIX®) ■ nonacog beta pegol (REFIXIA®) ■ albutrepenonacog alfa (IDELVION®) *Non-factor-therapies (NFT)/Non-Replacement therapies (NRT):* Concizumab (ALHEMO®): positive CHMP opinion on 17 October 2024 Marstacimab (HYMPAVZI®): positive CHMP opinion on 19 September 2024 Fitusiran (orphan designation) SerpinPC *Gene therapy:* Etranacogene dezaparvovec (HEMGENIX®) *Antifibrinolytic agents (Tranexamic acid): adjuvant therapy* *Local therapies (haemostyptics) and non-specific interventions*
O	**1. Clinical domains** *Efficacy* **Annual bleeding rate (ABR) for total bleeds (treated and untreated) from week 12 to month 15 vs. usual-care FIX prophylaxis regimen.** Annualised infusion rate (AIR) of exogenous FIX from week 12 to month 15 vs. AIR of FIX with usual-care FIX replacement regimen. Mean vector-derived FIX: C level at steady state (from week 12 to month 15) demonstrated to be >5%. Parameters compared with SoC FIX replacement regimen, comparing pre- and post-fidanacogene elaparvovec gene therapy from week 12 to month 15: ■ **Annualised FIX consumption.** ■ Annualised number of bleeding events of a specific type: spontaneous, traumatic, and untreated. ■ Frequency of target joint bleeds ■ Percentage of participants without bleeds Parameters compared with SoC FIX replacement regimen, comparing pre- and post-fidanacogene elaparvovec gene therapy at 12 months: ■ Change in joint health as measured by the HJHS instrument. **PROs** ■ **Haem-A-QoL Physical Health domain** ■ **HAL Complex Lower Extremity Activities Component Score**

[3] Products approved in Austria (BASG)

[4] Products approved in Austria (BASG)

Description of PICO elements	PICO
O *(continuation)*	*Safety* AEs **SAEs** Safety assessments included annual liver ultrasonography, vector shedding measurement, and immune response assessment directed at the AAV vector or the transgene product. **Mortality** **2. Non-clinical domains** *Economics* Drug (aquisition) costs Budget impact Cost-effectiveness/cost-utility *Ethical, social and organisational aspects* Structured patient questionnaire responses (AIHTA) Clinical expert consultations *Development costs and public contributions*

Abbreviations: AAV … adeno-associated virus, ABR … annual bleeding rate, AE … adverse event, AIR … annualised infusion rate, AIHTA … Austrian Institute for Health Technology Assessment, EHL … extended half-life, FIX … factor IX, FIX:C … circulating levels of factor IX, Haem-A-QoL … haemophilia-specific quality of life, HAL … haemophilia activities list, HJHS … Haemophilia Joint Health Score, NFT … Non-factor-therapies, NRT … Non-replacement therapies, PICO … population-intervention-comparator-outcome, PRO … patient-reported outcomes, SAE … serious adverse event, SHL … standard half-life, SoC … standard of care

Note: Outcomes written in **bold text** *represent patient-relevant endpoints*

4 Methods

4.1 Systematic literature search and study selection

Literature searches

Two systematic literature searches, one for the assessed drug (fidanacogene elaparvovec) and one for the competitor drug (etranacogene dezaparvovec), were conducted on 5 December 2024 in the following databases:

2 systematische Literatursuchen jeweils in 4 Datenbanken

- Medline via Ovid
- Embase
- The Cochrane Library
- INAHTA

The systematic searches were limited to articles published in English or German. After deduplication, a total of 297 citations were included. The specific search strategy employed can be found in Chapter 4 in the Appendix.

Ergebnis systematische Literatursuche: 297 Publikationen

Furthermore, to identify ongoing and unpublished studies, two searches in three clinical trials registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) for fidanacogene elaparvovec and etranacogene dezaparvovec were conducted on 9 December 2024, resulting in 22 potentially relevant hits.

Suche nach laufenden Studien

The marketing authorisation holder of the drug under assessment (fidanacogene elaparvovec, BEQVEZ®) has, on 19 December 2024, submitted a BEQVEZ® dossier, including a presentation on clinical data, BEQVEZ® European Public Assessment Report (EPAR), BEQVEZ® Product Information, one publication of the pivotal trial [29] with protocol and appendix and the BEQVEZ® risk management plan. One new citation was identified from the documents submitted. The dossier contained additional data: health-related quality of life (HRQoL), long-term follow-up efficacy and safety data, simulation of factor IX (FIX) activity, and indirect treatment comparison (ITC) of BEQVEZ® with standard of care (SoC). Additional data on the ITC were submitted upon request.

insgesamt 298 Publikationen identifiziert

No additional references were identified through manual searches.

Flow chart of study selection

Two independent researchers screened the 297 references on an abstract level, and the remaining full texts were screened independently again. In disagreement, a third researcher was involved in solving the differences. Based on the pre-defined inclusion criteria overall, one study [29] and the manufacturer dossier were included for the clinical effectiveness analyses, and one HTA report from the Canadian Agency for Drugs and Technologies in Health (CADTH) [3] was considered for the clinical effectiveness analysis and the summary of cost-effectiveness analyses. The selection process is displayed in Figure 4-1.

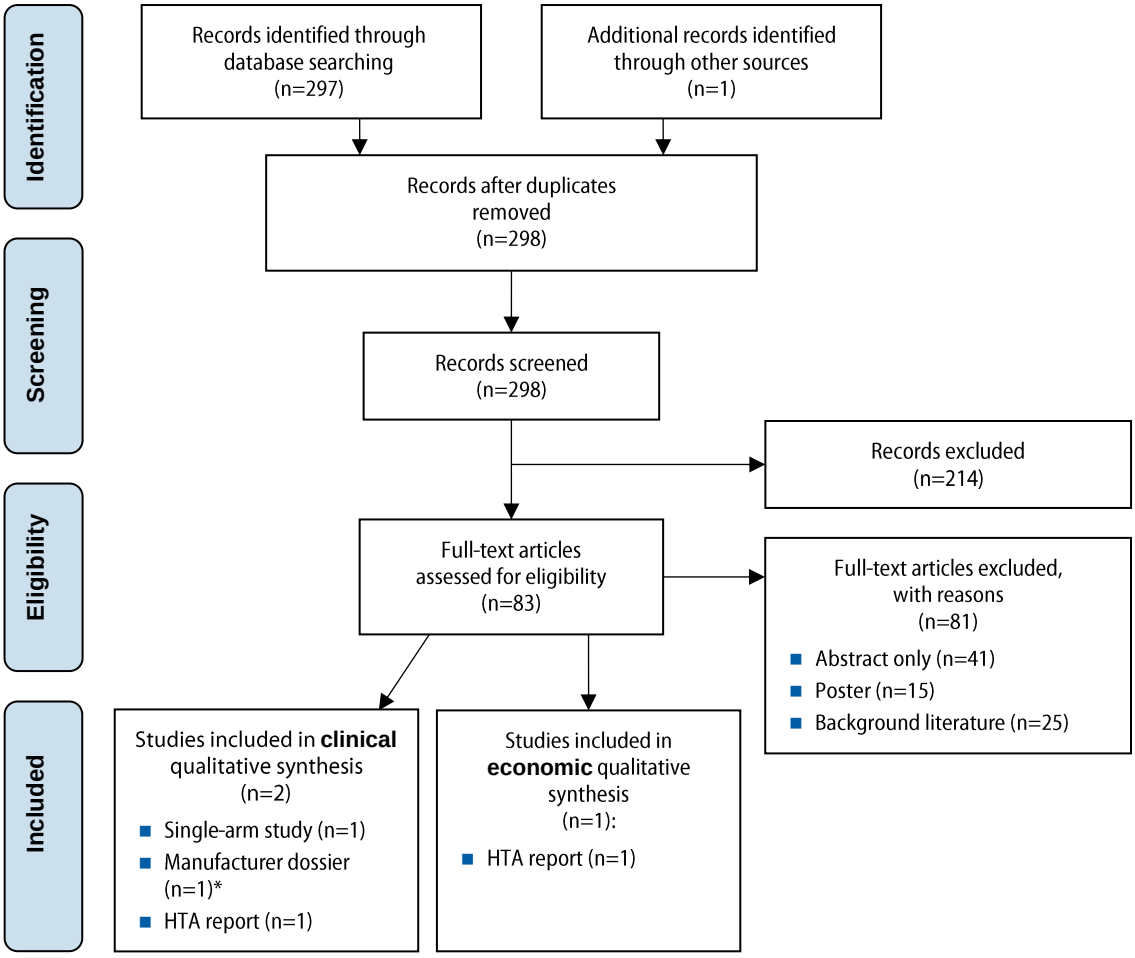
Literaturauswahl:

Wirksamkeitsanalyse (n=1)

Kosteneffektivität (n=1)

The following study designs were considered for inclusion/exclusion:

- Inclusion criteria: Double-blinded, randomised, placebo-controlled or single-arm studies (before-after case series).
- Exclusion criteria: Phase I/II clinical studies, case studies.



** The dossier was submitted to the AIHTA by the health technology developer on 19 December 2024. Additional data were requested and were submitted on 9 January 2025.*

Figure 4-1: Flow chart of study selection (PRISMA Flow Diagram)

The evidence for the ethical, social and organisational aspects and the aspects about public contributions were not collected through the systematic search and the according process is described later.

4.2 Methods of the relative clinical effectiveness and safety assessment

Data analysis and synthesis

Verzerrungsrisiko, Datenextraktion & Datenkontrolle nach dem 4-Augen Prinzip

Certainty was assessed using the Risk of Bias tool Institute of Health Economics (IHE) checklist for single-arm case-series (see Chapter 5 in the Appendix) [30]. Risk of bias (RoB) appraisal was conducted in duplicate by two reviewers (EM and NG); differences were settled via consensus. One reviewer (EM) systematically extracted relevant data from the included studies into data extraction tables. A second reviewer (NG) cross-checked the data extraction tables for accuracy. Due to the data quality (single-arm study), data are synthesised qualitatively only. The ITC from the applicant was critically reviewed according to the ISPOR Guideline 2011 [31] and PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses [32]. No further analysis on direct or indirect comparisons was conducted.

4.3 Methods of the economic chapters

Preis-Infos Fidanacogene elaparvovec internat.: GÖG

For the chapter about the treatment costs, budget impact analysis (BIA) and price comparison, we used different data sources:

1. Information on international prices of fidanacogene elaparvovec was retrieved by the Austrian National Public Health Institute (Gesundheit Österreich GmbH, GÖG).
2. Information on annual treatment costs for SoC was based on prices per package of relevant drugs from the health insurance, and dosing regimen based on product information
3. Since the manufacturer did not submit a BIA for Austria, we calculated a BIA using the following methods:
   - We identified information on the type and volume of medical services in connection with fidanacogene elaparvovec and on the SoC via the EPAR of fidanacogene elaparvovec, guidelines (Austrian Haemophilia Association, World Federation of Haemophilia, WFH) and clinical experts.
   - Currently, no price for fidanacogene elaparvovec is available in Europe; a price of € 3.4 million per intervention was assumed (based on the assumed price in the cost-utility analysis for the CADTH).
   - Information on the number of patients with the diseases in Austria came from clinical experts with access to Austrian registry data. Based on this information, the number of eligible patients for fidanacogene elaparvovec was retrieved and finally validated by clinical experts:
     - 25% of the moderate haemophilia B patients were assumed to receive FIX prophylaxis [12];
     - 60% of the adult patients who receive FIX prophylaxis were assumed to be not eligible for gene therapy due to AAV-neutralising anti-bodies [2];

Budgetfolgenanalyse:

Kostenkategorien aus Leitlinien & Befragung klinischer Expert:innen.

Preisannahme Fidanacogene elaparvovec: €3,4 Mio. pro Intervention

Annahmen zu potenziellen Pat.-Zahlen für basierend auf Expert:innen-Einschätzungen

Unit Costs: Sozialversicherung & Krankenhausverbünde ;

Gentherapie-Szenario vs. Standardtherapie-Szenario

  - 7.5% of the adult patients who receive FIX prophylaxis were assumed to be not eligible for gene therapy due to the development of FIX inhibitors [33];
  - Another 7.5% of the adult patients who receive FIX prophylaxis were assumed to be not eligible for gene therapy due to severe liver disease or missing compliance [12];
  - The market uptake of fidanacogene elaparvovec was assumed to be 20% in year 1, 30% in year 2 and 50% in year 3 [12].
- For calculating expenditure of FIX products in the outpatient sector we used data on total spending for all available products provided by the Austrian Federation of Social Insurances. Hospital providers in the nine federal states were contacted for cost items in the inpatient sector. Three providers (organisations) provided unit cost data for 2023. We used average values in case more than one unit cost information was available for a single cost item. The unit costs used for the analysis are presented in the Appendix (Chapter 6).

Brutto-, Netto-Budgetfolgen und zusätzliche Kosten im Rahmen der Verabreichung berechnet

- Cost categories with a minor contribution to the overall costs were excluded (e.g., costs of eligibility and monitoring testing and some treatments for adverse events). In addition, the analysis did not include additional treatments, such as local agents, and supportive treatments like pain therapy, physical therapy and orthopaedic treatments, as well as treatments of comorbidities.
- For the calculation of the yearly FIX-substitution costs per patients the outpatient costs of the three most frequently prescribed products were considered.

Übersicht internat. ökonomische Evaluationen: systematische Suche & Handsuchen; Preise konvertiert in € 2024 mit Online-Tool

- According to the implementing regulation § 4 (2) (Ausführungsbestimmungen gem. § 4 (2)) we calculated the 3-year gross drug budget impact (drug acquisition costs based on the eligible population and predicted market share), the net drug budget impact (drug acquisition costs and cost-offsets anticipated from the increased utilisation and/or displacement of other drugs) and additional costs, such as inpatient costs due to the application of the gene therapy, FIX prophylactic treatment after gene therapy and costs of very common adverse events. Economic consequences, especially potential cost-offsets of SoC beyond year three were taken from estimates in the international literature, considering the uncertainties of long-term effectiveness, market share and prices.
- To summarise existing economic evaluations of fidanacogene elaparvovec, we used the literature identified through the systematic search and additional manual searches via Google. US-dollars (2023) were converted into euros (2024) via an online tool using the International Monetary Fund data for purchasing power parities (PPP) [34].

4.4 Organisational (ethical, social, legal and environmental) aspects of new therapy

strukturiertes Herangehen nach dem EUnetHTA CoreModel®

To analyse non-clinical aspects of the intervention, we utilised the European Network for Health Technology Assessment (EUnetHTA) Core Model®. This framework provides structured questions to evaluate organisational, ethical and social dimensions systematically.

3 Quellen:

We gathered data from three complementary sources:

1. xpert interviews with six leading clinicians (interview guide available in in Chapter 4 in the Appendix)
2. Structured patient questionnaires (available in Chapter 4 in the Appendix)
3. Systematic literature review findings (methodology detailed in Chapter 3.2.1).

EInterviews mit führenden Kliniker:innen

schriftliche Befragung von Pat.

Literatur

We synthesised the data from these sources by mapping responses to the relevant categories within the EUnetHTA Core Model's® organisational, ethical and social domains. The findings were then narratively synthesised. Raw data from all sources is available upon request from the authors.

5 Pat./Angehörige haben Fragebögen ausgefüllt

A total of five participants completed the patient questionnaire (n=5), of whom three were male and two were female. All cases involved severe haemophilia B, with no representation of moderately severe cases. The participant distribution comprised three patients and two carers, with one carer completing the questionnaire on behalf of a patient and one carer completing it in addition to their patient's response. Four participants reported membership in patient organisations. The characteristics of the participants in this assessment are described in Table 4-1.

Table 4-1: Characteristics of participants of the structured patient questionnaires (n=5) conducted by the AIHTA

Patient characteristics	Total number of patients (n=5)
Sex	
Female	2
Male	3
Indication	
severe haemophilia B	5
moderately severe haemophilia B	0
Role	
Patient	3
Carer	2
Member of patient organisation	
Yes	4

4.5 Development costs and public contributions

Identification of generic or nonproprietary and proprietary designations

Identifizierung generischer oder nicht geschützter und geschützter Bezeichnungen

We started our research on product origins by thoroughly searching for product identifiers, including initial numbers and character combinations, generic or non-proprietary names of active ingredients, and trade or brand names usually given later in development. This search was conducted using AdisInsight. This ensures that we start the product search as early as possible for its history before the company gives the product a final brand name for marketing reasons.

Identification of originator and public contributions to the development

Identifizierung der Produktherkunft; wo und durch wen wurde Grundlagenforschung durchgeführt

Next, we searched for the earliest reference of these generic or non-proprietary names in publications to identify the origins of the products. Medline was searched to identify early basic R&D support, and the corresponding publications were searched for affiliations with academic institutions and research grants mentioned. Then, databases on clinical trials (https://clinicaltrials.gov/, https://eudract.ema.europa.eu/) and supranational institutions for research funding (https://cordis.europa.eu/; https://reporter.nih.gov/) were searched. Sponsor details, type of funding and amounts were extracted. This was followed by searching the European Commission Competition website (https://competition-cases.ec.europa.eu/search) to determine whether any EU member states provided funds to the companies developing gene therapies for haemophilia B.

Finanzierungsrunden, Fusionen und Übernahmen

Company-specific research was conducted using the official websites of the originators and collaborators to find additional information on funding rounds, sponsors and mergers, and acquisitions (M&A). We complemented our findings by extracting information on employee numbers, revenues and shareholders from 10-K reports.

Suche in Medien für zusätzliche Informationen (besonders in biotech Medien)

As a next and last step, we used Google, Forbes, Reuters to identify news articles about the products. We finished the search using various investor news sources (Statnews, BusinessInsider, Business Wire, FiercePharma, Pharmafile, Pharmatimes, Pharmaphorum, BioPharma Drive, BioWorld, Biospace, etc.). If the products or the knowledge that led to a product were acquired through an M&A, we also analysed the originator company if they received public contributions. For detailed information on search terms, see Chapter 6 in the Appendix.

5 Clinical effectiveness and safety assessment

5.1 Included studies

One clinical phase 3 study by Cuker et al. [29] was identified, see details in Table 5-1.

1 einarmige Studie

Table 5-1: Included studies – list of relevant studies used for the assessment

Study reference/ID study type	Sponsored or third-party study of the technology under assessment	Available documentation
PICO		
A single-arm study to evaluate the efficacy and safety of FIX gene therapy with PF-06838435 in adult males with moderately severe to severe haemophilia B (BENEGENE-2a,b,d)	Sponsored	CSR: not provided Registry entryc: NCT03861273 Publication or other reference: [29]

Abbreviations: CSR … clinical study report, NCT … national clinical trial, PICO … Population, Intervention, Comparison and Outcomes.

Notes:

[a] *study sponsored by the health technology developer (HTD) or in which the HTD participated financially in some other way*

[b] *in the following tables, the study is referred to as BENEGENE-2*

[c] *study registry entry, number (NCT-Number, EudraCT-Number)*

[d] *the study compared to the baseline from the BENEGENE-1 study*

5.2 Characteristics

Study design

BENEGENE-2 was a phase 3 study involving participants with moderately severe or severe haemophilia B conducted at 27 centres in 13 countries. Enrolled patients were men 18 to 62 years of age with haemophilia B (factor IX [FIX] level: ≤2%) who had received FIX prophylaxis therapy for at least six months during the BENEGENE-1 lead-in study (ClinicalTrials.gov number: NCT03587116) and who agreed to suspend prophylaxis after fidanacogene elaparvovec infusion.

BENEGENE-2: Phase 3, intra-individueller Vergleich von Pat. mit mittelschwerer bis schwerer Hämophilie B

The study began on 29 July 2019, and the primary completion date was 16 November 2022, with an updated data cutoff date of 30 August 2023. At this time point, 45 patients were analysed. Safety and efficacy data collection will continue until each participant has had six years of follow-up. The study is estimated to be completed in 2031. On day 1, the participants received a intravenous infusion of fidanacogene elaparvovec at a dose of 5×10^{11} vector genome copies/kg through an infusion pump.

Studie läuft noch bis 2031

The primary endpoint was the annualised bleeding rate (ABR, including treated and untreated bleeding episodes) from week twelve to month 15. When 40 participants completed at least 15 months of follow-up, the protocol specified a comparison of the ABR for total bleeding episodes for non-inferiority compared with prophylaxis (margin, 3.0 episodes per year) and a comparison for

primärer Endpunkt: jährliche Blutungsrate von Woche 12 bis Monat 15

superiority if noninferiority was achieved. This setting allowed for a 90% power, with a one-sided test at an alpha level of 0.025.

sekundäre Endpunkte

The primary and secondary efficacy endpoints were tested hierarchically to control for overall type I errors. Key secondary endpoints were the following: ABR for treated bleeding episodes, annualised infusion rate (AIR) of exogenous FIX and activity level of FIX. Detailed characteristics of the included study can be found in Table 5-2.

Table 5-2: Characteristics of the included study [29]

Study reference/ID	Study type and design	Study population	Study arms (number of randomised/ included patients)	Study duration, data cut off(s) and locations	Study endpoints
BENEGENE-2	Single-arm, open-label	Men 18 to 62 years of age with moderately severe or severe haemophilia B.	Group 1 (N = 45)	Study duration: 15 months Completion date (estimated): 09/01 2031 1. Data cut-off: 30 August 2023 (planned interim analysis) Number of centres by continent: 27 centres in 13 countries	Primary: ABR (treated and untreated bleeding episodes). Key secondary: ABR for treated bleeding episodes, AIR of exogenous FIX, activity level of FIX. Other: annualised FIX consumption, annualised number of bleeding events of a specific type, frequency of target joint bleeds, percentage of participants without bleeds, change in joint health as measured by the HJHS instrument, Haem-A-QoL Physical Health domain, HAL Complex Lower Extremity Activities Component Score.

Abbreviations: ABR … annualised bleeding rate, FIX … factor IX, Haem-A-QoL … Haemophilia Quality of Life Questionnaire for Adults, HAL … Haemophilia Activities List, HJHS … Haemophilia Joint Health Score, N … number of included patients.

3 Protokolländerungen

Three amendments were made to the protocol. The original protocol was from 13 December 2018. The first amendment to the study protocol was issued on 29 June 2022, and it revised the primary endpoint from the ABR for treated bleeds to the ABR for total bleeds. In the second and third protocol amendments, the start point for outcome analysis was revised from day one following fidanacogene elaparvovec infusion to week twelve post-infusion to correspond with the estimated onset of steady state circulating levels of FIX. All study endpoints, as defined in the study protocol after the third amendment, are presented in Table 5-3.

Table 5-3: Study endpoints as defined in the study protocol after the third amendment [29]

Study reference/ID Outcome category	Endpoints as defined in the study protocol
BENEGENE-2	
Primary endpoint	Annualised bleeding rate (ABR) for total bleeds (treated and untreated) from week twelve to month 15 vs. usual-care FIX prophylaxis regimen.
Key secondary efficacy endpoints	■ ABR for treated bleeding episodes from week twelve to month 15 vs. usual-care FIX prophylaxis regimen. ■ Annualised infusion rate of exogenous FIX from week twelve to month 15 vs. AIR of FIX with usual-care FIX replacement regimen. ■ The activity level of FIX

Study reference/ID Outcome category	Endpoints as defined in the study protocol
Secondary efficacy endpoints	■ Annualised FIX consumption ■ ABR of specific types of bleeding ■ Percentage of participants without bleeds ■ Haemophilia Joint Health Score ■ Haemophilia Quality of Life Questionnaire for Adults ■ Haemophilia Activities List ■ Immunogenicity
Other endpoints	■ Target joints ■ X-ray assessments to evaluate joints ■ Magnetic resonance imaging to evaluate joints ■ Haemophilia Life Impacts Questionnaire ■ EQ-5D-5L ■ Vector shedding ■ FIX Antigen Levels and Coagulation Activation Tests
Safety endpoints	■ Adverse events ■ Laboratory data ■ Vital signs and other safety endpoints ■ Concomitant medication ■ Liver ultrasound

Abbreviations: ABR … annualised bleeding rate, AIR … annualised infusion rate, EQ-5D-5L … European Quality of Life 5-Dimensions 5-levels, FIX … factor IX

primärer Endpunkt: Follow-up über 6 Jahre

The primary endpoint ABR (treated and untreated bleeding episodes) and the key secondary efficacy endpoint ABR for treated bleeding episodes were planned to be followed up for six years. Table 5-4 provides information on treatment duration and observation periods in the BENEGENE-2 study.

Table 5-4: Information on the follow-up for respective primary and secondary endpoints

Study reference/ID Outcome category	Planned follow-up	Median duration of follow-up [min; max] at the time of data cut-off
BENEGENE-2		
Annualised bleeding rate (treated and untreated bleeding episodes)	six years	3 years (1.0, 6.0 years)
Annualised rate of bleeding for treated bleeding episodes	six years	3 years (1.0, 6.0 years)

Study population

Studienpopulation: 45 Männer 18- 62 Jahre Hämophilie B (FIX ≤2 %)

alle Pat. hatten zuvor an der BENEGENE-1 Studie teilgenommen

The study population consisted of 45 men 18 to 62 years of age with haemophilia B (FIX level, ≤2%) who had received FIX prophylaxis therapy for at least six months during the BENEGENE-1 lead-in study (NCT03587116) and who agreed to suspend prophylaxis after fidanacogene elaparvovec infusion. FIX replacement therapy was permitted according to clinical need. In this BENEGENE-2 study, participants had a mean age of 33.2 years (range 18-62) and were predominantly White (73.3%) and non-Hispanic/Latino (77.8%), with participants from various regions including Europe (28.9%), North America (26.7%), and the Middle East (20.0%). The majority of participants (84.4%) had severe haemophilia B (<1% FIX level), and the mean Body mass index (BMI) was 27.85 kg/m^2. Previous viral infections were noted in some participants (Hepatitis C virus [HCV] 33.3%, Hepatitis B virus [HBV] 28.9%, human immunodeficiency virus [HIV] 6.7%), and 28.9% had target joints. Re-

garding factor IX therapy, most patients were on extended half-life (EHL) products (64.4%), followed by recombinant standard half-life (SHL) (33.3%) and plasma-derived products (4.4%). Detailed patient characteristics of the study population from the BENEGENE-2 study can be found in Table 5-5.

Table 5-5: Baseline Demographics and Disease Characteristics of Participants in the BENEGENE-2 Study [29]

Study reference/ID Characteristics Category	Study intervention
BENEGENE-2	**fidanacogene elaparvovec (N = 45)**
Age, years	
Mean (mean ±SD)	33.2 (10.9)
Median (range)	29.0 (18.0-62.0)
Male, n(%)	45 (100.0)
Race, n (%)*	
White	33 (73.3)
Black or African American	1 (2.2)
Asian	7 (15.6)
American Indian or Alaska Native	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)
Not reported	4 (8.9)
Multiracial	0 (0.0)
Ethnicity, n (%)	
Hispanic or Latino	2 (4.4)
Not Hispanic or Latino	35 (77.8)
Not reported	8 (17.8)
Region, n (%)	
Asia Pacific	6 (13.3)
Australia	2 (4.4)
Europe	13 (28.9)
Middle East	9 (20.0)
North America	12 (26.7)
South America	3 (6.7)
Body mass index, kg/m²	
n	45 (100.0)
Mean ±SD	27.85 (5.47)
Median (range)	27.70 (17.6-48.4)
Severity criteria, n (%)[5]	
<1%	38 (84.4)
1–2% (inclusive)	7 (15.6)
History of infection, n (%)1	
Hepatitis C virus	15 (33.3)
Hepatitis B virus	13 (28.9)

[5] Data are from the dossier submitted by the company on 19 December 2024.

Study reference/ID Characteristics Category	Study intervention
BENEGENE-2	**fidanacogene elaparvovec (N = 45)**
Human immunodeficiency virus	3 (6.7)
Target joints, n (%)	
Overall	13 (28.9)
One target joint	7 (15.6)
Two target joints	3 (6.7)
Three or more target joints	3 (6.7)
Category of factor IX therapy[2], n (%)	
Extended half-life	29 (64.4)
Plasma-derived	2 (4.4)
Recombinant standard half-life	15 (33.3)

Abbreviations: n … number of randomised patients, N … number of randomised patients, SD … standard deviation;

Notes:

** reported by the participant*

1 Counts and percentages of participants with positive laboratory results for the corresponding parameter

2 Participants may have been prescribed more than one type of factor IX replacement therapy.

45 Pat. haben eine Einzeldosis Fidanacogene elaparvovec erhalten, 43 davon nehmen an der laufenden Follow-up-Studie teil

Fifty-one participants completed the BENEGENE-1 lead-in study and were assessed for eligibility for BENEGENE-2. Among these 51 participants, six were not eligible due to various reasons: one had neutralising antibodies (nAB) titer above the established threshold, one did not complete ≥6 months of routine FIX prophylaxis therapy and had >50 lifetime exposure days to a FIX protein product, one was unable to adhere to scheduled visits, treatment plans, and laboratory tests, one had unstable liver or biliary disease at entry of study, one had screening laboratory values outside the acceptable range, and one withdrew consent. This resulted in 45 participants receiving a single dose of fidanacogene elaparvovec. Of these, 44 patients completed 15 months of follow-up, and one patient completed twelve months of follow-up. Ultimately, 43 participants continued the ongoing long-term follow-up study, while two withdrew consent (see Figure 5-2).

Ausschlusskriterien: anti-AAV-neutralisierende Antikörper, Nachweis von FIX-Inhibitoren, aktive/unkontrollierte chronische Infektionen

Key exclusion criteria of the BENEGENE-2 trial were detectable anti-adeno-associated virus (AAV) neutralising antibodies (nAB), a history of or positive test for FIX inhibitors, the presence of unstable or clinically significant disease other than haemophilia, a level of alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) that was more than twice the upper limit of the normal range, active hepatitis B or C status, and active HIV infection. Of note, one patient had a controlled HIV infection. At the time of data cut-off, 44 patients completed the 15 months of follow-up, and one patient completed twelve months of follow-up. For details on in- and exclusion criteria of the included study, see Table 5-6.

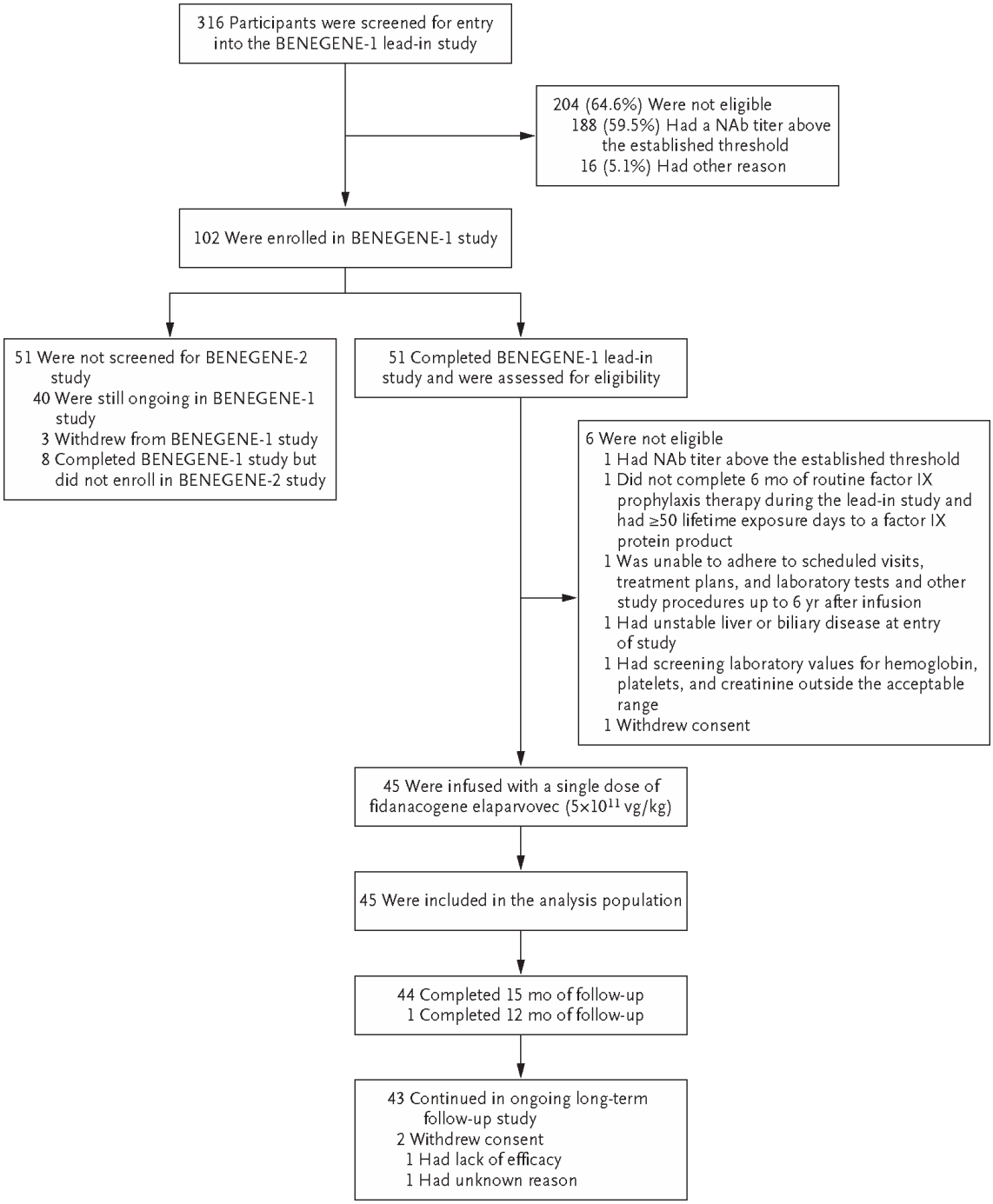


Figure 5-1: Diagram of patients in the study (extracted from [1])

Table 5-6: In- and exclusion criteria of the BENEGENE-2 trial [29]

Inclusion criteria	Exclusion criteria
Type of Participant and Disease Characteristics 1. Participants must have completed at least six months of routine FIX prophylaxis therapy during the lead-in study (C0371004) before providing consent at the screening visit for this study. 2. Participants who have documented moderately severe to severe haemophilia B, defined as FIX:C ≤2%. 3. Participants must agree to suspend prophylaxis therapy for haemophilia B after IP administration. FIX replacement therapy was allowed as needed. 4. Acceptable screening laboratory values are as follows: Haemoglobin ≥11 g/dL Platelets ≥100,000 cells/µL Creatinine ≤2.0 mg/dL **Sex** 5. Male. Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. Male participants are eligible to participate if they agree to the following for at least the time required for three consecutive ejaculate samples to test negative for vector shedding: Refrain from donating sperm. PLUS either: Be abstinent from heterosexual or homosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent. OR Must agree to use contraception/barrier as detailed below: Agree to use male condom when engaging in any activity that allows for the passage of ejaculate to another person. **Informed Consent** 6. Capable of giving signed informed consent as described in appendix 1, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol. **Allowed therapy** During the study, participants were requested to suspend their FIX prophylaxis regimen after infusion of fidanacogene elaparvovec, but were permitted to take: FIX replacement therapy, as needed. The infusion data (specific product, date, time, dosage, reason) was recorded in the eDiary. For a bleeding event, the Investigator/study staff recommended the appropriate dose of FIX to treat the bleed because the dose of factor concentrate was required to include the recent steady-state fidanacogene elaparvovec–induced FIX activity levels to avoid overdosing resulting in a potential thrombotic event. A participant could resume prophylaxis if the fidanacogene elaparvovec treatment was not efficacious, defined for this study as: FIX activity after 12 weeks of ≤2% (in the absence of a confirmed FIX inhibitor) as determined by the central laboratory on two consecutive samples collected within a 2-week period; and/or Over a 4-week period (in the absence of a confirmed FIX inhibitor): 2 or more spontaneous bleeds into a major joint and/or target joint OR 3 or more spontaneous bleeds (consisting of joint bleeds and/or significant soft tissue/muscle or other site bleeds). Significant spontaneous bleeds are defined as those that lead to a transient or persistent loss of function. The investigator was required to discuss the case with the sponsor's medical monitor prior to resumption of prophylaxis.	**Medical Conditions** 1. Anti-AAV nAbs, performed by a central laboratory during screening. 2. 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. 3. Known hypersensitivity to FIX replacement product or IVIg administration. 4. History of chronic infection or other chronic disease that the investigator deems as an unacceptable risk. 5. 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 behaviour (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 this study. 6. ALT, AST, ALP >2× ULN, based on central laboratory results. 7. Bilirubin >1.5× ULN (isolated bilirubin >1.5× ULN was acceptable if bilirubin is fractionated and direct bilirubin <35%), based on central laboratory results. 8. Current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, hepatic encephalopathy, coagulopathy, hypoalbuminemia, oesophagal 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. *Note:* Participants with a central laboratory test value that was outside the range specified by the exclusion criteria may have the test repeated by the central laboratory to determine eligibility; however, the result must be available before Baseline Visit/Visit 2. **Prior/Concomitant Therapy** 9. Currently on antiviral therapy for hepatitis B or C. 10. Any participant with a planned surgical procedure requiring FIX surgical prophylactic factor treatment in the next 15 months. 11. Participants using therapies that are restricted. See Section 6.5.2 for therapies not allowed during study participation. **Prior/Concurrent Clinical Study Experience** 12. 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. **Diagnostic Assessments** 13. Active hepatitis B or C; HBsAg, HBV-DNA positivity, or HCV-RNA positivity. 14. Significant liver disease, as defined by pre-existing diagnosis of portal hypertension, splenomegaly, or hepatic encephalopathy. Additionally, during screening, a serum albumin level below normal limits and/or significant liver fibrosis by any of the following diagnostic modalities: FibroScan score >8 kPa units, Fibro Test/FibroSURE >0.480F 1 or AST-to-Platelet Ratio Index (APRI) >1. In the Investigator's opinion, if there was concern regarding the FibroTest results due to a confounding medical history (e.g., proteinuria can impact FibroTest result), the Investigator can perform a different assessment of liver fibrosis (e.g., FibroScan or APRI) during the screening period. 15. Serological evidence of HIV-1 or HIV-2 infection with either CD4+ cell count ≤200 mm^3 or viral load >20 copies/mL. **Other Exclusion Criteria** 16. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the Investigator, or participants who are Pfizer employees, including their family members, directly involved in the conduct of the study.

Inclusion criteria	Exclusion criteria
Dosing of prophylaxis will take into account the current steady-state FIX activity level. A participant who resumes prophylaxis may choose to discontinue it; however, prior to discontinuation, the Investigator is to discuss with the Sponsor's medical monitor. Additional allowed therapies include the following: COX-2 inhibitors and topical NSAIDs, where medically necessary HIV therapy	17. Unable to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures for up to 6 years post infusion of fidanacogene elaparvovec, in the Investigator's judgment. 18. Sensitivity to heparin or heparin induced thrombocytopenia. 19. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator or the Sponsor's medical monitor, contraindicates participation in the study.

Abbreviations: AAV … adeno-associated virus, ALP … alkaline phosphatase, ALT … alanine aminotransferase, APRI … AST-to-Platelet Ratio Index, AST … aspartate aminotransferase, BU … Bethesda Units, CD4+ … cluster of differentiation 4 positive, COX-2 … cyclooxygenase-2, DNA … deoxyribonucleic acid, eDiary … electronic diary, Fibro Test/FibroSURE … Biomarkers Test for Liver Fibrosis, FIX … factor IX, FIX:C … circulating levels of factor IX, HbsAg … hepatitis B surface antigen, HBV-DNA … hepatitis B virus DNA, HCV-RNA … hepatitis C virus RNA, HIV … human immunodeficiency virus, HIV-1 … human immunodeficiency virus type 1, HIV-2 … human immunodeficiency virus type 2, ICF … international classification of functioning, disability and health, IP … investigational product, IVIg … intravenous immunoglobulin, nAbs … neutralising antibodies, NSAIDs … non-steroidal anti-inflammatory drugs, ULN … upper limit of normal.

Definition of critical outcomes

Critical efficacy outcomes for patients with severe and moderately severe haemophilia B

relevante Endpunkte zur Beurteilung der Wirksamkeit:

ABR for total bleeds (treated and untreated) from week twelve to month 15 versus usual-care FIX prophylaxis regimen:
This primary endpoint measured the occurrence of bleeding episodes, which the participants had to enter into a hand-held device. The investigator also documented the number of bleeds in the bleeding case report form. The bleed was treated with FIX infusion within 72 hours after the start of bleeding.

jährliche Blutungsrate (ABR) Woche 12 bis Monat 15

AIR of exogenous FIX from week twelve to month 15 versus AIR of FIX with usual-care FIX replacement regimen:
This secondary endpoint measured all FIX infusions administered for any purpose, including treatment of bleeding episodes, preventive measures, perioperative management, or resumption of prophylactic FIX regimen.

jährliche Infusionsrate (AIR) von exogenem FIX (Woche 12 bis Monat 15)

Mean vector-derived FIX: C level at steady state (from week twelve to month 15):
This endpoint was calculated for each participant as the geometric mean of all eligible FIX:C (circulating levels of factor IX) measures. The first one-stage assay was performed on the Behring Coagulation System analyser with an Actin-FSL reagent. The second one-stage assay used the same analyser but 'SynthAsil' as a reagent instead.

mittlerer, vom Vektor abgeleiteter FIX-Aktivitätsspiegel (Woche 12 bis Monat 15)

Annualised FIX consumption:
This outcome measured the dose of FIX therapy consumed in the unit of international units per kilogram (IU/kg) and total units.

jährlicher FIX-Verbrauch

Annualised number of bleeding events of a specific type: spontaneous, traumatic, and untreated. This outcome was measured similarly to ABR, with the type of bleed specified.

spontane, traumatische und unbehandelte Blutungen

Frequency of target joint bleeds:
A target joint is defined as a major joint (e.g., hip, elbow, wrist, shoulder, knee, and ankle) into which repeated bleeds occur (three or more spontaneous bleeds into a single joint within a consecutive 6-month period). Investigators will assess the health of the target joint(s), identified at baseline and other visits. This outcome was analysed using a repeated measures generalised linear model with negative binomial distribution and log link function.

Häufigkeit von Zielgelenkblutungen

Percentage of participants without bleeds:
For this outcome, the percentage of participants without bleeds was determined for the overall period. The occurrence of bleeding episodes was recorded by the participants, who were required to enter a bleed into a hand-held device. The investigator also documented the number of bleeds in the bleeding case report form.

Prozentsatz der Pat. ohne Blutungen

Change in joint health as measured by the Haemophilia Joint Health Score (HJHS) instrument:
For this outcome, a qualified healthcare professional assessed joints to derive modified HJHS, adapted from the original joint scoring system [35]. The HJHS v2.1 comprises an assessment of specific features, or items, of the six index joints and an assessment of global gait. For each of the six joints, the following items are scored: swelling (scored 0-3), duration of swelling (0-1), muscle atrophy (0-2), crepitus on motion (0-2), flexion loss (0-3), extension loss (0-3), joint pain (0-2), and strength (0-4). The maximum score for an individual index joint is 20, gait is scored 0 to 4, and the maximum HJHS total score is 124, with a higher score indicating worse joint health.

Veränderungen der Gelenkgesundheit

Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) Physical Health domain:
The Haem-A-QoL Questionnaire is designed for patients aged 17 and older with haemophilia. It contains 46 items with ten domains that assess health in the following areas: Physical Health (five items); Feelings (four items); View of Self (five items); Sports and Leisure (five items); Work and School (four items); Dealing with Haemophilia (three items); Treatment (eight items); Future (five items); Family Planning (four items); and Partnership and Sexuality (three items). The Physical Health domain was considered the primary domain in this questionnaire [36]. A seven-point reduction in the Total Score and a ten-point reduction in Physical Health and Sport & Leisure domain scores are considered clinically meaningful [28].

Messung der Lebensqualität

Haemophilia Activities List (HAL) Complex Lower Extremity Activities Component Score:
The HAL (version 2) is a multiple-domain measure of the impact of haemophilia on functional abilities in adults. The seven domains of this instrument contain 42 items in total, as follows: Lying/sitting/kneeling/standing (8); Lower (leg) functioning (9); Upper (arm) functioning (4); Transportation (3); Self-care (5); Household tasks (6); and Sports/Leisure (7). An overall sum score and three component scores can be calculated along with individual domain scores [37]. The minimal clinically meaningful change is 13.4 for the Complex Lower Extremity component score, 16.7 for the basic lower extremity component score, 9.2 for the upper extremity component score, and 10.2 for the HAL total sum score [28].

Messung der Funktionsfähigkeit der Extremitäten

European Quality of Life 5-Dimensions 5-levels (EQ-5D-5L)
Health status was assessed using the EQ-5D-5L questionnaire, which measures five dimensions of health, each on a 5-point scale. A score change of seven points is considered clinically meaningful. The EQ visual analogue scale (VAS) is an integral part of EQ-5D [28].

Gesundheitszustand durch EQ-5D-5L ermittelt

Critical safety outcomes for patients with severe and moderately severe haemophilia B

relevante Endpunkte zur Beurteilung der Sicherheit

Adverse events (AEs) and serious adverse events (SAEs):
AE summaries were presented by MedDRA System Organ Class and Preferred Term using frequency counts and percentages (i.e., number and percentage of subjects with an event).

(schwerwiegende) unerwünschte Ereignisse

Safety assessments included annual liver ultrasonography, vector shedding measurement, and immune response assessment directed at the AAV vector or the transgene product. All participants underwent ultrasound imaging of the liver at times specified. Vector shedding of fidanacogene elaparvovec in plasma, saliva, peripheral blood mononuclear cells, urine, and semen was assessed until three consecutive specimens reached below the detection limit for the given specimen type.

jährliche Lebersonographie, Messung der Vektorfreisetzung, Testung der Immunantwort

Mortality: All causes of mortality were recorded.

Mortalität

Available outcomes for patient population with severe and moderately severe haemophilia B

Outcomes that were identified as relevant in the PICO question and reported in the BENEGENE-2 study are presented in the Table 5-7. Several health-related quality of life (HRQoL) parameters were planned to be measured during the study, but were not included in the publication by Cuker et al. [29]: change in joint health as measured by the Haemophilia Joint Health Score (HJHS) instrument, Haemophilia Quality of Life Questionnaire (Haem-A-QoL) Physical Health domain, and Haemophilia Activities List (HAL) Complex Lower Extremity Activities Component Score. These parameters were subsequently submitted by the health technology developer to the AIHTA on 19 December 2024.

erhobene vs. berichtete Endpunkte

Table 5-7: Overview of outcomes assessed in the BENEGENE-2 study in relation to the PICO question

Outcomes	Reported in the study
Efficacy	
Annual bleeding rate for total bleeds (treated and untreated) from week 12 to month 15 vs. usual-care FIX prophylaxis regimen	*yes*
Annualised infusion rate (AIR) of exogenous FIX from week 12 to month 15 vs. AIR of FIX with usual-care FIX replacement regimen	*yes*
Mean vector-derived FIX: C level at steady state (from week 12 to month 15) demonstrated to be >5%	*yes*
Annualised FIX consumption.	*yes*
Annualised number of bleeding events of a specific type: spontaneous, traumatic, and untreated	*yes*
Frequency of target joint bleeds	*yes*
Percentage of participants without bleeds	*yes*
Change in joint health as measured by the HJHS instrument	*no*
Haem-A-QoL Physical Health domain	*no*
HAL Complex Lower Extremity Activities Component Score	*no*
Safety	
AEs	*yes*
SAEs	*yes*
Safety assessments included annual liver ultrasonography, vector shedding measurement, and immune response assessment directed at the AAV vector or the transgene product.	*yes*
Mortality	*yes*

Abbreviations: ABR … annualised bleeding rate, AIR … annualised infusion rate, AEs … adverse events, FIX … factor IX, HAL … Haemophilia Activities List, FIX:C (circulating levels of factor IX), Haem-A-QoL … Haemophilia Quality of Life Questionnaire for Adults, HJHS … Haemophilia Joint Health Score, PRO … patient-reported outcome, SAEs … serious adverse events.

5.3 Study results on relative effectiveness and relative safety

There is only partial evidence on the relative effectiveness and safety of fidanacogene elaparvovec for the treatment of severe and moderately severe haemophilia B (congenital FIX deficiency) in adult patients without a history of FIX inhibitors and detectable antibodies to variant AAV serotype Rh74. The evidence for relative effectiveness comprises the comparison data between the population treated with fidanacogene elaparvovec and an intra-individual comparison based exclusively on data from the same study participants during their treatment with prophylactic FIX therapy in BENEGENE-1 study. The detailed results of these comparisons are presented in the subsequent subchapter.

eingeschränkte Ergebnisse zur relativen Wirksamkeit und Sicherheit → basierend auf intra-individuellem Vergleich

Results for the patient population with severe and moderately severe haemophilia B (BENEGE-2 study)

Primary and key secondary efficacy study results

The results were compared between the patients who had received prophylaxis FIX treatment for at least six months in BENEGENE-1 study and those who consecutively entered BENEGENE-2 study and were treated with fidanacogene elaparvovec.

intra-individueller Vergleich

Primary endpoint

Primary efficacy analysis was conducted in 45 patients. The primary endpoint, the ABR for total bleeding episodes, decreased from 4.42 (95% CI, 1.80-7.05) during the prophylaxis period to 1.28 (95% CI, 0.57-1.98) from week 12 to month 15 after fidanacogene elaparvovec therapy. The treatment difference estimate was -3.15 episodes (95% CI, -5.46 to -0.83; p=0.008), demonstrating both non-inferiority (primary endpoint) and superiority (secondary endpoint) of gene therapy compared with factor IX prophylaxis. The mean ABR for total bleeding episodes was reduced after gene therapy with fidanacogene elaparvovec by 71% as compared with prophylaxis (p<0.001). Additionally, the proportion of patients who experienced no bleeding episodes increased from 29% (13 patients) during prophylaxis to 64% (29 patients) after gene therapy (Table 5-8).

45 auswertbare Pat.

mittlere ABR für Gesamtblutungen um 71 % reduziert

Key secondary endpoint

The ABR for treated bleeding episodes was 3.34 (95% CI, 1.70 to 4.98) in the prophylaxis period and 0.73 (95% CI, 0.23 to 1.23) after fidanacogene elaparvovec therapy for an estimated treatment difference of -2.61 (95% CI, -4.27 to -0.96; p=0.002). The proportion of patients without treated bleeding episodes increased from 36% (16 patients) to 73% (33 patients). The mean AIR decreased significantly from 58.83±29.06 to 4.54±10.03 (treatment difference: -54.29; 95% CI, -63.58 to -45.01; p<0.001), representing a 92.3% reduction. Similarly, the mean annualised total FIX consumption decreased from 3168.56±1635.55 IU/kg to 239.39±539.62 IU/kg (treatment difference: -2929.17; 95% CI, -3397.49 to -2460.85; p<0.001), representing a 92.4% reduction. Six out of 45 (13.3%) patients have resumed FIX-prophylaxis post fidanacogene elaparvovec infusion (primary reason: five due to low FIX:C and one due to bleed frequency), with time to resumption ranging from 5.1 months to 20.5 months (Table 5-8).

ABR für behandelte Blutungen reduziert

Pat. ohne behandlungspflichtige Blutungen:
vorher: 36 % (16)
nachher: 73 % (33)

13,3 %: Wiederaufnahme der Faktorgabe

Table 5-8: Efficacy results – primary and secondary efficacy endpoints of the BENGENE-2 trial

Time point Outcome Study reference/ID	Before FIX gene therapy, prophylaxis period (N = 45) Proportion of patients, n (%)	After FIX gene therapy, w 12 to m 15 (N = 45)	Treatment Difference	P Value	Percent reduction
BENEGENE-2					
The primary endpoint of noninferiority: all bleeding episodes[a]					
Model-derived annualised bleeding rate (95% CI)[b,c]	4.42 (1.80 to 7.05)	1.28 (0.57 to 1.98)	-3.15 (-5.46 to -0.83)	0.008	71.12 (50.09 to 83.29)
Participants without any bleeding episodes – no. (%)	13 (29)	29 (64)	-	-	-
Key secondary superiority endpoints: treated bleeding episodes and annualised infusion rate[d]					
Model-derived annualised bleeding rate (95% CI)[b,c]	3.34 (1.70 to 4.98)	0.73 (0.23 to 1.23)	-2.61 (-4.27 to −0.96)	0.002	78.15 (51.60 to 90.14)
Participants without any treated bleeding episodes – no. (%)	16 (36)	33 (73)	-	-	-
Mean annualised infusion rate[e]	58.83±29.06	4.54±10.03	-54.29 (-63.58 to -45.01)	<0.001	92.3[f]
Other secondary endpoints					
Participants who resumed prophylaxis – no. (%)	NA	6 (13)	-	-	-
Mean annualised total factor IX consumption – IU/kg	3168.56±1635.55	239.39±539.62	-2929.17 (-3397.49 to 2460.85)	<0.001	92.4[g]

Abbreviations: CI … confidence interval, FIX … factor IX, n … number of patients, m … month, NA … not available, w … week.

Notes:

[a] *Both spontaneous and traumatic bleeding episodes (treated or untreated) were counted, but procedural bleeding episodes were excluded. If the prophylaxis FIX regimen was resumed for a participant, then the period after the resumption of the prophylaxis regimen was excluded from the calculation of the endpoint of the annualised bleeding rate.*

[b] *The treatment difference and p-value were obtained from a repeated-measures generalised linear model with negative binomial distribution and identity-link function.*

[c] *The percentage reduction was obtained from a repeated-measures generalised linear model with negative binomial distribution and log-link function.*

[d] *Both spontaneous and traumatic bleeding episodes that resulted in FIX replacement treatment were counted, but procedural bleeding episodes were excluded. If the prophylaxis FIX regimen was resumed for a participant, then the period after the resumption of the prophylaxis regimen was excluded from the calculation of the endpoint of the annualised bleeding rate. If the prophylaxis FIX regimen was resumed for a participant, the time period after the resumption of the prophylaxis regimen was included in the calculation of the endpoint of the annualised infusion rate.*

[e] *The treatment difference was calculated as the rate after fidanacogene elaparvovec therapy minus the rate before gene therapy. The estimated 95% confidence interval and p-value were obtained from a paired t-test.*

[f] *The percent reduction was calculated as follows: 1 − (mean annualised infusion rate for FIX from week 12 to month 15 after fidanacogene elaparvovec therapy/the mean annualised infusion rate during standard-care factor IX replacement therapy) × 100% (in which the annualised infusion rate = number of infusions [for any reason] during the given period × 365.25/ [date of last day − date of first day + 1] in that period).*

[g] *The percent reduction was calculated as follows: 1 − (mean annualised FIX consumption [in IU per kg] for FIX from week 12 to month 15 after fidanacogene elaparvovec therapy/mean annualised FIX consumption [in IU per kg] during standard-care FIX replacement therapy) × 100%.*

Additional efficacy endpoints

Change in joint health from pre-infusion to post-gene therapy at 12 months using HJHS[6]

The change in joint health from pre-infusion to post-gene therapy at twelve months using HJHS was assessed.

Messung der Gelenkgesundheit mittels "Haemophilia Joint Health Score" (HJHS)

At baseline, the mean HJHS was 17.8 (standard deviation [SD]: 15.5; n=44). Among the 36 participants with HJHS data at year one, the mean HJHS change from baseline was -2.6 (95% CI: -4.7, -0.6; p=0.0117). The decrease was sustained in year two (-2.3 [95% CI: -4.4, -0.2; p=0.0322]). However, the clinical relevance of these results is uncertain [38].

HJHS-Score nach 1 Jahr um -2.6 Punkte verringert

Health-related quality of life (HRQoL)[6]

Statistically significant (p<0.05) improvements from pre-gene therapy through weeks twelve, 24, and 52 were seen for mean Haem-A-QoL Total Score and for individual Haem-A-QoL domains except Work and School (Week 12), Dealing with Haemophilia (weeks 24 and 52), and Partnership. The mean Haem-A-QoL Total Score was 29.1 (SD: 14.9) pre-gene therapy (n=40) and 17.2 (SD: 13.5) at week 52 (n=42). For the 37 participants with pre- and post-gene therapy data, the mean Total Score decreased by 11.2 (SD: 9.1) points (p<0.001) at week 52, indicating a clinically meaningful improvement in Haem-A-QoL. For the mean HAL total sum and component scores, statistically significant (p<0.05) improvements from pre-gene therapy to week 52 were seen. Additionally, improved responses to the EQ-5D-5L questionnaire were observed from pre- to post-gene therapy, indicating improved health status. The EQ-VAS (treatment difference [95% CI]) improved from pre- to Week 52 post-infusion by 5.8 (0.6-11.0; P=0.030) [39]. A score change of 7 points is considered clinically meaningful.

gesundheitsbezogene Lebensqualität durch spezifischen Fragebogen ermittelt (Haem-A-Qol): klinisch relevante Verbesserung

Hinweise auf verbesserten Gesundheitszustand nach der Gentherapie

Long-term effect of fidanacogene elaparvovec[6]

In the study BENEGENE-2, efficacy remained stable during years two to three post fidanacogene elaparvovec infusion regarding total ABR, AIR, and annualised FIX consumption. In contrast, the values were different for year four due to a low number of patients eligible for analysis (see Table 5-9).

Wirksamkeit der Gentherapie (bei ABR, AIR und FIX-Verbrauch) stabil bis 3 Jahre nach der Infusion

Table 5-9: Efficacy outcomes by year following fidanacogene elaparvovec administration in BENEGENE-2[a]

Outcome	Year 2 (15-24 m) (N=44)	Year 3 (24-36 m) (N=40)	Year 4 (36-48 m) (N=15)	Overall follow-up[b] (N=45)
ABRtotal				
Number (%) of patients without any bleeds	33 (84.6)	27 (79.4)	13 (86.7)	27 (60.0)
Mean (SD)	0.39 (1.110)	0.61 (1.624)	0.29 (0.776)	1.09 (2.208)
Median (min, max)	0.00 (0.0, 5.6)	0.00 (0.0, 8.2)	0.00 (0.0, 2.6)	0.00 (0.0, 9.9)
AIR				
Number (%) of patients without any treated bleeds	33 (75.0)	29 (72.5)	12 (80.0)	25 (55.6)
Mean (SD)	6.52 (18.697)	4.90 (14.871)	1.40 (4.691)	4.84 (11.085)
Median (min, max)	0.00 (0.0, 92.4)	0.00 (0.0, 81.2)	0.00 (0.0, 18.3)	0.00 (0.0, 53.3)

[6] Data are from the dossier submitted by the company on 19 December 2024.

Outcome	Year 2 (15-24 m) (N=44)	Year 3 (24-36 m) (N=40)	Year 4 (36-48 m) (N=15)	Overall follow-up[b] (N=45)
Annualised FIX consumption (IU/kg)				
Mean (SD)	301.34 (852.206)	219.01 (570.946)	56.28 (186.122)	230.51 (498.669)
Median (min, max)	0.00 (0.0, 4402.7)	0.00 (0.0, 2752.5)	0.00 (0.0, 724.7)	0.00 (0.0, 2304.8)
Number of participants resumed FIX prophylaxis (n)	1	0	0	6[c]

Abbreviations: ABR: annualised bleeding rate, AIR: annualised infusion rate, FIX: factor IX, m: months, n: number of patients, SD: standard deviation.

Notes:

[a] *Patients had varying lengths of follow-up post-infusion of fidanacogene elaparvovec, and bleeding and infusion rates were annualised within each period.*

[b] *From Week 12 to 30 Aug 2023.*

[c] *Five participants resumed FIX prophylaxis between month 5 and month 15. If the prophylaxis FIX regimen was resumed for a patient, then the period following the resumption of the prophylaxis regimen was excluded from the ABR endpoint calculation but still included in the AIR calculation.*

FIX activity simulation[7]

pharmakometrisches Modell zur Simulation der FIX-Aktivität entwickelt

A longitudinal pharmacometrics model of FIX activity (Actin FSL one-stage assay) was developed using data from fidanacogene elaparvovec phase 1-3 studies (BENEGENE-2, NCT03307980, NCT02484092), building on a previous approach for AAV-based gene therapies. FIX activity was simulated in 100,000 virtual individuals following 5×1011 vg/kg fidanacogene elaparvovec administration to generate the mean gene therapy response over 25 years (reference response). To compare this with standard therapy, FIX activity was also simulated for eftrenonacog alfa (ALPROLIX®), a recombinant FIX product, in 500 virtual individuals using a published population pharmacokinetic model.

welche Dosierung von ALPROLIX® ist notwendig, um den gleichen FIX-Aktivitätsspiegel zu erreichen wie durch Fidanacogene elaparvovec?

To assess comparative efficacy, two scenarios were simulated using a maximum likelihood estimation algorithm to determine eftrenonacog alfa dosing:

1. Weekly dosing with variable doses to match fidanacogene elaparvovec FIX activity.
2. Fixed 50 IU/kg dose with variable frequency.

Results for fidanacogene elaparvovec showed (Figure 5-2):

- Mean FIX activity remained >15 IU/dL in year 1, >8 IU/dL at year 10, and >4 IU/dL at year 25.
- Over 80% of the virtual population-maintained FIX activity >2 IU/dL during the first 10 years.
- More than 5% maintained levels above 20 IU/dL.
- Doses exceeding 100 IU/kg weekly in the first 10 years, or
- Dosing intervals shorter than 4.5 days with 50 IU/kg

benötigte Menge von ALPROLIX® würde die empfohlene Dosis übersteigen

These requirements exceed the recommended eftrenonacog alfa dosing regimen (50 IU/kg weekly or 100 IU/kg every ten days), suggesting that fi-danacogene elaparvovec achieves FIX activity levels not attainable within eftrenonacog alfa's labelled posology. These estimates are conservative as they don't include potential additional doses needed for breakthrough bleeding (Figure 5-3) [40].

[7] Data are from the dossier submitted by the company on 19 December 2024.

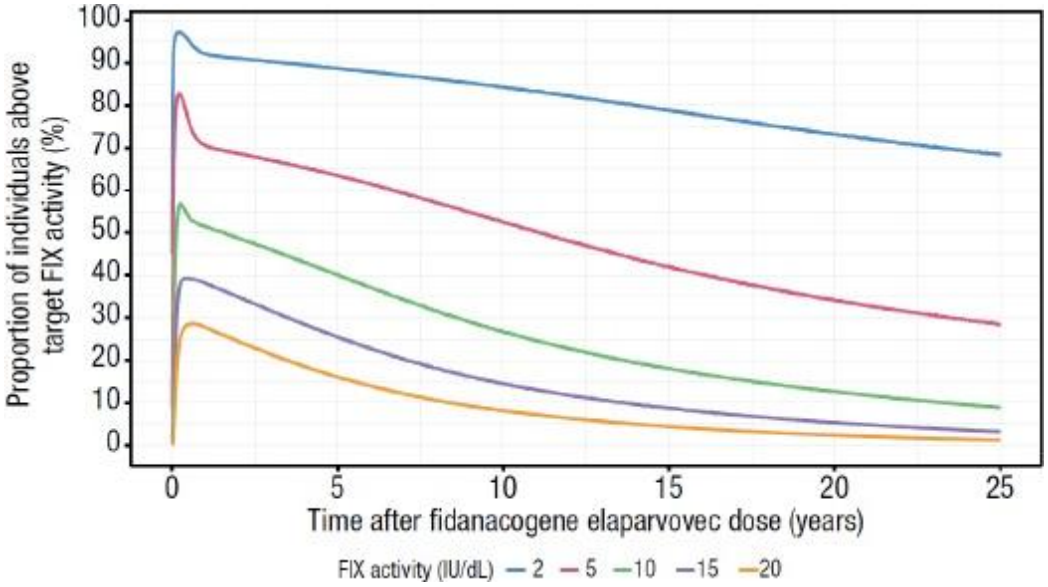


Figure 5-2: Proportion of individuals in the simulated population with predicted FIX activity above the selected target levels. FIX = factor IX (picture taken from [40])

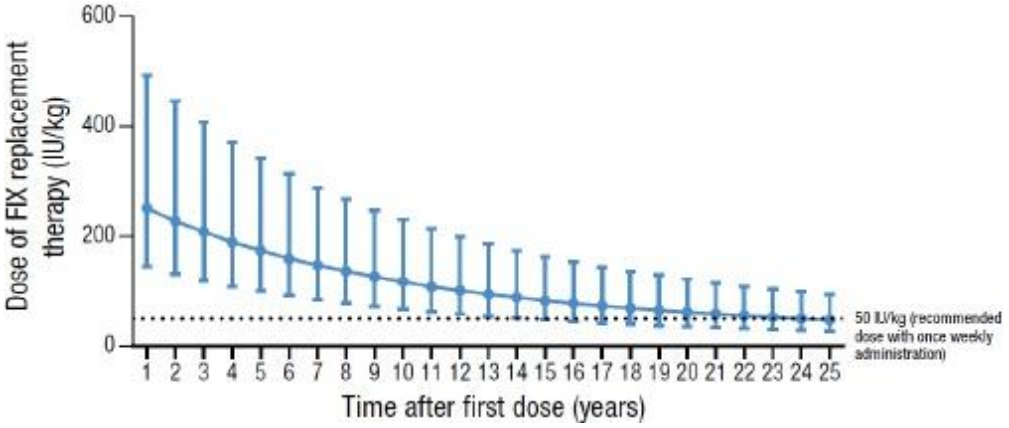


Figure 5-3: Median (90% PI) dose of FIX replacement therapy (eftrenonacog alfa; once weekly fixed frequency) required to maintain trough FIX activity at the time-matched mean fidanacogene elaparvovec response (picture taken from [40])

Simulation weist darauf hin, dass durch Gentherapie erreichter FIX-Aktivitätsspiegel durch ALPROLIX® in empfohlener Dosierung nicht erreicht werden kann

In conclusion, with an ALPROLIX® replacement therapy (eftrenonacog alfa), the simulated doses and frequencies required to maintain reference FIX activity trough levels comparable to fidanacogene elaparvovec exceeded recommended dosing regimens listed in the eftrenonacog alfa package insert (50 IU/kg once weekly or 100 IU/kg once every ten days). Assuming a fixed frequency of once weekly, required doses exceeded 100 IU/kg in the first 10 years. Assuming a fixed dose of 50 IU/kg, required frequencies were less than ~4.5 days between doses in the first ten years. These are conservative estimates; additional doses might be needed for on-demand treatment of bleeds. The findings suggest fidanacogene elaparvovec gene therapy results in FIX activity that is not achievable within the labelled posology for eftrenonacog alfa [40].

Results of safety outcomes for patient population with severe and moderately severe haemophilia B

Adverse Events (AEs) and serious adverse events (SAEs)

A total of 38 patients (84%) experienced AEs of any grade in severity. SAEs events occurred in seven patients (16%). The most common AE of any grade associated with fidanacogene elaparvovec therapy was an increased aminotransferase level (in 24 participants [53%]). A total of 28 participants (62%) received glucocorticoids for increased aminotransferase levels or decreased FIX levels (or both) (Table 5-10).

schwerwiegende unerwünschte Ereignisse (UE) bei 16%; häufigstes UE: erhöhter Aminotransferase-Spiegel

Mortality

No patient has died during the study from any cause (Table 5-10).

Table 5-10: Safety outcomes for patient population with severe and moderately severe haemophilia B

Study BENEGENE-2	Fidanacogene elaparvovec
	Participants (N=45)
Event	**Patients with event, n (%)**
Any adverse event	38 (84)
Increased levels of aminotransferase	24 (53)
Serious adverse event	7 (16)
Specific Serious adverse event	
Anaemia	2 (4.4)
Duodenal ulcer	1 (2.2)
Duodenal ulcer haemorrhage	1 (2.2)
Upper gastrointestinal haemorrhage	1 (2.2)
Drug-induced liver injury	1 (2.2)
COVID-19	1 (2.2)
COVID-19 pneumonia	1 (2.2)
Pilonidal disease	1 (2.2)
Alcohol poisoning	1 (2.2)
Femoral neck fracture	1 (2.2)
Coagulation factor IX level decreased	1 (2.2)
Hypokalaemia	1 (2.2)
Seizure	1 (2.2)
Infusion-related serious adverse event	0
Adverse event leading to study discontinuation	0
Adverse event leading to death	0

Abbreviations: n … number of patients.

Glucocorticoids initiation

The median time to glucocorticoid initiation was 37.5 days (range 11 to 123; Q1, Q3: 21.0, 69.0), and the median duration of glucocorticoid treatment was 95.0 days (range 41 to 276; Q1, Q3: 69.0, 138.5). The median total glucocorticoid dose was 3,558.75 mg (range 1,455.0 to 15,710.0). These data are based on 28 out of 45 participants who received glucocorticoid treatment (Table 5-11).

durchschnittlich 37,5 Tage bis zum Beginn einer Glukokortikoid-Therapie

Table 5-11: Corticosteroid treatment characteristics in BENEGENE-2

Study BENEGENE-2	Fidanacogene elaparvovec
	Participants (N=45)
Corticosteroid treatment parameters	
Time to corticosteroid initiation (days)[a]	
n	28
Mean (SD)	45.29 (30.101)
Median (Min, Max)	37.50 (11.0, 123.0)
(Q1, Q3)	(21.0, 69.0)
Total time on corticosteroid (days)[b]	
n	28
Mean (SD)	113.18 (58.814)
Median (Min, Max)	95.00 (41.0, 276.0)
(Q1, Q3)	(69.0, 138.5)
Total dose (mg)[c]	
n	28
Mean (SD)	4920.55 (39999.141)
Median (Min, Max)	3558.75 (1455.0, 15710.0)
(Q1, Q3)	(2377.5, 6032.5)

Abbreviations: n … number of participants, Q … quartile.

Notes:

[a] *Number of days from gene therapy with fidanacogene elaparvovec to the first onset of corticosteroid use for participants with corticosteroid treatment.*

[b] *Total time on corticosteroid is calculated as (date of stopping of corticosteroid – date of corticosteroid initiation +1) excluding any days without corticosteroid treatment and is calculated only for those participants who had corticosteroid treatment.*

[c] *An equivalent dose of prednisone is used to calculate the total corticosteroid dose.*

5.4 Quality of the evidence

Risk of Bias

Several risks of bias were identified for the BENEGENE-2 study (see Chapter 5 in the Appendix). The participants were not recruited consecutively but at once from the BENEGENE-1 study. Baseline documentation was incomplete, lacking previous treatment patterns and severity distribution.

unvollständige Pat.-Charakteristika, Unklarheit bzgl. Stadium der Erkrankung

Diskrepanzen bei Einschlusskriterien und Definition der Krankheitsschwere

The inclusion criteria (moderately severe to severe, FIX activity ≤2%) diverged from World Federation of Haemophilia definitions (severe <1%, moderate 1-5%) [13]. Moreover, FIX activity alone may not reflect clinical disease severity [2], as severity in clinical practice is defined by patient phenotype rather than FIX activity level alone [3].

fehlende Details im Behandlungsprotokoll, Bedenken hinsichtlich der Endpunkte (Bias Risiko, Änderung während der Studie)

Treatment protocol documentation showed limitations, with insufficient detail on allowed FIX replacement therapy (type and quantity) and variable corticosteroid administration and timing. Several endpoint-related concerns were identified: the primary endpoint (ABR) is subject to measurement bias [41], and its measurement consistency between BENEGENE-1 (baseline) and BENEGENE-2 was unclear. Additionally, there are documented differences in FIX activity measurements between one-stage and chromogenic assays, but these do not affect the results in the studies [42]. The clinical justification for the ABR non-inferiority margin 3.0 was missing, and the primary endpoint definition was changed during the study.

Limitationen durch Studiendesign: kurzes Follow-up, unverblindet

The study design had further limitations, including insufficient follow-up duration (15 months) for long-term safety and durability assessment and an unblinded design. These factors compromise the internal validity, resulting in a moderate risk of bias.

Inconsistencies in statistical analysis

3 Protokolländerungen und zahlreiche Änderungen des statistischen Analyseplans

Multiple amendments were made to the study protocol (three amendments) and statistical analysis plan [29]. Between the original protocol (13 December 2018) and the third amendment (29 June 2022), significant changes were made:

Originalprotokoll: 2 primäre Endpunkte

The original protocol (13 December 2018) specified two co-primary endpoints:

- Non-inferiority of ABR in the first 12 months post-infusion versus standard FIX prophylaxis.
- Vector-derived FIX:C levels at steady state (Week 12 to 12 months) exceeding 5%.

Änderungen nach 3. Überarbeitung

Third protocol amendment (29 June 2022) revised:

- Primary endpoint to total ABR (treated and untreated bleeds).
- Analysis period to week 12 through month 15 post-infusion.
- Start point of outcome analysis from day 1 to week 12 post-infusion to align with estimated FIX:C steady-state onset.

Inkonsistenz: 44 oder 45 Pat. bei Follow-up nach 15 Monaten?

These multiple amendments of the primary endpoint might have introduced a bias into results. An additional inconsistency was noted: while the applicant reported that 44 of 45 treated patients completed 15 months of follow-up, the final analysis included 15-month data for all 45 patients. This discrepancy remains unexplained.

External validity and applicability

Generalisierbarkeit der Studienergebnisse

The applicability of evidence from the BENEGENE-2 trial of fidanacogene elaparvovec in haemophilia B is addressed in the Appendix (Chapter 3.1.). For each domain, key trial characteristics are described and evaluated regarding their impact on the generalisability of results to routine clinical practice.

Heterogeneity and inconsistency across studies

Since only one clinical phase 3 study is available, no statement on heterogeneity or inconsistency can be made. On the quality of evidence, see chapter 5.

nur 1 Phase 3 Studie: keine Aussage zu Heterogenität und Inkonsistenz möglich

5.5 Indirect treatment comparison

Indirect treatment comparison (ITC) of fidanacogene elaparvovec to standard and gene therapy[8]

Methodology and included trials

In the absence of direct head-to-head comparisons between fidanacogene elaparvovec (BEQVEZ®, BENEGENE-2, Phase 3 trial), standard FIX prophylaxis therapy, and the approved gene therapy etranacogene dezaparvovec (HEMGENIX®), IQVIA, sponsored by Pfizer, conducted an indirect treatment comparison to evaluate fidanacogene elaparvovec against multiple available treatments for haemophilia B. The comparison was reported in a conference poster [43] and an abstract [44]. Based on the systematic literature research results and a feasibility assessment, five treatments were deemed feasible to compare with fidanacogene elaparvovec using an unanchored matching-adjusted indirect comparison (MAIC) approach. The methodology involved a systematic review of clinical trials (January 2000 to November 2023) and MAIC analyses. The matching criteria included age, disease severity, presence of prior bleeds, and presence of target joints. The primary outcomes were total ABR and proportion of patients with zero bleeding events (see Table 5-12) [28].

indirekter Vergleich von Fidanacogene elaparvovec mit 5 verfügbaren Behandlungsoptionen für Hämophilie B

Table 5-12: Trials selected for comparison with fidanacogene elaparvovec (adapted from [43])

Trial name (NCT)	Study type	Study Treatment	Description of population
BENEGENE-2 [29] (NCT03861273)	Phase 3, open-label, multicentre, single arm study to evaluate efficacy and safety	Fidanacogene elaparvovec (BEQVEZ®)	45 patients receiving prophylaxis (single dose)
Study B1821010 [45] (NCT01335061)	Phase 3, open-label, multicentre study to compare on-demand treatment to a prophylaxis regimen	Nonacog alfa (BENEFIX®)	25 patients receiving weekly prophylaxis (100 IU/kg)
B-LONG [46] (NCT01027364)	Phase 3, open-label, multicentre evaluation of the safety, pharmacokinetics, and efficacy	Eftrenonacog alfa (ALPROLIX®)	61 patients receiving weekly prophylaxis (50 IU/kg)
PROLONG-9FP [47] (NCT01496274)	Phase 2/3 open-label, multicentre, safety and efficacy study	Albutrepenonacog alfa (IDELVION®)	40 patients receiving weekly prophylaxis (35 to 50 IU/kg)
Paradigm 2 [48] (NCT01333111)	Phase 3, multicentre, single-blind trial evaluating safety and efficacy, including pharmacokinetics	Nonacog beta pegol (REFIXIA®)	29 patients receiving weekly prophylaxis (40 IU/kg)
HOPE-B [49] (NCT03569891)	Phase 3, open-label, single-dose, multicentre, multinational trial	Etranacogene dezaparvovec (HEMGENIX®)	54 patients receiving prophylaxis (single dose)

Abbreviation: IU … International Units.

Thirty-eight unique trials on the five comparators met the eligibility criteria and were included. However, after the feasibility assessment of these trials, only four trials (Study B1821010, B-LONG, PROLONG-9FP, and HOPE-B) assessing four interventions (BENEFIX®, ALPROLIX®, IDELVION®, and HEMGENIX®, respectively) were considered eligible for MAIC analyses. Another part of the report mentions that five trials were eligible for the compari-

5 Studien für indirekten Vergleich geeignet

[8] Data were submitted additionally by the company on 19.12.2024.

son (Study B1821010, B-LONG, PROLONG-9FP, HOPE-B and Paradigm 2) for five interventions (BENEFIX®, ALPROLIX®, IDELVION®, HEMGENIX®, and REFIXIA®, respectively). This inconsistency is discussed in the "Assessment of the ITC".

Baseline characteristics

After matching for age, disease severity, presence of prior bleed, and presence of target joints for the MAIC analysis, baseline characteristics were well-balanced (Table 5-13).

Baseline-Charakteristika ausgewogen

Table 5-13: Baseline characteristics in the BENEGENE-2 trial before and after matching to comparator trials (table taken from [44])

Baseline characteristic/group	Age (years, mean)	Age (years, SD)	Target joints, %	Severe disease <1%, %	Prior bleeds, %
BENEGENE-2 pre-matching	**33.2**	**11.0**	**28.9%**	**84.4%**	**71.1%**
fidanacogene elaparvovec (BENEGENE-2) vs. nonacog alfa [45]					
BENEGENE-2 (post-matching to Study B1821010	31.3	12.6	NA	88.0%	NA
Study B1821010	31.3	12.6	NA	88.0%	NA
fidanacogene elaparvovec (BENEGENE-2) vs. eftrenonacog alfa (B-LONG)					
BENEGENE-2 (post-matching to B-LONG[a])	50%	NA	57.1%	79.4%	NA
B-LONG[a]	50%	NA	57.1%	79.4%	NA
fidanacogene elaparvovec (BENEGENE-2) vs. albutrepenonacog alfa (PROLONG-9FP)					
BENEGENE-2 (post-matching to PROLONG-9FP)	31.6	15.2	52.5%	87.5%[b]	NA
PROLONG-9FP	31.6	15.2	52.5%	87.5%[b]	NA
fidanacogene elaparvovec (BENEGENE-2) vs. etranacogene dezaparvovec (HOPE-B)					
BENEGENE-2 (post-matching to HOPE-B)	41.5	15.8	18.5%	81.5%	81.5%
HOPE-B	41.5	15.8	18.5%	81.5%	81.5%

Abbreviations: NA … not available, SD … standard deviation.

Notes:

[a] *Age was matched on the percentage of patients older than 28 years for B LONG given only the median age reported.*

[b] *PROLONG-9FP only reported FIX activity level as ≤1 %*

Efficacy outcomes

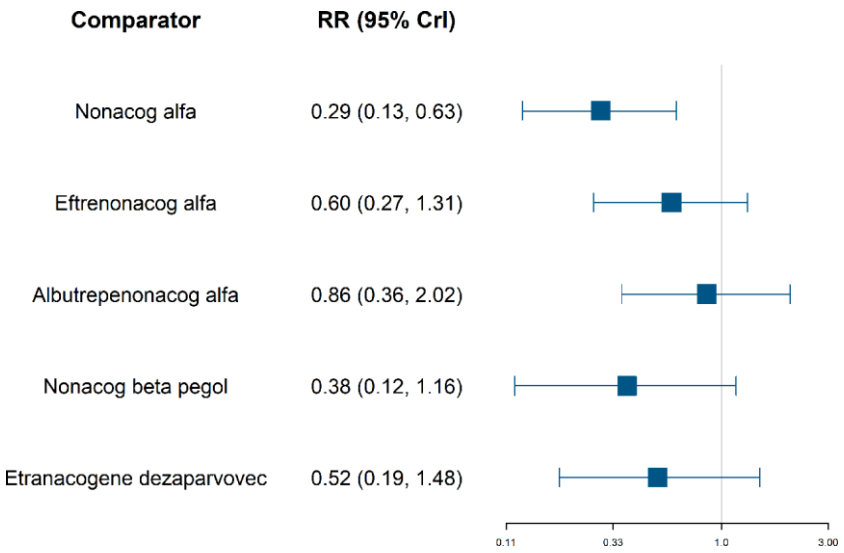
Annualised bleeding rate (ABR)

Fidanacogene elaparvovec showed a statistically significant lower total ABR compared to nonacog alfa (rate ratio [RR]: 0.29, 95% CI: 0.13-0.63). While total ABR was also numerically lower for fidanacogene elaparvovec when compared to eftrenonacog alfa (RR: 0.6, 95% CI: 0.27-1.31), albutrepenonacog alfa (RR: 0.86, 95% CI: 0.36-2.02), and etranacogene dezaparvovec (RR: 0.52, 95% CI: 0.19-1.48). These differences were not statistically significant (Figure 5-4).

Gesamt-ABR bei Fidanacogene elaparvovec statistisch signifikant niedriger als bei Nonacog alfa

Fidanacogene elaparvovec demonstrated a statistically significantly higher proportion of patients with zero bleeding events compared to both nonacog alfa (odds ratio [OR]: 3.55, 95% CI: 1.17-10.79) and eftrenonacog alfa (OR: 3.92, 95% CI: 1.48-10.39). While the proportion was also numerically higher compared to albutrepenonacog alfa (OR: 3.36, 95% CI: 0.78-14.48) and etranacogene dezaparvovec (OR: 1.74, 95% CI: 0.57-5.25), these differences were not statistically significant (Figure 5-5).

Fidanacogene elaparvovec: mehr Pat. ohne Blutungsereignisse verglichen mit Nonacog alfa und Eftrenonacog alfa



NOTE:
values less than 1 favour fidanacogene elaparvovec.

NOTE:
values greater than one favour fidanacogene elaparvovec.

Figure 5-4: Estimated effect of comparator treatments relative to fidanacogene elaparvovec with respect to total ABR (figure presented by [43]).

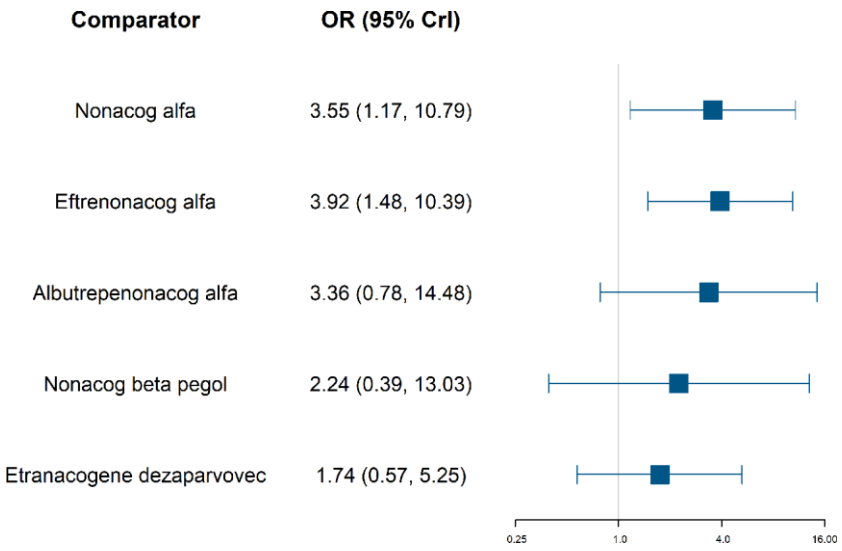


Figure 5-5: Estimated effect of comparator treatments relative to fidanacogene elaparvovec with respect to the proportion of patients with zero bleed events (figure presented by [43]).

Factor IX consumption

signifikanter Unterschied im FIX-Verbrauch zwischen Fidanacogene elaparvovec und Eftrenonacog alfa

The comparison of annualised FIX consumption between fidanacogene elaparvovec and eftrenonacog alfa (B-LONG) was analysed both before and after matching (Table 5-14). Before matching, the mean annualised FIX consumption was 235.04 IU/kg for fidanacogene elaparvovec compared to 2686.94 IU/kg for eftrenonacog alfa, showing a significant mean difference of -2451.90 (95% CI: -2712.21, -2191.59). After matching adjustment, the absolute mean difference in annualised FIX consumption remained statistically significant at -2301.21 [28].

Table 5-14: Fidanacogene elaparvovec (BENEGENE-2) versus eftrenonacog alfa (B-LONG): unadjusted and matching-adjusted treatment comparisons of annualised FIX consumption [28]

Source trial	Sample size or ESS	Annualized FIX consumption (IU/year)	Mean difference*	95% CI lower limit	95% CI upper limit	p-value
BENEGENE-2, unadjusted comparison	45	235.04	-2451.90	-2712.21	-2191.59	<0.0001
BENEGENE-2, matching-adjusted, base case	29.56	385.73	-2301.21	-2689.60	-1912.82	<0.0001
BENEGENE-2, matching-adjusted, sensitivity analysis	30.78	370.45	-2316.49	-2675.41	-1957.56	<0.0001
B-LONG	63**	2686.94	NA	NA	NA	NA

signifikanter Unterschied im FIX-Verbrauch zwischen Fidanacogene elaparvovec und Nonacog alfa

The comparison of annualised FIX consumption between fidanacogene elaparvovec and nonacog alfa (Study B1821010) was analysed both before and after matching (Table 5-15). Before matching, fidanacogene elaparvovec showed significantly lower mean annualised FIX consumption at 235.04 IU/kg compared to nonacog alfa (mean difference: -4749.96; 95% CI: -4932.00, -4567.91). After matching, two analyses were performed: in the base-case analysis, fi-

danacogene elaparvovec's consumption slightly increased to 254.54 IU/kg (mean difference: -4730.46; 95% CI: -4945.04, -4515.88), while in the sensitivity analysis, it slightly decreased to 232.40 IU/kg (mean difference: -4752.60; 95% CI: -4936.70, -4568.50). Both analyses showed statistically significant results favouring fidanacogene elaparvovec [28].

Table 5-15: Fidanacogene elaparvovec (BENEGENE-2) versus nonacog alfa (Study B1821010): unadjusted and matching adjusted treatment comparisons of annualised FIX consumption [28]

Source trial	Sample size or ESS	Annualized FIX consumption (IU/year)	Mean difference*	95% CI lower limit	95% CI upper limit	p-value
BENEGENE-2, unadjusted comparison	45	235.04	-4749.96	-4932.00	-4567.91	<0.0001
BENEGENE-2, matching-adjusted, base case	34.02	254.54	-4730.46	-4945.04	-4515.88	<0.0001
BENEGENE-2, matching-adjusted, sensitivity analysis	44.57	232.40	-4752.60	-4936.70	-4568.50	<0.0001
Study B1821010	25	4985	NA	NA	NA	NA

Results were consistent between the base case and sensitivity analyses for eftrenonacog alfa, nonacog beta pegol, and nonacog alfa comparisons.

Assessment of the ITC

unverankerte MAIC-Analyse

The applicant has delegated to IQVIA to conduct an unanchored MAIC [26] matching for age, disease severity, presence of prior bleeds, and target joints. This data is published in two conference contributions (a poster and an abstract, [43, 44]) to the 2024 International World Congress of the World Federation of Haemophilia (April, Madrid), both sponsored by the health technology developer.

5 Komparatoren

The ITC of fidanacogene elaparvovec (BEQVEZ®) has been conducted to compare with nonacog alfa (BENEFIX®), eftrenonacog alfa (ALPROLIX®), albutrepenonacog alfa (IDELVION®), nonacog beta pegol (REFIXIA®) and etranacogene dezaparvovec (HEMGENIX®). The manufacturer funded all information on ITC.

statistische Signifikanz nur für bestimmte Vergleiche

In addition to some statistically significant differences, the authors of the analysis further state that fidanacogene elaparvovec was numerically better than existing haemophilia B therapies. This statement, however, holds little value in the absence of statistical significance. The analysis has only shown that fidanacogene elaparvovec is better than nonacog alfa in terms of ABR, number of infusions, and percentage of participants with spontaneous bleeding events. Additionally, fidanacogene elaparvovec is favoured in reducing bleeding events and annualised FIX consumption compared to nonacog alfa and eftrenonacog alfa.

Limitationen des indirekten Vergleichs

The applicant who commissioned the analysis, identified some limitations himself: The main limitation of this analysis is that some factors that may be associated with outcomes (higher spontaneous bleeding event during the lead-in phase, more patients who returned to prophylaxis within the BENEGENE-2 trial) were not able to be adjusted for due to the limited information reported from the trials of comparator treatments. Furthermore, the FIX replace-

ment treatment trials did not report important baseline characteristics for matching, and matching was based only on matching variables with available data. In addition, B-LONG reported outcomes for 61 patients, while weighting was conducted based on 63 patients for which baseline data were reported, assuming there was no difference between these two groups. Although population matching was successful, the relatively low sample size in the BENEGENE-2 trial led to small effective sample sizes. As a result, wide confidence intervals were observed, suggesting imprecise and unstable results in many of the analyses. However, compared with eftrenonacog alfa, an EHL replacement therapy, and nonacog alfa, a SHL replacement therapy, statistically significant results were detected in favour of fidanacogene elaparvovec for ABR for treated bleeds [28].

von AIHTA identifizierte methodologische Einschränkungen

Furthermore, the AIHTA has also identified issues with the methods implemented; hence, the results should be taken with caution:

- Firstly, due to inconsistent and untransparent reporting, the applicant states that five treatments were deemed feasible to compare with BEQVEZ® using an unanchored MAIC approach: (BENEFIX®, ALPROLIX®, IDELVION®, HEMGENIX®, and REFIXIA®). Then later, the applicant stated that four trials with four different interventions (BENEFIX®, ALPROLIX®, IDELVION®, and HEMGENIX®) were eligible for MAIC analyses. Finally, in the results of MAIC, five trials are included with REFIXA®. Also, in the dossier, the applicant mentions that 38 trials met the eligibility criteria and were included, yet the ITC report says that ten out of 33 trials were included. These inconsistencies are not explained.
- Secondly, due to a lack of more detailed information on methodology, ABR is a subjective endpoint, and its measurement can vary among the trials [41]. It is not clear if ABR and bleeding events were measured consistently among the studies. Furthermore, not all parameters from the baseline characteristics are available for all included studies (prior bleeds, target joints). All the studies included were open-label, and some were single-arm studies. Three studies were non-randomised. The applicant does not discuss how to handle these biases.
- Furthermore, the following information on the MAIC analysis is missing (see Chapter 3.3. in the Appendix):
  - Methods
    - Detailed description of outcome measures.
    - Handling of potential bias/inconsistency.
  - Results
    - Detailed individual study data and detailed patient characteristics.
    - Justification of model results.
  - Discussion
    - Internal and external validity.

5.6 Ongoing Studies

derzeit 3 laufende klinische Studien

A total of 3 ongoing clinical studies with fidanacogene elaparvovec treatment were identified, all sponsored by the marketing authorisation holder. Among these is this report's pivotal study (highlighted in grey). The patients in this study are to be followed for six years. The study NCT03307980 is a long-term safety and efficacy follow-up study for participants with haemophilia B who were previously treated in the Phase 1/2a, open-label, single-dose, single-arm, multi-centre trial to assess the safety of fidanacogene elaparvovec in 15 subjects with haemophilia B. Additionally, this study is a dose-escalation substudy evaluating the safety, tolerability, and kinetics of a higher dose of fidanacogene elaparvovec with long-term safety and efficacy follow-up. The objective of study NCT05568719 is to learn about the long-term safety and efficacy of giroctocogene fitelparvovec or fidanacogene elaparvovec in patients with haemophilia A or haemophilia B, respectively, who have received treatment through prior participation in a Pfizer-sponsored clinical trial (see Table 5-16).

Table 5-16: List of ongoing studies with fidanacogene elaparvovec [50]

Title	Trial ID	Other IDs	Phase	Status	Estimated study completion date
A study to evaluate the efficacy and safety of FIX gene therapy with PF-06838435 in adult males with moderately severe to severe hemophilia B	NCT03861273	BENEGENE-2	Phase 3	Active, not recruiting.	9 January 2031
Long-term safety and efficacy study and dose-escalation substudy of PF 06838435 in individuals with hemophilia B	NCT03307980		Phase 2	Active, not recruiting.	6 June 2029
Safety and effectiveness of giroctocogene fitelparvovec or fidanacogene elaparvovec in patients with hemophilia A or B respectively	NCT05568719		Phase 3	Recruiting.	3 September 2039

The study included in this assessment is highlighted in grey.

5.7 International HTA reports

1 kanadischer HTA-Bericht

CDA-AMC empfiehlt Erstattung ausschließlich bei Einhaltung bestimmter Kriterien

One HTA report was identified from the Canada's Drug Agency (CDA-AMC) – Reimbursement recommendation [3, 51].

CDA-AMC recommends reimbursement of fidanacogene elaparvovec for the treatment of adults (aged 18 years or older) with moderately severe to severe haemophilia B (congenital factor IX deficiency) who are negative for nABto variant AAV serotype Rh74 (AAVRh74var), only if the conditions listed in Table 5-17 are met.

CDA-AMC concluded that fidanacogene elaparvovec might meet some of the needs of haemophilia B patients because it is a one-time gene therapy designed to provide an alternative active source of endogenous FIX that improves bleeding outcomes and reduces FIX use after treatment. The evidence from the BENEGENE-2 trial is associated with uncertainty because the comparative evidence is non-randomised, and potential sources of bias were identified (e.g., open-label design, self-reported bleeding events, subjective nature of some outcomes, assumptions of statistical models used for intrapatient comparisons). In addition, while patients expect gene therapy to be effective for at least ten years, the long-term efficacy of fidanacogene elaparvovec is unknown due to the limited duration of follow-up in the available evidence [3].

Table 5-17: Reimbursement conditions [3]

Reimbursement condition
1. Adults (aged ≥ 18 years) who meet all of the following criteria:
1.1. Documented moderately severe to severe haemophilia B based on FIX:C ≤ 2% and bleeding requiring ongoing prophylactic treatment
1.2. Negative for neutralising antibodies to variant AAV serotype Rh74.
2. Fidanacogene elaparvovec should not be reimbursed in patients who meet any of the following criteria:
2.1. Presence of FIX inhibitors
2.2. Previous receipt of gene therapy for the treatment of haemophilia B.
3. Treatment with fidanacogene elaparvovec is a one-time therapy.
4. Fidanacogene elaparvovec must be prescribed by specialists with expertise in treating haemophilia B.
5. A reduction in price.
6. The feasibility of the adoption of fidanacogene elaparvovec must be addressed.
7. The organisational feasibility of conducting anti-AAVRh74var nAbs testing must be covered by the sponsor.

Abbreviations: AAV … adeno-associated virus, FIX … factor IX, FIX:C … circulating levels of factor IX, nAB … neutralising antibodies.

6 Treatment costs, budget impact and price comparison

6.1 Price comparison and managed entry agreements

keine Preisinfos zu Fidanacogene elaparvovec vorhanden

The Austrian National Public Health Institute (Gesundheit Österreich GmbH, GÖG) found no price information for fidanacogene elaparvovec in moderately severe and severe haemophilia B in 15 European Union (EU) countries and the United Kingdom (UK). For Austria, the pharmaceutical company also reported no price for fidanacogene elaparvovec. For Austria, the pharmaceutical company also reported no price for fidanacogene elaparvovec (see Table 6-1).

Table 6-1: Price information fidanacogene elaparvovec

Country	Indication	Setting	Fidanacogene elaparvovec price	Managed entry agreements	Reference
AT	Moderately-sever and sever haemophilia B	NI	NI	NI	Information from manufacturer
BE, DE, DK, EL, ES, FI, FR, IE, IT, LU, NL, NO, PT, SE, UK	Moderately-sever and sever haemophilia B	NI	NI	NI	GÖG

Abbreviations: AT … Austria, BE … Belgium, CAN … Canada, DK … Denmark, EL … Greece, ES … Espagnole, FI … Finland, FR … France, GER … Germany, GÖG … Gesundheit Österreich GmbH, IE … Ireland, IT … Italy, LU … Luxemburg, NI … No information available, NL … Netherlands, NO … Norway, PT … Portugal, SE … Sweden, UK … United Kingdom

6.2 Budget impact analysis for the Austrian context before negotiations

Eligible population and market share in years 1-3

ca. 42 erwachsene Pat. in den kommenden 3 Jahren mit schwerer oder moderater Hämophilie B, davon 9 potenziell geeignet für Behandlung mit Fidanacogene elaparvovec: Jahr 1: 2 Pat. (20 %)
Jahr 2: 3 Pat. (30 %)
Jahr 3: 4 Pat. (50 %)

According to data from the Austrian haemophilia registry and information from clinical experts, there are currently around 130 persons living with haemophilia B in Austria. This number is assumed to stay the same over the next three years, as some patients will die, and some will be newly diagnosed. In total, 42 patients are older than 18 years of age and have severe or moderate haemophilia B. Of the patients with moderate haemophilia B, 25% are expected to receive prophylactic FIX treatment, resulting in 26 adult patients under FIX supplements. Based on expert information, 18 patients are expected not to be eligible for gene therapy due to AAV-neutralising anti-bodies, FIX inhibitors, severe liver disease or missing compliance, resulting in 9 potential fidanacogene elaparvovec candidates in the forthcoming three years with an assumed market uptake of 20%, 30% and 50% in the first to the third year. Based on the evidence, around 87% of the patients who received fidanacogene elaparvovec are expected to have a positive effect. In comparison, the remaining 13% will have no effect on the therapy, resulting in a return to the standard of care (SoC). Therefore, these patients and those not eligible for gene therapy still receive FIX prophylactic treatment. In comparison, the SoC scenario comprises all patients receiving FIX prophylaxis (n=39). The detailed patient numbers are displayed in Table 6-2.

Table 6-2: Population haemophilia B

Population	Year 1 (n)	Year 2 (n)	Year 3 (n)	Reference/assumption
A: Estimated patient population with HB in Austria, n	130			*[12]*
B: Patients with moderately severe to *severe* HB, n	61			*[12]*
C: Patients with moderately severe to severe HB who receive prophylactic FIX treatment, n	**39**			*Assumption: 25% of the moderate HB receive FIX prophylaxis [12]*
D: Patients with moderately severe to severe HB >18 years of age, n	42			*[12]*
E: Patients >18 years of age who receive prophylactic FIX treatment, n	**26**			*Assumption: 25% of the moderate HB receive FIX prophylaxis [12]*
F: Patients **NOT** eligible for fidanacogene elaparvovec due to AAV-neutralising anti-bodies, FIX inhibitors, severe liver disease or missing compliance (15%), n	14			*Assumption: AAV-neutralising anti-bodies: 60% [2]; FIX inhibitors: 7,5% [33], liver disease and missing compliance: 7,5% [12]*
G: Potential number of eligible patients for fidanacogene elaparvovec over 3 years, n	**9**			-
H: Potential number of eligible patients for fidanacogene elaparvovec per year, n	**2**	**3**	**4**	*Assumption based on clinical expert input: market uptake 20% year 1, 30% year 2, 50% year 3*
I: Patients with IV reactions leading to hospitalisation (0%), n	0	0	0	*[29]*
J: Patients with NO effect (13.3%) → return to SoC	0	0	1	*[52]*
K Patients **WITH** effect (86.7%) → no SoC needed (H-J)	2	3	3	*[52]*
L: Patients >18 years of age still receiving prophylactic FIX treatment per year, n (E-H)	24	21	17	-
M: Patients <18 years of age receiving FIX treatment per year, n (C-E)	13	13	13	-
N: **SoC-leftovers in gene therapy scenario:** patients still with SoC + WITHOUT treatment effect (L+J)	24	21	18	-
O: **SoC scenario: all patients receiving FIX prophylaxis (C)**	**39**	**39**	**39**	-

Abbreviations: FIX … factor IX; HB … haemophilia B, n … number of patients, SoC … standard of care

Treatment costs of therapy under evaluation per patient and gross budget impact (drug acquisition costs) year 1-3

Kosten Fidanacogene elaparvovec: €28.9 Mio. für 3 Jahre

Currently, there is no price available for fidanacogene elaparvovec in Europe. Based on assumptions of a Canadian cost-utility analysis, the price was assumed to be € 3.4 million per patient regardless of the dosage needed. For the estimated patient population in Table 6-2, the total drug acquisition cost would be around € 6.1 million in the first year, € 9.1 million in the second year and € 13.6 million in the third year, resulting in around € 28.9 million over the next three years.

SoC costs

jährliche Kosten pro Pat.: €80.000 – €500.000 abhängig von Produkt, Dosis & Körpergewicht

The annual costs of the FIX prophylaxis per patient range between around € 80,000 (cheapest product; minimum dosage; 70 kg body weight) and € 500,000 (most expensive product; maximum dosage; 80 kg) and depend on the dosage, annual consumption and price per pack.

Total Austrian SoC costs for the estimated patient population in Table 6-2, (based on total outpatient expenditure of the FIX treatments and inpatient expenditure for admissions related to haemophilia B) are currently around € 4.6 million per year and would be € 13.8 million over the next three years, if prices and prescription volumes remain stable. The inpatient on-demand FIX substitution accounts for <4% of the total costs (Table 6-3).

gesamte Kosten für SoC:
€ 4,6 Mio. pro Jahr

Table 6-3: Cost of severe and moderately severe haemophilia B (SoC scenario)

Cost categories	Year 1	Year 2	Year 3	Total	%
SoC prophylactic and on-demand outpatient treatments	€ 4,434,458	€ 4,434,458	€ 4,434,458	€ 13,303,375	96.2
On-demand FIX substitution in the inpatient sector	€ 174,878	€ 174,878	€ 174,878	€ 524,635	3.8
Total direct medical costs of SoC scenario WITHOUT fidanacogene elaparvovec	**€ 4,609,337**	**€ 4,609,337**	**€ 4,609,337**	**€ 13,828,010**	**100**

Abbreviation: FIX … factor IX, SoC … standard of care

Net drug-budget impact in year 1-3

Most patients in the clinical study (86,7%) treated with fidanacogene elaparvovec did not need SoC treatment (FIX prophylaxis). If this holds in real-world practice, the net budget impact (drug acquisition costs and cost offsets anticipated from the displacement of SoC drugs and treatments) would be € 5.9 million in year 1, € 8.8 million in year 2, € 13.2 million in year 3 and around €28 million over three years. The savings in SoC would be between € 181,926 and € 394,426 from year 1 until year 3, and € 917,364 over three years. In case of long-term effectiveness of fidanacogene elaparvovec, the savings would primarily affect the outpatient sector, while the inpatient sector would bear the additional costs of gene therapy.

ca. € 917.000 Einsparungen bei Standardtherapie innerhalb von 3 Jahren durch Fidanacogene elaparvovec

Additional costs

The additional costs in the fidanacogene elaparvovec scenario comprised the inpatient stay for the gene therapy application, the prophylactic FIX treatment over at least four weeks after gene therapy application (based on consultations with Austrian clinical experts) and the FIX prophylaxis for all patients with no effect of the gene therapy, resulting in a budget impact of around € 193,499 over three years. In addition, costs arise due to the very common adverse event "increased alanine transaminase or decreased FIX levels" in around 62% of the patients. However, the treatment costs of this adverse events were very low (see Table 6-4).

zusätzliche Kosten: stationärer Aufenthalt, FIX-Therapie 4 Wo nach Gentherapie FIX-Therapie für Pat. ohne Effekt:
ca. € 193.499 für 3 Jahre

The total direct medical costs of fidanacogene elaparvovec treatment, including additional costs next to drug acquisition costs would be around € 6.2 million for the first year, € 9.2 million for the second year, € 13.7 million for the third year, and € 29 million over all three years. The drug acquisition costs account for the greatest proportion with around 70% (Table 6-3).

gesamte direkte Kosten: € 29 Mio. für 3 Jahre

The total costs for treating the eligible patients with fidanacogene elaparvovec and all others with SoC would be € 10.6 million for year 1, rising to € 17.2 million in year three. Over three years, total treatment costs of € 41.0 million were estimated.

gesamte Kosten Gentherapie-Szenario:
€ 41.0 Mio. für 3 Jahre

Table 6-4: Cost of severe and moderately severe haemophilia B (fidanacogene elaparvovec scenario)

Cost categories	Year 1	Year 2	Year 3	Total	%

Cost categories	Year 1	Year 2	Year 3	Total	%
A: Drug acquisition cost	€ 6,120,000	€ 9,180,000	€ 13,600,000	€ 28,900,000	70.42
B: Additional costs (application, prophylactic treatments after gene therapy, FIX treatment for no effect)	€ 37,468	€ 62,878	€ 93,153	€ 193,499	0.47%
C: Adverse events	€ 54	€ 81	€ 121	€ 257	0.00
A-C: Direct medical costs of fidanacogene elaparvovec treatment	€ 6,157,522	€ 9,242,960	€ 13,693,274	€ 29,093,756	**70.89**
D: Costs of SoC and on-demand treatment	€ 4,394,548	€ 4,003,335	€ 3,549,401	€ 11,947,283	29.11
A-D: Total direct medical costs of fidanacogene elaparvovec scenario	€ 10,552,070	€ 13,246,295	€ 17,242,675	€ 41,041,039	**100**

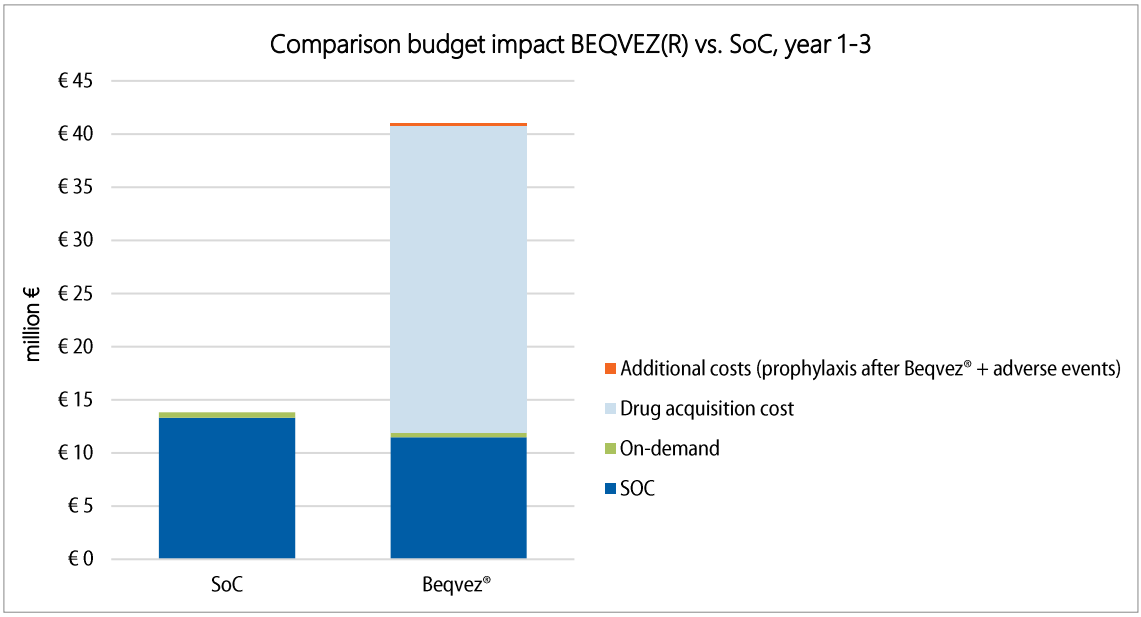
Abbreviation: SoC … standard of care

Comparison of fidanacogene elaparvovec scenario with current SoC

Fidanacogene elaparvovec Szenario mehr als 3x teurer als das Standardtherapie-Szenario über die nächsten 3 Jahre

In summary, based on the assumed number of patients potentially eligible for fidanacogene elaparvovec in Austria (n=9), total costs for all patients would rise per year, summing up to € 41.0 million for three years if fidanacogene elaparvovec is introduced and received by four patients (20%) in year 1, seven patients (30%) in year 2 and eleven patients (50%) in year 3, while the remaining patients would be treated as usual (FIX prophylaxis and if needed FIX on-demand treatment). Costs for acquiring fidanacogene elaparvovec and the additional costs associated with its administration account for roughly 71% of the total costs, while the treatment for the remaining patients with the current SoC accounts for 29.1%. In contrast, if fidanacogene elaparvovec is not introduced, and patients continue receiving SoC as usual, only around one-third of the budget (€ 13.8 million) would be needed (Abbreviation: SoC: standard of care

Figure 6-1).



Abbreviation: SoC: standard of care

Figure 6-1: Comparison SoC vs. fidanacogene elaparvovec scenario haemophilia B

7 Economic evaluation based on pharmaco-economic models

7.1 Summary of existing economic evaluations

Characteristics of the economic evaluations and applied models

We identified one health economic evaluation based on a decision-analytic model provided by the sponsor and appraised by Canadian Agency for Drugs and Technologies in Health (CADTH) [3, 51]. Table 5-1 in the Appendix summarises the main characteristics.

1 gesundheits-ökonomische Analyse identifiziert:

The provided cost-utility analysis examined the cost-effectiveness of fidanacogene elaparvovec compared to standard of care (SoC) (factor IX [FIX] prophylaxis treatments) in adult patients (aged 18 years and older) with moderately severe to severe haemophilia B. A Markov model with four health states based on an annual number of bleeds (0 bleeds, > 0 to < 3 bleeds, ≥ 3 to < 5 bleeds, ≥ 5 bleeds) and death, as well as a one-year cycle time horizon, was applied. Moreover, the model pictured the perspective of Canadian publicly funded healthcare payers and considered a lifetime horizon (77 years).

1 Markov Model (vom Sponsor erstellt) für moderate bis schwere Hämophilie B: 4 Gesundheitszustände, Zahlerperspektive & lebenslanger Zeithorizont

Outcomes were presented as life years (LYs) gained and quality-adjusted life years (QALYs) gained. The effectiveness data of fidanacogene elaparvovec originated from the BENEGENE-2 trial, while the effectiveness data of FIX prophylaxis treatments were taken from the BENEGENE-1 study. Regarding the costs, a placeholder price of $ 4,773,595.20 (€ 3,390,018.69) per administration (1×10^{13} vg/mL) was assumed, regardless of the number of vials required. Besides, administration costs associated with fidanacogene elaparvovec and cost and consequences of adverse events were not included, and neither was the neutralising antibody (nAb) testing since it was assumed to be covered by the sponsor. No indirect costs were considered. The coverage status of nAb testing is, however, uncertain. Cost and outcomes were applied with an annual discount rate of 1.5%.

Endpunkte: gewonnene Lebensjahre, QALYs,

angenommener Preis: € 3,4 Mio.

jährliche Diskontrate für Effekte und Kosten: 1,5 %

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. 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.

nach Gentherapie anhaltender Effekt für 25 Jahre angenommen

Results of the health economic evaluations

Base-case results of the sponsor's cost-utility analysis from a Canadian publicly funded healthcare payer perspective provide a mixed picture of the cost-effectiveness of fidanacogene elaparvovec in adult patients with moderately severe to severe haemophilia B (see Chapter 7 in the Appendix). The sponsor reported a gain of 1.08 QALYs compared to all comparators. While fidanacogene elaparvovec was not associated with any LY gains, the model predicted an incremental gain of 9.13 years in the "no bleeds" health state. Reported incremental costs between fidanacogene elaparvovec and FIX prophylaxis treatments ranged from € 2 million to € 4 million, depending on the type of FIX prophylaxis (standard half-life [SHL], extended half-life [EHL] or SHL-EHL basket).

Base-Case: inkrementelle Kosten: € 2,0 Mio. bis € 4,0 Mio. abhängig vom Vergleich

inkrementelle QALYs: 1,8; inkrementelle blutungsfreie Jahre: 9,13

Based on these results, fidanacogene elaparvovec was more effective and less costly (dominant) compared to SHL FIX prophylaxis, EHL FIX prophylaxis, and the basket of SHL and EHL FIX prophylaxis. At a willingness-to-pay threshold of $ 50,000 per QALY gained, there was a 97% probability of fidanacogene elaparvovec being cost-effective. The results were driven mainly by the acquisition cost of fidanacogene elaparvovec (90% of the total costs associated), as well as the predicted gain in QALYs and cost savings resulting from a reduction in bleeding events, FIX prophylaxis use, and healthcare resource use. Based on the model, the assumed acquisition cost of fidanacogene elaparvovec (€ 3,390,019 per administration) was predicted to be offset by savings after approximately 12 years.

Fidanacogene elaparvovec – dominante Therapie (effektiver & kostengünstiger) als FIX-Prophylaxe

hohe Kosten sollen nach 12 Jahren ausgeglichen sein

The sponsor conducted two scenario analyses that tested different outcome-based agreements based on the FIX prophylaxis infusions after gene therapy. The first scenario considered annuity payments, in which the annual cost of fidanacogene elaparvovec was applied to each patient who has received fidanacogene elaparvovec but has not initiated FIX prophylaxis infusion for 20 years. The second scenario considered lump-sum payments, in which the upfront cost of fidanacogene elaparvovec was applied to all patients who received fidanacogene elaparvovec, but a refund was applied if a patient needed to switch to FIX infusion during an eligibility period (18 years). In both outcome-based agreement scenarios, fidanacogene elaparvovec remained dominant over FIX prophylaxis.

2 Endpunkt-basierte Szenarien: Fidanacogene elaparvovec bleibt dominant gegenüber FIX

Overall, the CADTH concluded that the certainty of the evidence is low for most outcomes (see Chapter 7 in the Appendix) and noted that there is uncertainty in the magnitude and duration of the benefit of fidanacogene elaparvovec compared to FIX prophylaxis treatments due to the open-label, single-arm study design and the self-reporting of bleeding events. If the magnitude of benefit between fidanacogene elaparvovec and FIX prophylaxis is less than estimated or if the actual cost of FIX prophylaxis treatments is lower than incorporated in the model, it would take longer for any potential savings to be realised in the healthcare system [3].

CADTH-Bewertung: Ergebnisse unsicher, aufgrund der fehlenden Langzeit-Wirksamkeitsdaten & Kostenannahmen zu FIX-Prophylaxe

In the reanalysis of the economic evaluation, CADTH was unable to provide a more reliable estimate of the cost-effectiveness of fidanacogene elaparvovec.

Reanalyse von CADTH ergab keine zuverlässigeren Ergebnisse

7.2 Submitted pharmaco-economic model

The manufacturer has not submitted a model as requested as part of the dossier.

keine ökonomische Evaluation für AT übermittelt

8 Organisational, ethical, social and legal aspects of fidanacogene elaparvovec

8.1 Organisational aspects

Health delivery process & structure of the health care system

Versorgungsprozess: Screening und HUB-and-SPOKE-Modell

Implementing gene therapy for haemophilia involves complex care pathways integrating regular follow-up examinations and emergency care procedures. The patient journey begins with comprehensive screening, including neutralising antibody (nAb) testing for eligibility determination. Experts suggest implementing a HUB-and-SPOKE model to optimise treatment delivery, where specialised centres would serve as primary administration sites. In contrast, local centres could manage follow-up care [12, 33]. Under this model, eligible patients would receive a one-time infusion at designated HUB centres, followed by intensive initial monitoring in SPOKE centres with twice-weekly laboratory tests that gradually decrease frequency [3].

strukturierter stationärer Aufenthalt für Vorbereitung und Verabreichung

According to expert information, the implementation should include at least one inpatient hospital stay, independent of adverse reactions. This stay is suggested to be structured with Day 1 dedicated to preparation and Day 2 allocated for intravenous administration and subsequent monitoring [12]. Local treatment centres (spoke centres) could provide ongoing follow-up care; however, some patients may require additional inpatient admission to monitor acute infusion reactions [3, 12].

systematische Schulung des Fachpersonals für Therapiemanagement

Organisational requirements emphasise staff competence through systematic assessment and addressing of training needs [33]. Gene therapy implementation specifically requires multidisciplinary teams with expertise in administration and monitoring. Thus, healthcare providers necessitate specialised training to manage potential complications such as transaminitis and determine appropriate corticosteroid intervention timing [3].

Management Considerations

multidisziplinäre Eignungsprüfung und Berücksichtigung von Risiko-Pat.

Gene therapy for haemophilia requires comprehensive management strategies that address multiple complex dimensions. Eligibility determination involves nuanced clinical assessments by multidisciplinary teams at specialised haemophilia treatment centres, considering key factors such as neutralising antibodies, liver function, bleeding phenotype, and additional medical factors [3]. Particular attention is needed for vulnerable populations, including patients with chronic viral infections or age-related comorbidities [33].

koordinierte Überwachung zwischen Zentren und fachübergreifende Kommunikation

Implementing the recommended HUB-and-SPOKE model would require meticulous coordination between HUB infusion and SPOKE follow-up centres. Product transportation would occur directly from manufacturing facilities to these treatment centres, with associated costs typically covered by manufacturers. The ongoing monitoring protocol also encompasses regular assessments of factor IX (FIX) activity levels, liver function tests, bleeding events, and joint health evaluation. To support this monitoring, communication pathways must be maintained across multiple specialist disciplines, including haematologists, physiotherapists, hepatologists, and other healthcare providers.

Rapid laboratory result reporting and expert consultation systems become crucial for monitoring potential complications and determining appropriate interventions [3].

Langzeitbeobachtung durch verpflichtende Registereintragung und Pat.-Compliance

Given the complexity of gene therapy management and coordination, robust systems for long-term assessment are essential. The short follow-up period in the clinical study creates uncertainty about long-term benefits and risks, necessitating continued data collection. Mandatory clinical follow-up of all treated patients in the Austrian Haemophilia Registry is strongly recommended to address these uncertainties, enabling systematic evaluation of long-term outcomes. However, successful post-launch evidence generation depends on patient compliance with regular monitoring appointments.

Privacy and Data Protection

kontinuierliche Überwachung sensibler Pat.-Daten

The implementation of gene therapy introduces several important privacy and data protection considerations. Neutralising antibody testing will be conducted by US-based labs, necessitating specific privacy considerations and discussions with potential patients. Long-term monitoring and registry participation requirements have additional privacy implications that must be addressed through appropriate data protection measures. Regular monitoring and documentation requirements create an ongoing need to manage sensitive patient information carefully [3].

Culture

unterschiedlicher Informationsstand der Pat.-Gemeinschaft zur Gentherapie

Patient communities demonstrate significant interest in gene therapy as a potentially transformative treatment option [3]. However, patient-reported information gathered through questionnaires by the AITHA reveal varying levels of familiarity and acceptance. Three of five patients or caregivers surveyed were unfamiliar with the specific technology. In contrast, one caregiver had attended a lecture on gene therapy, and another patient had independently researched but expressed hesitancy toward using it [53].

Stakeholder-Perspektiven zur Gentherapie: Bewertung von Freiheit, Vertrauen & therapeutischem Mehrwert

In addition, recent qualitative research has revealed complex perspectives regarding the acceptance of gene therapy among stakeholders. Baas et al. [54] conducted interviews with Dutch stakeholders, including patients (n=13), parents (n=5), physicians (n=4), nurses (n=3), and other professionals, identifying three main themes affecting acceptance: freedom/independence, trust/altruism, and incremental benefits. While stakeholders generally embraced gene therapy's theoretical potential, several patients questioned the added value of current gene transfer products compared to existing treatments [54].

8.2 Ethical, social and legal aspects

Benefit-harm balance

umfassende Krankheitslast: physische Komplikationen & psychosoziale Herausforderungen

Haemophilia B imposes a substantial burden on affected individuals, encompassing both physical complications and psychosocial challenges. Spontaneous bleeding occurs in joints (70-80%) and muscles (10-20%). Central nervous system bleeds, although less common (<5%), carry severe risks, including seizures, impaired motor function, or death in up to 20% of cases [3]. These bleeding episodes and the resulting limitations often lead to social isolation and feelings of helplessness [53]. Furthermore, patients' lives are disrupted by the chronic nature of the condition, which impacts education, professional activities, and interpersonal relationships, adding to the overall disease burden [33].

Komplexität der aktuellen Behandlung & weitreichende Einschränkungen im täglichen Leben

The current treatments add substantial complexity to everyday life, particularly regarding travel and leisure activities. Frequent IV infusions present ongoing challenges due to scarring and pain at injection sites, often complicated by poor venous access. Patients encounter socio-economic challenges stemming from regular clinic visits, workplace absences for medical appointments, and issues related to travel and insurance coverage [3]. Moreover, joint damage from repeated internal bleeding leads to an increased need for mobility support and joint-replacement procedures over time, compounding the impact on social relationships and overall quality of life [33].

Patients' perspective on experiences of living with the conditions, symptoms and burden of disease

Einschränkungen im Lebensalltag: Auswirkungen auf Beruf, Mobilität & soziale Aspekte

Patients living with haemophilia and other haemorrhagic coagulation disorders face profound challenges that affect nearly every aspect of life. These conditions impair professional activities, physical mobility, and social evolution, significantly impacting self-confidence and life planning [33]. The restrictions imposed by the disease, including the need to avoid ladders and impact loads and the inability to participate in physical activities fully, exacerbate feelings of frustration and insecurity. Chronic pain, often requiring medication, is a frequent companion, along with arthrosis, which patients prioritise managing to maintain functionality and quality of life [53].

psychosoziale Belastungen von Kindheit an: Bewältigung von Scham & sozialer Isolation

In childhood, the disease often leads to feelings of shame due to being unable to participate in typical school activities, contributing to early social isolation – venous shunts, perceived as visually disturbing by some patients, further compound the psychosocial burden. One patient emphasised the importance of coping with the disease by adopting a positive mindset and being open with family, friends, and oneself. Despite such efforts, many patients struggle with the burden of being unable to engage in desired activities due to the risk of injury and the prolonged healing process associated with even minor injuries, such as haematomas or nosebleeds during a cold [53].

Expectations and wishes regarding the new therapy

Hoffnungen in neue Therapie → Verbesserung der Lebensqualität

Research by Baas et al. [54] and patient-reported information reveal that patients hold both hopes and concerns about new treatments. Their primary wish is for a solution that addresses all significant challenges associated with their condition, particularly the constant preoccupation with bleeding events, frequent injections, and risk avoidance in daily life [53].

konkrete Erwartungen → Behandlungsfreiheit & vereinfachte Therapieformen

Key expectations include long-term efficacy, eliminating bleeding events, improved quality of life, and reduced need for regular intravenous treatment. Patients also value the prospect of more flexibility in life planning, including professional opportunities, leisure activities, and vacations. A significant preference was expressed for alternative, less invasive administration methods than IV infusions, with discreet, simple, and affordable treatments being especially desirable [53].

Bedenken hinsichtlich der Langzeitfolgen & Therapiewechsel bei stabiler Einstellung

Alongside these hopes, patients expressed various concerns about new therapies. The most frequently mentioned worries were a lack of long-term data and uncertainty regarding potential side effects. Fear of liver disease and the potential ineffectiveness of new treatments were also cited as reasons for apprehension. Additionally, some patients reported reluctance to change their current medication regimen, mainly if it has been effective so far [53].

Justice and equity considerations

gerechte Ressourcenverteilung & Finanzierung wichtig zu berücksichtigen

Implementing gene therapy for haemophilia B raises significant questions about healthcare resource distribution and access equity within the Austrian healthcare system. The high upfront costs of fidanacogene elaparvovec require careful consideration against potential long-term savings from reduced FIX prophylaxis needs [3]. Alternative payment and reimbursement models might need to be considered within Austria's social insurance system to mitigate risks associated with uncertain long-term efficacy [33].

flächendeckende Koordination zwischen spezialisierten und lokalen Behandlungszentren notwendig

Resource distribution in Austria must account for both HUB centres and SPOKE facilities to ensure equitable access to treatment [12]. The successful implementation in the inpatient sector will require careful coordination between HUB and SPOKE centres to establish effective care pathways that serve all eligible patients, regardless of their location [3].

Patient autonomy and communication aspects

umfassende Pat.-Aufklärung & Schulungsprogramme zur Förderung der Autonomie

Treatment centres implement multiple mechanisms to support patient autonomy through comprehensive patient education and training [33]. For gene therapy specifically, robust informed consent and shared decision-making processes are essential, particularly given its nature as a one-time irreversible treatment [3]. Centres organise regular information events and training programs to enhance patient independence and understanding [33].

strukturierter Aufklärungsprozess & gemeinsame Entscheidungsfindung bei irreversibler Therapie

The informed consent process requires comprehensive communication of several key aspects. Patients must receive clear information about potential benefits, risks, and the possibility of needing to return to FIX prophylaxis if treatment effects diminish. Clinical providers must establish reasonable expectations by clearly communicating that gene therapies are not presently known to be curative. Additionally, providers must explain the potential need for immunosuppressive therapy, the requirements for frequent monitoring, and the implications of developing neutralising antibodies that could affect future treatment options [3].

große Bedeutung von Ärzt:innen-Pat.-Beziehung für Therapieentscheidungen

Treatment decisions heavily rely on trusted physician-patient relationships. Patients strongly prefer receiving information about gene therapy options from their regular treating physician due to established trust relationships [54]. Patient-reported information from the questionnaire conducted by the AIHTA reinforces this finding, emphasising the critical importance of clear and transparent communication [53].

Environmental Safety Considerations for Vector-Based Gene Therapy

Umweltsicherheit: AAV-Vektor Kontrolle, Standardprotokolle, Abfallmanagement, Virusüberwachung

The implementation of fidanacogene elaparvovec, an AAV-based gene therapy, involves specific environmental safety considerations. Current evidence indicates that AAV vectors demonstrate limited environmental impact due to their biological characteristics and replication patterns [55]. Treatment centres should implement standardised environmental risk assessment and monitoring protocols as part of their operating procedures. These should include specific handling protocols during preparation and administration, waste management procedures, and viral shedding monitoring. Both HUB and SPOKE centres should follow consistent safety protocols to maintain environmental protection standards. While research data on AAV vectors indicates limited horizontal transmission patterns, centres should maintain ongoing monitoring programmes to collect data on long-term environmental interactions [55].

8.3 Registries and documentation of the application

Indikationsregister dokumentieren jegliche Interventionen in definierten Patient:innen-Gruppen

Disease-specific registries contain data on patients with specific clinical indications. Unlike epidemiological registries, they do not collect data on prevalence or incidence. Unlike product-specific registries for medicinal products, indication registries are open to any intervention within the respective patient group. Inclusion in a disease-specific registry typically occurs during routine care [56]. One indication registry for haemophilia is available in Austria: the Austrian Haemophilia Register ("Österreichisches Hämophilie Register") [57].

Zweck und Aufgaben des österreichischen Hämophilie-Registers

The Austrian Haemophilia Registry is the country's sole indication registry. It represents a collaborative initiative between the Austrian Haemophilia Society (ÖHG), the scientific advisory board, haemophilia treatment centres, and the Medical University of Vienna. This comprehensive database fulfils international documentation requirements for the European Union (EU), World Health Organization (WHO), and World Federation of Haemophilia (WFH). The registry evaluates the quality of haemophilia therapy in Austria. It collects scientific data on inherited blood coagulation disorders, enabling optimal planning for coagulation factor concentrate supply and early detection of adverse effects such as inhibitor development and infections [57].

Finanzierung & teilnehmende Behandlungszentren

Funded by donations from pharmaceutical companies in Austria's haemophilia sector, the registry ensures its independence through strict data access restrictions. Its network includes treatment centres across Austria – in Bregenz, Graz, Innsbruck, Klagenfurt, Linz, Salzburg, St. Pölten, and Vienna – ensuring nationwide coverage [57].

Datenerfassung & digitale Dokumentation

Data collection occurs through multiple channels: centralised entry by a study physician at the Medical University of Vienna, local entry at treatment centres, and patient-reported data via electronic treatment diaries. The recently implemented "Haemoassist" smartphone application allows consenting patients to directly document treatment and bleeding events, with automatic data transfer to the registry [57].

9 Development costs and public contributions

9.1 Own development costs, acquisitions and licences

Pfizer has not published the development costs of fidanacogene elaparvovec.
Table 9-1 provides an overview fidanacogene elaparvovec.

Table 9-1: Overview of fidanacogene elaparvovec (BEQVEZ®)

Originator	Developer	Information on acquisitions	Public contribution	Type of public funding
BEQVEZ® *Active substance:* Fidanacogene Elaparvovec *Alternative names:* AAV8 factor IX gene therapy, AAV8 hFIX18, DURVEQTIX, Haemophilia B gene therapy – Spark Therapeutics PF-06838434, rAAV-Spark100-hFIX-Padua, SPK 9000, SPK-FIX *Pharmacotherapeutic group:* Antihemorrhagics *Therapeutic area:* Hemophilia B *Orphan designation:* NO *Categorization:* ATMP *Additional monitoring:* YES *Conditional approval:* YES *Accelerated assessment:* NO *PRIME: priority medicines:* YES *Marketing authorisation issued:* 24.07.2024				
Spark Therapeutics, Children's Hospital of Philadelphia	Pfizer	**Patent deal in 2014:** Pfizer licensed BEQVEZ® from Spark Therapeutics for $20 million with up to $260 million in milestone payments **Acquisition 2019:** Roche acquires Spark Therapeutics for $4.3 billion	Basic research is mostly publicly funded Early clinical development in cooperation with publicly funded research institutes and hospitals	Basic, applied and translational research support

Basic Research and clinical development

Grundlagenforschung für Fidanacogene elaparvovec

Factor IX (FIX) gene therapy development for treating haemophilia B emerged primarily from public research institutions, as shown in Chapter 6 in the Appendix and visualised in Figure 9-1. The basic research began at public institutions in the early 2000s, with key studies at Children's Hospital of Philadelphia (CHOP) and other academic centres pioneering adeno-associated virus (AAV)-based gene therapy approaches (St. Jude Children's Research Hospital and Perelman School of Medicine).

Forscherin von CHOP, die Mitbegründerin von Spark Therapeutics ist

Several researchers made significant contributions to the development: Katherine A. High at CHOP (and later Spark Therapeutics as co-founder) led many pivotal studies, including early AAV-based gene therapy trials. Valder R. Arruda at CHOP contributed extensively to understanding AAV vectors for haemophilia treatment. In 2006, Catherine S. Manno and colleagues published crucial findings on AAV-FIX transduction in haemophilia patients, noting challenges with immune responses. Adam Cuker at the University of Pennsylvania later led key clinical studies demonstrating fidanacogene elaparvovec's efficacy in reducing bleeding in haemophilia B patients.

Durchbruch in der Forschung

A pivotal advancement came in 2015 when Amit C. Nathwani and colleagues at University College London (UCL) Cancer Institute, Royal Free NHS Trust, and St. Jude Children's Research Hospital demonstrated the long-term safety

and efficacy of factor IX gene therapy in haemophilia B patients. Their work showing sustained factor IX expression over a median 3.2-year period helped bridge basic research to therapeutic applications, leading to increased industry involvement.

Spark Therapeutics führte Phase 1 Studien durch

The initial clinical trial in 2012 was conducted by Spark Therapeutics (NCT-01620801) in partnership with mostly publicly funded institutions, including Children's Hospital of Philadelphia, University of Pittsburgh, Royal Prince Alfred Hospital in Sydney, and St. James's Hospital in Ireland. Subsequently, Pfizer proceeded with the later-stage clinical trials (NCT02484092 in 2015, NCT03307980 in 2017, NCT03861273 in 2019, NCT05568719 in 2022), expanding the research network to include multiple international centres. The research sites included public and private institutions, with a significant presence of academic medical centres and public hospitals across Europe, Asia, and North America.

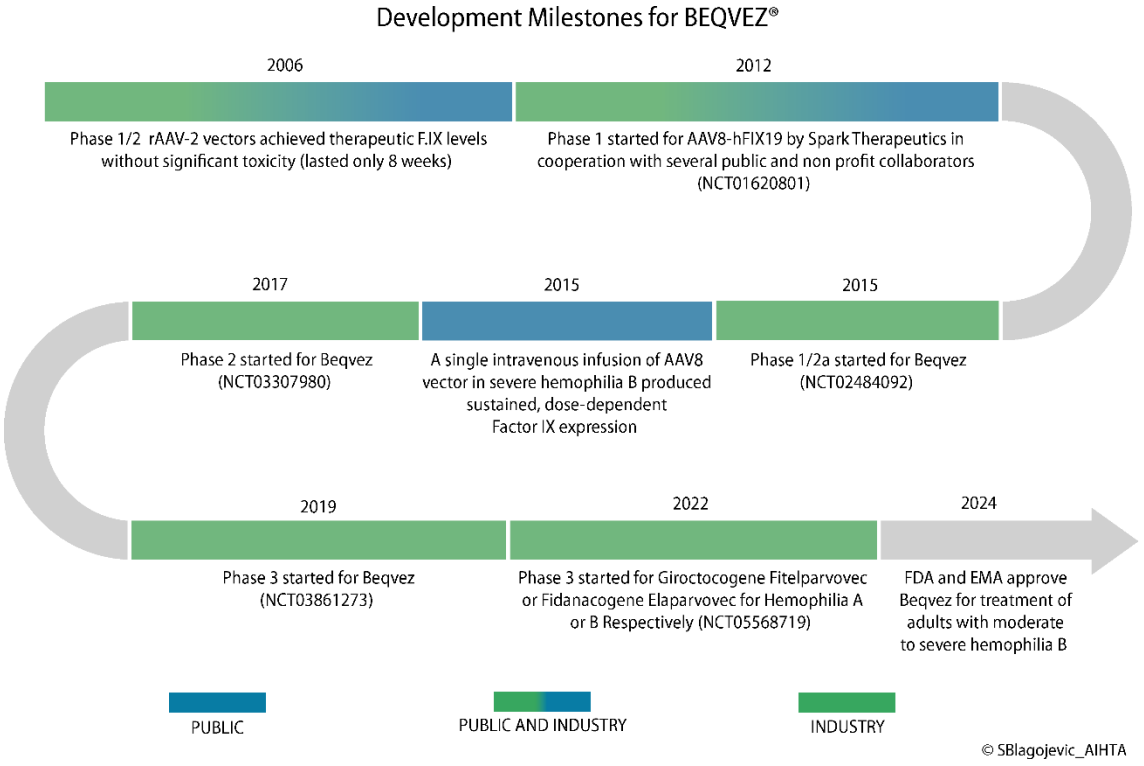


Figure 9-1: Timeline of the development milestones of BEQVEZ®

9.2 Public contributions on drug development

CHOP erhielt $ 38.5 Millionen → Hämophilie B Forschung

Chapter 6 in the Appendix demonstrate substantial public funding support for haemophilia B gene therapy research, particularly from the US-state-funded National Heart, Lung and Blood Institute (NHLBI). The CHOP received numerous grants between 1994-2022, with funding directed toward projects ranging from basic biochemistry of FIX to clinical applications of gene therapy. Adding up all National Institutes of Health (NIH) grants to CHOP related to haemophilia B gene therapy research, as shown in Chapter 6 in the Appendix, the total public funding amounted to approximately $ 38.5 million. This public funding played a crucial role in advancing the basic science that would eventually lead to fidanacogene elaparvovec's development.

St. Jude Children's Research Hospital erhielt $ 8.1 Mio.

While a lesser involvement in the development of fidanacogene elaparvovec, St. Jude Children's Research Hospital received roughly $ 8.1 million from 2005-2015 in public funding from the US-funded NHLBI for their Haemophilia B and FIX research, which helped researchers worldwide to better understand AAV-based gene therapies.

Pfizer kaufte das Recht auf Fidanacogene elaparvovec von Spark Therapeutics für $ 20 Millionen

Industry interest spiked in 2014 when Spark exclusively licensed fidanacogene elaparvovec to Pfizer for $ 20 million upfront with the potential for $ 260 million in milestone payments. The agreement included a provision where Spark Therapeutics conducted Phase 1 and 2 trials, and Pfizer then proceeded with the development.

9.3 Financial information

Pfizer Unternehmensdaten

Pfizer's organizational structure, as shown Chapter 6 in the Appendix, reveals that Pfizer's revenues dwindled over time from roughly $ 49,6 billion in 2014 to $ 41,2 billion in 2019. However, the company has shown significant growth in employee numbers, from 78,300 in 2014 to 88,300 in 2019, indicating organisational expansion.

Spark Therapeutics Unternehmensdaten

Spark Therapeutics has consistently operated at a revenue loss from 2014 to its acquisition by Roche in 2019. However, its employee numbers show that the company has experienced significant growth at the same time, from 50 in 2014 to 368 in 2018.

Besitzverhältnisse von Pfizer

The ownership structure of Pfizer reveals that venture capital is the most important financier, as seen in Chapter 6 in the Appendix. The Vanguard Group holds the largest stake with 9.1%. BlackRock follows with 5.8%, State Street Corporation maintains 5.1% total ownership, and Wellington Trust holds 2.9%. The "Big Three" index fund is with Wellington Trust, the most important shareholder.

9.4 Landscape overview on further gene therapies (in development)

No further gene therapies in development could be identified. However,

- *Verbrinacogene setparvovec*, (FLT180a), a gene therapy developed by Freeline Therapeutics was paused after the Phase 1/2 clinical trial in 2022 for strategic reasons unless a partner could be found to move the gene therapy into phase 3 testing. Freeline was acquired by Syncona in 2023, and it remains unclear if there are plans to continue developing the therapy.

1 andere Gentherapie, Verbrinacogene setparvovec wurde in Phase 1/2 pausiert

- As mentioned previously, *etranacogene dezaparvovec* (HEMGENIX® by CSL Behring), approved by the European Commission (EC) in February 2023, is investigated in a phase 3b trial (NCT06003387) aiming at assessing the risk of bleeding due to failure of the expected pharmacological action of CSL222 in adults with detectable pretreatment AAV5 nabs. The estimated primary completion is October 2028. It is unclear whether this trial would change the authorised indication for etranacogene dezaparvovec, which does not explicitly exclude patients with AAV5 nab. If so, a label change is estimated for August 2029.

1 weitere Gentherapie, Etranacogene dezaparvovec, wurde 2023 in Europa zugelassen

Some further therapies have recently been approved or are under investigation:

weitere Therapien in Entwicklung oder kürzlich zugelassen:

- *Marstacimab* (HYMPAVZI® by Pfizer) was authorised in December 2024. Marstacimab is an antibody that binds to and blocks the tissue factor pathway inhibitor (TFPI), a protein that normally prevents blood clotting. Release of this molecular brake is expected to help prevent or reduce the number of bleeds, making it a possible alternative to replacement therapy. Based on this mechanism of action, *marstacimab* is expected to be equally effective in haemophilia A and B without inhibitor status.

Marstacimab weiterer Anti-TFPI-Antikörper Dez. 2024 zugelassen

- *Concizumab* (ALHEMO® by Novo Nordisk) was authorised in December 2024. Concizumab is another anti-TFPI antibody for prophylaxis across all haemophilia subtypes that acts independently from FVIII and FIX by enhancing the initiation phase of coagulation through increased FXa production, allowing sufficient thrombin generation (TG) to prevent bleeds. Based on this mechanism of action, concizumab is expected to be equally effective in haemophilia A and B, regardless of inhibitor status.

Concizumab Anti-TFPI-Antikörper Dez. 2024 zugelassen

- *Fitusiran* (by Sanofi) is a small interference RNA therapeutic designed to lower antithrombin (AT), a protein that inhibits blood clotting, with the goal of promoting thrombin generation to rebalance haemostasis and prevent bleeds. It interferes with AT translation by binding and degrading messenger RNA-AT, silencing AT gene expression, and preventing AT synthesis. Fitusiran was studied in two completed phase 3 trials (ATLAS-INH and ATLAS-A/B). The phase 3 ATLAS-A/B trial was designed to investigate fitusiran prophylaxis versus episodic (on-demand) treatment; the phase 3 ATLAS-INH was to determine the frequency of bleeding episodes in participants receiving fitusiran as prophylactic treatment of haemophilia compared to participants who were assigned to continue with their regular medication. In a June 2024 Sanofi press release, the company indicated that regulatory submissions had been completed in China, Brazil, and the US; however, no

Fitusiran RNA-Therapeutikum in Entwicklung (Zulassung erwartet: Jan. 2026)

SerpinPC Biologikum in Entwicklung (Zulassung erwartet: Jan. 2027)

BE-101 B-Zell-Medikament in Entwicklung

indication of a potential timeline for an EMA regulatory submission could be identified. Assuming a December 2024 EMA submission, the estimated EC authorisation date is January 2026.

- *SerpinPC* (by Centessa Pharmaceuticals) is a biologic of the serpin family of proteins designed to allow more thrombin to be generated by inhibiting activated protein C (APC). SerpinPC reduces levels of APC, which generally controls coagulation by limiting the generation of thrombin, an enzyme involved in the final stages of blood clotting. In doing so, SerpinPC helps increase thrombin production, facilitating blood clotting. Assuming a December 2025 EMA submission, the estimated EC authorisation date is January 2027.
- *BE-101* (by Be Biopharma) is an autologous first-in-class B cell medicine (BCM) that is engineered to insert the human FIX gene into primary human B cells, allowing for the expression of active FIX for the treatment of haemophilia B. BE-101 has the potential to express sustained therapeutic FIX activity levels with a single infusion with the flexibility to be re-dosed, if needed. Dates for marketing authorisation approval submission are currently unknown.

10 Discussion

In the following chapter, the findings of this report will be interpreted and discussed on a chapter-by-chapter basis.

Interpretation & Diskussion der Ergebnisse

Discussion of relative clinical effectiveness and safety analysis

Haemophilia B treatment has historically relied on factor IX (FIX) replacement therapies [15]. The treatment landscape changed with the 2023 EU market entry of etranacogene dezaparvovec [23] as the first gene therapy, followed by fidanacogene elaparvovec [27] as a second gene therapy option. These gene therapies represent a paradigm shift from regular FIX replacement to potential one-time treatments.

Etranacogene dezaparvovec als erste Gentherapie zur Behandlung der Hämophilie B

The efficacy and safety of fidanacogene elaparvovec were investigated in a single-arm phase 3 study, BENEGENE-2 (NCT03861273) [29]. Patients enrolled on the study were men 18 to 62 years of age with haemophilia B (factor IX level, ≤2%) who had received FIX prophylaxis therapy for at least 6 months during the BENEGENE-1 lead-in study (NCT03587116) [58] and who agreed to suspend prophylaxis after fidanacogene elaparvovec infusion.

einarmige Phase 3 BENEGENE-2 Studie

The pivotal trial results suggest efficacy of fidanacogene elaparvovec, demonstrated in the form of reduced annualised bleeding rate (ABR) by 71%, remaining stable up to 48 months in 15 patients, and a clinically meaningful improvement of health-related quality of life (HRQoL) [28]. Yet, 84% of patients experienced adverse events (AEs) of any grade in severity. Serious adverse events (SAEs) occurred in seven patients (16%). The most common AE of any grade was an increased aminotransferase level (53%). Furthermore, the manufacturer sponsored an unanchored matching-adjusted indirect treatment comparison (MAIC), suggesting some benefits compared to first-generation FIX products.

Fidanacogene elaparvovec vs. Standardtherapie: statistisch signifikante Reduktion der Blutungsrate von 4,42 auf 1,28
indirekter Vergleich: potenzielle Vorteile gegenüber Prophylaxe

The strength of the evidence is severely limited by the study design of the pivotal trial and intransparency, both in the pivotal trial and in the indirect comparison. The BENEGENE-2 [29] is characterised by a small number of patients and the lack of a placebo group. Additionally, the study was uncontrolled and open label. The baseline characteristics of the patients were incomplete. It was unclear whether the participants were enrolled at a similar point of the disease, as the duration of the disease was not reported. There are also differences in the definition of haemophilia B severity between the BENEGENE-2 study (moderate to severe, FIX activity ≤2%) and the severity defined by the World Federation of Haemophilia (severe <1%, moderate 1-5% FIX activity) [13]. The allowed FIX replacement therapy was not described in detail, and there was also variability in the application and timing of corticosteroid treatment.

Qualität der Studie (BENEGENE-2) stark eingeschränkt, z. B. unkontrolliertes Studiendesign, Unklarheiten bzgl. der Pat.-Charakteristika

Further methodological concerns relate to the study endpoints and measurements. The primary endpoint, ABR, is prone to subjectivity [41], and it was unclear if it was measured consistently among BENEGENE-2 [29] and BENEGENE-1 [58] studies, which provided the baseline values. Moreover, the primary endpoint changed throughout the study. Clinical justification for the non-inferiority margin of 3.0 for ABR is missing. There are also documented differences in the measurement of FIX activity through one-stage and chromogenic assays [42]. The follow-up of the study (15 months) was not long

Subjektivität des primären Endpunkts

enough to evaluate the long-term safety and durability of the effect. These factors negatively affect the internal validity and constitute a moderate risk of bias [30].

fehlende Langzeitdaten – laufende Studien

The durability of the effect of fidanacogene elaparvovec in the treatment of haemophilia B is currently unknown, and long-term safety data are not available. An interim clinical study report including a six-year follow-up of BENEGENE-2 is expected no later than December 2028 [24].

mehrere methodologische Unklarheiten

Additionally, the methodological quality of the indirect comparison analysis raises several concerns. Inconsistencies in reporting of included trials and interventions undermine transparency, with varying numbers of eligible trials reported across different sections of the documentation. The matching process was hampered by incomplete baseline characteristics across trials and inability to adjust for important outcome-related factors. The relatively small sample size in BENEGENE-2 resulted in wide confidence intervals, suggesting imprecise effect estimates.

Limitationen durch Studiendesign

Additional methodological limitations include the subjective nature of the primary endpoint (ABR) [41], potential measurement inconsistencies across trials, and the open-label design of included studies. The analysis lacks critical methodological information, including detailed outcome measure descriptions, bias handling methods, and adequate internal and external validity assessment.

indirekte Vergleiche für Etranacogene dezaparvovec verfügbar

Two indirect treatment comparisons are available for the competing product etranacogene dezaparvovec, both showing more comprehensive reporting than the fidanacogene elaparvovec analysis. The Canadian Agency for Drugs and Technologies in Health (CADTH) analysis [21] provides transparent documentation of methods and limitations, including persistent between-population differences after matching and uncertainty in effect magnitude due to missing prognostic factors. Similarly, the Klamroth analysis [22] showed favourable results for etranacogene dezaparvovec versus standard therapies but acknowledged potential biases from differences in outcome definitions and follow-up periods.

Limitationen des indirekten Vergleichs

Both gene therapies face similar challenges in their comparative evidence base, including the inherent limitations of unanchored comparisons and the need for long-term efficacy data. While the CADTH analysis [21] notes that 20-25 years of follow-up may be needed to establish long-term efficacy, current evidence for both treatments is limited to much shorter periods. This underscores the importance of continued monitoring to establish the durability of treatment effects for both gene therapies.

Discussion of economic chapters

Fidanacogene elaparvovec kein Markteintritt in EU

Currently, no price is yet available for fidanacogene elaparvovec in Europe. According to press information, fidanacogene elaparvovec will not enter the European market as Pfizer has discontinued this haemophilia treatment (BEQVEZ®) and removed it from their gene therapy portfolio [59].

fehlender Preis & Annahmen zu Pat.-Anzahl → BIA-Ergebnisse unsicher

Due to the absence of a listed price for fidanacogene elaparvovec in Europe and the assumptions made regarding the patient population likely to receive the intervention, the results of the budget impact analysis (BIA)[9] are highly uncertain:

- The number of patients expected to receive fidanacogene elaparvovec and its market uptake is based on assumptions (year 1: 20%, year 2: 30%, year 3: 50%). These estimates are, therefore, uncertain and may either overestimate or underestimate the actual figures.
- Experts assumed and recommended that the HTD would cover the costs associated with testing for nAbs; however, this remains uncertain. Additionally, the assumptions regarding the costs of FIX prophylaxis and on-demand treatments might be underestimated or overestimated, which would, in turn, influence the net budget impact.
- Since no price for fidanacogene elaparvovec is currently available in Europe, the calculation was based on a placeholder price of € 3.4 million per administration. However, as the drug's price represents the most significant cost driver, the finally negotiated price and the size of the treated population, namely, whether more or fewer patients receive the treatment, would substantially affect the overall budget.

nAbs-Test sollten von vertriebsberechtigten Unternehmen organisiert & bezahlt werden

Annahmen zu FIX-Behandlungskosten beeinflussen Netto-Budgetfolgen

grobe Einschätzung der Budgetfolgen nach Einführung der Gentherapie → Kostenverschiebung in den intramuralen Bereich

Due to the various assumptions made, the BIA only roughly estimates the cost impact of fidanacogene elaparvovec being introduced as a treatment alternative for moderately severe and severe haemophilia B patients. In addition, it shows that the introduction of fidanacogene elaparvovec comes with cost savings in the outpatient sector (reduced standard of care [SoC] costs) but increased costs for the inpatient sector. A limitation of the analysis is the short time horizon of three years, which does not cover the full potential of cost-offset in case of long-term sustainability of the clinical benefit. However, since several long-term factors, such as long-term effectiveness and market dynamics, are unknown, any estimation beyond three years would be highly uncertain.

identifizierte Kosteneffektivitäts-ergebnisse für Kanada sehr unsicher → eigene Analyse für Österreich notwendig

Regarding the cost-effectiveness of fidanacogene elaparvovec, in the absence of an economic evaluation from the HTD, we only identified one cost-utility analysis from the HTD for Canada, which was assessed by the CADTH. Based on the model, fidanacogene elaparvovec was more effective and less costly (dominant) compared to SHL FIX prophylaxis, EHL FIX prophylaxis, and the basket of SHL and EHL FIX prophylaxis. The assumed acquisition costs of fidanacogene elaparvovec (€ 3.4 million) were predicted to be offset by savings after approximately twelve years, assuming a gene therapy effect of at least 25 years. However, the cost-effectiveness results are highly uncertain when considering the magnitude and duration of the benefit of fidanacogene elaparvovec compared to FIX prophylaxis treatments due to the open-label, single-arm study design and the self-reporting of bleeding events. Consequently, the results are not transferable to other contexts. In conclusion, whilst an economic evaluation specific to the Austrian context would be necessary, this was not submitted by the HTD and thus was unavailable for assessment.

[9] Calculated by the AIHTA as the manufacturer did not send a BIA.

Discussion of social, organisational, ethical and legal aspects

organisatorische Herausforderungen: HUB-and SPOKE-Modell, Personalschulung & Infrastrukturentwicklung, Datenschutzaspekte bei der Implementierung

Implementing fidanacogene elaparvovec presents multifaceted organisational challenges within the Austrian healthcare system. The proposed HUB-and SPOKE-model requires careful coordination between specialised administration centres and local follow-up facilities, necessitating robust communication pathways and standardised protocols [12, 33]. While potentially efficient for resource allocation, this model demands significant investment in staff training and infrastructure development to manage complex monitoring requirements and potential complications. The implementation strategy must also address privacy concerns, particularly regarding neutralising antibody testing in US-based laboratories while ensuring comprehensive data protection measures for long-term patient monitoring [3].

ethische & soziale Implikationen: Pat.-Perspektive zur Gentherapie, Abwägung zwischen bestehenden & neuen Therapieoptionen, Ressourcenallokation und Kostenfragen im Gesundheitssystem

The ethical implications of fidanacogene elaparvovec extend beyond clinical considerations to encompass broader social and equity concerns. Patient perspectives reveal a complex landscape of hopes and anxieties, with some expressing optimism about reduced treatment burden and improved quality of life. In contrast, others raise concerns about uncertain long-term efficacy and potential side effects [53]. The management of haemophilia B through existing therapeutic options and their effectiveness must be carefully weighed against the potential benefits of innovative treatments [3]. This evaluation becomes particularly significant when considering the high upfront costs and uncertain long-term outcomes, which raise important questions about resource allocation, healthcare equity and potential disadvantages for other patients.

Pat.-Autonomie & Aufklärung: Skepsis gegenüber Therapiemehrwert, Notwendigkeit transparenter Kommunikation

Research by Baas et al. [54] highlights the critical role of patient autonomy and informed decision-making in gene therapy implementation. Their findings emphasise that while stakeholders generally embrace the theoretical curative potential of gene therapy, many patients question its added value compared to existing treatments [54]. This scepticism underscores the importance of comprehensive patient education and transparent communication about treatment expectations, particularly regarding the potential need for ongoing monitoring or return to traditional prophylaxis [3].

Langzeitbeobachtung & Systemintegration

A successful implementation of fidanacogene elaparvovec within the Austrian healthcare system would require careful consideration of both immediate and long-term implications. Given the limited follow-up period in clinical studies and uncertainties about long-term benefits and risks, mandatory clinical follow-up of all treated patients in the Austrian Haemophilia Registry is strongly recommended for systematic evaluation of long-term outcomes (e.g., the need for FIX prophylaxis and FIX activity) [3]. Establishing effective care pathways that serve all eligible patients, regardless of their geographic location, remains a crucial challenge [12]. Furthermore, developing alternative payment models may be necessary to address the treatment's financial implications and uncertain long-term efficacy [33].

Discussion of public investment

Grundlagenforschung für Fidanacogene elaparvovec wurde teilweise öffentlich finanziert

The development of fidanacogene elaparvovec illustrates the critical role of public funding and academic institutions in advancing medical treatments. The journey from basic research to approved therapy spans over two decades, with public institutions, particularly the Children's Hospital of Philadelphia (CHOP), playing a pivotal role in its development. The substantial public investment in basic and translational research is evident from the approximately € 38.5 million in National Institute of Health (NIH) grants awarded to CHOP

between 1994 and 2022. St. Jude Children's Research Hospital also received $ 8.1 million in public funding from the National Heart, Lung, and Blood Institute (NHLBI), contributing to the broader understanding of AAV-based gene therapies. This long-term public commitment to research provided the foundation for later commercial development.

öffentliche vs. private Investionen

This case study raises important questions about balancing public and private investment in drug development. While public funding and academic institutions bore much of the early research risks and costs, private companies largely accrued the commercial benefits. Additionally, the successful development of fialso demonstrates how public-private partnerships can effectively translate basic research into approved therapies.

Fidanacogene elaparvovec durchlief das klassische Muster in der Forschung und Entwicklung

The development pathway of fidanacogene elaparvovec exemplifies a common pattern in modern drug development: public institutions and funding drive early-stage research and discovery, while private companies provide the resources and expertise needed for late-stage development and commercialisation. This model has proven effective in bringing treatments to market, though it also raises questions about equitable returns on public investment in pharmaceutical research.

11 Conclusion

- Fidanacogene elaparvovec received European Commission (EC) approval in July 2024 under conditional marketing authorisation and is included in the EMA Priority Medicines (PRIME) scheme. It is the second gene therapy approved for haemophilia B after etranacogene dezaparvovec (HEMGENIX®). The approval is based on a single-arm study comparing intra-individual data. A long-term observation is ongoing (6-year follow-up study, BENEGENE-2).

Fidanacogene elaparvovec (PRIME) seit Juli 2024 von der EMA zugelassen

- The approved indication is for adult patients with severe and moderately severe haemophilia B without a history of factor IX (FIX) inhibitors and detectable antibodies to variant adeno-associated virus (AAV) serotype Rh74. According to clinical experts, of the 130 haemophilia B patients in Austria, around nine patients could be eligible for fidanacogene elaparvovec treatment in the next three years.

für Pat. mit mittelschwerer & schwerer Hämophilie, ohne FIX-Inhibitoren & AAVRh74 Antikörper

- The prognosis for patients with haemophilia B has significantly improved over recent decades due to comprehensive care with FIX replacement therapies. However, the disease remains associated with a substantial burden through regular prophylactic treatment, bleeding events, and joint damage affecting quality of life. The therapeutic alternatives are standard and extended half-life FIX concentrates and one other gene therapy.

Standardtherapie = FIX-Prophylaxe → trotzdem reduzierte Lebensqualität

- The efficacy and safety of fidanacogene elaparvovec have been investigated in one prospective open-label study compared to intra-individual data with 45 patients and a maximum follow-up of 15 months. The study demonstrated a 71% reduction in annual bleeding rate compared to prior FIX prophylaxis. The most common adverse event was increased aminotransferase levels (53% of patients). Around 13% of treated patients needed to resume FIX prophylaxis due to insufficient treatment effects.

Zulassungsstudie (einarmig, n=45): 71 %-Reduktion der jährlichen Blutungsrate

- The manufacturer-sponsored indirect treatment comparison demonstrated statistically significant advantages of fidanacogene elaparvovec only in specific comparisons versus some first-generation FIX products. However, several methodological limitations affect the reliability of these results, including incomplete baseline matching, small sample sizes leading to imprecise estimates, and the subjective nature of bleeding rate measurements. Long-term comparative effectiveness data will be crucial for establishing the relative benefits of gene therapies in haemophilia B treatment.

indirekte Vergleichsanalysen mit methodischen Limitierungen & begrenzter Evidenz

- Treatment with fidanacogene elaparvovec consists of a single intravenous infusion. Implementation requires careful patient selection, a structured hospital stay for administration and monitoring, and long-term follow-up. Therefore, comprehensive patient education, expectation management regarding uncertainties, and compliance with monitoring requirements are essential prerequisites.

strikte Pat.-Auswahl & organisierte Administration bzw. Nachsorge wichtig

- Fidanacogene elaparvovec requires specialised centres for administration and monitoring. A HUB-and SPOKE-model with coordination between specialised administration centres (HUBs) and local follow-up facilities (SPOKEs) is recommended. Implementation demands significant investment in staff training and infrastructure.

Aufbau von HUB- & SPOKE-Zentren

- With an assumed price of € 3.4 million per patient, fidanacogene elaparvovec would incur drug acquisition costs of around € 29 million over three years. Additional costs for administration and prophylactic treatment would add to around 193,000. While some cost offsets through reduced FIX consumption are expected (around € 917,000), the total direct medical costs would increase more than threefold compared to current treatment costs (€ 13.8 million). Given long-term effectiveness of gene therapy, the implementation of fidanacogene elaparvovec therapy would induce significant cost-shifting from the outpatient to the inpatient sector. International cost-effectiveness analyses predicted that the assumed acquisition cost of fidanacogene elaparvovec (€ 3.4 million per administration) can be offset by savings after approximately 12 years. However, these results are highly uncertain and a transfer to the Austrian context would be highly uncertain.

3-Jahreskosten der Gentherapie: € 41,0 Mio., Einsparungen bei der Standardtherapie von ca. € 917.000 über 3 Jahre

- Basic research and development emerged primarily from public institutions, particularly the Children's Hospital of Philadelphia, which received approximately € 38.5 million in public funding. The commercial development proceeded through licensing agreements between Spark Therapeutics and Pfizer.

Grundlagen-R&D zum Großteil öffentlich finanziert

- Fidanacogene elaparvovec represents a potentially transformative treatment option. However, several uncertainties remain:
  - Long-term durability of treatment effect beyond the current 15-month follow-up data
  - Long-term safety profile and potential delayed adverse events
  - Comparative effectiveness versus standard care and other gene therapy options
  - Transferability of clinical trial results to real-world populations
  - Economic sustainability, given high upfront costs
  - Therefore, regular monitoring and documentation in registries, preferably in combination with risk-sharing models, will be essential to address these uncertainties.

Fidanacogene elaparvovec neue Therapieoption für genannte Population, jedoch Unsicherheiten zu berücksichtigen & Langzeitdokumentation in Register notwendig

- Finally, the remaining uncertainties must be balanced against the potential benefits of the reduced treatment burden and improved quality of life for patients with haemophilia B, while ensuring equitable access and sustainable resource allocation within the healthcare system.

Unsicherheiten müssen den potenziellen Benefits der Therapie gegenübergestellt werden

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13 List of abbreviations

AAV.....adeno-associated virus
AE.....adverse event
ABR.....annualised bleeding rate
AFP .....alpha-fetoprotein
AIHTA .....Austrian Institute for Health Technology Assessment
AIR.....annualised infusion rate
ALP .....alkaline phosphatase
ALT.....alanine aminotransferase
APRI.....AST-to-platelet ratio index
aPTT .....activated partial thromboplastin time
AST .....aspartate transaminase
AT.....Austria
ATC.....anatomical therapeutic chemical
ATMP.....advanced therapy medicinal product
BE.....Belgium
BIA .....budget impact analysis
BU .....bethesda unit
CADTH .....Canadian Agency for Drugs and Technologies in Health (former Canada's Drug Agency)
CAN .....Canada
CAD .....Canadian dollar
CAT.....Committee for Advanced Therapies
CBC.....complete blood count
CDA-AMC.....Canada's Drug Agency
CD4+.....cluster of differentiation 4 positive
CHMP.....Committee for Human Medicinal Products
CHOP.....Children's Hospital of Philadelphia
CNS.....central nervous system
COX-2 .....cyclooxygenase-2
CPK.....creatine phosphokinase
CRP.....c-reactive protein
CSR .....clinical study report
CVD .....cardiovascular disease
DNA.....deoxyribonucleic acid
DE .....Denmark
eDiary .....electronic diary
EHL .....extended half-life
EKO .....Erstattungskodex
EL.....Greece
EMA.....European Medicines Agency
EPAR .....European public assessment report
EQ-5D-5L.....European quality of Life 5-dimensions 5-levels
ES .....Espagnole
EU .....European Union
EUnetHTA .....European Network for Health Technology Assessment
FI.....Finland
FIX.....factor IX
FIX:C .....circulating levels of factor IX
FR.....France
FVIII .....factor VIII
GER.....Germany
GÖG .....Gesundheit Österreich GmbH
HAL .....hemophilia activities list
Haem-A-QoL...haemophilia quality of life questionnaire for adults
HBsAg.....hepatitis B surface antigen
HBV .....hepatitis B virus
HCV .....hepatitis C virus
HCCC .....haemophilia comprehensive care centre
HIV.....human immunodeficiency virus
HIV-1 .....human immunodeficiency virus type 1
HIV-2 .....human immunodeficiency virus type 2
HJHS.....haemophilia joint health score
HRQoL .....health-related quality of life
HTA .....Health Technology Assessment
HTC .....Haemophilia Treatment Centre
HTD.....health technology developer
ICF .....international classification of function, disability and health
ICH .....intracranial haemorrhage
IE.....Ireland
IgG.....immunoglobulin G
IHE.....Institute of Health Economics

INAHTA.....The International Network of Agencies for Health Technology Assessment
INN.....international non-proprietory name
IP.....investigational product,
IVD.....in-vitro diagnostic
IT.....Italy
ITC.....indirect treatment comparison
IU.....international unit
IV.....intravenously
IVIg.....intravenous immunoglobulin
ITC.....indirect treatment comparison
LIS.....lot information sheet
LU.....Luxemburg
LY.....life years
MAIC.....matching-adjusted indirect comparison
MedDRA.....Medical Dictionary for Regulatory Activities
N.....number of patients
nAbs.....neutralising antibodies
NCRR.....National Center for Research Resources
NCT.....national clinical trial
NFT.....non-factor therapy
NHLBI.....National Heart, Lung and Blood Institute
NI.....no information available
NIAID.....National Institute of Allergy and Infectious Diseases
NIH.....National Institutes of Health
NL.....Netherlands
NO.....Norway
NRT.....non-replacement therapy
NSAIDs.....non-steroidal anti-inflammatory drugs
ÖHG.....österreichische Hämophilie Gesellschaft
ÖHR.....österreichisches Hämophilie Register
OR.....odds ratio
PBMC.....peripheral blood mononuclear cells
PEG.....polyethylene glycol
PICO.....population-intervention-comparator-outcome
PPP.....Purchasing Power Parties
PRIME.....PRIority MEdicines
PRO.....patient-reported outcome
PT.....prothrombin time
PT.....Portugal
QALY.....quality-adjusted life year
QoL.....quality of life
rFIXFc.....recombinant factor IX-Fc fusion protein
rIX-FP.....recombinant factor IX albumin fusion protein
RNA.....ribonucleic acid
RoB.....risk of bias
SAE.....serious adverse event
SE.....Sweden
SHL.....standard half-life
SoC.....standard of care
TFPI.....tissue factor pathway inhibitor
TT.....thrombin time
UCL.....University College London
UK.....United Kingdom
ULN.....upper limit of normal
US.....United States
vg.....vector genomes
WFH.....World Federation of Hemophilia
WHO.....World Health Organization

HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH