Medicinrådet

Baggrund for Medicinrådets anbefaling vedrørende vonicog alfa som mulig standardbehandling til von Willebrand sygdom

Versionsnr.: 1.0

Medicinrådet

Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner.

Medicinrådet vurderer, om nye lægemidler og nye indikationer kan anbefales som mulig standardbehandling og udarbejder fælles regionale behandlingsvejledninger.

Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

De fælles regionale behandlingsvejledninger er vurderinger af, hvilke lægemidler der er mest hensigtsmæssige til behandling af patienter inden for et terapiområde og dermed grundlag for ensartet høj kvalitet for patienterne på tværs af sygehuse og regioner.

Om anbefalingen

Anbefalingen er Medicinrådets vurdering af, om omkostningerne ved behandling lægemidlet er rimelige i forhold til lægemidlets kliniske værdi.

Lægemidlet vurderes efter Metodehåndbog for Medicinrådets arbejde med at udarbejde fælles regionale vurderinger af nye lægemidlers og nye indikationers kliniske merværdi – version 1. Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	10. april 2019
Ikrafttrædelsesdato	10. april 2019
Dokumentnummer	46551
Versionsnummer	1.0

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 10. april 2019

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Veyvondi
Generisk navn	Vonicog alfa
Firma	Shire/Takeda
ATC-kode	B02BD10
Virkningsmekanisme	Rekombinant von Willebrand faktor (rvWf)
Administration/dosis	Infusion af 40-80 IE/kg hver 8.-24. time indtil ønsket faktorniveau og hæmostatisk effekt er opnået.
EMA-indikation	Voksne (≥ 18 år) med von Willebrand sygdom, når behandling med desmopressin alene er ineffektiv eller ikke er indiceret til behandling af spontan blødning, kirurgisk blødning samt forebyggelse af kirurgisk blødning.

2 Medicinrådets anbefaling

Medicinrådet **anbefaler** vonicog alfa (Veyvondi) som mulig standardbehandling til:

- On-demandbehandling og ved mindre kirurgiske indgreb hos voksne patienter, som har normalt eller let nedsat faktor VIII-niveau.
- Blødning hos voksne patienter, som i forbindelse med større kirurgiske indgreb får behov for at skifte til et faktorpræparat med lavere indhold af faktor VIII.

Medicinrådet **anbefaler ikke** vonicog alfa (Veyvondi) som mulig standardbehandling til:

- On-demandbehandling af voksne patienter med lavt faktor VIII-niveau eller ved blødning hos voksne patienter, som gennemgår større kirurgiske indgreb, hvor der i begge tilfælde også er behov for et faktor VIII-præparat.

De kliniske spørgsmål, som ligger til grund for anbefalingen, er som følger:

1. *Hvad er den kliniske merværdi af vonicog alfa (Veyvondi), i forhold til plasmaderiveret vWf, ved behandling af blødning hos patienter med von Willebrand sygdom og med normalt eller let nedsat FVIII-niveau (> 30 %)?*
2. *Hvad er den kliniske merværdi af vonicog alfa (Veyvondi), i forhold til plasmaderiveret vWf, ved behandling af blødning hos patienter med von Willebrand sygdom og lavt FVIII-niveau (< 30 %)?*
3. *Hvad er den kliniske merværdi af vonicog alfa (Veyvondi), i forhold til plasmaderiveret vWf, ved forebyggelse og behandling af blødninger ved mindre kirurgiske indgreb hos patienter med von Willebrand sygdom?*

4. *Hvad er den kliniske merværdi af vonicog alfa (Veyvondi), i forhold til plasmaderiveret vWf, ved forebyggelse og behandling af blødning ved større kirurgiske indgreb hos patienter med von Willebrand sygdom?*

3 Formål

Formålet med Baggrund for Medicinrådets anbefaling vedrørende vonicog alfa (Veyvondi) som mulig standardbehandling til von Willebrand sygdom er at skabe gennemsigtighed om det materiale, der ligger til grund for Medicinrådets anbefaling.

4 Baggrund

Veyvondi er et rekombinant von Willebrand faktorpræparat, som er godkendt til behandling af voksne (≥ 18 år) med von Willebrand sygdom til behandling af spontan blødning, kirurgisk blødning samt forebyggelse af blødning i forbindelse med kirurgiske indgreb, når behandling med desmopressin alene er ineffektiv eller ikke er indiceret.

4.1 Sagsbehandlingstid og proces for Medicinrådets vurdering

Medicinrådets sagsbehandlingstid er på denne sag 12 uger.

I Medicinrådets vurdering af klinisk merværdi for vonicog alfa til behandling af von Willebrand sygdom – vers. 1.1 er datoen for modtagelse af den endelige ansøgning fejlagtigt angivet som den 29. januar 2019. Den korrekte dato for modtagelsen af den endelige ansøgning er den 17. januar 2019.

5 Medicinrådets vurdering af samlet klinisk merværdi

Medicinrådet vurderer, at vonicog alfa (Veyvondi) til voksne patienter (≥ 18 år) med von Willebrand sygdom giver:

- **Ingen klinisk merværdi** ved on-demandbehandling til patienter med lavt FVIII-niveau (< 30 %) sammenlignet med plasmaderiveret von Willebrand faktor.
- **Ingen klinisk merværdi** ved forebyggelse og behandling af blødning under mindre kirurgiske indgreb sammenlignet med plasmaderiveret von Willebrand faktor.
- **Ikkedokumenterbar klinisk merværdi** ved forebyggelse og behandling af blødning under større kirurgiske indgreb sammenlignet med plasmaderiveret von Willebrand faktor.

Evidensens kvalitet er meget lav for alle kliniske spørgsmål.

Den kliniske merværdi for voksne patienter i on-demandbehandling, som har normalt eller let nedsat FVIII-niveau (> 30 %), kan ikke vurderes.

6 Høring

Ansøger har den 20. marts 2019 meddelt, at de ikke har indvendinger imod Medicinrådets kategorisering af den kliniske merværdi for Veyvondi.

7 Resumé af økonomisk beslutningsgrundlag

Amgros har ikke vurderet vonicog alfa for voksne patienter med normalt eller let nedsat FVIII-niveau. Ved sammenligning udelukkende af lægemiddelprisen er behandling med vonicog alfa ikke forbundet med meromkostninger sammenlignet med Willfact.

For patienter med lavt FVIII-niveau er behandling med vonicog alfa forbundet med betydelige meromkostninger. Amgros vurderer, at der ikke er et rimeligt forhold mellem omkostningerne og den kliniske merværdi af vonicog alfa sammenlignet med Haemate og Wilnativ.

For patienter, som gennemgår et mindre kirurgisk indgreb, er behandling med vonicog alfa forbundet med begrænsede meromkostninger. Amgros vurderer, at der er et rimeligt forhold mellem omkostningerne og den kliniske merværdi af vonicog alfa sammenlignet med Willfact.

For patienter, som gennemgår et større kirurgisk indgreb, er behandling med vonicog alfa forbundet med meromkostninger. Amgros vurderer, at der er et rimeligt forhold mellem omkostningerne og den kliniske merværdi af vonicog alfa sammenlignet med Willfact men ikke for Haemate eller Wilnativ.

Budgetkonsekvenserne er begrænsede, da en anbefaling af vonicog alfa medfører en populationsudvidelse på 5-10 ekstra patienter.

Amgros' beslutningsgrundlag og sundhedsøkonomiske analyse er vedlagt som henholdsvis bilag 1 og 2.

8 Overvejelser omkring alvorlighed/forsigtighed

Medicinrådet har ikke fundet anledning til at inddrage forhold vedrørende alvorlighed eller forsigtighed i anbefalingen.

9 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende blødersygdomme

Forvaltningslovens § 4, stk. 2, har været anvendt i forbindelse med udpegning af medlemmer til dette fagudvalg.

Formand	**Indstillet af**
Eva Funding Overlæge	Lægevidenskabelige Selskaber og Region Hovedstaden
Medlemmer	**Udpeget af**
Har ikke en relevant specialist til fagudvalget	Region Nordjylland
Anne-Mette Hvas Professor, overlæge, ph.d.	Region Midtjylland
Lone Hvitfeldt Poulsen Overlæge	Region Midtjylland
Jesper Farup Revsholm Afdelingslæge	Region Syddanmark
Rune Larsen Overlæge	Region Sjælland
Marie Louise Schougaard Christiansen Afdelingslæge, klinisk farmakolog, ph.d.	Dansk Selskab for Klinisk Farmakologi (DSKF)
Jennifer A.F. Andresen Farmaceut	Dansk Selskab for Sygehusapoteksledelse (DSS)
Kan ikke udpege en kandidat, der opfylder Medicinrådets habilitetskrav	Dansk Selskab for Klinisk Biokemi
Marianne Hutchings Hoffmann Overlæge	Dansk Pædiatrisk Selskab
Finder det ikke længere relevant at have en kandidat i fagudvalget	Dansk Selskab for Anæstesiologi og Intensiv Medicin
Peter Kampmann Overlæge, lægefaglig teamleder	Dansk Selskab for Trombose og Hæmostase
2 patienter/patientrepræsentanter	Danske Patienter

Medicinrådets sekretariat

Medicinrådet Dampfærgevej 27-29, 3. th. 2100 København Ø + 45 70 10 36 00 medicinraadet@medicinraadet.dk
Sekretariatets arbejdsgruppe: Mette Hollensted (projekt- og metodeansvarlig) Dorte Glintborg (projektdeltager) Anne Sofie Gram (projektdeltager) Ilse Linde (fagudvalgskoordinator) Jan Odgaard-Jensen (biostatistiker) Bettina Fabricius Christensen (informationsspecialist) Kirsten Holdt Henningsen (teamleder)

10 Versionslog

Version	Dato	Ændring
1.0	10.04.2019	Godkendt af Medicinrådet.

11 Bilag

Bilagsliste:

- Amgros' beslutningsgrundlag
- Amgros' sundhedsøkonomiske analyse
- Høringssvar fra ansøger
- Vurdering af den kliniske merværdi af vonicog alfa (Veyvondi)
- Ansøgers endelige ansøgning
- Protokol for vurdering af den kliniske merværdi af vonicog alfa (Veyvondi)

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Beslutningsgrundlag til Medicinrådet

Dette dokument er Amgros' vurdering af vonicog alfa (Veyvondi) indiceret til voksne (≥ 18 år) med von Willebrand sygdom (vWD) når behandling med desmopressin (DDAVP) alene er ineffektiv eller ikke er indiceret til behandling af hæmorrhagi og kirurgisk blødning samt forebyggelse af kirurgisk blødning. Vurderingen er baseret på lægemidlets gennemsnitlige inkrementelle omkostninger (baseret på SAIP) sammenholdt med Medicinrådets vurdering af den kliniske merværdi.

Dato for Medicinrådsbeslutning	10-04-2019
Firma	Shire (ansøger)
Lægemiddel	Vonicog alfa (Veyvondi)
Indikation	Voksne (≥ 18 år) med von Willebrands sygdom (vWD) når behandling med desmopressin (DDAVP) alene er ineffektiv eller ikke er indiceret til behandling af hæmorrhagi og kirurgisk blødning samt forebyggelse af kirurgisk blødning.

Amgros' vurdering

- Amgros har **ikke** vurderet forholdet mellem meromkostningerne og den kliniske merværdi for vonicog alfa (Veyvondi) som mulig standardbehandling til patienter på ≥ 18 år med vWD og et FVIII-niveau >30 % (P1)

- Amgros vurderer, at der **ikke** er et rimeligt forhold mellem meromkostningerne og den kliniske merværdi for vonicog alfa (Veyvondi) som mulig standardbehandling til patienter på ≥18 år med vWD og et FVIII-niveau < 30 % (P2)

- Amgros vurderer, at der **er** et rimeligt forhold mellem meromkostningerne og den kliniske merværdi for vonicog alfa (Veyvondi) som mulig standardbehandling til patienter på ≥18 år med vWD, som gennemgår et mindre kirurgisk indgreb (P3)

- Amgros vurderer, at der **er** et rimeligt forhold mellem meromkostningerne og den kliniske merværdi for vonicog alfa (Veyvondi) som mulig standardbehandling til patienter på ≥18 år med vWD, som gennemgår et større kirurgisk indgreb (P4) ved sammenligning med vWf, mens der **ikke** er et rimeligt forhold ved sammenligning med vWf i kombination med FVIII.

Overordnet konklusion

Medicinrådet har vurderet, at vonicog alfa (Veyvondi) sammenlignet med de mulige komparatorer giver:

- **Ikke kan vurderes** til patientpopulation P1
- **Ingen klinisk merværdi** til patientpopulation P2
- **Ingen klinisk merværdi** til patientpopulation P3
- **Ikkedokumenterbar klinisk merværdi** patientpopulation P4

Amgros har **ikke** vurderet forholdet mellem den kliniske merværdi og omkostningerne for P1.

Behandling med vonicog alfa (Veyvondi) er forbundet med meromkostninger sammenlignet med komparatorer ved P2. Amgros vurderer, at forholdet mellem klinisk merværdi og omkostning **ikke** er rimeligt for P2.

Behandling med vonicog alfa (Veyvondi) medfører meromkostninger af begrænset omfang ved sammenligning komparator. Amgros vurderer, at forholdet mellem kliniske merværdi og omkostninger **er** rimeligt for P3.

Behandling med vonicog alfa (Veyvondi) medfører høje meromkostninger ved sammenligning med plasmaderiveret vWf i kombination med FVIII, mens det medfører begrænset meromkostninger ved sammenligning med vWf alene. Amgros vurderer, at forholdet mellem kliniske merværdi og omkostninger:

- **er** rimeligt for P4 ved sammenligning med Willfact (vWf)
- **ikke** er rimeligt for P4 ved sammenligning med Heamate og Wilnativ (vWf i kombination med FVIII)

Andre overvejelser

[redacted]

[redacted]

Konklusion for populationen

Tabel 1 Merværdi, meromkostninger og Amgros' vurdering (baseret på SAIP)

Population	Komparator	Merværdi	Usikkerhed for klinisk merværdi	Amgros' konklusion om forholdet mellem meromkostninger og merværdi
P1: Patienter på 18 år eller derover med vWD og et FVIII-niveau > 30 %	Plasmaderiveret vWf	Kan ikke vurderes	-	Ikke vurderet
P2: Patienter på ≥ 18 år med vWD og et FVIII-niveau < 30 %	Plasmaderiveret vWf + FVIII i kombination	Ingen klinisk merværdi	Meget lav evidens kvalitet	Ikke rimeligt
P3: Patienter på ≥ 18 år med vWD, som gennemgår et mindre kirurgisk indgreb	Plasmaderiveret vWf	Ingen klinisk merværdi	Meget lav evidens kvalitet	Rimeligt
P4: Patienter på ≥ 18 år med vWD, som gennemgår et større kirurgisk indgreb	Plasmaderiveret vWf	Ikkedokumenterbar klinisk merværdi	Meget lav evidenskvalitet	Rimeligt
	Plasmaderiveret vWf + FVIII i kombination	Ikkedokumenterbar klinisk merværdi	Meget lav evidenskvalitet	Ikke rimeligt

Supplerende informationer (resumé af resultaterne fra afrapporteringen)

Konklusion på omkostnings- og budgetkonsekvensanalyserne

Amgros' afrapportering af omkostnings- og budgetkonsekvensanalyser er baseret på SAIP for vonicog alfa (Veyvondi). Resultatet fra Amgros' afrapportering på omkostningsanalyserne er gengivet i det følgende. For uddybende gennemgang af analyse og resultater henvises til afrapporteringen på http://www.amgros.dk.

Amgros' afrapportering - Inkrementelle omkostninger per patient

Behandling med vonicog alfa (Veyvondi) er forbundet med meromkostninger sammenlignet med behandling med komparatorer for P2.

Amgros' hovedanalyse for P2 resulterer i gennemsnitlige meromkostninger for vonicog alfa (Veyvondi) på ca. [redacted] og [redacted] sammenlignet med hhv. Wilnativ og Haemate, se tabel 2.

Hvis analysen udføres på baggrund af AIP, bliver lægemiddelomkostningerne for vonicog alfa (Veyvondi) ca. 1,45 mio. DKK, mens de inkrementelle omkostninger bliver ca. 1,04 mio. DKK og 1,03 mio. DKK per patient ved sammenligning med hhv. Wilnativ og Haemate.

Tabel 2: Resultatet af Amgros' hovedanalyse for P2, DKK (SAIP).

	Vonicog alfa (Veyvondi) og rFVIII	Wilnativ	Haemate
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Inkrementelle omkostninger	-	[redacted]	[redacted]

Behandling med vonicog alfa (Veyvondi) er forbundet med begrænsede meromkostninger sammenlignet med behandling med komparator for P3.

Amgros' hovedanalyse for P3 resulterer i gennemsnitlige meromkostninger for vonicog alfa (Veyvondi) på ca. [redacted] sammenlignet med Willfact, se tabel 3.

Hvis analysen udføres på baggrund af AIP, bliver lægemiddelomkostningerne for vonicog alfa (Veyvondi) på ca. 153.000 DKK, mens de inkrementelle omkostninger bliver ca. 12.000 DKK per patient.

Tabel 3: Resultatet af Amgros' hovedanalyse for P3, DKK (SAIP).

	Vonicog alfa (Veyvondi)	Willfact
Lægemiddelomkostninger	[redacted]	[redacted]
Inkrementelle omkostninger	-	[redacted]

Behandling med vonicog alfa (Veyvondi) er forbundet med meromkostninger sammenlignet med behandling med alle komparator for P4.

Amgros' hovedanalyse for P4 resulterer i gennemsnitlige meromkostninger for vonicog alfa (Veyvondi) på ca. [redacted], [redacted] og [redacted] sammenlignet med hhv. Willfact, Haemate og Wilnativ, se tabel 4.

Hvis analysen udføres på baggrund af AIP bliver lægemiddelomkostningerne for vonicog alfa (Veyvondi) ca. 363.000 DKK, mens de inkrementelle omkostninger bliver ca. 38.000 DKK, 236.000 DKK og 240.000 DKK per patient ved sammenligning med hhv. Willfact, Haemate og Wilnativ.

Tabel 4: Resultatet af Amgros' hovedanalyse for P4, DKK (SAIP).

	Vonicog alfa (Veyvondi) evt. rFVIII	Willfact	Haemate	Wilnativ
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]	[redacted]
Inkrementelle omkostninger	-	[redacted]	[redacted]	[redacted]

Amgros' afrapportering – Budgetkonsekvenser

Amgros vurderer, at anbefaling af vonicog alfa (Veyvondi) som mulig standardbehandling, vil resultere i følgende budgetkonsekvenser for populationerne:

- P2: [redacted] per år
- P3: [redacted] per år
- P4: [redacted] per år

Hvis analysen udføreres på baggrund af AIP bliver budgetkonsekvenserne følgende for populationerne:

- P2: 0 DKK per år
- P3: 3.000 DKK per år
- P4: 99.000 DKK per år

VONICOG ALFA (VEYVONDI)

VON WILLEBRANDS SYGDOM

AMGROS 28. marts 2019

AMGROS

OPSUMMERING

Baggrund

Vonicog alfa (Veyvondi) er indiceret til voksne (≥ 18 år) med von Willebrand sygdom (vWD) når behandling med desmopressin (DDAVP) alene er ineffektiv eller ikke er indiceret til behandling af hæmorrhagi og kirurgisk blødning samt forebyggelse af kirurgisk blødning.

Omkring 250 patienter er registreret ved de højt specialiserede hæmofilicentre i København og Aarhus. Amgros' vurdering tager udgangspunkt i dokumentation indsendt af Shire.

Analyse

I analysen estimeres de inkrementelle omkostninger forbundet med vonicog alfa (Veyvondi) sammenlignet med:

- P1: plasmaderiveret vWf ved behandling af blødning hos patienter med vWD og med normalt eller let nedsat FVIII-niveau (>30 %)
- P2: plasmaderiveret vWf + FVIII i kombination ved behandling af blødning hos patienter med vWD og lavt FVIII-niveau (<30 %)
- P3: plasmaderiveret vWf ved forebyggelse og behandling af blødninger ved mindre kirurgiske indgreb hos patienter med vWD
- P4: plasmaderiveret vWf + FVIII i kombination ved forebyggelse og behandling af blødninger ved større kirurgiske indgreb hos patienter med vWD

Inkrementelle omkostninger og budgetkonsekvenser

Amgros har vurderet de gennemsnitlige meromkostninger per patient ved brug af vonicog alfa (Veyvondi) sammenlignet med komparator. De inkrementelle omkostninger er angivet i SAIP og AIP.

I scenariet Amgros mener er mest sandsynligt, er de gennemsnitlige meromkostninger i SAIP for vonicog alfa (Veyvondi) følgende for hhv. P2, P3 og P4:

- P1: Amgros har ikke vurderet omkostningerne da sammenligningen ikke er fundet meningsfuld grundet manglende data for populationen
- P2: Ca. [redacted] og [redacted] sammenlignet med hhv. Haemate og Wilnativ
- P3: Ca. [redacted] sammenlignet med Willfact
- P4: Ca. [redacted], [redacted] og [redacted] sammenlignet med hhv. Willfact, Haemate og Wilnativ

Hvis analysen udføres på baggrund af AIP bliver de inkrementelle omkostninger:

- P2: Ca. 1,03 mio. DKK og 1,04 mio. DKK sammenlignet med hhv. Haemate og Wilnativ
- P3: Ca. 12.000 DKK sammenlignet med Willfact
- P4: Ca. 38.000 DKK, 236.000 DKK og 240.000 DKK sammenlignet med hhv. Willfact, Haemate og Wilnativ

Konklusion

Behandling med vonicog alfa (Veyvondi) er forbundet med meromkostninger af varierende størrelse sammenlignet med samtlige komparatorer. Da analysen udelukkende inkluderer omkostninger til lægemidler, tilskrives meromkostningerne udelukkende prisen for vonicog alfa (Veyvondi).

Den vurderede analyse er baseret på en narrativ sammenligning af flere kliniske studier, hvilket fører til stor usikkerhed ved analysens resultat.

Liste over forkortelser

AIP	Apotekernes indkøbspris
DKK	Danske kroner
DRG	Diagnose Relaterede Grupper
SAIP	Sygehusapotekets indkøbspriser

INDHOLD

LOG

Ansøgning	
Lægemiddelfirma:	Shire
Handelsnavn:	Veyvondi
Generisk navn:	Vonicog alfa
Indikation:	Voksne (≥ 18 år) med von Willebrands sygdom (vWD) når behandling med desmopressin (DDAVP) alene er ineffektiv eller ikke er indiceret til behandling af hæmorrhagi og kirurgisk blødning samt forebyggelse af kirurgisk blødning.
ATC-kode:	B02BD10

Proces	
Ansøgning modtaget hos Amgros:	29-01-2019
Endelig rapport færdig:	14-03-2019
Sagsbehandlingstid fra endelig ansøgning:	44 dage
Arbejdsgruppe:	**Pernille Winther Johansen** Lianna Geertsen Line Brøns Jensen Louise Greve Dal Mark Friborg

Priser
Denne rapport bygger på analyser udført på baggrund sygehusapotekernes indkøbspriser (SAIP). Enkelte steder er analysens resultat yderligere angivet på baggrund af listepriser (AIP).

1 BAGGRUND

Vonicog alfa (Veyondi) er indiceret til voksne (≥ 18 år) med von Willebrand sygdom (vWD) når behandling med desmopressin (DDAVP) alene er ineffektiv eller ikke er indiceret til behandling af hæmorrhagi og kirurgisk blødning samt forebyggelse af kirurgisk blødning.

Shire (herefter omtalt som ansøger) er markedsføringstilladelsesindehaver af vonicog alfa (Veyvondi) og har den 29.01.2019 indsendt en ansøgning til Medicinrådet om anbefaling af vonicog alfa (Veyvondi) som standardbehandling på danske hospitaler af den nævnte indikation. Som et led i denne ansøgning vurderer Amgros, på vegne af Medicinrådet de økonomiske analyser, ansøger har sendt som en del af den samlede ansøgning til Medicinrådet. Denne rapport er Amgros' vurdering af de fremsendte økonomiske analyser (herefter omtalt som analysen).

1.1 Problemstilling

Formålet med analysen er at estimere de inkrementelle omkostninger forbundet med behandling af Voksne (≥ 18 år) med vWD når behandling med desmopressin alene er ineffektiv eller ikke er indiceret til behandling af hæmorrhagi og kirurgisk blødning samt forebyggelse af kirurgisk blødning, i form af de gennemsnitlige inkrementelle omkostninger per patient og de samlede budgetkonsekvenser for regionerne ved anbefaling vonicog alfa (Veyvondi) som standardbehandling på danske sygehuse af den nævnte indikation. I analyserne sammenlignes behandling med vonicog alfa (Veyvondi) med behandling med plasmaderiveret vWf og vWf + FVIII i kombination.

1.2 Patientpopulation

Von Willebrands sygdom er den hyppigste bløddersygdom i Danmark. Incidens og prævalens er ikke fuldstændig kendt, da mange milde tilfælde ikke diagnosticeres. Der er registreret i alt ca. 250 patienter med vWD ved de højt specialiserede hæmofilicentre i København og Aarhus (1).
vWD skyldes mangel på virksom von Willebrand faktor (vWf). Von Willebrand faktor er et glykoprotein, der medierer blodpladeaggregation og -adhæsion ved karskade som led i den primære hæmostase, og dermed blodets evne til at størkne og standse blødninger. Von Willebrand faktor (vWF) er bærerprotein for koagulationsfaktor VIII (FVIII), og vWf-mangel er derfor ofte associeret med nedsat FVIII. Svær vWD vil også medføre svær FVIII-mangel og sekundær hæmostasedefekt som ved hæmofili A.
vWD klassificeres ift. vWf-aktivitet og -niveau (2), og vWD inddeles i 3 typer: vWD type 1 er defineret ved nedsat vWf-mængde, vWD type 2 ved nedsat funktion af vWf, mens vWD type 3 defineres ved fuldstændig mangel på vWf. For at stille diagnosen vWD, skal der foruden nedsat vWf være en familiehistorie med blødning og klinisk betydende blødningstendens.

1.3 Nuværende behandling

Behandlingen af vWD omfatter infusion af et vWf-præparat. Udfordringerne ved det nuværende behandlingsregime er at opnå en god hæmostase, dvs. at standse spontan blødning samt sikre, at patienter som gennemgår kirurgi, ikke oplever større blødning under det kirurgisk indgreb ift. patienter uden vWD.
De aktuelt tilgængelige vWF er alle plasmaderiverede. Rekombinante præparater er generelt at foretrække fremfor plasmaderiverede præparater. Dette skyldes, at der i plasmaderiverede præparater er risiko for patogener, som ikke nødvendigvis inaktiveres ved virusinaktivering. Udviklingen af virusinaktiverende metoder har minimeret risikoen for smitte med HIV og hepatitis C, men udbruddet af variant Creutzfeldt-Jakob sygdom i Storbritannien i 1997, som skyldtes prioner, der ikke destrueres ved virusinaktiverende behandling, var en påmindelse om, at det kun er muligt at screene for og inaktivere kendte patogener (1).
De forskellige plasmaderiverede vWf-præparater varierer med hensyn til FVIII-indhold. I henhold til den gældende behandlingsvejledning (3) tilbydes danske patienter med vWD som 1. valg behandling med Haemate, som indeholder vWf og FVIII i forholdet 2,4:1. Som 2. og 3. valg tilbydes patienter med vWD henholdsvis Wilnativ, der indeholder vWf og FVIII i forholdet 1:1 eller Willfact, der indeholder vWf og FVIII i forholdet ≥ 10:1.
Behandling af vWD i henhold til type 1, 2 og 3 er vist i tabel 1.

Tabel 1: Behandling af vWD inddelt efter type vWD.

Type vWD	Årsag	Sværhedsgrad	Behandling
Type 1	Nedsat mængde vWf	Svær, moderat eller mild	On-demand behandling med desopressin (DDAVP) eller vWf ved behov for gentagne doser
Type 2	Nedsat funktion af vWf	Svær, moderat eller mild	Enkelte i profylakse, de fleste i on-demand behandling med DDAVP eller vWf
Type 3	Fuldstændig mangel på vWf	Altid svær	Profylakse eller on-demand behandling med vWf

1.4 Behandling med vonicog alfa (Veyvondi)

Indikation

Vonicog alfa (Veyvondi) er indiceret til behandling af Voksne (≥ 18 år) med von Willebrands sygdom (vWD) når behandling med desmopressin (DDAVP) alene er ineffektiv eller ikke er indiceret til behandling af hæmorrhagi og kirurgisk blødning samt forebyggelse af kirurgisk blødning.

Virkningsmekanisme

Vonicog alfa er et rekombinant vWf (rvWf)-præparat, der virker som endogen vWf. Vonicog alfa er fremstillet i chinese hamster ovarieceller uden brug af humant protein.

Dosering

Vonicog alfa kan doseres som monoterapi eller i kombination med FVIII, og dosering bestemmes individuelt efter personens vægt, blødningstype og sværhedsgrad samt ud fra monitorering af relevante kliniske og klinisk biokemiske parametre. Ved behandling af blødninger bør den initiale dosis af vonicog alfa være på 40 til 80 IE/kg. Ifm. kirurgi bør FVIII-niveauet vurderes inden for 3 timer forud for indledning af kirurgisk procedure.

1.4.1 Komparator

Medicinrådet har defineret plasmaderiveret vWf som komparatorer for P1 og P3. For P2 er plasmaderiveret vWf + FVII i kombination komparator, mens komparator for P4 er både plasmaderiveret vWf alene og i kombination med FVIII. Populationer og de respektive komparatorer er vist i tabel 2.

Tabel 2: Definerede populationer og komparatorer.

Population	Komparator
P1: Patienter på 18 år eller derover med vWD og et FVIII-niveau > 30 %	Plasmaderiveret vWf
P2: Patienter på ≥ 18 år med vWD og et FVIII-niveau < 30 %	Plasmaderiveret vWf + FVIII i kombination
P3: Patienter på ≥ 18 år med vWD, som gennemgår et mindre kirurgisk indgreb	Plasmaderiveret vWf
P4: Patienter på ≥ 18 år med vWD, som gennemgår et større kirurgisk indgreb	Plasmaderiveret vWf og Plasmaderiveret vWf + FVIII i kombination

1.5 Medicinrådets kliniske spørgsmål

Medicinrådet har vurderet den kliniske merværdi af Vonicog alfa (Veyvondi) som behandling for følgende populationer:

- **P1:** Hvad er den kliniske merværdi af vonicog alfa, i forhold til plasmaderiveret vWf, ved behandling af blødning hos patienter med vWD og med normalt eller let nedsat FVIII-niveau (> 30 %)
- **P2:** Hvad er den kliniske merværdi af vonicog alfa, i forhold til plasmaderiveret vWf, ved behandling af blødning hos patienter med vWD og lavt FVIII-niveau (< 30 %)
- **P3:** Hvad er den kliniske merværdi af vonicog alfa, i forhold til plasmaderiveret vWf, ved forebyggelse og behandling af blødninger ved mindre kirurgiske indgreb hos patienter med vWD
- **P4:** Hvad er den kliniske merværdi af vonicog alfa, i forhold til plasmaderiverede vWf, ved forebyggelse og behandling af blødning ved større kirurgiske indgreb hos patienter med vWD

2 VURDERING AF INDSENDT ØKONOMISK ANALYSE

2.1 Model, metode og forudsætninger

Ansøger har indsendt en analyse der estimerer de inkrementelle omkostninger ved vonicog alfa (Veyvondi) sammenlignet med komparatorer for fire populationer. Medicinrådet angiver i rapporten for klinisk merværdi af vonicog alfa (Veyvondi) at det ikke er muligt at vurdere den kliniske merværdi for P1, grundet manglende data for on-demand behandling af denne patientpopulation. Af denne årsag indeholder Amgros' afrapportering ikke resultater for denne population.

2.1.1 Modelbeskrivelse

Ansøger har indsendt en meget simpel omkostningsanalyse, der kun inkluderer omkostninger til lægemidler. Analysen er udarbejdet på baggrund af en narrativ sammenligning, hvor en række forskellige kliniske studier er inddraget.
Ansøger har baseret en række antagelser i den indsendte analyse på udsagn fra en klinisk ekspert.
Der antages ikke at være forskel i ressourcer mellem vonicog alfa (Veyvondi) og de forskellige komparatorer, hverken ved indlæggelsestid, ambulante besøg, patienttid, transport, tværsektorielt eller personaletid på hospitalet. Ansøger argumenterer at der er en forventning om, at vonicog alfa (Veyvondi) kræver færre ressourcer end komparatorerne og derfor er dette en konservativ tilgang.

Ansøger redegør for at forekomsten af alvorlige bivirkninger i forbindelse med vonicog alfa (Veyvondi) og komparatorer er meget lav og i nogle tilfælde ikke eksisterende i de anvendte kliniske studier. På denne baggrund vælger ansøger ikke at medtage omkostninger til bivirkninger i analysen.

Amgros' vurdering

Ansøgers analyse er baseret på en narrativ sammenligning, som Amgros anser som en metode det bidrager til stor usikkerhed ved den pågældende analyse.
Ansøger har ikke været villig til at oplyse hvem den konsulterede kliniske ekspert, der har bidraget til antagelserne der ligge bag ansøgningen er. Derfor har Amgros konsulteret to kliniske eksperter, hvis udsagn/estimater vil erstatte ansøgers antagelser i analysen. Analysen med disse antagelser vil blive præsenteret som Amgros' hovedanalyse.

De kliniske eksperter Amgros har konsulteret i forbindelse med validering af ansøgers analyse, angiver begge at forekomsten af bivirkninger er meget sjældne.

Ansøgers tilgang accepteres, men Amgros udarbejder egen hovedanalyse hvor alle estimater og antagelser valideres af kliniske eksperter. Hvis estimater eller antagelser findes i uoverensstemmelse med disse eksperters udsagn ændres de.

2.1.2 Analyseperspektiv

Ansøger har indsendt en omkostningsanalyse. Analysens tidshorisont er livstidsperspektiv, hvor omkostninger der ligger efter det første år, er diskonteret med en faktor på 4 %.

Amgros' vurdering

Analysen er et meget forsimplet billede af de reelle omkostninger forbundet med den pågældende behandling.
Amgros accepterer ansøgers tidshorisont og simple tilgang.

2.1.3 Omkostninger

Det følgende afsnit om omkostninger redegør for hvordan og hvilke omkostninger ansøger har inkluderet i analysen.

Lægemiddelomkostninger

Som det eneste omkostningselement inkluderer ansøger lægemiddelomkostninger. Priserne for de lægemidler ansøger anvender i analysen, er angivet i tabel 3. Alle priser er fra Amgros.

Tabel 3: Anvendte lægemiddelpriser, SAIP (Fra Amgros 14-03-2019).

Lægemiddel	Hætteglasstørrelse [IE]	Pris [DKK]
Veyvondi	1.300	[redacted]
	650	[redacted]
Willfact	1.000	[redacted]
Haemate	2.400	[redacted]
	1.200	[redacted]
Wilnativ	1.000	[redacted]
	500	[redacted]
Advate	3.000	[redacted]
	2.000	[redacted]
	1.500	[redacted]
	1.000	[redacted]
	500	[redacted]
	250	[redacted]

Til at estimere gennemsnitligt antal infusioner anvender ansøger en række studier. Til at estimere gennemsnitligt antal infusioner ved Haemate anvender ansøger median-værdier fra to forskellige studier. Det gennemsnitlige eller for tilfældet med Haemate, mediane antal infusioner er vist i tabel 4. Ansøger angiver at dosis for lægemidlerne er hentet i produkternes respektive SPC'er. Anvendte doser kan ligeledes ses i tabel 4.

Tabel 4: Lægemiddel doser og antal administrationer per blødning estimeret af ansøger.

	Lægemiddel	Antal administrationer	Første dosis [IE/kg]	Efterfølgende Doser [IE/kg]
P2	Veyvondi	1,24	60	50
	Haemate	2,0	80	60
	Wilnativ	2,0	65	35
P3	Veyvondi	4,25	50	60
	Willfact	4,39	60	60
P4	Veyvondi	8,7	50	50
	Willfact	17,14	60	60
	Haemate	9,0	80	60
	Wilnativ	11,0	65	35

Amgros' vurdering

Amgros forholder sig meget kritisk til den narrative sammenligning der er lavet mellem de studier ansøger anvender, da de forskellige studier bygger på forskellige metoder og populationer anses sammenligning ikke at medføre et meningsfuldt resultat. I Medicinrådets vurdering af den kliniske merværdi angives det, at der ikke vurderes at være forskel i antal infusioner for vonicog alfa (Veyvondi) i forhold til komparator ved P2 og P3. For P4 vurderer fagudvalget vedrørende blødersygdom, at der kan være en reduktion i antallet af antal infusioner i forhold til komparatorer. Ansøger har dog baseret dele af analysen på median-værdier som ifølge Amgros' metodevejledning ikke må benyttes i omkostningsanalyserne.

Ansøger angiver at anvendte doser er fra lægemidlernes SPC. I produkternes SPC er doser angivet som et spænd og ansøger argumenterer eller dokumenterer hvorfor de valgte antagelser omkring dosis gør sig gældende. I Medicinrådets vurderingsrapport angiver fagudvalget sammenlignelige doser for de anvendte lægemidler.

Amgros' udarbejder egen hovedanalyse hvor antal infusioner er ens for vonicog alfa (Veyvondi) og komparatorer for alle populationer. I denne analyse vil de sammenlignelige doser Medicinrådets vurderingsrapport blive anvendt.

2.2 Følsomhedsanalyser

Ansøger præsenterer resultaterne af en række følsomhedsanalyser i deres tekniske dokument. Variation i følgende parametre undersøges:

- Reduceret kropsvægt på gennemsnitspatienten
- Øget kropsvægt på gennemsnitspatienten
- Ens dosis ved første og efterfølgende infusioner (P2)
- Ens dosis ved præ- og postoperative infusioner (P3 og P4)

Amgros' vurdering

Ansøgers følsomhedsanalyser er ikke inkluderet i Excel-dokumentet indeholdende analysen, men skal manuelt genskabes, hvis resultatet ønskes undersøgt. På baggrund af dette vil resultaterne af følsomhedsanalyserne ikke blive præsenteret. Dog findes følsomhedsanalyserne relevante og som tidligere nævnt.

3 RESULTATER

3.1 Ansøgers hovedanalyse

3.1.1 Population 2

Ansøgers hovedanalyse resulterer i gennemsnitlige meromkostninger for vonicog alfa (Veyvondi) på ca. [redacted] og [redacted] sammenlignet med hhv. Wilnativ og Haemate. Resultatet er præsenteret i tabel 5.

Tabel 5: Resultatet af ansøgers hovedanalyse for P2, DKK (SAIP).

	Vonicog alfa (Veyvondi) og rFVIII	Wilnativ	Haemate
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Inkrementelle omkostninger	-	[redacted]	[redacted]

3.1.2 Population 3

Ansøgers hovedanalyse resulterer i gennemsnitlige omkostninger for vonicog alfa (Veyvondi) på ca. [redacted] sammenlignet med Willfact. Resultatet er præsenteret i tabel 6.

Tabel 6: Resultatet af ansøgers hovedanalyse for P3, DKK (SAIP).

	Vonicog alfa (Veyvondi)	Willfact
Lægemiddelomkostninger	[redacted]	[redacted]
Inkrementelle omkostninger	-	[redacted]

3.1.3 Population 4

Ansøgers hovedanalyse resulterer i gennemsnitlige omkostninger for vonicog alfa (Veyvondi) på ca. [redacted], [redacted] og [redacted] sammenlignet med hhv. Willfact, Haemate og Wilnativ. Resultaterne er præsenteret i tabel 7.

Tabel 7: Resultatet af ansøgers hovedanalyse for P4, DKK (SAIP).

	Vonicog alfa (Veyvondi) evt. rFVIII	Willfact	Haemate	Wilnativ
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]	[redacted]
Inkrementelle omkostninger	-	[redacted]	[redacted]	[redacted]

3.2 Amgros' hovedanalyse

Baseret på Amgros' kritiske vurdering af den tilsendte model, har Amgros udarbejdet sin egen hovedanalyse. Forudsætningerne er som i ansøgers analyse bortset fra følgende:

- Antal infusioner ved behandling af blødninger med vonicog alfa (Veyvondi) og komparatorer er ens for alle populationer
- Sammenligningsdoser fra Medicinrådet rapport for vurdering af klinisk merværdi anvendes for alle lægemidler

Resultaterne fra Amgros' hovedanalyse præsenteres i de følgende afsnit for de forskellige populationer.

3.2.1 Population 2

Amgros' hovedanalyse for P2 resulterer i gennemsnitlige meromkostninger for vonicog alfa (Veyvondi) på ca. [redacted] og [redacted] sammenlignet med hhv. Wilnativ og Haemate, se tabel 8.

Hvis analysen udføres på baggrund af AIP, bliver lægemiddelomkostningerne for vonicog alfa (Veyvondi) ca. 1,45 mio. DKK, mens de inkrementelle omkostninger bliver ca. 1,04 mio. DKK og 1,03 mio. DKK per patient ved sammenligning med hhv. Wilnativ og Haemate.

Tabel 8: Resultatet af Amgros' hovedanalyse for P2, DKK (SAIP).

	Vonicog alfa (Veyvondi) og rFVIII	Wilnativ	Haemate
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]
Inkrementelle omkostninger	-	[redacted]	[redacted]

3.2.2 Population 3

Amgros' hovedanalyse for P3 resulterer i gennemsnitlige meromkostninger for vonicog alfa (Veyvondi) på ca. [redacted] sammenlignet med Willfact, se tabel 9.

Hvis analysen udføres på baggrund af AIP, bliver lægemiddelomkostningerne for vonicog alfa (Veyvondi) på ca. 153.000 DKK, mens de inkrementelle omkostninger bliver ca. 12.000 DKK per patient.

Tabel 9: Resultatet af Amgros' hovedanalyse for P3, DKK (SAIP).

	Vonicog alfa (Veyvondi)	Willfact
Lægemiddelomkostninger	[redacted]	[redacted]
Inkrementelle omkostninger	-	[redacted]

3.2.3 Population 4

Amgros' hovedanalyse for P4 resulterer i gennemsnitlige meromkostninger for vonicog alfa (Veyvondi) på ca. [redacted], [redacted] og [redacted] sammenlignet med hhv. Willfact, Haemate og Wilnativ, se tabel 10.

Hvis analysen udføres på baggrund af AIP bliver lægemiddelomkostningerne for vonicog alfa (Veyvondi) ca. 363.000 DKK, mens de inkrementelle omkostninger bliver ca. 38.000 DKK, 236.000 DKK og 240.000 DKK per patient ved sammenligning med hhv. Willfact, Haemate og Wilnativ.

Tabel 10: Resultatet af Amgros' hovedanalyse for P4, DKK (SAIP).

	Vonicog alfa (Veyvondi)	Willfact	Haemate	Wilnativ
Lægemiddelomkostninger	[redacted]	[redacted]	[redacted]	[redacted]
Inkrementelle omkostninger	-	[redacted]	[redacted]	[redacted]

4 BUDGETKONSEKVENSER

4.1 Ansøgers estimater

4.1.1 Patientpopulation og markedsandel

Med udgangspunkt i et RADS' baggrundsnotat fra 2016, vurderer ansøger at ca. 40 patienter om året vil være kandidater til at modtage vonicog alfa (Veyvondi) ved anbefaling både for P2, P3 og P4.

Amgros' vurdering af estimeret antal patienter

Amgros har adspurgt danske klinikere om forventede patientantal ved de forskellige populationer. Klinikernes vurderede patientantal er ikke fundet i overensstemmelse med ansøgers estimat.

Amgros udarbejder egen budgetkonsekvensanalyse, hvor patientantal baseres på de adspurgte klinikers udsagn.

4.1.2 Estimat af budgetkonsekvenser

Ansøger har inkluderet de samme omkostninger i budgetkonsekvensanalysen, som der er inkluderet i omkostningsanalysen dog uden diskontering af omkostninger efter første år.
I de følgende afsnit bliver budgetkonsekvenserne for de forskellige populationer præsenteret samt antagelser der gør sig gældende for de enkelte populationer.

Patientpopulation 2

Det antages at 50 % af blødninger forekommer hos personer med normalt eller let nedsat FVIII-niveau, mens 50 % forekommer hos personer med lavt FVIII-niveau.
Med de indlagte antagelser estimerer ansøger, at anvendelse af vonicog alfa (Veyvondi) vil resultere i budgetkonsekvenser på ca. [redacted] per år. Ansøgers estimat af budgetkonsekvenserne fremgår af tabel 11.

Tabel 11: Ansøgers hovedanalyse for totale budgetkonsekvenser for P2, mio. DKK, ikke-diskonterede tal (SAIP).

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Patientpopulation 3

Det antages at 50 % af de kirurgiske indgreb der forekommer i Danmark årligt, er mindre indgreb.
Med de indlagte antagelser estimerer ansøger, at anvendelse af vonicog alfa (Veyvondi) vil resultere i budgetkonsekvenser på [redacted] per år. Ansøgers estimat af budgetkonsekvenserne fremgår af tabel 12.

Tabel 12: Ansøgers hovedanalyse for totale budgetkonsekvenser for P3, mio. DKK, ikke-diskonterede tal (SAIP).

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Patientpopulation 4

Det antages at 50 % af de kirurgiske indgreb der forekommer i Danmark årligt, er større.
Med de indlagte antagelser estimerer ansøger, at anvendelse af vonicog alfa (Veyvondi) vil resultere i budget-konsekvenser på [redacted] per år. Ansøgers estimat af budgetkonsekvenserne fremgår af tabel 13.

Tabel 13: Ansøgers hovedanalyse for totale budgetkonsekvenser for P4, mio. DKK, ikke-diskonterede tal (SAIP).

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4.2 Amgros' estimater af budgetkonsekvenser

Amgros har korrigeret følgende estimater i forhold til ansøgers analyse:

- Antagelser fra Amgros' hovedanalyse benyttes
- Det årlige patientantal baseres på adspurgte klinikers estimater

Patientpopulation 2

Adspurgte klinikere forventer ikke at nogle patienter i P2 vil være kandidat til at modtage behandling med vonicog alfa (Veyvondi) ved anbefaling. Dermed estimeres det, at anvendelse af vonicog alfa (Veyvondi) resultere i budgetkonsekvenser på 0 DKK.

Patientpopulation 3

Adspurgte klinikere estimerer at antallet af patienter i P3 der er kandidat til at modtage behandling med vonicog alfa (Veyvondi) ved anbefaling er ca. 5 patienter årligt.

Med de indlagte antagelser estimeres det, at anvendelse af vonicog alfa (Veyvondi) vil resultere i budgetkonsekvenser på ca. [redacted] per år. Amgros' estimat af budgetkonsekvenserne fremgår af tabel 14.

Hvis analysen udføres på baggrund af AIP bliver de årlige budgetkonsekvenser ca. 3.000 DKK.

Tabel 14: Amgros' hovedanalyse for totale budgetkonsekvenser for P3, mio. DKK, ikke-diskonterede tal (SAIP).

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Patientpopulation 4

Adspurgte klinikere estimerer at antallet af patienter i P4 der er kandidat til at modtage behandling med vonicog alfa (Veyvondi) ved anbefaling er ca. 10 patienter årligt.

Med de indlagte antagelser estimerers det, at anvendelse af vonicog alfa (Veyvondi) vil resultere i budgetkonsekvenser på ca. [redacted] per år. Amgros' estimat af budgetkonsekvenserne fremgår af tabel 15.

Hvis analysen udføres på baggrund af AIP bliver de årlige budgetkonsekvenser ca. 99.000 DKK.

Tabel 15: Amgros' hovedanalyse for totale budgetkonsekvenser for P4, mio. DKK, ikke-diskonterede tal (SAIP).

	År 1	År 2	År 3	År 4	År 5
Anbefales	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anbefales ikke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Totale budgetkonsekvenser	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5 DISKUSSION

Ansøger har indsendt en analyse baseret på en narrativ sammenligning af kliniske studier. Der er stor variation studierne imellem på flere vigtige parametre, hvilket medfører stor usikkerhed til analysen.

Antagelser i analysen er baseret på udsagn fra en klinisk ekspert, hvis identitet er ukendt da ansøger ikke har været villig til at oplyse denne. Det medfører ligeledes store usikkerheder, da det ikke giver Amgros mulighed for at validere disse udsagn med personen.

Alle lægemidler inkluderet i analysen har vægtbaseret dosis, men ikke identiske hætteglasstørrelse. Derfor vil patientens vægt, i tilfælde hvor priserne for to forskellige lægemidler er tæt på ens, være afgørende for hvilket produkt der er billigst.

6 REFERENCER

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2. Von Willebrands sygdom | Danmarks Bløderforening [Internet]. [cited 2019 Mar 14]. Available from: https://www.bloderforeningen.dk/blodersygdom/von-willebrands-sygdom

3. Behandlingsvejledning inklusiv laegemiddelrekommandation for behandling af haemofili [Internet]. [cited 2019 Mar 14]. Available from: https://medicinraadet.dk/media/7027/laegemiddelrekommandation-haemofili-vers-12.pdf

AMGROS

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Høringssvar fra ansøger

PM

on 20-03-2019 15:29

Pode Milwertz, Anders <Anders.Pode-Milwertz@takeda.com>

SV: Medicinrådets endelige vurdering af klinisk merværdi for vonicog alfa

Til Mette Hollensted

Cc Dorte Glintborg; Anne Sofie Gram

Du svarede på denne meddelelse den 22-03-2019 11:20.

Kære Mette.

Tak for din mail.

Som nævnt under vores telefonsamtale, så har vi ingen indvendinger mod kategoriseringen af den kliniske merværdi.

Men jeg har to kommentar til specifikke forhold i vurderingsrapporten, se venligst nedenfor:

1. Hvad er begrundelsen for at Fagudvalget har undladt stillingtagen til Veyvondi sammenlignet med Willfact i relation til spørgsmål 4 – større blødninger.?
Ansøger har i afsnit 5.4.1 som førte afsnit henvist til afsnit 5.3 for s¨å vidt angår data for Veyvondi sammenlignet med Willfact. De fornødne data herunder antal af infusinoer ved større blødninger fremgår af afsnit 5.3.3 (p. 32ff) samt tabel 17 (p.33)

2. I behandlingen af klinisk spørgsmål #3 synes der at være en diskrepans i omtalen af andelen af patienter, som har type 3 VWD.
På s. 18, linje 6 fra neden anføres, at "i Veyvondi studiet er en overrepræsentation af patienter med von Willebrand sygdom type 3 i forhold til studiet med Willfact (53% vs 25%)", mens der på s. 19. linje 2 fra neden anføres ,at der er flere patienter med von Willebrand sygdom i Willfact-studiet sammenlignet med Veyvondi-studiet. Det er således korrekt at der numerisk er flere patienter med type 3 i Willfact studiet, men andelen af patienter med type 3 er større i Veyvondi studiet (53 % vs 32%).

I tabel 16 er der under opgørelsen af type sygdom anført , at der er 14 patienter (af 44) med type 3 i Willfact-studiet, men procentsatsen er angivet til 25%.
Antallet af patienter er korrekt, men den korrekte procentdel er 32 % (31,8%) som anført i ansøgningens tabel 15 (s.30)

Disse forhold giver ikke indvendinger mod kategoriseringen af den kliniske merværdi, men ville være godt at få forklaret.

Mvh Anders

Best regards,

Anders Pode Milwertz
Market Access and External Affairs Lead

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Medicinrådet

Medicinrådets vurdering af klinisk merværdi for vonicog alfa til behandling af von Willebrand sygdom

Versionsnr.: 1.1

Medicinrådet

Om Medicinrådet

Medicinrådet er et uafhængigt råd, som udarbejder anbefalinger og vejledninger om lægemidler til de fem regioner.

Medicinrådet vurderer, om nye lægemidler og nye indikationer kan anbefales som mulig standardbehandling og udarbejder fælles regionale behandlingsvejledninger.

Nye lægemidler vurderes i forhold til effekt, eksisterende behandling og pris. Det skal give lavere priser og lægemidler, der er til størst mulig gavn for patienterne.

De fælles regionale behandlingsvejledninger er vurderinger af, hvilke lægemidler der er mest hensigtsmæssige til behandling af patienter inden for et terapiområde og dermed grundlag for ensartet høj kvalitet for patienterne på tværs af sygehuse og regioner.

Om vurderingen af klinisk merværdi

Vurderingen af klinisk merværdi er Medicinrådets vurdering af, hvor effektiv og sikkert lægemidlet er i forhold til andre lægemidler til den samme gruppe patienter.

Vurderingen af klinisk merværdi indgår, når Medicinrådet skal beslutte, om lægemidlet anbefales som mulig standardbehandling.

Se Medicinrådets metodehåndbog for yderligere information.

Dokumentoplysninger	
Godkendelsesdato	13. marts 2019
Ikrafttrædelsesdato	13. marts 2019
Dokumentnummer	45292
Versionsnummer	1.1

Medicinrådet, Dampfærgevej 27-29, 3. th., 2100 København Ø
www.medicinraadet.dk
Sprog: dansk
Format: pdf
Udgivet af Medicinrådet, 13. marts 2019

Indhold

1 Lægemiddelinformationer

Lægemidlets oplysninger	
Handelsnavn	Veyvondi
Generisk navn	Vonicog alfa
Firma	Shire
ATC-kode	B02BD10
Virkningsmekanisme	Rekombinant von Willebrand faktor (rvWf)
Administration/dosis	Infusion af 40-80 IE/kg hver 8.-24. time indtil ønsket faktorniveau og hæmostatisk effekt er opnået.
EMA-indikation	Voksne (≥ 18 år) med von Willebrand sygdom, når behandling med desmopressin alene er ineffektiv eller ikke er indiceret til behandling af spontan blødning, kirurgisk blødning samt forebyggelse af kirurgisk blødning.

2 Medicinrådets konklusion vedrørende klinisk merværdi

Medicinrådet vurderer, at vonicog alfa (Veyvondi) til voksne patienter (≥ 18 år) med von Willebrand sygdom giver:

- **Ingen klinisk merværdi** ved on-demand behandling til patienter med lavt FVIII-niveau (< 30 %) sammenlignet med plasmaderiveret von Willebrand faktor.
- **Ingen klinisk merværdi** ved forebyggelse og behandling af blødning under mindre kirurgiske indgreb sammenlignet med plasmaderiveret von Willebrand faktor.
- **Ikkedokumenterbar klinisk merværdi** ved forebyggelse og behandling af blødning under større kirurgiske indgreb sammenlignet med plasmaderiveret von Willebrand faktor.

Evidensens kvalitet er meget lav for alle kliniske spørgsmål.

Den kliniske merværdi for patienter i on-demandbehandling, som har normalt eller let nedsat FVIII-niveau (> 30 %), kan ikke vurderes.

Medicinrådet kategoriserer lægemidlers kliniske merværdi i en af følgende kategorier:

Kategori 1. Stor merværdi: Vedvarende og stor forbedring i effektforhold, der ikke tidligere er opnået med et relevant behandlingsalternativ. Eksempler herpå er sygdomsremission, markant stigning i overlevelsestid, langvarigt fravær af alvorlige sygdomssymptomer eller udtalt fravær af alvorlige bivirkninger.

Kategori 2. Vigtig merværdi: Markant forbedring, eksempelvis lindring af sygdomstilstand, moderat stigning i overlevelsestid, lindring af alvorlige symptomer, fravær af alvorlige bivirkninger og væsentligt fravær af andre bivirkninger.

Kategori 3. Lille merværdi: Moderat forbedring, f.eks. reduktion i ikkealvorlige sygdomssymptomer eller fravær af bivirkninger.

Kategori 4. Ingen merværdi: Ingen merværdi sammenlignet med standardbehandling/andre behandlinger.

Kategori 5. Negativ merværdi: Negativ merværdi sammenlignet med standardbehandling/andre behandlinger.

Kategori 6. Ikkedokumenterbar merværdi: Ikkedokumenterbar merværdi sammenlignet med standardbehandling/ andre behandlinger. Effektforskellen kan ikke kvantificeres ud fra det videnskabelige datagrundlag.

3 Forkortelser

aPTT	Partiel tromboplastintid
EMA:	*European Medicines Agency*
EPAR:	*European public assessment report*
FVIII:	Koagulationsfaktor VIII
GRADE:	System til vurdering af evidens (*Grading of Recommendations Assessment, Development and Evaluation*)
IA:	Ikke angivet
IE:	Internationale enheder
IVR:	*In vivo recovery*
RCo:	Ristocetin co-faktor
rFVIII:	Rekombinant koagulationsfaktor VIII
rvWf:	Rekombinant von Willebrand faktor
vWf:	von Willebrand faktor

4 Formål

Formålet med Medicinrådets vurdering af klinisk merværdi af vonicog alfa (Veyvondi) til voksne (≥ 18 år) med von Willebrand sygdom er at vurdere den kliniske merværdi i forhold til et eller flere lægemidler til samme patientgruppe (komparator(-er)).

Med udgangspunkt i den kliniske merværdi og en omkostningsanalyse udarbejdet af Amgros vurderer Medicinrådet, om Veyvondi anbefales som mulig standardbehandling.

5 Baggrund

Von Willebrand sygdom

Von Willebrand sygdom er den hyppigste blødersygdom i Danmark, men incidens og prævalens er ikke kendt, da mange milde tilfælde ikke diagnosticeres. Der er registreret i alt ca. 300 patienter med von Willebrand sygdom ved de to hæmofilicentre i henholdsvis København og Aarhus [1].

Von Willebrand sygdom skyldes mangel på virksom von Willebrand faktor (vWf), som er vigtig for blodets hæmostatiske effekt, dvs. blodets evne til at størkne og dermed standse blødning. vWf er bærerprotein for koagulationsfaktor VIII (FVIII), og vWf-mangel er derfor ofte forbundet med nedsat FVIII-niveau. Svær von Willebrand sygdom vil derfor også medføre svær FVIII-mangel og sekundær hæmostasedefekt som ved hæmofili A.

Von Willebrand sygdom klassificeres i forhold til vWf-aktivitet og -niveau [2] og inddeles i type 1-3, som beskrevet i tabel 1. For at stille diagnosen von Willebrand sygdom skal der, foruden nedsat vWf, være en familiehistorie med blødning og klinisk betydende blødningstendens.

Opdelingen af von Willebrand sygdom i henhold til type 1-3 er listet i tabel 1:

Tabel 1: Typer af von Willebrand sygdom

Type von Willebrand sygdom	**Årsag**	**Sværhedsgrad**	**Behandling**
Type 1	Nedsat mængde vWf	Svær, moderat eller mild	On-demand behandling med desmopressin eller vWf ved behov for gentagne doser
Type 2*	Nedsat funktion af vWf	Svær, moderat eller mild	Enkelte i profylakse, de fleste i on-demand behandling med desmopressin eller vWf
Type 3	Fuldstændig mangel på vWf	Altid svær	Profylakse eller on-demand behandling med vWf

*Undertyper inkluderer 2A, 2B, 2M og 2N.

Nuværende behandling

Von Willebrand sygdom behandles i dag med desmopressin, som virker ved at øge mængden af vWf og FVIII i blodet. Patienter, som ikke opnår hæmostase med desmopressin, behandles med infusion af et vWf-præparat. Målet med behandlingen er at opnå hæmostase, dvs. at standse blødning samt sikre, at patienter, som gennemgår kirurgi, ikke har større blødning under det kirurgisk indgreb eller i det postoperative forløb end patienter uden von Willebrand sygdom.

De tre hidtil tilgængelige vWf-præparater er alle plasmaderiverede, og behandling med disse lægemidler kan derfor potentielt medføre en smitterisiko. Rekombinante præparater er derfor generelt at foretrække fremfor plasmaderiverede præparater. Udviklingen af virusinaktiverende metoder har minimeret risikoen for smitte med HIV og hepatitis C. Dog var udbruddet af variant Creutzfeldt-Jakob sygdom i Storbritannien i 1997, som skyldtes prioner, dvs. misfoldede proteiner, en påmindelse om, at det kun er muligt at screene for og inaktivere kendte patogener [1].

Plasmaderiverede vWf-præparater indeholder forskellig mængde FVIII. Da lægemidlerne ikke har entydige generiske navne, benævnes de i denne rapport med handelsnavne. Ifølge RADS' vejledning [3] er første valg behandling med Haemate, som indeholder vWf og FVIII i forholdet 2,4:1. Andet og tredje valg er henholdsvis Wilnativ med vWf og FVIII i forholdet 1:1 eller Willfact med vWf og FVIII i forholdet ≥ 10:1.

Anvendelse af det nye lægemiddel

Veyvondi er et rekombinant vWf (rvWf)-præparat, der virker som kroppens naturlige vWf. Veyvondi er fremstillet i ovarieceller fra kinesiske hamstere uden brug af humant protein. Veyvondi indeholder ikke FVIII.

Veyvondi er godkendt til behandling af voksne (≥ 18 år) med von Willebrand sygdom til behandling af spontan blødning, kirurgisk blødning samt forebyggelse af blødning i forbindelse med kirurgiske indgreb, når behandling med desmopressin alene er ineffektiv eller ikke er indiceret.

Veyvondi kan doseres som monoterapi eller i kombination med rekombinant FVIII (rFVIII), og dosering bestemmes individuelt efter patientens vægt, blødningstype, sværhedsgraden af von Willebrand sygdom samt ud fra monitorering af relevante kliniske og klinisk biokemiske parametre. Ved behandling af blødninger bør den initiale dosis af Veyvondi være på 40 til 80 IE/kg. I forbindelse med kirurgi bør FVIII-niveauet vurderes inden for tre timer forud for indledning af det kirurgiske indgreb.

6 Metode

De præspecificerede metoder i protokollen er udarbejdet af Medicinrådet. Ansøgningen er valideret af Medicinrådet.

Ansøger har anvendt og fulgt den præspecificerede metode, jf. protokol, som blev godkendt i Medicinrådet 30. oktober 2018, og har foretaget en narrativ gennemgang af data for alle effektmål. Ansøger har 29. januar 2019 indsendt den endelige ansøgning.

Fagudvalget har genovervejet baggrunden for, at afgræsningen mellem patienter med normalt og nedsat FVIII-niveau i protokollen blev sat til netop 30 %. Idet definitionsgrænsen for mild hæmofili er et FVIII-niveau på 40 %, vurderer fagudvalget, at afgræsningen, som blev fastsat for klinisk spørgsmål 1 og 2, i stedet burde være 40 %. Da en ændring til 40 % ikke vil have praktisk betydning for vurderingen af den kliniske merværdi for Veyvondi, vurderer fagudvalget dog, at afgrænsningen på 30 % bibeholdes i vurderingen af Veyvondi.

Fra evidens til kategori. Medicinrådet vurderer den kliniske merværdi af et lægemiddel ud fra den indsendte endelige ansøgning, evt. suppleret med andet materiale. I protokollen blev effektmålene angivet som "kritiske", "vigtige" og "mindre vigtige". I vurderingen af klinisk merværdi vægter de kritiske højest, de vigtige næsthøjest og de mindre vigtige indgår ikke.

Den kliniske merværdi kategoriseres først enkeltvis pr. effektmål, hvorefter der foretages en vurdering af den samlede kategori for lægemidlet på tværs af effektmålene. Kategoriseringen pr. effektmål foretages på baggrund af absolutte og relative værdier for det enkelte effektmål. Den relative effekt beskrives med et estimat og et konfidensinterval, der sammenholdes med generiske væsentlighedskriterier. Den absolutte effekt sammenholdes med den i protokollen beskrevne "mindste klinisk relevante forskel". Den endelige kategorisering af lægemidlets kliniske merværdi er en delvis kvalitativ proces, hvor der foretages en vurdering af det samlede datagrundlag på tværs af effektmålene.

Vurdering af evidensens kvalitet foretages med udgangspunkt i GRADE og udtrykker tiltroen til evidensgrundlaget for de enkelte effektstørrelser og den endelige kategori for klinisk merværdi. Evidensens kvalitet inddeles i fire niveauer: høj, moderat, lav og meget lav. GRADE-metoden er et internationalt anerkendt redskab til systematisk vurdering af evidens og udarbejdelse af anbefalinger. I denne vurdering er metoden anvendt til at vurdere evidensens kvalitet.

7 Litteratursøgning

Ansøger har udført en systematisk litteratursøgning og identificeret ni publikationer (jf. tabel 2). Fagudvalget har foruden disse ni publikationer identificeret og inkluderet endnu et relevant studie [4] samt orienteret sig i *European public assessment report* (EPAR) og produktresuméerne for Veyvondi, Haemate, Wilnativ og Willfact [5–9].

Tabel 2: Studier anvendt til at besvare klinisk spørgsmål 1-4

Reference	Titel	Klinisk spørgsmål	Lægemiddel
Gill et al., 2015 [10]	Haemostatic efficacy, safety, and pharmacokinetics of a recombinant von Willebrand factor in severe von Willebrand disease.	1, 2	Veyvondi
Peyvandi et al., 2018 [11]	A Phase 3 Study of Recombinant von Willebrand Factor in Patients with Severe von Willebrand Disease Who Are Undergoing Elective Surgery.	3, 4	Veyvondi
Borel-Derlon et al., 2007 [12]	Treatment of severe von Willebrand disease with a high-purity von Willebrand factor concentrate (Wilfactin): a prospective study of 50 patients.	1, 3	Willfact
Gill et al., 2003 [13]	Successful treatment of urgent bleeding in von Willebrand disease with factor VIII/VWF concentrate (Humate-P): use of the ristocetin cofactor assay (VWF:RCo) to measure potency and to guide therapy.	2	Haemate
Berntorp et al., 2009 [14]	Treatment and prevention of acute bleedings in von Willebrand disease--efficacy and safety of Wilate, a new generation von Willebrand factor/factor VIII concentrate.	2	Wilnativ
Castaman et al., 2013 [4]	Efficacy and safety during formulation switch of a pasteurized VWF/FVIII concentrate: Results from an Italian prospective observational study in patients with von Willebrand disease	2	Haemate
Lethagen et al., 2007 [15]	von Willebrand factor/factor VIII concentrate (Haemate P) dosing based on pharmacokinetics: a prospective multicentre trial in elective surgery.	4	Haemate

Gill et al., 2011 [16]	von Willebrand factor/factor VIII concentrate (Humate-P) for management of elective surgery in adults and children with von Willebrand disease.	4	Haemate
Windyga et al., 2011 [17]	Efficacy and safety of a new generation von Willebrand factor/factor VIII concentrate (Wilate®) in the management of perioperative haemostasis in von Willebrand disease patients undergoing surgery.	4	Wilnativ
Srivastava A, et al., 2017 [18]	Efficacy and safety of a VWF/FVIII concentrate (Wilate®) in inherited von Willebrand disease patients undergoing surgical procedures	4	Wilnativ

8 Databehandling

Medicinrådet har ikke fundet anledning til at foretage ændringer af beregninger foretaget af ansøger eller supplere med yderligere beregninger.

Da publicerede studier kun muliggør en narrativ gennemgang af data for alle effektmål, kan Medicinrådet ikke beregne relative effektestimater men kun forholde sig til absolutte værdier i vurderingen af effektmålene.

Ansøger ikke har indsendt data for patienter med normalt eller let nedsat FVIII-niveau. Den kliniske merværdi af Veyvondi kan derfor ikke vurderes for denne population (jf. klinisk spørgsmål 1).

9 Klinisk merværdi

9.1 Konklusion klinisk spørgsmål 1

Hvad er den kliniske merværdi af vonicog alfa (Veyvondi), i forhold til plasmaderiveret vWf, ved behandling af blødning hos patienter med von Willebrand sygdom og med normalt eller let nedsat FVIII-niveau (> 30 %)?

Fagudvalget vurderer, at Veyvondi til patienter med von Willebrand sygdom og normalt eller let nedsat FVIII-niveau (> 30 %) **ikke kan vurderes**, da der ikke er data for on-demand behandling til denne patientpopulation.

Datagrundlag

Ansøger henviser til data fra et studie af Veyvondi med 22 patienter, hvoraf langt størsteparten havde von Willebrand sygdom type 3 og dermed fuldstændig mangel på FVIII [10]. Det var planlagt, at patienter fik en initialdosis af FVIII uanset FVIII-niveau. Da langt størstedelen af patientpopulationen har intet FVIII, kan data ikke besvare dette kliniske spørgsmål.

9.2 Konklusion klinisk spørgsmål 2

Hvad er den kliniske merværdi af vonicog alfa (Veyvondi), i forhold til plasmaderiveret vWf, ved behandling af blødning hos patienter med von Willebrand sygdom og lavt FVIII-niveau (< 30 %)?

Fagudvalget vurderer, at Veyvondi ved on-demand behandling til patienter (≥ 18 år) med von Willebrand sygdom og lavt FVIII-niveau (< 30 %) giver **ingen klinisk merværdi** sammenlignet med plasmaderiveret von Willebrand faktor (meget lav evidenskvalitet).

9.2.1 Gennemgang af studier

Der er fundet et studie af Veyvondi [10] og tre studier af et plasmaderiveret vWf-præparat med indhold af FVIII [4,13,14], som ligger til grund for vurderingen.

Karakteristika

Gill et al., 2015 [10]: Et ukontrolleret fase 3-studie, hvor 31 patienter blev allokeret til seks måneders on-demand behandling. 22 patienter blev behandlet for en blødning i observationsperioden. I alt blev der behandlet 192 blødninger. Uanset patientens FVIII-niveau blev der givet en initialdosis med rvWf i en dosis ratio på 1,3:1 i forhold til FVIII (vWf:ristocetin co-faktor (RCo)/FVIII:C). Det vigtigste primære endepunkt var andel patienter, der opnåede succesfuld behandling af blødninger. Sekundære endepunkter inkluderede andelen af patienter, der opnåede 'meget god' eller 'god' hæmostatisk effekt, antal infusioner af rvWf:rFVIII og/eller rvWf per blødning, antal tilfælde af udvikling af inhibitor (heriblandt mod vWf og/eller FVIII), tromboemboliske hændelser samt uønskede hændelser.

Gill et al., 2003 [13]**:** Et prospektivt ukontrolleret open-label studie med 33 patienter i on-demandbehandling fra 19 centre, som havde til formål at evaluere effekt og sikkerhed ved behandling med FVIII og vWf-kombinationspræparatet Humate-p (Haemate). Studiet varede ni måneder. Patienterne blev ikke fulgt men blev inkluderet ved alvorlig blødning, og en enkelt patient kunne inkluderes flere gange. I alt blev der behandlet 53 blødninger i studiet. Den gennemsnitlige ratio vWf:RCo til FVIII:C aktivitet for Humate-P er 2,5:1. Hver investigator var i besiddelse af doseringsguidelines, men den endelige dosering var op til hver enkelt investigator. Studiets primære effektmål var hæmostatisk effekt, og derudover blev der rapporteret blødningstyper, sværhedsgrad af blødningerne og alvorlige bivirkninger.

Berntorp et al., 2009 [14]**:** Berntorp et al. rapporterer data fra fire prospektive, ukontrollerede, ikke-randomiserede multicenter fase 2/3 -studier (n = 44), der havde til formål at evaluere effekten og sikkerhedsprofilen ved behandling med Wilate (Wilnativ). Wilnativ er et vWf kombinationspræparat med en gennemsnitlig ratio vWf:RCo til FVIII:C aktivitet på ca. 0.9. I studiet anføres en anbefalet dosis på 20–50 internationale enheder (IE) Wilate/kg. Faktisk dosis og behandlingstid var dog afhængigt af den enkelte patients kliniske situation (dvs. sværhedsgrad og fysisk placering af blødning). Studiets primære effektmål var hæmostatisk effekt, og derudover blev der rapporteret blødningstyper, sværhedsgrad af blødningerne og alvorlige bivirkninger.

Castaman et al., 2013 [4]: Et prospektivt, observationelt open-label studie, som blev foretaget på tværs af 20 hæmofilicentre i Italien. Studiets formål var at undersøge den kliniske effekt samt sikkerhedsprofilen ved behandling med Haemate. Hver patient blev vurderet ved baseline og herefter 1-4 gange årligt. Behandling med Haemate blev givet både som on-demand ved blødning og/eller som sekundær profylakse og til forebyggelse og behandling i forbindelse med kirurgi. Opfølgningstiden var 24 mdr. Primære endepunkter inkluderede hæmostatisk effekt samt uønskede hændelser.

Tabel 8 viser studiekarakteristika for de fire studier [4,10,13,14].

Tabel 8: Studiekarakteristika for relevante studier vedrørende on-demand behandling

	Veyvondi	**Haemate**	**Haemate**	**Wilnativ**
	Gill et al., 2015 [10]	Gill et al., 2003 [13]	Castaman et al., 2013 [4]	Berntorp et al., 2009 [14]
Design	Fase 3, ikke-randomiseret, cross-over, open-label studie	Prospektivt, multicenter, ikke-randomiseret open-label-studie	Prospektivt, observationelt open-label-studie	Prospektivt, ikke-kontrolleret, ikke-randomiseret multicenter fase 2/3-studie
Varighed af on-demand behandling	6 mdr.	Patienter blev fulgt indtil tre dage efter den sidste infusion med interventionen, og hvis investigator vurderede, at patienten ikke ville have gavn af flere infusioner	24 mdr.	IA
Dosis (IE/kg)				
Initialdosis	Mindre blødninger: 40-60 IE vWf:RCo/kg Større blødninger: op til 80 IE vWf:RCo/kg	60-80 IE vWf:RCo (27-26 IE FVIII:C)/kg	vWf:RCo, 40–80 IE/kg og FVIII:C, 20–40 IE/kg	20-50 IE/kg (både vWf:RCo og FVIII:C)
Vedligeholdelses-dosis	IA	40-60 IE vWf:RCo (18–27 IE FVIII:C)/kg	IA	20-50 IE/kg (både vWf:RCo og FVIII:C)
Median dosis i studiet	46,5 IE/kg vWf:RCO	67 IE/kg vWf:RCO - efterfølgende 74 IE	IA	29 IE
Samtidig administration af FVIII:				
Initialdosis	Ja*	Nej¤	IA	Nej
Vedligeholdelses-dosis	Nej, hvis klinisk forsvarligt	Nej¤	IA	Nej
Median dosis i studiet	33,6 IE/kg FVIII	IA	IA	IA

* Ved en fejl blev der ikke administreret FVIII ved 10 behandlinger af blødninger hos 3 patienter. Disse blødninger blev alligevel vurderet til 'meget god' hæmostatisk effekt. Samlet blev der givet tillæg af FVIII i 95 % af alle blødninger.
¤ Patienter, hvis FVIII:C-niveauer var for lave i forhold til klinisk praksis og dermed skulle have øget mængde FVIII, modtog en øget dosis af lægemidlet (Humate P). IA, ikke angivet.

Population

Gill et al., 2015 [10]**:** Inklusionskriterier var svær von Willebrand sygdom defineret ved: type 1 (vWf:RCo < 20 IE/dL); type 2A (vWf:RCo < 20 IE/dL), type 2B (diagnosticeret ved genetisk udredning), type 2N (FVIII:C < 10 % og genetisk udredning, type 2M, type 3 (vWf antigen ≤ 3 IE/dL) eller svær von Willebrand sygdom med tidligere behandling med et vWf-præparat. Patienter måtte ikke være gravide op til studiestart, og der skulle anvendes prævention undervejs i studiet. Eksklusionskriterier inkluderede andre blødningssygdomme, tidligere immunologiske eller kardiovaskulære sygdomme, tromboemboliske hændelser samt udvikling af inhibitor mod vWf eller FVIII.

Gill et al 2003., [13]**:** Inklusionskriterier var von Willebrand sygdom, hvor behandling med desmopressin ikke var effektiv, men sværhedsgraden af vWf er ikke defineret. Derudover var inklusionskriteriet en alvorlig, livs- eller legemsdelstruende blødning. Patienter med inhibitor mod vWf blev ekskluderet.

Berntorp et al., 2009 [14]**:** Inklusionskriterier var alle typer von Willebrand sygdom, hvor behandling med desmopressin ikke har været effektiv. Eksklusionskriterier inkluderede: graviditet, amning, inhibitor mod vWf eller FVIII, overfølsomhed overfor plasmaderiverede vWf-præparater samt alvorlig sygdom, herunder i nyrer eller lever.

Castaman et al., 2013 [4]: Inklusionskriterier inkluderede alle typer von Willebrand sygdom, begge køn og alle aldre. Patienterne skulle tidligere have modtaget behandling med Haemate.

Populationskarakteristika for de relevante studier [4,10,13,14] er beskrevet i tabel 9:

Tabel 9: Populationskarakteristika for relevante studier vedrørende on-demand behandling.

	Veyvondi	**Haemate**	**Haemate**	**Wilnativ**
	Gill et al., 2015 [10]	Gill et al., 2003 [13]	Castaman et al., 2013 [4]	Berntorp et al., 2009 [14]
Aldersafgrænsning	≥ 18 år ≥ 65 år	Patienter i alle aldre	Patienter i alle aldre	≥ 5 år
Patienter i on-demand behandling	22[a]	33	75¤	44
von Willebrand sygdom type (n) **1** **1 eller 2** **2A** **2B** **2M** **2N** **3** **Ikke specificeret**	 - - 1 - - 4 17 (77 %) -	 9 (27 %) - 4 4 - - 12 (36 %) 4	 29 - 5 14 1 - 25 (33 %) -	 8 (18 %) - 6 4 - 2 24 (55 %) -
Alder, år **Median (range)** **Gns (range)**	 37 (18-64)* IA	 31,0 IA	 41,0 (1-79)* IA	 IA 31,9 (5-73)
Vægt, kg **Median (range)** **Gns (range)**	 73,0 (44,0-142,7)* IA	 67.0 IA	 IA IA	 IA 62 (19-104)
Behandling forud for inklusion, n (%) **On-demand**	 27 (73,0)§	 IA	 101 (83,5%)*	 IA

Profylakse **Kombination af on-demand og profylakse**	3 (8,1)§ 7 (18,9)§	IA IA	16 (13,2%)* IA	IA IA
Antal blødninger 12 mdr. forud for studie, median (range)	0,7 (0,0-6,0)#	IA	IA	IA

[a] Inklusionskriterier blev baseret på følgende afgrænsninger: svær type 3 eller svær type 1 og type 2A (vWf:RCo, 20 IE/dL), type 2B, type 2N, type 2M, eller type 3 (vWf:Ag ≤ 3 IE/dL). 31 patienter blev allokeret til on-demand behandling, men kun 22 af disse patienter oplevede blødninger. ¤Af de 75 patienter, som var i on-demand behandling for blødning, var 26 patienter i profylaktisk behandling, mens de 49 patienter kun fik on-demand behandling. *Baseret på den fulde patientpopulation, som modtog vWf (n = 37 for [10] og n = 121 for [4]).
§Vurderet 24 måneder forud for inklusion.
#n = 36. IA, ikke angivet.

I studiet af Veyvondi er der flere patienter med von Willebrand sygdom type 3 i forhold til studierne af Haemate og Wilnativ. Størstedelen af patienterne i studiet af Veyvondi (77 %) har von Willebrand sygdom type 3, mens andelen i studierne af Haemate og Wilnativ er henholdsvis 36 %, 33 % og 55 %. Tidligere behandling samt antallet af blødninger 12 måneder forud for inklusion i studiet er ikke rapporteret i studierne af Haemate og Wilnativ. I studiet af Veyvondi har 95 % af patienterne modtaget samtidig administration af FVIII. Haemate og Wilnativ er kombinationsbehandlinger, men der var mulighed for samtidig administration af FVIII i det ene studie af Haemate [13]. Fagudvalget vurderer, at populationerne i alle tre studier svarer til den prædefinerede population i klinisk spørgsmål 2 (patienter med lavt FVIII-niveau).

9.2.2 Resultater og vurdering

Resultater og vurdering af de effektmål, som fagudvalget har præspecificeret som henholdsvis kritiske og vigtige, følger nedenfor.

Jf. protokollen skal klinisk spørgsmål 2 besvares med en sammenligning af Veyvondi med plasmaderiveret vWf. Datagrundlaget tillader ikke indirekte sammenlignende analyser, hvorfor data sammenstilles i en narrativ sammenligning.

Hæmostatisk effekt (ved blødning og kirurgi) (kritisk)

Målet med behandlingen er at opnå hæmostase og derved standse blødningen på stedet for den vaskulære skade.

Tabel 10. Vurdering af klinisk merværdi: Hæmostatisk effekt (ved blødning og kirurgi)

	Forhåndsdefineret grundlag for vurdering	Resultater			
		Veyvondi [10]	**Haemate** [13]	**Haemate** [4]	**Wilnativ** [14]
Absolutte forskelle	10 procentpoint forskel i antal blødninger, hvor patienten opnår "meget god" eller "god" hæmostatisk effekt	97,9 %* [98,1;100]	98 % [88,1;100]	95,4 % [IA;IA]	96 % [IA;IA]
Evidensens kvalitet	Meget lav				

ANM: Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data på de absolutte værdier fra resultatafsnittet, som indgår i Medicinrådets vurdering. *Data fra Veyvondi EPAR [6]. IA, ikke angivet.

For Veyvondi var andelen af patienter, der opnåede god eller meget god hæmostatisk effekt 97,9 %. I de to studier af Haemate var andelen henholdsvis 98 % og 95.4 % (gns. 96,7 %), mens andelen var 96 % for Wilnativ. Data indikerer dermed, at der ikke er en klinisk relevant forskel mellem lægemidlerne, idet den hæmostatiske effekt er høj (96-97,9 %) for både Veyvondi, Haemate og Willfact.

Samlet vurderer fagudvalget, at Veyvondi har **ingen klinisk merværdi** vedrørende hæmostatisk effekt sammenlignet med Haemate og Wilnativ (meget lav evidenskvalitet).

Antal infusioner per blødning (kritisk)

Antallet af nødvendige infusioner til behandling af en blødning er et kritisk effektmål, da umiddelbar behandlingseffekt skaber hurtigere klinisk bedring, og da et lavere antal infusioner forventes at minimere den praktiske ulempe.

Tabel 11. Vurdering af klinisk merværdi: Antal infusioner per blødning

	Forhåndsdefineret grundlag for vurdering	Resultater			
		Veyvondi [10]	**Haemate** [13]	**Haemate** [4]	**Wilnativ** [14]
Absolutte forskelle	En infusion	1 (1-4)*	2 (1-36)*	1 (1-28)*	1**
Evidensens kvalitet	Meget lav				

ANM: Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data fra ansøgningen, som indgår i Medicinrådets vurdering. *Median (range). **Gennemsnitligt antal behandlingsdage.

For Veyvondi rapporteres én median infusion per blødning sammenlignet med to og en i de to studier af Haemate. Der rapporteres ikke antal infusioner per blødning for Wilnativ. Antallet af infusioner per blødning varierer fra 1-28 og 1-36 i de to studier af Haemate sammenlignet med 1-4 for Veyvondi. Fagudvalget vurderer, at variationen i antal infusioner skyldes forskel i sværhedsgrad af blødningerne i studierne. I studiet af Veyvondi var 122 ud af 192 blødninger klassificeret som mindre ('minor'), mens inklusionskriteriet i det ene studie af Haemate var alvorlig blødning, og kun tre ud 53 blødninger blev efterfølgende klassificeret som milde [13]. I dette studie af Haemate indgik både akut ortopædkirurgi, en patient i motorcykelulykke og behandling af en intrakraniel blødning [13]. I det andet studie af Haemate [4] var de typiske blødningstyper næseblod, blødninger i tandkød, ledblødninger, kraftige menstruationer og gastrointestinal blødning. Ca. en

tredjedel af patienterne, der fik on-demand behandling for en blødning, var i profylaktisk behandling, mens de resterende patienter kun fik on-demand behandling. Hæmostatisk effekt er opgjort samlet, og profylaktisk behandling kan påvirke opgørelsen af infusioner per blødning.

Fagudvalget vurderer på den baggrund, at Veyvondi har **ingen klinisk merværdi** vedrørende antal infusioner per blødning sammenlignet med Haemate og Wilnativ (meget lav evidenskvalitet).

Inhibitor mod vWf (kritisk)

Patienter med von Willebrand sygdom kan ved behandling med et vWf-præparat udvikle neutraliserende antistoffer (inhibitor) mod vWf, hvorved vWf-præparatet gøres uvirksomt.

Tabel 12: Vurdering af klinisk merværdi: Inhibitor mod vWf

	Forhåndsdefineret grundlag for vurdering	Resultater			
		Veyvondi [10]	**Haemate** [13]	**Haemate** [4]	**Wilnativ** [14]
Absolutte forskelle	2 hændelser i hvert af de aktuelle studier	0	IA	0	IA
Evidensens kvalitet	Meget Lav				

ANM: Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data fra ansøgningen, som indgår i Medicinrådets vurdering. IA, ikke angivet.

Forekomst af inhibitor er opgjort til 0 tilfælde for Veyvondi. For Haemate er der registreret 0 tilfælde af inhibitor i det ene studie [4], mens der ikke er oplysninger vedrørende inhibitor i det andet studie [13]. Der er ikke oplysninger om inhibitor for Wilnativ. Samlet vurderer fagudvalget, at Veyvondi har **ingen klinisk merværdi** vedrørende inhibitor mod vWf sammenlignet med Haemate og Wilnativ (meget lav evidenskvalitet).

Anafylaksi (vigtig)

Patienter med von Willebrand sygdom, som udvikler inhibitor mod vWf, kan foruden en større risiko for blødningsepisoder have en risiko for at udvikle livstruende anafylaksi i forbindelse med behandling med et vWf-præparat. Anafylaksi udgør dermed en alvorlig bivirkning.

Tabel 13. Vurdering af klinisk merværdi: Anafylaksi

	Forhåndsdefineret grundlag for vurdering	Resultater			
		Veyvondi [10]	**Haemate** [13]	**Haemate** [4]	**Wilnativ** [14]
Absolutte forskelle	To hændelser i hvert af de aktuelle studier	0	IA	IA	IA
Evidensens kvalitet	Meget lav				

ANM: Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data fra ansøgningen, som indgår i Medicinrådets vurdering. IA, ikke angivet.

Forekomst af anafylaksi er opgjort til 0 tilfælde for Veyvondi. Der er ikke oplysninger om anafylaksi for Haemate og Wilnativ. Samlet vurderer fagudvalget, at Veyvondi har **ingen klinisk merværdi** vedrørende anafylaksi sammenlignet med Haemate og Wilnativ (meget lav evidenskvalitet).

Alvorlig venøs tromboemboli (vigtig)

Fagudvalget ønsker jf. protokollen, at udvikling af venøs tromboemboli rapporteres udelukkende i forhold til alvorlige episoder, hvilket omfatter proksimal dyb venetrombose, lungeemboli, trombose i centralnervesystemet eller andre vitale organer.

Tabel 14. Vurdering af klinisk merværdi: Alvorlig venøs tromboemboli

	Forhåndsdefineret grundlag for vurdering	Resultater			
		Veyvondi [10]	**Haemate** [13]	**Haemate** [4]	**Wilnativ** [14]
Absolutte forskelle	To hændelser i hvert af de aktuelle studier	0	0	0	0
Evidensens kvalitet	Meget lav				

ANM: Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data fra ansøgningen, som indgår i Medicinrådets vurdering.

Der er i de inkluderede studier af Veyvondi, Haemate og Wilnativ rapporteret 0 tilfælde af alvorlig venøs tromboemboli.

Fagudvalget vurderer derfor, at Veyvondi har **ingen klinisk merværdi** vedrørende alvorlig venøs tromboemboli sammenlignet med Haemate og Wilnativ (meget lav evidenskvalitet)

9.2.3 Evidensens kvalitet

Evidensens kvalitet for klinisk spørgsmål 2 er samlet set vurderet som værende **meget lav**. Overvejelser vedrørende evidensens kvalitet kan ses i bilag 2.

I evidensgennemgangen for sammenligningen af Veyvondi, Haemate og Wilnativ foreligger der ikke direkte sammenlignende studier. Der er derfor ikke estimater for relativ effekt. Da der er tale om en narrativ sammenligning af data fra forskellige studier, vil evidenskvaliteten i udgangspunktet være lav. Den vurderede risiko for bias er moderat, og forskelle i patientkarakteristika og sværhedsgraden af blødninger medfører minimum nedgradering med yderligere ét niveau for '*indirectness'*. Samlet set vil evidenskvaliteten derfor som minimum blive meget lav, og der er derfor ikke udarbejdet GRADE-profiler. Risiko for bias-vurderinger af de enkelte studier kan ses i bilag 2.

9.2.4 Konklusion for klinisk spørgsmål 2

Fagudvalget vurderer, at Veyvondi som on-demand-behandling til patienter med von Willebrand sygdom og lavt FVIII-niveau (< 30 %) giver **ingen klinisk merværdi** sammenlignet med plasmaderiveret von Willebrand faktor (meget lav evidenskvalitet).

I den samlede vurdering vægter fagudvalget, at der ikke er fundet klinisk relevante forskelle mellem lægemidlerne for de kritiske effektmål hæmostatisk effekt, antal infusioner per blødning og inhibitor mod vWf samt for de vigtige effektmål alvorlig venøs tromboemboli og anafylaksi. Fagudvalget finder på denne

baggrund, at Veyvondi har ingen klinisk merværdi til on-demand behandling af patienter med von Willebrand sygdom og lavt FVIII-niveau sammenlignet med plasmaderiveret vWf.

Evidenskvaliteten er samlet set meget lav for alle effektmålene, hvorfor den samlede evidenskvalitet er meget lav.

9.3 Konklusion klinisk spørgsmål 3

Hvad er den kliniske merværdi af vonicog alfa (Veyvondi), i forhold til plasmaderiveret vWf, ved forebyggelse og behandling af blødninger ved mindre kirurgiske indgreb hos patienter med von Willebrand sygdom?

Fagudvalget vurderer, at Veyvondi ved forebyggelse og behandling af blødninger ved mindre kirurgiske indgreb hos patienter med von Willebrand sygdom giver i**ngen klinisk merværdi** sammenlignet med plasmaderiveret von Willebrand faktor (meget lav evidenskvalitet).

9.3.1 Gennemgang af studier

Der er fundet et studie af Veyvondi [11] og et studie af et rvWf-præparat uden indhold af FVIII [12], som ligger til grund for vurderingen.

Karakteristika

Peyvandi et al., 2018 [11]: et ukontrolleret fase 3-studie, der havde til formål at evaluere den hæmostatiske effekt og bivirkningsprofil ved behandling af Veyvondi hos patienter med svær von Willebrand sygdom, der gennemgår et elektivt kirurgisk indgreb. I alt blev 15 patienter inkluderet og fulgt i 14 dage efter det kirurgiske indgreb. Studiets primære endemål var hæmostatisk effekt (vurderet på en 4-trinsskala), mens sekundære endemål inkluderede udvikling af inhibitor og tromboemboliske hændelser.

Borel-Derlon et al., 2007 [12] rapporterer to separate studier (kaldet henholdsvis 'Fransk studie' og 'Europæisk studie') på fire separate studiepopulationer: on-demand (n = 26), kirurgi (n = 44), korttidsprofylakse og langtidsprofylakse. Den første studiedel (Fransk studie) blev udført på seks centre i Frankrig og er et ikke-randomiseret farmakokinetisk studie med det formål at undersøge effekt og sikkerhedsprofil ved behandling med Willfact. Tillæg af FVIII blev administreret, hvis baseline FVIII-niveauer var < 20 IE/dL eller i tilfælde af kraftig blødning.

Den anden studiedel (Europæisk studie) er et randomiseret, open-label, farmakokinetisk crossover-studie, som foregik på fem europæiske centre. Studiet sammenlignede behandling med Willfact med behandling med andre vWf-præparater hos patienter med alvorlig von Willebrand sygdom. Ved blødning blev tillæg af FVIII administreret for at bibeholde vWf:RCo og FVIII-niveauer ≥ 30 IE/dL eller i tilfælde af kraftig blødning.

Borel-Derlon et al., 2007 rapporterer ikke forhåndsdefinerede endepunkter, men de vigtigste fund i studiet forholder sig bl.a. til antal infusioner, antal blødninger, median infusionsdosis vWf:RCo IE/kg og 'meget god' eller 'god' hæmostatisk effekt.

Studiekarakteristika for de relevante studier er beskrevet i tabel 15:

Tabel 15: Studiekarakteristika for relevante studier vedrørende forebyggelse og behandling af blødninger ved mindre kirurgiske indgreb

	Veyvondi	**Willfact**
	Peyvandi et al., 2018 [11]	Borel-Derlon et al., 2007 [12]
NCT-nummer	NCT02283268	NA
Design	Prospektivt fase 3, open-label, ukontrolleret, ikke-randomiseret studie	Prospektivt ukontrolleret ikke-randomiseret multicenterstudie
Definition af mindre kirurgiske indgreb (kirurgi minor)	Inkluderede placering af i.v. adgang, fjernelse af mindre hudforandringer, artroskopi, gastrokopi, coloskopi, eller keglesnit	Ikke klart defineret. Dog angives det, at gastroskopi, coloskopi, hysteroskopi, koronar angiografi og tandrensning blev anset som mindre indgreb
Loadingdosis vWf 12-24 timer forud for indgreb	Alle patienter modtog 40–60 IE/kg vWf:RCo med ønsket målsætningsniveau på ≥ 30 IE/dL	Patienter med baseline FVIII-niveau <60 IE/dL modtog en infusion af vWf-koncentrat (50 eller 60 IE/kg)
Dosis vWf 1-2 timer forud for indgreb	Hvis FVIII:C målsætningsniveau blev opfyldt, blev alene rvWf administreret	Alle patienter modtog en infusion af vWf-koncentrat (50 eller 60 IE/kg)
Samtidig administration af FVIII 1-2 timer forud for indgreb	Hvis ikke FVIII:C målsætningsniveauer blev opfyldt, så blev rFVIII (Advate) administreret	Ikke prædefineret. Dog angives det, at tillæg af FVIII blev givet ved operationer, som ikke var planlagt. I disse tilfælde var målsætningen at opnå FVIII-niveau på 60 IE/dL
Vurdering af hæmostatisk effekt	24 timer efter sidste perioperative infusion af lægemidlet eller ved det afsluttende besøg 14 dage efter indgreb (alt efter, hvad der kom først for den enkelte patient)	Ved afslutning af det kirurgiske indgreb samt ved udskrivelse fra hospitalet

Population

Peyvandi et al., 2018 [11]**:** Inklusionskriterier inkluderede svær von Willebrand sygdom defineret ved: type 1 (VWF:RCo <20 IE/dL, type 2A, type 2B (genetisk udredning), type 2N (FVIII:C < 10 % og genetisk udredning, type 2M eller type 3 (vWf antigen (vWf:Ag) ≤ 3 IE/dL). Eksklusionskriterier inkluderede alder < 18 år, graviditet, amning, inhibitor mod vWf eller FVIII, overfølsomhed overfor komponenter i interventionen, tidligere kendte immunologiske sygdomme, sygdomme i nyrer eller lever, tromboemboliske hændelser og lavt blodpladetal.

Borel-Derlon et al., 2007 [12]**:** For begge de inkluderede studier var inklusionskriterierne arvelige former af von Willebrand sygdom, hvor behandling med desmopressin var ineffektiv samt tidligere behandling med pdvWf-præparater eller røde blodceller. Endvidere var der specifikke inklusionskriterier for de to studier:
Fransk studie: Patienter med vWf:RCo < 30 IE/dL eller FVIII < 30 IE/dL for type 2 N.
Europæisk studie: Patienter med svær von Willebrand sygdom blev inkluderet, hvis de havde (i) en klinisk blødningshistorik (> én blødningsepisode) og ii) mindst én af følgende: a) blødningstid > 15 minutter, b) vWf:RCo < 10 IE/dL eller c) FVIII koaguleringsaktivitet < 20 IE/dL. I begge studier blev patienter med udvikling af inhibitor mod vWf eller FVIII ekskluderet.

Populationskarakteristika for de relevante studier er beskrevet i tabel 16:

Tabel 16: Populationskarakteristika for relevante studier vedrørende forebyggelse og behandling af blødninger ved mindre kirurgiske indgreb

	Veyvondi	**Willfact**
	Peyvandi et al., 2018 [11]	Borel-Derlon et al., 2007 [12]
Aldersafgrænsning	≥ 18 år	≥ 5 år
Patienter, n **Mindre kirurgiske indgreb (kirurgi minor), n**	15 4	44 IA
von Willebrand sygdom type (n) **1** **1 eller 2** **2** **2A** **2B** **2M** **2N** **3** **Ikke specificeret**	 3 - - 2 1 1 - 8 (53 %) -	 5 - - 14 9 1 1 14 (32 %) -
Alder, år [median (range)]	40 (20-70)	37 (5-81)¤
Vægt, kg [median (range)]	73,5 (52-127,2)	62 (24-102)¤
BMI [median (range)]	25,6 (17,1-38)	IA
vWf:RCo, median	IA	< 10 (10-33)¤
FVIII:C **Median** **Gns. (SD), IE/dL** **Alle typer von Willebrand sygdom** **Type 1** **Type 2A** **Type 2B** **Type 2M** **Type 3**	 IA 16,4 (19,9) (n = 15) 17 (4) (n = 3) 34,5 (23,3) (n = 2) 36 (IA) (n = 1) 66 (IA) (n = 1) 3,0 (1,5) (n = 8)*	 27 (< 1-63)¤ IA IA IA IA IA IA

¤baseret på den fulde patientpopulation (n=50), IA. ikke angivet.

Fagudvalget vurderer, at patienterne i studierne er repræsentative for danske hæmofilipatienter. Selvom der i studiet af Veyvondi er en overrepræsentation af patienter med von Willebrand sygdom type 3 i forhold til studiet af Willfact (53 % versus 32 %), så vurderer fagudvalget, at patienter med von Willebrand sygdom type 3 også er den patientgruppe, som er mest behandlingskrævende i dansk klinisk praksis.

9.3.2 Resultater og vurdering

Resultater og vurdering af de effektmål, som fagudvalget har præspecificeret som henholdsvis kritiske og vigtige, følger nedenfor.

Jf. protokollen skal klinisk spørgsmål 3 besvares med en sammenligning af Veyvondi med plasmaderiveret vWf. Datagrundlaget tillader ikke indirekte sammenlignende analyser, hvorfor data sammenlignes i en narrativ sammenligning.

Hæmostatisk effekt (ved blødning og kirurgi) (kritisk)

Målet med behandlingen er at opnå hæmostase og derved standse skaden (blødningen).

Tabel 17. Vurdering af klinisk merværdi: Hæmostatisk effekt (ved blødning og kirurgi)

	Forhåndsdefineret grundlag for vurdering	Resultater	
		Veyvondi [11]	**Willfact** [12]
Absolutte forskelle	10 procentpoint forskel i antal blødninger, hvor patienten opnår "meget god" eller "god" hæmostatisk effekt	100 %	100 %
Evidensens kvalitet	Meget Lav		

ANM: Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data på de absolutte og relative værdier fra resultatafsnittet, som indgår i Medicinrådets vurdering.

For både Veyvondi og Willfact var andelen af patienter, der opnåede 'god' eller 'meget god' hæmostatisk effekt, 100 %. Data indikerer dermed ikke, at der er en klinisk relevant forskel på lægemidlerne. Fagudvalget bemærker dog, at hæmostatisk effekt af Veyvondi blev vurderet 24 timer efter sidste perioperative infusion, mens hæmostatisk effekt for Willfact blev vurderet ved udskrivelse fra hospitalet.

Samlet vurderer fagudvalget derfor, at Veyvondi har **ingen klinisk merværdi** vedrørende hæmostatisk effekt sammenlignet med Willfact, idet effekten ligger på samme niveau (meget lav evidenskvalitet).

Antal infusioner per blødning (kritisk)

Antallet af nødvendige infusioner til behandling af en blødning er et kritisk effektmål, da umiddelbar behandlingseffekt skaber hurtigere klinisk bedring, og da et lavere antal infusioner forventes at minimere den praktiske ulempe.

Tabel 18. Vurdering af klinisk merværdi: Antal infusioner per blødning

	Forhåndsdefineret grundlag for vurdering	Resultater	
		Veyvondi [11]	**Willfact** [12]
Absolutte forskelle	En infusion	3-5* (2-5)	2-9* (1-21)
Evidensens kvalitet	Meget lav		

ANM: Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data fra ansøgningen, som indgår i Medicinrådets vurdering. *Data er opgjort kombineret for orale indgreb og mindre kirurgiske indgreb og angives derfor som interval og range (lavest til højest antal infusioner per blødning ved de to typer kirurgi).

Fagudvalget ønsker at gøre opmærksom på nedenstående forskelle i datagrundlaget i de to studier: Antallet af infusioner per blødning er for Veyvondi rapporteret for henholdsvis orale og mindre kirurgiske indgreb [11]. Ansøger har kombineret data for disse to typer kirurgi, og den absolutte medianværdi er derfor angivet som et interval. Antal infusioner per blødning er for Willfact rapporteret for henholdsvis generelle, dentale, biopsi og invasive procedurer [12], og ansøger har opgjort en samlet værdi og range for disse typer kirurgi. Fagudvalget bemærker, at variationen i antal infusioner kan være relateret til forskelle i typen af kirurgi og til sværhedsgraden af von Willebrand sygdom i de to studier. Andelen af patienter med type 3 von Willebrand sygdom er større i Veyvondi-studiet sammenlignet med Willfact-studiet. Patienter med von Willebrand

sygdom type 3 vil ofte have brug for mere behandling, dvs. flere infusioner. For Veyvondi rapporteres antal infusioner for større (”*major*”), mindre (”*minor*”) og orale indgreb, mens der for Willfact rapporteres for typen af indgreb. Derudover opgives det samlede antal infusioner for Veyvondi inklusive den 12-24 timers præoperative infusion, mens denne infusion ikke er medtaget i opgørelsen for Willfact.

Samlet vurderer fagudvalget, at Veyvondi har **ingen klinisk merværdi** vedrørende antal infusioner per kirurgisk indgreb sammenlignet med Willfact (meget lav evidenskvalitet).

Inhibitor mod vWf (kritisk)

Patienter med von Willebrand sygdom kan ved behandling med et vWf-præparat udvikle neutraliserende antistoffer (inhibitor) mod vWf, hvorved vWf-præparatet gøres uvirksomt. Fagudvalget har vurderet, at to hændelser i hvert studie udgør den mindste klinisk relevante forskel.

Tabel 19. Vurdering af klinisk merværdi: Inhibitor mod vWf

	Forhåndsdefineret grundlag for vurdering	Resultater	
		Veyvondi [11]	**Willfact** [12]
Absolutte forskelle	2 hændelser i hvert af de aktuelle studier	0	0*
Evidensens kvalitet	Meget lav		

ANM: Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data fra ansøgningen, som indgår i Medicinrådets vurdering. *Kun von Willebrand sygdom type 3 patienter (n=18) er screenet.

Data for udvikling af inhibitor overfor vWf er for Willfact kun rapporteret for vWf type 3-patienter. Datagrundlaget tillader derfor ikke en sammenligning, men fagudvalget bemærker, at der i de tilgængelige data ikke rapporteres tilfælde af inhibitor.

Samlet vurderer fagudvalget, at Veyvondi har **ingen klinisk merværdi** vedrørende inhibitor mod vWf sammenlignet med Willfact (meget lav evidenskvalitet).

Anafylaksi (vigtig)

Patienter med von Willebrand sygdom, som udvikler inhibitor mod vWf, kan foruden en større risiko for blødningsepisoder have en risiko for at udvikle livstruende anafylaksi i forbindelse med behandling med et vWf-præparat, og anafylaksi udgør dermed en alvorlig bivirkning.

Tabel 20. Vurdering af klinisk merværdi: Anafylaksi

	Forhåndsdefineret grundlag for vurdering	Resultater	
		Veyvondi [11]	**Willfact** [12]
Absolutte forskelle	To hændelser i hvert af de aktuelle studier	0	IA
Evidensens kvalitet	Meget lav		

ANM: Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data fra ansøgningen, som indgår i Medicinrådets vurdering. IA, ikke angivet.

Forekomst af anafylaksi er opgjort til 0 tilfælde for Veyvondi. Der er ikke oplysninger om anafylaksi for Willfact. Samlet vurderer fagudvalget, at Veyvondi har **ingen klinisk merværdi** vedrørende anafylaksi sammenlignet med Willfact (meget lav evidenskvalitet).

Alvorlig venøs tromboemboli (vigtig)

Fagudvalget ønsker jf. protokollen, at udvikling af venøs tromboemboli udelukkende rapporteres i forhold til alvorlige episoder, hvilket omfatter proksimal dyb venetrombose, lungeemboli, trombose i centralnervesystemet eller andre vitale organer.

Tabel 21. Vurdering af klinisk merværdi: Alvorlig venøs tromboemboli

	Forhåndsdefineret grundlag for vurdering	Resultater	
		Veyvondi [11]	**Willfact** [12]
Absolutte forskelle	To hændelser i hvert af de aktuelle studier	1	0
Evidensens kvalitet	Meget lav		

ANM: Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data fra ansøgningen, som indgår i Medicinrådets vurdering.

Der er for Veyvondi rapporteret ét tilfælde af alvorlig venøs tromboemboli (en dyb venøs tromboemboli). I EPAR'en vurderes det, at hændelsen ikke har en sandsynlig relation til lægemidlet [6]. Der blev ikke rapporteret tilfælde af alvorlig venøs tromboemboli for Willfact, og data indikerer dermed, at der ikke er en klinisk relevant forskel mellem de to lægemidler.

Fagudvalget vurderer, at Veyvondi har **ingen klinisk merværdi** vedrørende alvorlig venøs tromboemboli sammenlignet med Willfact, idet hændelsesraterne er sammenlignelige (meget lav evidenskvalitet).

9.3.3 Evidensens kvalitet

Evidensens kvalitet for klinisk spørgsmål 3 er samlet set vurderet som værende **meget lav**. Overvejelser vedrørende evidensens kvalitet kan ses i bilag 2.

I evidensgennemgangen for sammenligningen af Veyvondi og Willfact foreligger der ikke direkte sammenlignende studier. Da der er tale om en narrativ sammenligning af data fra forskellige studier, vil evidenskvaliteten i udgangspunktet være lav. Den vurderede risiko for bias er moderat, og forskelle i patientkarakteristika medfører minimum nedgradering med yderligere ét niveau for *indirectness.* Samlet set vil evidenskvaliteten derfor som minimum blive meget lav, og der er derfor ikke udarbejdet GRADE-profiler. Risiko for bias vurderinger af de enkelte studier kan ses i bilag 2.

9.3.4 Konklusion for klinisk spørgsmål 3

Fagudvalget vurderer, at Veyvondi til forebyggelse og behandling af blødninger ved mindre kirurgiske indgreb hos patienter med von Willebrand sygdom giver **ingen klinisk merværdi** sammenlignet med plasmaderiveret von Willebrand faktor (meget lav evidenskvalitet).

I den samlede vurdering vægter fagudvalget, at der ikke er fundet klinisk relevante forskelle mellem lægemidlerne for de kritiske effektmål hæmostatisk effekt, antal infusioner per blødning og inhibitor mod vWf samt for de vigtige effektmål alvorlig venøs tromboemboli og anafylaksi. Fagudvalget bemærker, at datagrundlaget for sammenligningen er usikkert, og der er store forskelle i definitionen af mindre kirurgiske indgreb samt i opgørelsen af antal infusioner for lægemidlerne. Med udgangspunkt i fagudvalgets kliniske erfaring og lægemidlernes ens virkningsmekanismer vurderer fagudvalget, at Veyvondi har **ingen klinisk merværdi** til forebyggelse og behandling af blødninger ved mindre kirurgiske indgreb hos patienter med von Willebrand sygdom sammenlignet med plasmaderiveret von Willebrand faktor.

Evidenskvaliteten er meget lav for alle effektmålene, og samlet set er evidensens kvalitet derfor meget lav.

9.4 Konklusion klinisk spørgsmål 4

Hvad er den kliniske merværdi af vonicog alfa (Veyvondi), i forhold til plasmaderiveret vWf, ved forebyggelse og behandling af blødning ved større kirurgiske indgreb hos patienter med von Willebrand sygdom?

Fagudvalget vurderer, at Veyvondi ved forebyggelse og behandling af blødninger ved større kirurgiske indgreb hos patienter med von Willebrand sygdom giver en **ikkedokumenterbar klinisk merværdi** sammenlignet med plasmaderiveret von Willebrand faktor (meget lav evidenskvalitet).

9.4.1 Gennemgang af studier

Der blev fundet et studie af Veyvondi [11] og fire studier af plasmaderiverede vWf-præparater med indhold af FVIII [15–18], som vil indgå i vurderingen.

Karakteristika

Peyvandi et al., 2018 [11]**:** Se afsnit 9.3.1.

Gill et al., 2011 [16]: Et prospektivt open-label fase 4-studie, der havde til formål at vurdere effekten, bivirkningsprofilen og optimal dosis ved behandling med Humate-P (Haemate) hos patienter med von Willebrand sygdom, som får foretaget elektive kirurgiske indgreb. Studiets primære endemål var hæmostatisk effekt, anslået blodtab, antal infusioner og tromboemboliske hændelser.

Lethagen et al., 2007 [15]: Et prospektivt, open-label, multicenterstudie, der havde til formål at vurdere muligheden for at dosere Haemate baseret på farmakokinetiske analyser ved behandling af patienter med von Willebrand sygdom, der får foretaget kirurgiske indgreb. Loadingdosis blev beregnet ud fra den enkelte patients farmakokinetiske analyser, mens postoperativ dosis blev besluttet af den behandlende læge. Studiets primære endemål er ikke angivet, men publikationen rapporterer bl.a. hæmostatisk effekt.

Srivastava et al., 2017 [18]: Et prospektivt open-label multicenter fase 3-studie, der havde til formål at evaluere effekt og bivirkningsprofil ved behandling med Wilate (Wilnativ) ved kirurgiske indgreb. Primære endemål inkluderede hæmostatisk effekt (vha. en 4-trinsskala), mens sekundære endemål inkluderede intraoperativ og postoperativ hæmostatisk effekt samt udvikling af inhibitor og alvorlige bivirkninger.

Windyga et al., 2011 [17] rapporterer data fra fire prospektive open-label, ukontrollerede, ikke-randomiserede multicenter fase 2/3-studier, der havde til formål at evaluere effekt og bivirkningsprofil ved behandling med Wilnativ til forebyggelse og behandling af blødning i forbindelse med kirurgiske indgreb. Primære endemål inkluderer hæmostatisk effekt (vha. en 4-trinsskala, dog med forskellig definition på tværs af de fire studier) og uønskede hændelser.

Studiekarakteristika for de relevante studier [11,15–18] er beskrevet i tabel 22:

Tabel 22: Studiekarakteristika for relevante studier vedrørende forebyggelse og behandling af blødning ved større kirurgiske indgreb

	Veyvondi	**Haemate**	**Haemate**	**Wilnativ**	**Wilnativ**
	Peyvandi et al., 2018 [11]	Gill et al., 2011 [16]	Lethagen et al., 2007 [15]	Srivastava et al., 2017 [18]	Windyga et al., 2011 [17]
NCT-nummer	NCT02283268	NCT00168090	NA	NCT01365546	NA
Design	Prospektivt fase 3, open-label, ukontrolleret, ikke-randomiseret studie	Prospektivt fase 4, open-label, multinationalt studie	Prospektivt open labe, multicenter kohorte-studie	Prospektivt fase 3, open-label, multinationalt, multicenterstudie	Pooled data fra fire prospektive fase 2/3, open-label, ikke-kontrollerede, ikke-randomiserede multicenterstudier
Definition af større kirurgiske indgreb (kirurgi major)	*"Those that carried a significant risk of large volume blood loss or blood loss into a confined anatomical space, such as major orthopaedic-, abdominal-, gynaecologic-, head and neck-, intracranial-, cardiovascular- or spinal-surgery, and extraction of impacted third molars".*	*"Operation involving considerable hazard or risk to life or limb, frequently involving general anaesthesia, multiple (>2) tooth extractions and removal of >1 impacted wisdom tooth".*	*"Arthroscopic removal of osteosynthesis material, total knee replacement, hysterectomy, Hysterectomy-adnexectomy, adnexectomy, extraction of greater than or equal to four teeth, laparoscopic cholecystectomy, removal of basalioma, mandibular osteotomy".*	*"Orthopaedic, obstetric/gynaecological, gastrointestinal, dental and ear, nose and throat surgeries".*	*"Requirement for general or spinal anaesthesia, surgical opening into the great body cavities, procedures where severe haemorrhage was possible, orthopaedic interventions involving joints (ankle, knee, hip, wrist, elbow, shoulder), 3rd molar extraction, surgeries or conditions in which the subject's life was considered at risk".*
Opfølgningstid	Dag 14 efter indgreb	24 timer efter sidste infusion eller på dag 14 efter indgreb, alt efter hvad der kom først for den enkelte patient	Dag 14 efter indgreb	Afhængigt af evt. postoperativ blødning blev vurderingen foretaget umiddelbart efter indgrebet eller indtil 24 timer efter sidste infusion af lægemidlet	Vurderingen blev foretaget efter komplet heling efter indgrebet (ved investigators diskretion)
Præoperativ dosis vWf forud for indgrebet (IE/kg)	Alle patienter modtog en dosis 12-24 timer forud for indgrebet, og en dosis 1-2 timer forud for indgrebet Mean præoperativ dosis 12-24 timer før 49.3 IE/kg	Dosis var individuel og blev beregnet ud fra patientens farmakokinetiske værdier. Loading dosis blev fastsat for at opnå plasma VWF:RCo niveau på 50–60 IE/dL for oral/kirurgi	Dosis var individuel og blev beregnet ud fra patientens farmakokinetiske værdier.	Alle patienter modtog i *in vivo recovery* undersøgelsen 60 IE/kg Wilate til beregning af den optimale dosis til det kirurgiske indgreb. Følgende guidelines var aktuelle:	I ét af studierne blev dosis besluttet af den behandlende læge. I de tre andre studier blev følgende anbefalinger fulgt: kirurgi major: dosis givet dagligt eller hver anden dag med formal om at holde FVIII:C > 50 IE/dl indtil heling efter indgreb. Kirurgi minor: dosis givet dagligt eller hver anden dag med formål

Dosis ved efterfølgende infusioner	Mean loading dose 1-2 timer før 37.6 IE/kg Efterfølgende kumuleret dosis 214 IE/kg	minor kirurgi, og 80–100 IE/dL for kirurgi major Mean 61.2 IE/kg Efterfølgende dosis 47 IE/kg svær von Willebrand sygdom (35 IE/kg ikke svær) Gange antal infusioner = 10	Mean 66.5 IE/kg Efterfølgende kumuleret dosis 307 IE/kg Dag 0-2: 46,1 Dag 3-6: 43,1 Dag > 6: 42,3	Kirurgi major: loadingdosis på 40–60 vWf:RCo IE/kg Mean 54.7 IE/kg Efterfølgende dosis 30.0 IE/kg	om at holde FVIII:C > 30 IE/dl indtil heling efter indgreb. Mean 49 IE/kg Efterfølgende dosis 21 IE/kg Gange antal infusioner = 10
Kumulativ dosis for hele indgrebet*	307 IE/kg	531,2 IE/kg	373,5 IE/kg	368,8 IE/kg	280 IE/kg
Samtidig administration af FVIII 1-2 timer forud for indgreb	Hvis ikke FVIII:C var høj nok tre timer før indgrebet, blev der suppleret med rFVIII (Advate) (aktuelt for patienter)	IA	IA	IA	IA
Tidspunkt for vurdering af hæmostatisk effekt	24 timer efter sidste perioperative infusion af lægemidlet eller ved dag 14 efter indgreb, alt efter hvad der kom først for den enkelte patient	24 timer efter sidste infusion af vWf/FVIII koncentrat eller på dag 14, alt efter hvad der kom først for den enkelte patient	Prædefineret tidspunkt ikke angivet. I publikationen rapporteres effekt ved dag 0 (kirurgi), dag 1 og dag 14	Vurderet af kirurg efter afsluttet operation samt post-operativt (fra afsluttet operation indtil 24 timer efter sidste infusion af lægemidlet) af investigator	Efter fuldstændig heling efter kirurgi (ved investigators diskretion).

*Beregnet ud fra oplysninger vedrørende mediane doser angivet i studierne.

Population

Peyvandi et al., 2018 [11]**:** Se afsnit 9.3.1.

Gill et al., 2011 [16]**:** Inklusionskriterier inkluderede von Willebrand sygdom, hvor behandling med desmopressin ikke havde været effektivt samt påkrævet behandling med vWf og FVIII i forbindelse med kirurgi. Eksklusionskriterier inkluderede anden blødersygdom, inhibitor mod vWf eller FVIII, akut kirurgi, overfølsomhed for Humate-P, anden behandling for vWf modtaget inden for fem dage forud for studiestart, graviditet > 20. svangerskabsuge.

Lethagen et al., 2007 [15]**:** Inklusionskriterier inkluderede diagnose med von Willebrand sygdom, historiske blødninger, alder > 5 år samt et planlagt kirurgisk indgreb forventet til at kræve hospitalsindlæggelse i mindst 24 timer. Eksklusionskriterier inkluderede inhibitor mod vWf eller FVIII samt blodpladetype von Willebrand sygdom.

Srivastava et al. 2017 [18]**:** Inklusionskriterier inkluderede alder > 6 år, diagnose med von Willebrand sygdom samt påkrævet behandling med et vWf-præparat i forbindelse med et større kirurgisk indgreb. Eksklusionskriterier inkluderede anden blødersygdom, kendt forekomst af inhibitor mod vWf eller FVIII, overfølsomhed overfor Wilnativ eller andre vWf-præparater, samt graviditet indtil 20. graviditetsuge.

Windyga et al., 2011 [17]**:**Inklusionskriterier inkluderede diagnose med von Willebrand sygdom, hvor behandling med desmopressin var ineffektiv. Tre af studierne inkluderede patienter > 12 år, mens det ene studie inkluderede patienter ≤ 12 år. Eksklusionskriterier inkluderede graviditet og amning, kendt forekomst af inhibitor mod vWf eller FVIII, overfølsomhed overfor plasmaderiverede- eller blodpræparater samt lever- eller nyresygdom.

Populationskarakteristika for de relevante studier [11,15–18] er beskrevet i tabel 23:

Tabel 23: Populationskarakteristika for relevante studier vedrørende forebyggelse og behandling af blødning ved større kirurgiske indgreb

	Veyvondi	**Haemate**	**Haemate**	**Wilnativ**	**Wilnativ**
	Peyvandi et al., 2018 [11]	Gill et al., 2011 [16]	Lethagen et al., 2007 [15]	Srivastava et al., 2017 [18]	Windyga et al., 2011 [17]
Aldersafgrænsning	≥ 18 år	Alle aldre	> 5 år	≥ 6 år	Alle aldre
Patienter, totalt (n)	15	42	28	28	32
Patienter, kirurgi major (n)	10	25	16	21	27
von Willebrand sygdom type (n)*					
1	3	17	10	7	4
2	-	-	-	2	9
2A	2	2	10	-	-
2B	1	4	-	-	-
2M	1	6	1	-	-
3	8	13	8	21	19
Alder, år [median (range)]	40 (20-70)	21 (1-75)	NA (5-65+)	36,0 (12-74)#	50 (6-77)
Vægt, kg [median (range)]	73,5 (52-127,2)	IA	IA	63,7 (39-126)#	67 (28-104)
BMI [median (range)]	25,6 (17,1-38)	24,9 (13,3-63,6	IA	26,6 (IA)	IA
vWf:RCo, IE/dL [median (range)]	IA	13 (6-124)	18,0 (6,7-32,0)	22,5 (3-38)#	10 (0-86)§
FVIII:C, IE/dL [median (range)]	IA	39 (0,5-96)	36,0 (14,0-46,0)	43,0 (2-65)#	10 (2-125)§

FVIII:C, mean (SD), IE/dL					
Alle von Willebrand sygdom typer (n=15)	16,4 (19,9)	IA	2,4 (1,8-3,0)**	IA	IA
Type 1 (n = 3)	17 (4)		2,4 (1,8-2,6)**		
Type 2A (n = 2)	34,5 (23,3)		2,2 (1,7-3,2)**		
Type 2B (n = 1)	36		IA**		
Type 2M (n = 1)	66		3,3 (3,3-3,3)**		
Type 3 (n = 8)*	3,0 (1,5)		2,3 (2,1-3,6)**		

*Opgjort for den totale studiepopulation. **Median og IQR. #Opgjort for intention-to-treat populationen (n = 30). §Manglende data for en patient. IA, ikke angivet.

I alle studierne ses en overrepræsentation af patienter med von Willebrand sygdom type 3 i forhold til den samlede danske population, omend overrepræsentationen er mest udtalt for Wilnativ. En gennemsnitlig dansk population med von Willebrand sygdom vil muligvis have behov for lavere vWf-doser end i studierne.

9.4.2 Resultater og vurdering

Resultater og vurdering af de effektmål, som fagudvalget har præspecificeret som henholdsvis kritiske og vigtige, følger nedenfor.

Jf. protokollen skal klinisk spørgsmål 4 besvares med en sammenligning af Veyvondi med plasmaderiveret vWf. Datagrundlaget tillader ikke indirekte sammenlignende analyser, og data sammenlignes derfor i en narrativ sammenligning.

Hæmostatisk effekt (ved blødning og kirurgi) (kritisk)

Målet med lægemiddelbehandlingen er at opnå hæmostase og derved standse skaden (blødningen).

Tabel 24. Vurdering af klinisk merværdi: Hæmostatisk effekt (ved blødning og kirurgi)

	Forhåndsdefineret grundlag for vurdering	Resultater				
		Veyvondi [11]	**Haemate** [16]	**Haemate** [15]	**Wilnativ** [18]	**Wilnativ** [17]
Absolutte forskelle	10 procentpoint forskel i antal blødninger, hvor patienten opnår "meget god" eller "god" hæmostatisk effekt	100 %	91,4 %* 94,3 %§	96,3 %# 100 %¤	96,7 %	96 %
Evidensens kvalitet	Meget lav					

ANM: Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data på de absolutte og relative værdier fra resultatafsnittet, som indgår i Medicinrådets vurdering. *Vurderet umiddelbart post-operativt, §vurderet senere end post-operativt, #vurderet på dagen for indgrebet; ¤vurderet dag 1 post-operativt.

For Veyvondi, Haemate og Wilnativ var andelen af patienter, der opnåede 'god' eller 'meget god' hæmostatisk effekt 91,4-100 %. Data indikerer derfor ikke, at der er en klinisk betydende forskel imellem lægemidlerne. Fagudvalget bemærker, at både klassificeringen af større kirurgiske indgreb (kirurgi major) samt tidspunktet for vurdering af den hæmostatiske effekt varierer mellem de inkluderede studier.

Samlet vurderer fagudvalget derfor, at Veyvondi har **ingen klinisk merværdi** vedrørende hæmostatisk effekt sammenlignet med Haemate og Wilnativ (meget lav evidenskvalitet).

Antal infusioner per blødning (kritisk)

Antallet af nødvendige infusioner til behandling af en blødning er et kritisk effektmål, da umiddelbar behandlingseffekt skaber klinisk bedring, og da et lavere antal infusioner forventes at minimere den praktiske ulempe.

Tabel 25. Vurdering af klinisk merværdi: Antal infusioner per blødning ved større kirurgiske indgreb

	Forhåndsdefineret grundlag for vurdering	Medicinrådets vurdering				
		Veyvondi [11]	**Haemate** [16]	**Haemate** [15]	**Wilnativ** [18]	**Wilnativ** [17]
Absolutte forskelle	En infusion	7,5 (4-15) median, (range)	10 (4-55) median, (range)	7 (4.5-11.5 IQR) *8 (inkl. loadingdosis)*	IA	12 (1-29) median, (range)
Evidensens kvalitet	Meget lav					

ANM: Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data fra ansøgningen, som indgår i Medicinrådets vurdering.

Det rapporterede mediane antal infusioner ved større kirurgiske indgreb er lavere for Veyvondi end for Haemate og Wilnativ, og den mindste klinisk relevante forskel er opnået til fordel for Veyvondi. Der rapporteres en mindre variation i antallet af infusioner med Veyvondi sammenlignet med de to komparatorer. Der blev givet samtidig administration af FVIII i studiet af Veyvondi. Det er ikke oplyst for de øvrige studier, men FVIII-niveauet var lavere blandt patienter, der blev behandlet med Wilnativ [17].

Fagudvalget bemærker, at der i Gill et al. 2011 [16] rapporteres en range på 4-55 infusioner per blødning ved større kirurgiske indgreb, og to type 2 patienter rapporteres at have fået kirurgiske komplikationer i forbindelse med operationerne. Disse to patienter havde de længste behandlingstider (henholdsvis 19 og 26 dage), og den tidskrævende behandling af disse to patienter kan være medvirkende til den brede range.

Fagudvalget vurderer, at større kirurgiske indgreb kan gennemføres med færre doser Veyvondi end Wilnativ og Haemate, især når man påtænker, at to doser ud af de i alt syv gives præoperativt henholdsvis 12-24 og 1-2 timer før indgrebet. De farmakokinetiske studier af Veyvondi tyder også på længere halveringstid, både målt som vW:rcof og stigning i endogen FVIII. Omvendt er den kumulerede dosis af vWf lavest i studiet med Wilnativ, der samtidig har det højeste antal infusioner men samtidig det laveste forbrug af FVIII ([17], tabel 22). Studiet af Haemate [16] med den højeste kumulative dosering havde højere målværdi for vWf og FVIII, og flere patienter opnåede kliniske værdier, som ligger over det normale kliniske niveau. Fagudvalget vurderer, at forskellen mellem studierne ikke udelukkende kan tilskrives en større effekt af Veyvondi, men dokumenterer, at patienter kan opnå effektiv hæmostase ved større kirurgiske indgreb med færre doser af Veyvondi. Datagrundlaget er usikkert, og derfor vurderer fagudvalget, at Veyvondi har en **ikkedokumenterbar klinisk merværdi** vedrørende antal infusioner per kirurgisk indgreb sammenlignet med Haemate og Wilnativ (meget lav evidens kvalitet).

Inhibitor mod vWf (kritisk)

Patienter med von Willebrand sygdom kan ved behandling med et vWf-præparat udvikle neutraliserende antistoffer (inhibitor) mod vWf, hvorved vWf-præparatet gøres uvirksomt.

Tabel 26. Vurdering af klinisk merværdi: Inhibitor mod vWf

	Forhåndsdefineret grundlag for vurdering	Medicinrådets vurdering				
		Veyvondi [11]	**Haemate** [16]	**Haemate** [15]	**Wilnativ** [18]	**Wilnativ** [17]
Absolutte forskelle	2 hændelser i hvert af de aktuelle studier	0	IA	0	0	0
Evidensens kvalitet	Meget Lav					

ANM: Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data fra ansøgningen, som indgår i Medicinrådets vurdering. IA, ikke angivet.

I protokollen har fagudvalget vurderet, at to hændelser af inhibitorudvikling mod vWf i hvert studie udgør den mindste klinisk relevante forskel. Data for udvikling af inhibitor overfor vWf er rapporteret inkonsistent, og i de tilgængelige data rapporteres ingen tilfælde af inhibitor. Data tyder derfor på, at der ikke er en klinisk betydende forskel mellem lægemidlerne.

Samlet vurderer fagudvalget, at Veyvondi har **ingen klinisk merværdi** vedrørende inhibitor mod vWf sammenlignet med Haemate og Wilnativ (meget lav evidenskvalitet).

Anafylaksi (vigtig)

Patienter med von Willebrand sygdom, som udvikler inhibitor mod vWf, kan foruden en større risiko for blødningsepisoder have en risiko for at udvikle livstruende anafylaksi i forbindelse med behandling med et vWf-præparat. Anafylaksi udgør dermed en alvorlig bivirkning.

Tabel 27. Vurdering af klinisk merværdi: Anafylaksi

	Forhåndsdefineret grundlag for vurdering	Medicinrådets vurdering				
		Veyvondi [11]	**Haemate** [16]	**Haemate** [15]	**Wilnativ** [18]	**Wilnativ** [17]
Absolutte forskelle	2 hændelser i hvert af de aktuelle studier	0	IA	IA	IA	IA
Evidensens kvalitet	Meget lav					

ANM: Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data fra ansøgningen, som indgår i Medicinrådets vurdering. IA, ikke angivet

Forekomst af anafylaksi er opgjort til 0 tilfælde for Veyvondi. Der er ikke oplysninger om anafylaksi for Haemate og Wilnativ. Samlet vurderer fagudvalget, at Veyvondi har **ingen klinisk merværdi** vedrørende anafylaksi sammenlignet med Haemate og Wilnativ (meget lav evidenskvalitet).

Alvorlig venøs tromboemboli (vigtig)

Fagudvalget ønsker jf. protokollen, at udvikling af venøs tromboemboli rapporteres udelukkende i forhold til alvorlige episoder, hvilket omfatter proksimal dyb venetrombose, lungeemboli, trombose i centralnervesystemet eller andre vitale organer.

Tabel 28. Vurdering af klinisk merværdi: Alvorlig venøs tromboemboli

	Forhåndsdefineret grundlag for vurdering	Medicinrådets vurdering				
		Veyvondi [11]	**Haemate** [16]	**Haemate** [15]	**Wilnativ** [18]	**Wilnativ** [17]
Absolutte forskelle	2 hændelser i hvert af de aktuelle studier	1	0	1	0	0
Evidensens kvalitet	Meget lav					

ANM: Første kolonne indeholder de i protokollen og metodehåndbogen præspecificerede grundlag for vurderingen. Anden kolonne indeholder data fra ansøgningen, som indgår i Medicinrådets vurdering.

Der er for Veyvondi rapporteret ét tilfælde af alvorlig venøs tromboemboli (en dyb venøs tromboemboli). I EPAR'en vurderes det, at hændelsen ikke har en sandsynlig relation til lægemidlet [6]. For Haemate er der rapporteret ét tilfælde af alvorlig venøs tromboemboli (en lungeemboli), der af investigator blev vurderet til sandsynligvis at være relateret til lægemidlet. Der blev ikke rapporteret tilfælde af alvorlig venøs tromboemboli for Wilnativ. Data indikerer dermed, at der ikke er forskel i risiko for alvorlig venøs tromboemboli for Veyvondi sammenlignet med Haemate og Wilnativ.

Samlet vurderer fagudvalget, at Veyvondi har **ingen klinisk merværdi**, da hændelsesraterne vedrørende alvorlig venøs tromboemboli er sammenlignelige for Veyvondi, Haemate og Wilnativ (meget lav evidenskvalitet).

9.4.3 Evidensens kvalitet

Evidensens kvalitet for klinisk spørgsmål 4 er samlet set vurderet som værende **meget lav**. Overvejelser vedrørende evidensens kvalitet kan ses i bilag 2.

I evidensgennemgangen for sammenligningen af Veyvondi, Haemate og Wilnativ foreligger der ikke direkte sammenlignende studier. Da der er tale om en narrativ sammenligning af data fra forskellige studier, vil evidenskvaliteten i udgangspunktet være lav. Den vurderede risiko for bias er i alle studier moderat, hvilket primært skyldes studiernes uklare beskrivelser af studiedesign, herunder patientallokering, dosis og opfølgningstid samt manglende data. Derudover medfører forskelle i patientkarakteristika, herunder von Willebrand sygdomstype og operationskarakteristika, som minimum nedgradering med yderligere ét niveau for '*indirectness'*. Samlet set vil evidenskvaliteten derfor som minimum blive meget lav, og der er derfor ikke udarbejdet GRADE-profiler. Risiko for bias-vurderinger af de enkelte studier kan ses i bilag 2.

9.4.4 Konklusion for klinisk spørgsmål 4

Fagudvalget vurderer, at Veyvondi til forebyggelse og behandling af blødninger ved større kirurgiske indgreb hos patienter med von Willebrand sygdom giver en i**kkedokumenterbar klinisk merværdi** sammenlignet med plasmaderiveret von Willebrand faktor (meget lav evidenskvalitet).

I den samlede vurdering vægter fagudvalget, at der er fundet klinisk relevante forskelle mellem lægemidlerne for det kritiske effektmål antal infusioner per større kirurgiske indgreb. Der er ikke fundet forskel for effektmålene hæmostatisk effekt og tromboemboli. Datagrundlaget for det vigtige effektmål anafylaksi tillod ikke fagudvalget at foretage en vurdering af den kliniske merværdi for Veyvondi. Fagudvalget finder på denne baggrund, at Veyvondi har en **ikkedokumenterbar klinisk merværdi** til forebyggelse og blødninger i forbindelse med større kirurgiske indgreb hos patienter med von Willebrand sygdom sammenlignet med plasmaderiveret von Willebrand faktor.

Evidenskvaliteten er samlet set meget lav for alle effektmålene. Fagudvalget vurderer på den baggrund, at den samlede evidenskvalitet er meget lav.

10 Andre overvejelser

Anvendelse af rekombinant vs. plasmaderiveret vWf -præparat

Veyvondi er det første rekombinante vWf-præparat til patienter med von Willebrand sygdom. Plasmaderiverede produkter anses i dag for sikre, og der er ikke registreret overførsel af nye tilfælde af HIV eller hepatitis C siden 1993. Andre patogener, f.eks. parvovirus B19, er dog relativt resistente for alle kendte virusinaktiveringsmetoder, og der kan desuden kun screenes og behandles for kendte smitteagens. Ved brug af rekombinante præparater er risikoen for blodbårne virus derimod elimineret. På den baggrund vurderer fagudvalget, at rekombinante præparater som udgangspunkt er mere sikre og derfor foretrækkes.

Samtidig administration af FVIII

Hos patienter, der har behov for både vWf og FVIII (patienter med FVIII < 30 %), vil det af praktiske hensyn være en fordel at anvende et kombinationspræparat fremfor Veyvondi. Veyvondi er fortrinsvis undersøgt hos patienter med type 3, som har total mangel på FVIII, og næsten alle patienter i on-demand behandling fik også tillæg af FVIII. Da Veyvondi kun indeholder rvWf, vil patienter med lavt FVIII-niveau have brug for to præparater ved on-demand behandling. Fagudvalget vurderer derfor, at der for patienter med lavt FVIII-niveau vil være en anseelig praktisk ulempe forbundet med Veyvondi ved on-demand behandling.

Valg af vWf-præparat ved kirurgi

Ved kirurgiske indgreb vil det være nødvendigt at påbegynde behandling med Veyvondi eller Willfact 12-24 timer før indgrebet og kontrollere niveauet af FVIII tre timer før indgrebet med henblik på eventuel yderligere infusion af FVIII. Ved behandling med Haemate og Wilnativ behøver man ikke påbegynde behandling før 30-60 minutter forud for indgrebet.

Fagudvalget vurderer, at der ved kirurgi foretrækkes brug af det vWf-præparat, som patienten forud for det kirurgiske indgreb har anvendt til on-demand eller profylakse. Dosis og effekt af vWf-præparatet vil dermed allerede være testet og afprøvet hos den enkelte patient, og virkningen af vWf-præparatet vil være forudsigelig uden behov for monitorering umiddelbart før indgrebet. Ved behov for skift til et præparat med lavere indhold af FVIII foretrækkes Veyvondi, da det er rekombinant.

Sammenligningsgrundlag for doser

Effekten af 20 enheder Wilnativ er sammenlignelig med effekten af 40 enheder af de øvrige lægemidler. Lavest anbefalede doser fra produktresuméerne (fra enten EMA eller Lægemiddelstyrelsen) for lægemidlerne [5,7–9] er angivet i tabellen nedenfor. Dette stemmer overens med fagudvalgets kliniske erfaring, og de ækvieffektive doser for Haemate, Willfact, Wilnativ og Veyvondi er derfor 40, 40, 20 og 40 IE/kg.

Lægemiddel	**Sammenligningsdosis**
Haemate	40 IE/kg
Willfact	40 IE/kg
Wilnativ	20 IE/kg
Veyvondi	40 IE/kg

Lægemiddelhåndtering

De patienter, der har det laveste forbrug, bør have det vWf-præparat, der har længst holdbarhed for at minimere spild. Både Veyvondi, Haemate og Willfact har en holdbarhed på 3 år ved stuetemperatur (defineret som henholdsvis højst 30 °C, 25 °C og 25 °C for de tre lægemidler). Wilnativ har en holdbarhed på 3 år på køl (2-8 °C) og 2 måneder ved stuetemperatur (højst 25 °C). Med sin korte holdbarhedstid ved stuetemperatur kan Wilnativ derfor være mere relevant for on-demand behandling af patienter med et højt forbrug.

Virusinaktiveringsmetoder

Veyvondi fremstilles i rekombinante ovarieceller fra kinesiske hamstere (CHO) uden brug af humane eller animalske materialer, som måtte indeholde risiko for virus eller prionkontaminering. Cellemedium filtreres desuden for potentielle vira. Alle materialer, som bruges i fremstillingen af Veyvondi, testes i overensstemmelse med specificerede farmakopémonografier.

Rekonstitutionssystem

Rekonstitutionssystemet for Veyvondi er det samme, som anvendes ved de plasmaderiverede præparater: Haemate, Willfact og Wilnativ (Mix2vial). Fagudvalget vurderer derfor, at Veyvondi ikke adskiller sig på denne parameter.

Tilgængelighed af forskellige styrker

Veyvondi: 650 IE (5 mL opløsning) og 1300 IE (10 mL opløsning) vWf
Haemate: 1200 IE (10 mL opløsning) og 2400 IE (15 mL opløsning) vWf
Wilnativ: 500 IE (5 mL opløsning) og 1000 IE (10 mL opløsning) vWf
Willfact: 500 IE (5 mL opløsning), 1000 IE (10 mL opløsning) og 2000 IE (20 mL opløsning) vWf.

Fagudvalget vurderer, at styrkerne for de forskellige præparater er sammenlignelige.

Monitoreringsmetoder

Rutinemæssig monitorering af vWf:RCo og FVIII-aktivitet med henblik på evt. dosisjustering er nødvendig ved behandling, idet de enkelte patienter kan have variationer i deres respons. vWf:RCo aktivitet bestemmes i forhold til WHO-standard vWf-niveau. Det er ikke nødvendigt med et produktspecifikt referenceniveau ved bestemmelse af FVIII-aktivitet med en 1-trins-koagulationsanalyse baseret på en aktiveret partiel tromboplastintid (aPTT).

Pakningens størrelser

Pakningerne for Veyvondi (650 IE og 1300 IE) måler henholdsvis 107x61x57 mm, svarende til et volumen på 0,372 L og en vægt på 69 g og 123x61x72 mm, svarende til et volumen på 0,540 L og en vægt på 97 g. Pakningernes størrelser vurderes at være håndterbar for patienten, og det vurderes ikke, at der er forskel mellem lægemidlerne.

Medfølgende utensilier

Pulver i et hætteglas (type I-glas) med gummiprop, 5 ml eller 10 ml solvens i et hætteglas (type I-glas) med gummiprop og et rekonstitutionssæt (Mix2Vial).

Konklusion vedrørende andre overvejelser

Fagudvalget vurderer, at der er praktiske fordele ved et vWf-kombinationspræparat i de kliniske situationer, hvor der er behov for både vWf og FVIII. Dog er alle de vWf-kombinationspræparater, som er tilgængelige i dag plasmaderiverede, og disse præparater medfører derfor en teoretisk, om end meget lille risiko for smitteoverførsel. Samlet set vurderer fagudvalget, at de praktiske fordele ved et kombinationspræparat opvejer fordelen ved et rekombinant præparat.

11 Fagudvalgets vurdering af samlet klinisk merværdi og samlet evidensniveau

Fagudvalget vurderer, at vonicog alfa (Veyvondi) til voksne (≥ 18 år) med von Willebrand sygdom giver:

- **Den kliniske merværdi kan ikke vurderes** ved on-demand behandling til patienter med von Willebrand sygdom og normalt eller let nedsat FVIII-niveau (> 30 %) sammenlignet med plasmaderiveret von Willebrand faktor. Fagudvalget vurderer, at Veyvondi vil være lige så effektivt som plasmaderiverede præparater og derfor vil være at foretrække hos patienter, hvor der ikke er behov for tillæg af FVIII.
- **Ingen klinisk merværdi** ved on-demand behandling til patienter med von Willebrand sygdom og lavt FVIII-niveau (< 30 %) sammenlignet med plasmaderiveret von Willebrand faktor. Evidensens kvalitet vurderes at være meget lav. Fagudvalget vurderer, at et kombinationspræparat er at foretrække fremfor behandling med to særskilte præparater (Veyvondi + FVIII), da den praktiske fordel ved et kombinationspræparat langt opvejer den lille fordel ved et rekombinant produkt.
- **Ingen klinisk merværdi** ved forebyggelse og behandling af blødning ved mindre kirurgiske indgreb hos patienter med von Willebrand sygdom sammenlignet med plasmaderiveret von Willebrand faktor. Evidensens kvalitet vurderes at være meget lav. Fagudvalget foretrækker at anvende samme vWf-præparat, som patienten plejer ved on-demand eller profylaktisk behandling, da dosis og effekt er testet og dermed er forudsigelig i den enkelte patient.
- **Ikkedokumenterbar klinisk merværdi** ved forebyggelse og behandling af blødning ved større kirurgiske indgreb hos patienter med von Willebrand sygdom sammenlignet med plasmaderiveret von Willebrand faktor. Evidensens kvalitet vurderes at være meget lav. Fagudvalget foretrækker at anvende samme præparat, som patienten plejer ved on-demand eller profylaktisk behandling, da dosis og effekt er testet og dermed er forudsigelig i den enkelte patient. Fordelen ved færre infusioner opvejer ikke ulempen ved behovet for at påbegynde behandling med Veyvondi 12-24 timer før indgrebet og for blodprøvekontrol tre timer før indgrebet. Ved behov for skift til præparat med lavere indhold af FVIII foretrækkes Veyvondi, da det er rekombinant.

Fagudvalgets kliniske vurdering er, at lægemidlerne (Veyvondi, Haemate, Wilnativ og Willfact) er sammenlignelige, hvad angår hæmostatisk effekt, udvikling af inhibitor mod vWf og sikkerhed (risiko for anafylaksi og alvorlige tromboemboliske hændelser). Vurderingen er baseret på fagudvalgets kliniske erfaringer med lægemidlerne og lægemidlernes ens virkningsmekanisme.

12 Rådets vurdering af samlet klinisk merværdi og samlet evidensniveau

Medicinrådet vurderer, at vonicog alfa (Veyvondi) til voksne (≥ 18 år) med von Willebrand sygdom giver:

- **Ingen klinisk merværdi** ved on-demand behandling til patienter med lavt FVIII-niveau (< 30 %) sammenlignet med plasmaderiveret von Willebrand faktor.
- **Ingen klinisk merværdi** ved forebyggelse og behandling af blødning ved mindre kirurgiske indgreb sammenlignet med plasmaderiveret von Willebrand faktor.
- **Ikkedokumenterbar klinisk merværdi** ved forebyggelse og behandling af blødning ved større kirurgiske indgreb sammenlignet med plasmaderiveret von Willebrand faktor.

Evidensens kvalitet er meget lav for alle kliniske spørgsmål.

Den kliniske merværdi kan ikke vurderes for patienter i on-demandbehandling, som har normalt eller let nedsat FVIII-niveau (> 30 %).

13 Relation til eksisterende behandlingsvejledning

Der foreligger en samlet behandlingsvejledning fra RADS på von Willebrand sygdom, hæmofili A og hæmofili B. Medicinrådet har i 2019 igangsat udarbejdelse af en særskilt behandlingsvejledning for von Willebrand sygdom.

Danske patienter med von Willebrand sygdom tilbydes i nuværende behandlingsalgoritme Haemate som førstevalg. Som andet- og tredjevalg tilbydes henholdsvis Wilnativ og Willfact. Fagudvalget vil i den opdaterede behandlingsvejledning tage stilling til, hvordan Veyvondi skal indplaceres i den nuværende behandlingsalgoritme.

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15 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende blødersygdomme

Forvaltningslovens § 4, stk. 2, har været anvendt i forbindelse med udpegning af medlemmer til dette fagudvalg.

Formand	**Indstillet af**
Eva Funding Overlæge	Lægevidenskabelige Selskaber og Region Hovedstaden
Medlemmer	**Udpeget af**
Har ikke en relevant specialist til fagudvalget	Region Nordjylland
Anne-Mette Hvas Professor, overlæge, ph.d.	Region Midtjylland
Lone Hvitfeldt Poulsen Overlæge	Region Midtjylland
Jesper Farup Revsholm Afdelingslæge	Region Syddanmark
Rune Larsen Overlæge	Region Sjælland
Marie Louise Schougaard Christiansen Afdelingslæge, klinisk farmakolog, ph.d.	Dansk Selskab for Klinisk Farmakologi (DSKF)
Jennifer A.F. Andresen Farmaceut	Dansk Selskab for Sygehusapoteksledelse (DSS)
Kan ikke udpege en kandidat, der opfylder Medicinrådets habilitetskrav	Dansk Selskab for Klinisk Biokemi
Marianne Hutchings Hoffmann Overlæge	Dansk Pædiatrisk Selskab
Finder det ikke længere relevant at have en kandidat i fagudvalget	Dansk Selskab for Anæstesiologi og Intensiv Medicin
Peter Kampmann Overlæge, lægefaglig teamleder	Dansk Selskab for Trombose og Hæmostase
2 patienter/patientrepræsentanter	Danske Patienter

Medicinrådets sekretariat

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16 Versionslog

Version	Dato	Ændring
1.0	13.03.2019	Godkendt af Medicinrådet.
1.1	27.03.2019	På side 18 er procentsatsen for type 3 patienter i studiet med Willfact rettet fra 25 % til 32 %, og teksten på side 19 er justeret, så denne fordeling er korrekt beskrevet.

17 Bilag 1: GRADE-evidensprofiler

For alle de kliniske spørgsmål er der tale om narrative sammenligninger af data fra forskellige studier, og evidenskvaliteten vil derfor i udgangspunktet være lav. Der er derfor udelukkende lavet vurderinger af risiko for bias.

17.1 Cochrane Risk of Bias

Cochrane risk of bias for In Non-Randomized Studies of Interventions (Robins-I) assessment tool.

Veyvondi, NCT01410227

(Hemostatic efficacy, safety, and pharmacokinetics of a recombinant von Willebrand factor in severe von Willebrand disease, Gill et al., 2015)

Bias	Risk of bias	Elaboration
Confounding	• Unclear	There is no information on confounder and therefore the risk of bias is unclear.
Selection of participants into the study	• Moderate	1 out of 3 treatment arms (the 4th does not include on-demand treatment and therefore is not of interest here) were randomized, and the rest of patients were only "allocated at the investigator's discretion". The study is prospective. The risk of bias is due to these factors judged as moderate.
Classification of interventions	• Low	The intervention is relatively clearly defined.
Deviations from intended interventions	• Low	Nothing suggests that the intervention received deviated essentially from the intended intervention.
Missing data	• Moderate	Only 4/8 (50 %) patients from the first treatment arm were analyzed.
Measured outcomes		
Hemostatic efficacy	• Low	The hemostatic efficacy is analyzed by means of an objective rating scale, and therefore we judged the risk of bias as being low.
FVIII activity	• Low	No concern. Based on primary pharmacokinetic parameters.
Adverse events	• Low	No concern. Safety was evaluated by clinical assessments of adverse events, hematology panels, coagulation panels, serum chemistry, urinalysis, viral serology, and immunologic assessments.
Selection of reported results	• Low	At Clinicaltrials.gov (ID NCT01410227) were defined 66 outcome measures, however, nothing suggests that the selection of reported results was biased.
Overall bias	• **Moderate**	**Concern regarding potential confounding and the selection of patients to the treatment arms. Only half of the patients in one of the arms were included in the analyses, therefore there is also a moderate risk of bias regarding the missing data.**

Veyvondi, NCT02283268

(Study of Recombinant von Willebrand Factor in Patients with Severe von Willebrand Disease Who Are Undergoing Elective Surgery, Peyvandi et al., 2018)

Bias	Risk of bias	Elaboration
Confounding	• Moderate	It is not possible to assess confounding in a single arm study, and therefore there is a risk of bias per definition.
Selection of participants into the study	• Low	Patients aged ≥ 18 years with severe von Willebrand disease of all types who had planned elective surgery were eligible for the study. Nothing suggests selection bias.
Classification of interventions	• Low	The intervention is clearly defined.
Deviations from intended interventions	• Low	Nothing suggests that the intervention received deviated essentially from the intended intervention.
Missing data	• Moderate	There is a moderate risk of bias as only 11 out of 15 patients (73,3 %) were included in the PK/PD analyses.
Measured outcomes		
Hemostatic efficacy	• Moderate	Intraoperative hemostatic efficacy was assessed by the surgeon using the four-point efficacy rating scale, which has definitions worded by e.g. "as good or better than that expected" or "was probably as good as that expected" which is not too specific and could be subjective, and therefore poses a moderate risk of bias.
FVIII activity	• Low	No concern. Based on primary pharmacokinetic parameters.
Adverse events	• Low	No concern. Inhibitor is detected via clinical laboratory tests.
Selection of reported results	• Low	Nothing suggests bias in the selection of reported results. (Clinicaltrials.gov ID NCT02283268).
Overall bias	• **Moderate**	**Concern regarding potential confounding and missing data. The main outcome of interest, hemostatic efficacy, is decided by surgeon, which could be subjective.**

Willfact

(Treatment of severe von Willebrand disease with a high-purity von Willebrand factor concentrate (Wilfactin): a prospective study of 50 patients, Borel-Derlon et al., 2007)

Bias	Risk of bias	Elaboration
Confounding	• Moderate	It is not possible to assess confounding in a single arm study (more specifically studies, as there are two similar ones described together), therefore there is a risk of bias per definition.
Selection of participants into the study	• Low	As the protocols of the two studies (European and French) were comparable, they were merged into one article. There were 20 participants in the European study and 33 participants in the French study, while three patients took part in both studies, making it 50 participants altogether. However, nothing suggests risk of selection bias here.
Classification of interventions	• Low	The interventions are clearly defined.
Deviations from intended interventions	• Low	Nothing suggests that the interventions received deviated essentially from the intended interventions.
Missing data	• Low	Three patients out of 50 were lost to follow-up after the surgery, not finishing the European study. This, due to the small percentage (6 %), does not pose a risk of bias due to missing data.
Measured outcomes		
Efficacy	• Moderate	Treatment efficacy was assessed using a subjective four-point scale (excellent, good, moderate or none). For bleeding episodes treated at home, efficacy was assessed by the patients or their custodians, while for the patients in the hospital, efficacy was assessed by the attending physicians. The risk of bias is because of the subjectivity and various types of assessment judged as moderate.
FVIII activity	• Low	No concern. Based on primary pharmacokinetic parameters.
Adverse events	• Low	No concern. Inhibitor is detected via clinical laboratory tests.
Selection of reported results	• Unclear	The risk of bias regarding the selection of reported results is unclear, as the original study protocols are not available/mentioned in the study.
Overall bias	• **Moderate**	**Concern regarding potential confounding and selection of reported results. One of the main outcomes of interest, treatment efficacy, is assessed by the surgeon or patients themselves, which could also pose risk of bias.**

Haemate

(Successful treatment of urgent bleeding in von Willebrand disease with factor VIII/VWF concentrate (Humate-P_): use of the ristocetin cofactor assay (VWF:RCo) to measure potency and to guide therapy, Gill et al., 2003)

Bias	Risk of bias	Elaboration
Confounding	• Moderate	As the study is a single arm study with on demand treatment, there is by definition a potential of risk of bias.
Selection of participants into the study	• Low	Patients were males or females of any age with a diagnosis of congenital von Willebrand disease in whom desmopressin was known or suspected to be inadequate. They were expected to respond to exogenously administered VWF and to have a serious, life- or limb-threatening hemorrhage. Patients known to have inhibitors to VWF were excluded. The risk of bias is judged low.
Classification of interventions	• Moderate	Dosing recommendations included a loading dose, followed by maintenance doses. Each investigator was asked to follow the study dosing guidelines, but the final decisions on dosing were based on the investigators' clinical judgment. Maintenance doses could be extended longer than 7 days in unusual circumstances. A patient's study participation was completed if, in the opinion of the investigator, he or she would not benefit from further infusions of the study medication. As a result of this study design, the interventions could not be defined in detail, and therefore there is a moderate risk of bias regarding their classification.
Deviations from intended interventions	• Low	Nothing suggests that the interventions deviated from those intended, despite of the study design.
Missing data	• Low	This article summarizes the results of treatment for the 33 patients. Of these, nine patients were enrolled more than once (two to eight times) for multiple events. A total of 53 serious bleeding events were evaluated; 48 (91 %) had complete follow-up; five (9 %) discontinued prior to completion [consent withdrawn, lost to follow-up (two events), doctor's decision, and scheduling conflicts]. The risk of bias due to missing data is judged low.
Measured outcomes		
Hemostatic efficacy	• Moderate	Hemostatic efficacy was measured by the investigator's daily rating for each treatment event as well as an overall rating, following completion of the study treatment. The rating was subjective (with clinical assessment worded as e.g. "Similar hemostasis to that expected for persons without known bleeding disorders" or "Less hemostasis than expected for persons without known bleeding disorders") and therefore it poses a moderate risk of bias.
FVIII activity	• Low	No concern. Based on primary pharmacokinetic parameters.
Adverse events	• Low	No concern. The safety of FVIII/VWF concentrate was assessed by analyzing the incidence of unexpected and treatment-related AEs. Physical examination and vital sign data were collected for each patient.
Selection of reported results	• Unclear	The risk of bias regarding the selection of reported results is unclear, as the original study protocols are not available/mentioned in the article.
Overall bias	• **Moderate**	**Concern regarding potential confounding, the classification of interventions and the subjective assessment of the hemostatic**

		efficacy. The risk of bias regarding the selection of the reported results is unclear as a consequence of the trial number not being included in the article.

Haemate

(Efficacy and safety during formulation switch of a pasteurized VWF/FVIII concentrate: results from an Italianprospective observational study in patients with von Willebrand disease, Castaman et al., 2013)

Bias	Risk of bias	Elaboration
Confounding	• Unclear	As no confounders are mentioned in the article, the risk of bias is judged unclear.
Selection of participants into the study	• Low	No concern regarding the selection of participants.
Classification of interventions	• Moderate	The study was non-interventional and patients were treated with volume-reduced study drug based on their clinical needs, as judged by the investigator. This means a moderate bias due to the possible subjectivity in investigator's decisions.
Deviations from intended interventions	• Low	No concern regarding the deviations from intended interventions.
Missing data	• Low	No concern regarding the missing data.
Measured outcomes		
Hemostatic efficacy	• Moderate	Hemostatic efficacy was rated at each follow-up visit by the treating physician on a four-point scale of excellent, good, moderate, or none. The scale was not defined in detail and therefore the physicians' ratings could be subjective/biased.
Adverse events	• Low	Adverse events related to the treatment were recorded in a standardized case report form. No concern of bias.
Selection of reported results	• Unclear	The risk of bias regarding the selection of reported results is unclear, as the original study protocols are not available/mentioned in the article.
Overall bias	• **Moderate**	**There is overall moderate concern of bias. The bias regarding the confounding and selective reporting of results is unclear due to the missing information about these, while the bias regarding the classification of interventions and hemostatic efficacy (one of the outcomes) is judged as moderate due to possible subjectivity of physician's decisions.**

Haemate

(von Willebrand factor/factor VIII concentrate (Humate-P) for management of elective surgery in adults and children with von Willebrand disease, Gill et al., 2011)

Bias	Risk of bias	Elaboration
Confounding	• Moderate	As the study is an open-label, prospective single arm study with elective surgery treatment, there is by definition a potential of risk of bias.
Selection of participants into the study	• Low	Adults and children with a clinical and laboratory diagnosis of von Willebrand disease who were scheduled for elective surgery and expected to require at least two consecutive days of perioperative treatment with a VWF/FVIII concentrate, were eligible to enroll. Subjects were to be withdrawn from the study for uncontrollable bleeding, failure to attain sufficient plasma levels of VWF and FVIII after administration of Humate-P, or detection of antibodies against VWF and/or FVIII. There is no concern regarding the risk of bias due to selection of participants.
Classification of interventions	• Moderate	Each subject underwent a PK analysis in the steady state before surgery, with the results used to determine the initial preoperative loading and maintenance dosing. Concomitant medications were administered at the discretion of the investigator. As a result of this study design, the interventions could not be defined in detail, and therefore there is a moderate risk of bias regarding their classification.
Deviations from intended interventions	• Low	Nothing suggests that the interventions deviated from those intended, despite of the study design.
Missing data	• Low	Thirty-five subjects underwent surgery as planned and were included in the full-analysis population. There is no concern of risk of bias regarding the missing data.
Measured outcomes		
Hemostatic efficacy	• Moderate	Hemostatic efficacy was assessed by the treating physician on a 4-point scale, which included e.g. following formulations: Excellent – hemostasis not significantly different from normal, Good – mildly abnormal hemostasis, such as mild oozing; which are subjective. Risk of bias is therefore judged as moderate.
FVIII activity	• Low	No concern. The analyses were performed at a central laboratory.
Adverse events	• Low	No concern. The safety of FVIII/VWF concentrate was assessed by analyzing the incidence of unexpected and treatment-related AEs. Physical examinations were performed at baseline and at day 14. Vital sign data were evaluated at baseline. All adverse events, including new intercurrent illness or worsening of existing illness, were reported and documented.
Selection of reported results	• Unclear	The risk of bias regarding the selection of reported results is unclear, as the original study protocols are not available/mentioned in the article.
Overall bias	• **Moderate**	**Concern regarding potential confounding, the classification of interventions and the subjective assessment of the hemostatic efficacy. The risk of bias regarding the selection of the reported results is unclear as a consequence of the trial number not being included in the original article.**

Haemate

(von Willebrand factor/factor VIII concentrate (Haemate P) dosing based on pharmacokinetics: a prospective multicenter trial in elective surgery, Lethagen et al., 2007)

Bias	Risk of bias	Elaboration
Confounding	• Moderate	As the study is single arm study with elective surgery treatment, there is by definition a potential of risk of bias.
Selection of participants into the study	• Low	The subjects were evaluated at 12 centers, while 11 additional participating centers did not enroll any subjects. Candidates for study entry must have presented with a clinical and laboratory diagnosis of von Willebrand disease and a history of abnormal bleeding. Both males and females > 5 years old with hereditary von Willebrand disease were eligible. Enrollment was restricted to subjects scheduled for elective surgery requiring a hospital stay of at least 24 h. There is no concern of risk of bias regarding the selection of participants.
Classification of interventions	• Moderate	Each subject had an individually calculated loading dose. Moreover, postoperative doses were given at the discretion of the investigator. As a result of this study design, the interventions could not be defined in detail, and therefore there is a moderate risk of bias regarding their classification.
Deviations from intended interventions	• Low	Nothing suggests that the interventions deviated from those intended, despite of the study design.
Missing data	• Low	No concern. All 29 enrolled subjects received a PK infusion, while one subject was excluded from the PK analysis as a result of a protocol deviation, and another subject was lost to follow-up after the PK phase of the study. During the perioperative phase, 28 subjects received the individually calculated loading doses, and 27 subsequently underwent a surgical procedure. 25 subjects (86 %) had available all data.
Measured outcomes		
Hemostatic efficacy	• Moderate	Assessment of hemostatic effectiveness was based on laboratory assays, bleeding time, transfusion requirements and rating of hemostasis by the investigator. Bleeding time was determined using the Ivy method with the Simplate device. Hemostatic efficacy was rated daily by the treating physician on a four-point scale of excellent, good, moderate, or none. There, the concern was due to the subjective assessment of the daily ratings, as the scale was not defined in detail and therefore the physicians' ratings could be biased.
FVIII activity	• Low	No concern. The analyses were performed at a laboratory.
Adverse events	• Low	No concern. Subjects were monitored for adverse events from the time of informed consent until postoperative day 14 or until the end of treatment with the VWF/FVIII concentrate if treatment extended beyond day 14.
Selection of reported results	• Unclear	The risk of bias regarding the selection of reported results is unclear, as the original study protocols are not available/mentioned in the article.
Overall bias	• **Moderate**	**Concern regarding potential confounding, classification of interventions and the subjective assessment of the hemostatic**

		efficacy. The risk of bias regarding the selection of the reported results is unclear as a consequence of the trial number not being included in the original article.

Wilnativ

(Treatment and prevention of acute bleedings in von Willebrand disease – efficacy and safety of Wilate, a new generation von Willebrand factor/factor VIII concentrate, Berntorp et al., 2009)

Bias	Risk of bias	Elaboration
Confounding	• Moderate	Risk of bias regarding the confounding is judged as moderate due to the studies being single arm.
Selection of participants into the study	• Unclear	The risk of bias is judged as unclear due to the article referring to four studies at once as if they were the same, without enough specifications. The fact that only one of the studies recruited kids (participants of 12 years old or younger) suggests, that the inclusion criteria might have been different for each of the studies, which suggests risk of bias. Moreover, from the description it is not possible to judge the risk of bias for the individual studies.
Classification of interventions	• Moderate	A general dosing recommendation of Wilate per kilogram bodyweight was given for the treatment or prevention of spontaneous or trauma-induced hemorrhages. However, the actual dose and duration of treatment depended on the individual clinical situation and were at the discretion of the treating physician. Due to the possible subjectivity in dosing is the risk of bias judged as moderate.
Deviations from intended interventions	• Low	Nothing suggests that the interventions deviated from those intended.
Missing data	• Unclear	The article summarizes the results of 4 studies, where in total participated 44 patients (some of them took part in more than one study). From the article it is unclear, whether there is risk of bias regarding the missing data, as the specific study results and numbers of patients in the four studies are not provided.
Measured outcome		
Hemostatic efficacy	• Moderate	Hemostasis was monitored routinely by measuring plasma FVIII:C levels. In addition, investigators and/or patients had to rate the efficacy of the treatment using a 4-point verbal scale. This could be subjective, and the hemostatic efficacy is therefore judged as with moderate risk of bias.
Adverse events	• Moderate	AEs were reported by patients or their parents (and assessed using a 4-point verbal rating scale), and therefore is the risk of bias due to possible subjectivity judged as moderate.
Selection of reported results	• Unclear	The risk of bias regarding the selection of reported results is unclear, as the original study protocols are not linked in the article.
Overall bias	• **Moderate**	**Moderate concern regarding potential confounding, the classification of interventions and the subjective assessment of the hemostatic efficacy and AEs. Unclear risk of bias regarding the selection of participants, missing data and selective reporting. Overall is the risk of bias judged as moderate.**

Wilnativ, NCT01365546 (WONDERS)

(Efficacy and safety of a VWF/FVIII concentrate (wilate®) in inherited von Willebrand disease patients undergoing surgical procedures, Srivastava et al., 2017)

Bias	Risk of bias	Elaboration
Confounding	• Moderate	Risk of bias regarding the confounding is judged as moderate due to the study being single arm.
Selection of participants into the study	• Low	This prospective, open-label multinational clinical study documents 28 individuals who underwent 30 surgical procedures managed with wilate®. Twenty-one patients had von Willbrand disease type 3, and 21 surgeries were major. No concern of risk of bias due to selection of participants.
Classification of interventions	• Moderate	The dosing recommendations were adjusted for each patient using the results of the baseline IVR and at the investigator's discretion based on the clinical situation. Due to the possible subjectivity in dosing is the risk of bias judged as moderate.
Deviations from intended interventions	• Low	The study originally planned to examine up to 41 surgical procedures, while a single interim analysis was planned after 30 procedures. In the end, 28 patients underwent 30 surgeries. Nothing suggests that the interventions deviated from those intended.
Missing data	• Low	All 39 enrolled patients were included in the safety analysis as well as all received an infusion of wilate® for IVR determination, but not all underwent surgery. Overall no concern regarding the missing data.
Measured outcome		
Hemostatic efficacy	• Low	The study used stringent, objective efficacy criteria to assess efficacy during and after surgical procedures, as well as blinded adjudication of all efficacy assessments by the IDMC and statistical analysis, to provide a conservative, unbiased efficacy assessment of wilate®. The use of objective assessment criteria for surgical prophylaxis in this study is in line with recently developed objective efficacy criteria in non-surgical settings.
Adverse events	• Low	No concern. Clinical tolerability was assessed by monitoring vital signs, laboratory parameters (including VWF inhibitors and virus markers) and adverse events.
Selection of reported results	• Low	Nothing suggests bias in the selection of reported results. (Clinicaltrials.gov ID NCT01365546).
Overall bias	• **Moderate**	**Moderate concern regarding potential confounding (due to the nature of the study) and the classification of interventions (as dosing was at investigator's discretion). There is no concern of bias regarding the rest of the domains.**

Wilnativ

(Efficacy and safety of a new generation von Willebrand factor/factor VIII concentrate (Wilate®) in the management of perioperative haemostasis in von Willebrand disease patients undergoing surgery, Windyga et al., 2011)

Bias	Risk of bias	Elaboration

Confounding	• Moderate	The risk of bias judged originates from four European, prospective, open-label, non-controlled, non-randomized, multicenter phase II or phase III clinical trials. For ethical reasons, a placebo control group was not included, and the studies are single arm, as a result of what is risk of bias judged as moderate by definition.
Selection of participants into the study	• Unclear	The risk of bias is judged as unclear due to the article referring to four studies at once as if they were the same, without enough specifications. The fact that only one of the studies recruited kids (participants of 12 years old or younger) suggests, that the inclusion criteria might have been different for each of the studies, which suggests risk of bias. Moreover, from the description it is not possible to judge the risk of bias for the individual studies.
Classification of interventions	• Moderate	Dosing was calculated according to the investigator's discretion in one study and according to the recommendations in three studies. As a result of the possible subjectivity in the first study, the risk of bias is judged as moderate.
Deviations from intended interventions	• Low	Nothing suggests that the interventions deviated from those intended.
Missing data	• Unclear	A total of 57 surgical procedures were performed in 32 patients. Hemostatic efficacy data were missing for three minor surgeries of one patient, as this patient underwent a minor surgical procedure but did not receive the drug. The risk of bias regarding missing data is judged as unclear, as the article only mentions the available data for all studies together, omitting the availability of the data for the four separate studies.
Measured outcome		
Hemostatic efficacy	• Moderate	Hemostatic efficacy was rated by the investigator using a four-point scale (excellent, good, moderate or none). Three studies used definitions for assessment, while one was assessed to the Investigator's discretion. Therefore, the assessment could have been subjective and is therefore judged as having moderate risk of bias.
Adverse events	• Moderate	All adverse events that occurred during the trials and baseline AEs that worsened during the trials were recorded. AEs were classified using the standard Medical Dictionary Regulatory Activities (MedDRA) coding dictionary. Tolerability was also assessed by investigators and patients using a four-point rating scale (very good, good, satisfactory and unsatisfactory). The risk of bias is judged as moderate, as the assessing of tolerability of adverse events is subjective and therefore could have been subject of bias in the study/studies.
Selection of reported results	• Unclear	The risk of bias regarding the selection of reported results is unclear, as the original study protocols are not linked in the article.
Overall bias	• **Moderate**	**Possible bias regarding the confounding, classification of interventions and some of the measured outcomes. Unclear bias regarding the selection of participants into the studies (due to article summarizing 4 studies into one), missing data (as this is not specified for individual studies) and selection of reported results. Overall moderate concern.**

VEYVONDI® (Vonicog alfa)

Final application to the Medicine Council

Shire Denmark A/S
Larsbjørnsstræde 3
1454 København K
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Contents

List of tables

1 Basic information

Table 1 Contact information

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Table 2 Overview of the pharmaceutical

[1]

Proprietary name	**VEYVONDI®**
Generic name	Vonicog alfa
Marketing authorization holder in Denmark	Baxalta Innovations GmbH, Industriestrasse 67, 1221, Vienna, Austria
ATC code	B02BD10
Pharmacotherapeutic group	Antihaemorrhagics, blood coagulation factor von Willebrand factor
Active substance(s)	Recombinant von Willebrand Factor (rVWF)
Pharmaceutical form(s)	Powder and solvent for solution for injection. The powder is a white top off-white lyophilized powder. The solvent is a clear and colourless solution.
Mechanism of action	Veyvondi is a recombinant human von Willebrand factor (rVWF). Veyvondi behaves in the same way as endogenous von Willebrand factor. Administration of Veyvondi allows correction of the haemostatic abnormalities exhibited by patients who suffer from von Willebrand factor deficiency (von Willebrand's disease) at two levels: • Veyvondi re-establishes platelet adhesion to the vascular sub-endothelium at the site of vascular damage (as it binds both to the vascular sub-endothelium matrix (e.g. collagen) and to the platelet membrane), providing primary haemostasis as shown by the shortening of the bleeding time. This effect occurs immediately and is known to depend to a large extent on the level of polymerisation of the protein. • Veyvondi produces delayed correction of the associated factor VIII deficiency. Administered intravenously, Veyvondi binds to endogenous factor VIII (which is produced normally by the patient), and by stabilising this factor, avoids its rapid degradation. Because of this, administration of Veyvondi restores the FVIII:C level to normal as a secondary effect. After the first infusion, the FVIII:C rises above 40% within 6 hours and peaks within 24 hours in a majority of patients, depending on the baseline FVIII:C level. VEYVONDI is a rVWF that contains ultra-large multimers in addition to all of the multimers found in plasma as it is not exposed to proteolysis by ADAMTS13 during the manufacturing process.
Dosage regimen	<u>*On demand treatment*</u> *Start of treatment* The first dose of VEYVONDI should be 40 to 80IU/kg body weight.

Replacement levels of VWF:RCo >0.6IU/mL (60%) and FVIII:C >0.4IU/mL(40%) should be achieved. Dosing guidelines for treatment of minor and major haemorrhages are provided in the SmPC.

VEYVONDI should be administered with recombinant factor VIII if the FVIII:C levels are<40%, or are unknown, to control bleeding. The rFVIII dose should be calculated according to the difference between the patient's baseline plasma FVIII:C level, and the desired peak FVIII:C level to achieve an appropriate plasma FVIII:C level based on the approximate mean recovery of 0.02 (IU/mL)/(IU/kg). The complete dose of VEYVONDI should be administered followed by rFVIII within 10minutes.

Calculating dose:

VEYVONDI dose [IU] = dose [IU/kg] x weight [kg]

Subsequent infusions:

A subsequent dose of 40IUto 60IU/kg of VEYVONDI should be infused every 8 to 24hours as per the dosing ranges in Table1 in the SmPC, or as long as clinically appropriate. In major bleeding episodes, maintain trough levels of VWF:RCo greater than 50% for as long as deemed necessary.

Based on experience from clinical studies, once VWF has been replaced, endogenous FVIII levels will remain normal or near normal as long as VEYVONDI is continued to be administered.

Detailed guidance is tabulated in the SmPC.

Prevention of bleeding in surgery

Prior to Surgery:

In patients with inadequate levels of FVIII, a dose of 40-60 IU/kg VEYVONDI should be administered 12-24 hours prior to initiating elective surgery(pre-operative dose), to ensure pre-operative endogenous FVIII levels of at least 0.4IU/mL for minor and at least 0.8IU/mL for major surgery.

For prevention of excessive bleeding in case of elective surgery, within 3 hours prior to initiation of any surgical procedure, the FVIII:C levels should be assessed. If the FVIII:C levels are at the recommended target level of:

- at least 0.4IU/mL for minor and oral surgery and

- at least 0.8IU/mL for major surgery,

a dose of VEYVONDI alone should be administered within 1hour prior to the procedure.

If the FVIII:C levels are not at the recommended target levels ,rFVIII should be administered in addition to Veyvondi to raise VWF:RCo and FVIII:C, within 1 hour prior to the procedure. Please refer to Table 2 in the SmPC for FVIII:C recommended target levels. The dose depends on VWF and FVIII levels of the patient, the type and severity of the expected bleeding.

During and after surgery

After the initiation of the surgical procedure, the VWF:RCo and FVIII:C plasma levels should be monitored, and the intra-and post-operative substitution regimen should be individualised according to the PK results, intensity and duration of the haemostatic challenge, and the institution's standard of care. In general, the frequency of VEYVONDI dosing for post-

	operative substitution should range from twice a day to every 48hours. Detailed guidance is tabulated in the SmPC.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	VEYVONDI is indicated in adults (age 18 and older) with von Willebrand Disease (VWD), when desmopressin (DDAVP) treatment alone is ineffective or not indicated for the: • Treatment of haemorrhage and surgical bleeding • Prevention of surgical bleeding VEYVONDI should not be used in the treatment of Haemophilia A.
Other approved therapeutic indications	N/A
Will dispensing be restricted to hospitals?	BEGR
Combination therapy and/or co-medication	N/A
Packaging – types, sizes/number of units, and concentrations	VEYVONDI 650 IU powder and solvent for solution for injection Each pack contains: - powder in a vial (type I glass), with a butyl rubber stopper - 5mL of solvent in a vial (type I glass), with a rubber stopper (chlorobutyl) - one reconstitution device (Mix2Vial) VEYVONDI 1300 IU powder and solvent for solution for injection Each pack contains: - powder in a vial (type I glass), with a butyl rubber stopper - 10mL of solvent in a vial (type I glass), with a rubber stopper (bromobutyl) - one reconstitution device (Mix2Vial)
Orphan drug designation	No

2 Abbreviations and Acronyms

Please note that the comparators are marketed under different brand names as follows Haemate (Humate), Wilnativ (Wilate) and Willfact (Willfactin)

The original name of the products has been maintained in citations and in quotes from original publications.

Table 3 Abbreviations

AE: Adverse event	N/A: not applicable
CHMP: Committee for Medicinal Products for Human Use	Pd: plasma derived
CI: 95 % Confidence interval	PK/PD: Pharmacokinetic/pharmacodynamic
DDAVP: Desmopressin	RCo: Ristocetin co-factor
EMA: European Medicines Agency	rFVIII: Recombinant coagulation factor VIII
EPAR: European Public Assessment Report	rvWf Rekombinant von Willebrand factor
EUVWD: European Group on von Willebrand disease	SAE: Serious adverse event
FVIII: coagulation factor VIII	SD: Standard deviation
FVIII:C: Factor VIII coagulation activity	SmPC: Summary of Product Characteristics
HA: Hemophilia A	ULM: Ultra large multimers
HB: Hemophilia B	vWD: von Willebrand disease
IQR: Interquartile Range	vWf: von Willebrand factor
IU: International Units	vWF:RCo: von Willebrand factor:ristocetin cofactor
IVR: In vivo recovery	

3 Summary

Summary

This application concerns Veyvondi® (vonicog alfa) the first recombinant von Willebrand factor, that can be administered as monotherapy or in combination therapy with recombinant FVIII, if needed as on demand treatment for spontaneous or traumatic bleeds and to prevent bleeding during elective surgery in patients with von Willebrand disease.

Based on the Medicines Council protocol a systematic literature review protocol, it became evident that published data was not reported in manner that allowed for addressing the clinical questions as defined in the protocol. This was in particular caused by the lack of data for FVIII values above/below 30%, and to a major extent the incomplete or lack of definitions of minor/major bleeds as well as minor/major surgery in the identified literature. This probably caused by the fact that the majority of these studies and publications are up to 15 years old.

It was therefore agreed with the Medicines Council secretariat to present the available data in the format used in this submission.

To the extent possible data have been extracted and presented to allow for a comparison of VWF monotherapy (Veyvondi compared to Willfact) and VWF+FVIII (Veyvondi plus Advate compared to Haemate and Wilnativ) for the outcomes defined in the protocol.

Data for the three safety outcomes (serious venous thromboembolic events, anaphylaxis and inhibitor) are presented separately due to limited availability of data.

In clinical question # 1 data were requested for Veyvondi monotherapy compared to Willfact monotherapy. Such data are however not available for Veyvondi as the design of the on-demand phase III study mandated co-administration of rFVIII at the first infusion of Veyvondi.

However, the pharmacological properties of Veyvondi are similar to the properties of Willfact why the effect level must be considered equivalent.

Interestingly though, a comparison of data for Veyvondi in combination with rFVIII to Willfact in combination with FVIII show a difference in haemostatic effect (97.9% vs 89%) in favour of Veyvondi. The number of infusions as well as the range of infusions per bleed was 1.0 (1-4) for Veyvondi compared to 3.0 (1-46) for Willfact.

In clinical question #2 data were requested for Veyvondi in combination with rFVIII compared to the plasma derived combinations products Haemate and Wilnativ in on demand treatment.

For Veyvondi 188 of 192 (97.9%) the haemostatic effect was rated as either excellent (95.8%) or good (2.1%). For Haemate the 52 of 53 (98 %) evaluable bleed treatments were rated excellent/good, and for Wilnativ 96% (of 1095 bleed treatments) were rated excellent/good.

The median number of infusions with Veyvondi was 1.0 (1-4), which is lower than the 2.0 (1-36) reported for Haemate. Data for number of infusions per bleed is not reported for Wilnativ, but other data reported (#infusion days) indicate a median number of 1 (1-29) with at least one infusion per day.

The number of infusions required for Veyvondi is thus 1 lower than for Haemate. In addition, the range of infusions needed is apparently much narrower for Veyvondi than for Haemate [2.0 (1-36)] and Wilnativ [1 (1-29)].

Overall it seems as if the haemostatic efficacy is similar for Veyvondi and the two comparators while the required numbers of infusions with Veyvondi is lower and with a much narrower range.

In clinical question # 3 data were requested for Veyvondi monotherapy compared to Willfact monotherapy in the prevention of bleeding in patients undergoing minor surgery. Due to the variability in the reporting of the data between the two studies data have been described separately for minor and major surgery as well as the type (anatomical location) of surgery.

The overall haemostatic efficacy was 100% for both Veyvondi and Willfact. Efficacy for Veyvondi was evaluated 24 h post last infusion while efficacy for Willfact was evaluated at the day of discharge.

The overall number of infusions needed was 5 for Veyvondi and 3 for Willfact. The overall number is however skewed by the distribution of major and minor surgery between two studies. When looking at subgroups of major surgery the number of infusions need for Veyvondi is 7.5 (4-15) and 5.5 to 22 for Willfact depending of type of major surgery. In minor surgery the number of infusions needed seem similar.

In addition, the range for number of infusions needed is much narrower for Veyvondi than for Willfact.

In clinical question #4 data were requested for Veyvondi in combination with rFVIII compared to Willfact the plasma derived combinations products Haemate and Wilnativ in the prevention of bleeding in patients undergoing major surgery.

The haemostatic effect (percentages reaching a rating of excellent/good) ranges from 100% for Veyvondi to 94.3% for Wilnativ.

The median number of infusions in major surgeries is 7.5 (4-15) infusions for Veyvondi compared to 10 (4-55) and 7 (4.5-11.5 IQR) for the two Haemate studies and with 25 (10-79) for Wilnativ in similar types of major surgeries.

This comparison highlights two important points; a) the median number of infusions required in major surgery seems on par or lower with Veyvondi than with the comparators and b) the range of infusions needed with Veyvondi is narrower than for the comparators.

The incidence of the three safety outcomes (serious venous thromboembolic events, anaphylaxis and inhibitor) is low.

The narrative description of data indicates that the haemostatic efficacy of Veyvondi is at least at the level of the comparators both in on demand treatment and in the prevention of bleeds in elective surgery.

The number of infusions needed seems to be lower in major surgery and similar in minor surgery, while the range of infusions needed is much narrower and thereby more predictable for Veyvondi than for the comparators.

4 Literature search

A systematic literature search has been performed for relevant literature concerning von Willebrand disase in on demand treatment and elective surgery for Veyvondi, plasma derived VWF (Willfact/Wilfactin) and plasma derived combinations of FVIII and VWF (Haemate (Humate), Wilnativ (Wilate))

Electronic search in was performed on January 14th, 2019 in BIOSIS Previews®, Embase®, MEDLINE® and (via ProQuest) and CENTRAL via Cochrane Library.

The search included terms descriptive to the area (von Willebrand disease, bleedings, surgery) and the defined intervention and comparators. The eligibility criteria are presented in section 8.1.

Two employees screened all references by title and abstract in an electronic reference tool according to the pre-defined in- and exclusion criteria. In case of uncertainty of inclusion/exclusion, full text publications were reviewed. Excluded full text references with reason for exclusion are listed in section 8.1.2.

The entire search definition is presented in the PRISMA flow diagram in section 8.1.1 and the search strings in section 8.1.3.

16 articles were retrieved for full text review, seven were excluded and nine included in the present report.

4.1 Relevant studies

The outcome of the systematic literature search is a total of 5 publications relevant for questions related to the on-demand indication and 4 publications relevant for questions related to the surgery indication.

Confounders in the selection of publications

There are a number of confounders regarding identification of the specific studies underlying the publications concerning the comparators. This is caused by the fact that

a) The majority of studies were conducted prior to the implementation of the requirement for registering clinical studies at www.clinicaltrials.gov in 2006, and
b) the description in the publication of the studies underlying the data reported in the publication is somewhat incomplete

It should be noted that two of the publications (Berntorp 2009 and Windyga 2011) are pooled analyses of 4 studies conducted with Wilnativ. *[2, 3]* It has not been possible to identify information on the individual studies from e.g. clinicaltrials.gov. In addition, it has not been possible to verify if there is an overlap or duplicate publication of data from any of the individual studies. However, as these publications seem to be the only publications reporting from prospective intervention trials in Wilnativ, they have been included.

In order to provide a relevant and comprehensive overview of the data, it is assumed that each publication represents one study for the medicine in question.

European Public Assessment Reports and SmPCs

The European Assessment Report is only available for Veyvondi.[4] The comparator products have all been approved through the national regulatory procedures, where the assessment reports are not publicly available.

SmPCs for both intervention and comparators have been developed in accordance with the standard wordings provided in the CHMP Guideline for Core SmPC for Human Derived von Willebrand Factor (CPMP/BPWG/278/02), why they are very similar in most content. The clinical section 5.1 contains no clinical data relevant for this application. [1, 5-8]

Studies included in the assessment

The studies included in the assessment are listed in Table 4.

Table 4 Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Relevant for clinical question <x>*
Gill JC, et al. Haemostatic efficacy, safety, and pharmacokinetics of a recombinant von Willebrand factor in severe von Willebrand disease. Blood. 2015 Oct 22;126(17):2038-46[9]	*Pharmacokinetics, Safety and Efficacy of Recombinant Von Willebrand Factor (rVWF) in the Treatment of Bleeding Episodes in Von Willebrand Disease (VWD).* *In this application the study will be referred to as "Gill 2015"*	*NCT01410227*	*Nov 2011 to Nov 2014*	*1 + 2*
Borel-Derlon A, et al. Treatment of severe von Willebrand disease with a high-purity von Willebrand factor concentrate (Wilfactin): a prospective study of 50 patients. J Thromb Haemost. 2007 Jun;5(6):1115-24.[10]	*No specific name reported.* *In this application the study will be referred to as "Borel-Derlon 2007"*	*Not reported*	*Not reported*	*1* *3*
Gill JC, et al. Successful treatment of urgent bleeding in von Willebrand disease with factor VIII/VWF concentrate (Humate-P): use of the ristocetin cofactor assay (VWF:RCo) to measure potency and to guide therapy. Haemophilia. 2003 Nov;9(6):688-95. [11]	*No specific name reported.* *In this application the study will be referred to as "Gill 2003"*	*Not reported*	*Inclusion of patients happened between NOV1998 to AUG1999.*	*2*
Berntorp E, Windyga J; European Wilate Study Group. Treatment and prevention of acute bleedings in von Willebrand disease--efficacy and safety of Wilate, a new generation von Willebrand factor/factor VIII concentrate. Haemophilia. 2009 Jan;15(1):122-30. [2]	*No specific name reported.* *In this application the study will be referred to as "Berntorp 2009"*	*Not reported*	*Not reported*	*2*
Peyvandi F, et al. Phase 3 Study of Recombinant von Willebrand Factor in Patients With Severe von Willebrand Disease Who Are Undergoing Elective Surgery. J Thromb Haemost. 2018 Oct 25. doi: 10.1111/jth.14313. [Epub ahead of print] PubMed PMID: 30362288 [12]	*A Phase 3, Prospective, Multicenter Study to Evaluate Efficacy and Safety of Recombinant Von Willebrand Factor (rVWF) With or Without ADVATE in Elective Surgical Procedures in Subjects With Severe Von Willebrand Disease.* *In this application the study will be referred to as "Peyvandi 2018"*	*NCT02283268*	*01APR2015 to 06JULY2016* *[clinicaltrials.gov (NCT02283268)]*	*3+4*
Srivastava A, et al. Efficacy and safety of a VWF/FVIII	*WONDERS* *In this application the study will*	*NCT01365546*	*JUN2011 to APR2014*	*4*

concentrate (wilate(®)) in inherited von Willebrand disease patients undergoing surgical procedures. Haemophilia. 2017 Mar;23(2):264-272.[13]	*be referred to as "Srivastava 2017"*		*[clinicaltrials.gov (NCT02283268)]*	
Gill JC, Shapiro A, Valentino LA, Bernstein J, Friedman C, Nichols WL, Manco-Johnson M. von Willebrand factor/factor VIII concentrate (Humate-P) for management of elective surgery in adults and children with von Willebrand Disease. Haemophilia. 2011 Nov;17(6):895-905. [14]	*Study of Safety and Efficacy of Antihemophilic Factor/Von Willebrand Factor Complex in Surgical Subjects With Von Willebrand Disease (vWD). [CT.GOV]* *In this application the study will be referred to as "Gill 2011"*	*NCT00168090* *(this is not verified as neither the publication nor any other source has confirmed this) [CT.GOV]*	*OCT2001 to OCT2006* *[clinicaltrials.gov (NCT02283268)]*	*4*
Windyga J, von Depka-Prondzinski M; European Wilate® Study Group. Efficacy and safety of a new generation von Willebrand factor/factor VIII concentrate (Wilate®) in the management of perioperative haemostasis in von Willebrand disease patients undergoing surgery. Thromb Haemost. 2011 Jun;105(6):1072-9. [3]	*No specific name reported.* *In this application the study will be referred to as "Windyga 2011"*	*Not reported*	*Not reported*	*4*
Lethagen S, Kyrle PA, Castaman G, Haertel S, Mannucci PM; HAEMATE P Surgical Study Group. von Willebrand factor/factor VIII concentrate (Haemate P) dosing based on pharmacokinetics: a prospective multicenter trial in elective surgery. J Thromb Haemost. 2007 Jul;5(7):1420-30.[15]	*No specific name reported.* *In this application the study will be referred to as Lethagen 2007.*	*Not reported*	*Oct 2001 to May 2003*	*4*
****when multiple clinical questions are defined in the protocol***				

4.2 Main characteristics of included studies

The main characteristics of the studies are presented in Table 37 to Table 45 in section 8.2.

In general, the majority of publications is characterized by a high variability in both structure, definitions and content. Every effort has been made to ensure an aligned description across the studies, but several inconsistencies remain.

5 Clinical questions

Following the initial review of the available literature in the area, it became evident that data was not reported in manner that allowed for addressing the clinical questions as defined in the protocol. This was specifically caused by the lack of data for FVIII values above/below 30%, and to a major extent the incomplete or lack of definitions of minor/major bleeds as well as minor/major surgery.

It was therefore agreed with the Medicines Council secretariat to present the available data as described below:

Each clinical question will be answered separately for the outcome measures “haemostatic effect” and “number of infusions per bleed”.

Subsequently the outcomes “inhibitor”, “anaphylaxis” and “serious venous thromboembolic events” will be addressed combined as the reporting in the publications is incomplete.

5.1 What is the clinical added value of vonicog alfa compared to plasma derived vWF for the treatment of bleeding in patients with vWD and with a normal or mildly reduced level of Factor VIII (>30%)?

The reporting in the identified publications does not fully match the definitions in the clinical question with regard to neither the FVIII-level nor the use of the intervention and comparator as monotherapy only.

Therefore, the response to this question will include an overview of the effect of on demand Veyvondi and Willfact on bleedings episodes in patients with all levels of FVIII with or without co-administration of FVIII.

To the extent possible data will be described as close as possible to the definition in the clinical question.

5.1.1 Presentation of relevant studies

The following studies are used in the assessment of this clinical question:

Veyvondi: Gill JC, et al. Haemostatic efficacy, safety, and pharmacokinetics of a recombinant von Willebrand factor in severe von Willebrand disease. Blood. 2015 Oct 22;126(17):2038-46. *[9]*

In addition, data from the EPAR is included, when applicable. The SmPC does not contain any clinical efficacy data.

Willfact: Borel-Derlon A, et al. Treatment of severe von Willebrand disease with a high-purity von Willebrand factor concentrate (Wilfactin): a prospective study of 50 patients. J Thromb Haemost. 2007 Jun;5(6):1115-24. *[10]*

No EPAR is available for Willfact. The SmPC does not contain any clinical efficacy data.

Vonicog alfa:

No formal data are available for Veyvondi as monotherapy in on demand treatment of bleeding episodes.

The phase III on demand study for Veyvondi *[9]* was designed to evaluate treatment with Veyvondi *with* mandatory co-administration of FVIII at the time of the initial does of Veyvondi regardless of baseline FVIII-level. The study did thus not formally evaluate the use of Veyvondi in monotherapy for on demand treatment of bleeds. *[9]*

A detailed description of the study can be found in connection with the response to clinical question # 2 and in Table 37.

Data for 3 patients with a total of 10 bleeds who were inadvertently treated with Veyvondi as monotherapy will be presented below.

In addition, as the publication for Willfact includes data for the efficacy in patients with both minor and major bleeds treated with co-administration of FVIII, data for combined use of Willfact and FVIII will be

described to allow for a thorough evaluation of the efficacy of the two medicines also when used in combination with FVIII.

Plasma derived von Willebrand factor (Willfact)

Data for pdVWF as monotherapy for on demand treatment of bleeds is reported in Borel-Derlon 2007, which is a publication reporting two separate studies on 4 separate study populations: on demand, surgery, short term prophylaxis and long-term prophylaxis. *[10]*

A brief summary is provided below. A detailed description of the study can be found in Table 38.

This prospective trial was conducted in two parts. The first part (called the French study) was conducted at six French centres in the form of a crossover PK study comparing for bioequivalence the study product (Willfact) and the earlier one (Facteur Willebrand-LFB®) in patients with type 3 VWD. [16] The second part (called the European study) was conducted at five European centres as a crossover PK study comparing Willfact with FVIII/VWF concentrates currently licensed for treatment of VWD in patients with severe VWD (see definition below). The French study was not randomized, open label, while the European study was randomized open label. [17]

Fifty patients (32 females and 18 males) were originally enrolled: 5 had type 1, 16 type 2A, 9 type 2B, 1 type 2 M, 1 type 2 N, and 18 type 3 VWD.

For the overall study population (N=50), the median age was 37 years (range 5–81) and body weight ranged from 24 to 102 kg (median 62). Three children were less than 15 years old. The median plasma levels of VWF:RCo was < 10 (10-33), and FVIII 27 (< 1-63). The baseline levels of VWF:RCo were less than 10 IU/dL in 36 patients (72%) and those of FVIII were less than 20 IU/dL in 23 patients (46%).

The 26 patients (15 type 3, 1 type 1, 7 type 2A and 3 type 2B) participating in the on-demand part of the study received a total of 733 infusions of Willfact over 565 exposure days for 139 bleeding episodes.

All patients were to receive pdVWF according to predefined dosage schedules. For patients with a FVIII level <20 IU/dl or with severe bleeding, FVIII was to be co-administered with the first pdVWF infusion.

5.1.2 Results per study

Note: Data for and comparison of the outcomes anaphylaxis, inhibitor and serious thromboembolic events are presented combined for all four clinical questions in section 5.5 as the format and content of the reported data in the publications does not allow for addressing these data individually for each clinical question.

The results for the outcomes haemostatic effect and number of infusions are presented in this section.

Haemostatic effect – results per study

Veyvondi:

No formal data for Veyvondi monotherapy in the defined patient population is available due to the dosing requirements in the phase III on demand study. *[9]*

However, for 10 bleeding episodes in 3 patients where the investigator staff inadvertently did not co-administer FVIII, the haemostatic efficacy was rated excellent/good in all episodes (10 of 10). *[9]*

Whilst no data are available for Veyvondi in monotherapy for on demand treatment of bleeding episodes, the mode of action for von Willebrand Factor in general strongly supports the use of Veyvondi as monotherapy for on demand treatment of bleedings episodes.

It should be noted that the EMA in the approved SmPC is fully in line with the recommendation that patients with FVIII levels ≥40IU/dl should not have FVIII co-administered with Veyvondi.[1]

It is considered that haemostasis can be ensured if Factor VIII coagulant activity (FVIII:C) is at least 0.4IU/mL (≥40%of normal activity). Initial (primary) haemostasis is dependent upon elevation of the plasma VWF:RCo activity to normal, but longer-term secure haemostasis is dependent on a normal level of Factor VIII [18]. Infused VWF must first stabilize endogenous FVIII produced in these patients.

The PK assessments in the on demand pivotal studies for Veyvondi have shown that the endogenous FVIII (FVIII:C) increased above 40% within 6 hours post-infusion, reached a peak at 86 U/dL 24 hours post-infusion and will result in sustaining levels above 40IU/dL up to 72hours post infusion. *[9]*

The Principles of care for the diagnosis and treatment of von Willebrand disease published by the European Group on von Willebrand disease (EUVWD) in 2013 have recommended in the treatment of spontaneous bleeding episodes that FVIII:C levels have to be maintained above 30 % or U/dL (table below). [19]These recommendations are in line with the 2012 recommendations by the Nordic Hemophilia Council. [20]

Table 5 Suggestions for replacement therapy of von Willebrand disease

1.	VWD diagnosis should be considered within the context of an appropriate personal and/or familial bleeding history. The use of a standardized questionnaire for history collection is advisable to appreciate the severity of the bleeding tendency.
2.	Other common hemostatic defects should be excluded by performing a platelet count, APTT, PT and PFA-100 (or bleeding time).
3.	If personal and/or familial bleeding history is significant, VWF:RCo assay should be carried out at this stage. If not possible, VWF:Ag assay or VWF:CB assay should be performed. VWF:Ag < 3 U/dL suggests type 3 VWD. VWF:Ag and VWF:RCo and FVIII:C should be measured on the same sample to assess the presence of a reduced VWF:RCo/VWF:Ag ratio (a ratio < 0.6 suggest type 2 VWD) or FVIII:C/VWF:Ag (a ratio < 0.6 suggests type 2N VWD, to be confirmed by binding study of FVIII to patient's VWF).
4.	If any of these tests is below 40 U/dL, the diagnosis of VWD should be strongly considered.
5.	Other family members with a possible bleeding history should be evaluated. Finding another member with bleeding and reduced VWF strongly supports the likelihood of diagnosis.
6.	Aggregation of patient platelet-rich plasma in the presence of increasing concentrations of ristocetin (0.25, 0.5, 1.0 mg/mL, final concentration) should be assessed. Aggregation at low concentration (< 0.5 mg) suggests type 2B (or platelet type) VWD.
7.	Multimer pattern using an intermediate resolution gel should be evaluated. Lack of high molecular weight multimers suggests type 2A and/or 2B. Presence of full complement of multimers suggests type 1 (or 2N, 2M). Absence of multimers in type 3. Analysis of the triplet structure will help identify variants with increased or decreased cleavage. Repetition of the multimer gel in low resolution agarose may be helpful in confirming the presence/lack of HMW multimers.
8.	VWF genetic analysis could be advisable for differential diagnosis of mild hemophilia A *vs.* 2N VWD in males, hemophilia A carriership *vs.* 2N VWD in females and for type 2B VWD *vs.* platelet type-VWD.
9.	VWF genetic analysis may be required for prenatal diagnosis in type 3.

Since we consider the use of VWF as monotherapy in patients with FVIII>40%, a co-administration of FVIII is not recommended.

In conclusion it is expected that the efficacy of Veyvondi monotherapy will be at least as effective as other available VWF products for monotherapy in patients with FVIII levels ≥40.

Willfact (pdVWF)

In Borel-Derlon 2007 the outcomes haemostatic effect was evaluated by the investigator at 6h and 24h after the infusion using a subjective four-point scale (excellent, good, moderate or none; no further definition is reported). *[10]*

Combined success rate for vWF alone and in combination with FVIII

The reported overall success rate of 89.1 % is the combined success rate for patients with major or minor bleeds with or without co-administration of FVIII and combined for treatment at home (evaluated 24 post infusion) or during hospitalization (evaluated at discharge). *[10]*

As efficacy for patients treated in hospital is evaluated at the time of discharge, it is to be expected that the efficacy rating for this group of patients will be higher than if the evaluation was performed at 24 h post infusion. *[10]*

The overall success rate is therefore not necessarily fully representative for the success rate for vWF administered as monotherapy. *[10]*

The publication also reports data for 18 major and 121 minor bleeds separately. *[10]*

vWF in combination or as monotherapy for minor bleeds

Patients used Willfact at home for the treatment of 121 minor bleeding episodes. The percentage of excellent/good responses to treatment 6 and 24 h post infusion was 88% and 89%, respectively. Most of these episodes (86) episodes occurred in patients with baseline FVIII levels below 20 IU/dL and, as prescribed, these patients self-administered a priming dose of FVIII together with the first VWF dose. *[10]*

vWF as monotherapy for minor bleeds

In 40/86 episodes, the patient did not co-administer FVIII. In this group, efficacy was rated as excellent or good in 87% and as moderate in 13% 6 h post infusion, then as excellent or good in 97% and moderate in 3% 24 h post infusion. *[10]*

vWF in combination or as monotherapy for major bleeds

Among the 18 severe bleeding episodes, 13 occurred in patients with baseline FVIII levels below 20 IU/dL. The recommended concomitant priming FVIII dose was infused with the first VWF dose in seven of the 13 episodes (56%). Efficacy was excellent for 16 of 18 (89%) episodes but is not reported separately for the patient receiving only vWF. It should be noted that the evaluation of haemostatic efficacy for hospitalized patients was performed at discharge from the hospital. *[10]*

Number of infusions – outcomes per study

The outcomes *number of infusions* is reported both for Veyvondi and for pdVWF (Willfact).

Veyvondi

All subjects but 3 (with 10 bleeds) received co-administration of FVIII with the initial infusion of rVWF.

The median # of infusions for the 192 bleeding episodes in 22 subjects was 1.0 (90% CI 1.0-1.0; range 1-4) per bleed. *[9]*

81.8 % (157/192) of all bleeding episodes required only one infusion. Only one patient required 4 infusions. *[9]*

Plasmaderived von Willebrand factor (Willfact)

Co-administration of FVIII with the first vWF infusion happened in 53 of 139 (38.1%) bleeding episodes, however data for treatments without co-administration of FVIII is not reported separately. *[10]*

The median number of infusions for the 139 bleeding episodes in 26 subjects was 3.0 (1-46). The highest required number of infusions was 46. *[10]*

5.1.3 Comparative analyses

The approved dosing schedule for Veyvondi and for Willfact is shown in Table 6

Table 6 Dosing for Veyvondi and Willfact

	Veyvondi [1]	Willfact [6]
On Demand		
Initial dose, minor bleeds	40-50 IU/kg	40-80 IU/kg
Initial dose, major bleeds	40-80 IU/kg	
Subsequent doses, minor	40-50 IU/kg every 8-24 h	40-80 IU/kg every 12-24 h
Subsequent doses, major	40-60 IU/kg every 8-24 h	
Surgery		
Initial dose 12-24 h before surgery	40-60 IU/kg	40-80 IU/kg
Pre-surgery dose (1h)	40-60 IU/kg	40-80 IU/kg
FVIII co-administration	Depending on FVIII levels	

Haemostatic efficacy

Due to the limited data available for Veyvondi (10 bleeds in 3 patients) a comparison for monotherapy alone has limited value. *[9]*

Therefore, the reported data for haemostatic efficacy for Veyvondi and Willfact when co-administered with FVIII has been included in Table 7 below.

Table 7 Outcome: Haemostatic effect per bleed type

[9] [10]	**Minor**	**Moderate**	**Severe**	**Unknown**
Haemostatic efficacy rated Excellent/good; % (with and without FVIII)				
Veyvondi; % (# bleeds evaluated)	100% (122)	100% (61)	100% (7)	100% (2)
Willfact; % (# bleeds evaluated)	89% (121)	NR	89 % (18)	NR
Haemostatic efficacy rated Excellent/good; % (*without* FVIII)				
Veyvondi; % (# bleeds evaluated)	NR	NR	NR	100% (10)
Willfact; % (# bleeds evaluated)	97% (40)	NR	NR	NR

NR: Not reported

The discrepancy between the reported haemostatic effect of 100% in Gill 2015 and the 97.9% in the EPAR is caused by the fact that EMA requested an additional evaluation of the investigator assessment of the haemostatic effect. The re-evaluation led to a reclassification of four investigator efficacy assessments lowering the percentage for haemostatic efficacy from 100% to 97.9%. [4]

A sub-analysis of the 130 bleeds that were evaluated <u>prospectively</u> by the investigator showed that the proportion of bleeds rated excellent/good was 97.7% (127/130; 95% CI: 93.4-99.5), emphasizing the robustness of the data. This result is consistent with the results for all evaluated bleeds (N=192). [4]

There are however several confounding factors, hereunder the proportion of patients receiving co-administration of FVIII, variations in bleeding site and others that will be addressed in the following section.

Number of infusions

As the reported data include data for both monotherapy and with co-administration, the data are not immediately comparable. Therefore, data for available sub-analyses have been presented in this section in addition to the overall data.

The overall data shows that the median number of infusions for Veyvondi was 1.0 compared to 3.0 for Willfact. *[9] [10]*

Table 8 Outcome: Number of infusions per bleed

Number of infusions/bleeds	# patients	# treated bleeds	**# infusions per bleed; median (range)**
Veyvondi *[9]*	22	192	**1.0 (1-4)**
Willfact *[10]*	26	139	**3.0 (1-46)**

For a more comprehensive evaluation of both haemostatic effect and the required number of infusions several parameters that may influence the comparison must be considered.

This would include distribution of bleeds per bleed site, percentage of patients receiving co-administration with FVIII, the infused dose as well as the previously described distribution across bleed severity.

In order to identify differences between the efficacy across different locations of bleeds, the selected data have been tabulated.

Data per bleed site for Veyvondi

Table 9 Data per bleed site for Veyvondi

[9]	**Joint**	**GI**	**Mucosal**	**Other†**	**Total**
# bleeds	59	6	106	37	192‡
# infusions per bleed; median (range)	1 (1-3)	1 (1-2)	1 (1-4)	1 (1-4)	1 (1-4)
Median (range) infusion dose VWF:RCO (IU/kg)	48.2 (23.8-139.6)	60.0 (53.6-121.1)	43.3 (23.8-184.9)	52.2 (25.2-184.9)	46.5 (23.8-184.9)
# FVIII co-admin at first dose	NR All – as per protocol	NR	NR	NR	NR
Efficacy rating (excellent/good)	100 % (57/2)	100 % (5/1)	100% (103/3)	100% (36/1)	100% (186/6)

†Other includes e.g. soft tissue, superficial bleeds

‡ The discrepancy between number of bleeds and bleeding episodes elsewhere in the material is due to the fact that some bleeding episodes concerned more than one bleeding site

Data per bleed site for Willfact

Table 10 Data per bleed site for Willfact

[10]	Musculo-skeletal	Naso-pharynx	Genital tract	GI tract	Oral cavity	Other	Total
# bleeds	44	41	29	11	13	1	139
# infusions per bleed; median (range)	4.0 (1-46)	2.0 (1-7)	9.0 (1-32)	5.0 (1-18)	1.0 (1-3)	1	3.0 (1-46)

Median (range) infusion dose VWF:RCO (IU/kg)	37.5 (24.3–57.3)	39.7 (14.2–74.5)	53.2 (35.6–68.3)	41.0 (20.8–72.8)	38.3 (24.9–71.1)	17.1	41.8 (14.2–74.5)
# bleeds w/FVIII co-admin at first dose	25	9	11	6	2	0	53 (38.1%)
Efficacy rating (% excellent/good)	77.3	95.1	92.9	90.0	100	100	89.1

Comments on the outcome Haemostatic effect

For bleeding episodes where VWF is administered alone, the limited data available for Veyvondi limits the possibilities of making a relevant comparison.

For bleeding episodes where FVIII is co-administered with Veyvondi and Willfact respectively, there is a difference in 11 percentage points (100 % vs. 89 %) in favour of Veyvondi. *[9] [10]*

As the total number of bleeding episodes evaluated is 192 for Veyvondi and 139 for Willfact this difference may be considered relatively robust. *[9] [10]*

Comment on the outcome Number of infusions

For Veyvondi the number of infusions needed to control bleeding episodes is low 1 (1-4) and consistent across anatomical bleeding site. *[9]*

For Willfact the number of infusions required to control bleeding episodes is 3.0 (1-46) which is not only higher, but also has a much wider range. The higher number of infusions needed seems relatively consistent across anatomical bleeding site. *[10]*

The median (range) infusion dose VWF:RCO is slightly higher for Veyvondi (46.5 vs 41.8 IU/kg/infusion). *[9, 10]* Though the reported data do not allow for a precise calculation the difference in median number of infusions is in favour of Veyvondi.

A confounding factor is the fact that FVIII was co-administered with Veyvondi in 95 % (182 of 192) of the bleeding episodes, but only co-administered with Willfact in 38.1 % of the bleeding episodes. *[9] [10]*

Serious thromboembolic events, anaphylaxis and inhibitor

The data and comparative analysis for the outcomes “Serious thromboembolic events”, “anaphylaxis” and “inhibitor” are separately presented in section 5.5.

5.2 What is the clinical added value of vonicog alfa compared to plasma derived vWF for the treatment of bleeding in patients with vWD and low level of Factor VIII (<30%)?

5.2.1 Presentation of relevant studies

Studies included in the response to clinical question # 2 are

Veyvondi: Gill JC, et al. Haemostatic efficacy, safety, and pharmacokinetics of a recombinant von Willebrand factor in severe von Willebrand disease. Blood. 2015 Oct 22;126(17):2038-46. *[9]*

In addition, data from the EPAR is included, when applicable. The SmPC does not contain any clinical efficacy data. The study is described in section 8.2.1.

Haemate: Gill JC, et al. Humate-P Study Group. Successful treatment of urgent bleeding in von Willebrand disease with factor VIII/VWF concentrate (Humate-P): use of the ristocetin cofactor assay (VWF:RCo) to measure potency and to guide therapy. Haemophilia. 2003 Nov;9(6):688-95.

The study is described in section 8.2.3. No EPAR is available for Haemate. The SmPC does not contain any efficacy data.

Wilnativ: Berntorp E, et al. European Wilate Study Group. Treatment and prevention of acute bleedings in von Willebrand disease--efficacy and safety of Wilate, a new generation von Willebrand factor/factor VIII concentrate. Haemophilia. 2009 Jan;15(1):122-30. *[2]*

The study is described in Table 40. No EPAR is available for Wilnativ. The SmPC does not contain any efficacy data.

Veyvondi

The phase III on demand study was published by Gill 2015. *[9]*

The phase III study on Veyvondi for on demand treatment of spontaneous bleeds was a Phase III, non-randomized, cross-over assignment, open label study in patients with type 1, 2 or 3 VWD. *[9]*

For the main part of the study (following a PK-part) the intervention for bleeding episodes (37 patients with a total of 192 bleeding episodes), was as follows: *[9]*

- An initial infusion of 40 to 60 IU/kg rVWF:RCo rVWF for minor to moderate bleeds and up to 80 IU/kg rVWF:RCo for major bleeds*[9]*

To ensure an immediate haemostatic level of FVIII:C, the initial dose of rVWF was to be administered together with rFVIII (Advate) at a ratio of 1.3:1 ± 0.2 VWF:RCo/FVIII:C and subsequently without rFVIII as long as therapeutic FVIII:C levels were maintained. *[9]*

The primary endpoint was the Percentage of Participants with Treatment Success for Treated Bleeding Episodes. *[9]*

Secondary endpoints included percentage of treated bleeding episodes with an efficacy rating of excellent or good, and the number of infusions of rVWF and rFVIII per bleeding episode. *[9]*

Further details can be found in the description of differences and similarities of studies in Table 11 below.

Haemate

Data for Haemate has been published in Gill 2003. *[11]*

This was a prospective, multicentre, open-label, nonrandomized study in patients with type 1, 2 or 3 VWD. *[11]*

A total of 33 patients were treated for 53 bleeding events. *[11]*

Dosing instructions defined a loading dose Haemate (combined pdVWF/pdVWF) of 60 to 80 IU VWF:RCo (27–36 IU FVIII:C) per kilogram (kg) body weight, followed by maintenance doses of 40–60 IU VWF:RCo (18–27 IU FVIII:C) per kg every 8–12 h for 3 days. *[11]*

The primary endpoint was haemostatic effect rated on a 3-point scale (excellent/good; fair/poor; none). Other endpoints included amongst others number of infusions required. *[11]*

Further details can be found in the description of differences and similarities of studies in Table 11.

Wilnativ

Data for Wilnativ has been published in Berntorp 2009. *[2]*

The publication reports on pooled data for 4 individual studies (not further defined) designed as prospective, open, noncontrolled, non-randomized, multicentre phase II- or phase III-trials with objective to evaluate clinical efficacy, safety and tolerability of Wilnativ in patients with inherited VWD of all disease types.

The studies also included a patient population treated with Wilnativ for prevention of bleedings in surgeries. These data are reported separately in Windyga 2011, which is further described in the response to the clinical question #4.

In the on-demand part of the studies 44 patients received a total of 1095 infusions.

A general dosing recommendation of 20–50 IU Wilnativ per kilogram bodyweight was given for the treatment or prevention of spontaneous or trauma induced haemorrhages.

Actual dose and duration of treatment depended on the individual clinical situation (e.g. severity and location of bleeding, VWD type) and were at the discretion of the treating physician.

The publication does not specifically specify pre-defined endpoints in a formalized manner. In the publication the following data is reported:

Response to treatment was rated by the investigator, or by the patients or their parents in case of home treatment, using a 4-point verbal scale (excellent, good, moderate, none).

Outcomes are as number of treated bleeds, dose per treatment day (mean/median), no of treatment days (mean/median), and percentage efficacy (excellent/good) per bleeding site.

Other outcomes reported per type of VWD include: Number (mean/median) of treatment days per bleeding episode, mean and median dose per kg per day, mean and median loading dose per kg per day, mean and median maintenance dose per kg per day

The publication does not report the number of infusions needed per treatment episode.

Further details can be found in the description of differences and similarities of studies in Table 11.

Table 11 Overview of Study Characteristics related to Clinical Question #2

On demand studies	Veyvondi *[9]*; **[4]**	Haemate *[11]*	Wilnativ *[2]*
VWD type	N=37, distributed by type (n;%): 1: 2 (5.4%) 2A: 5 (13.5%) 2N: 1 (2.7%) 3: 29 (78.4%)	N=33 distributed by type (n;%): 1: 9 (27%) 2A: 4 (12%) 2B: 4 (12%) 3: 12 (36%) Unspecified: 4 (12%)	N=44 distributed by type (n;%): 1: 8 (18%) 2A: 6 (14%) 2B: 4 (9%) 2N: 2 (5%) 3: 24 (55%)
Drug combination	rVWF and rFVIII was administered separately. The initial dose of rVWF was to be administered together with rFVIII at a ratio of 1.3:1 ± 0.2 VWF:RCo/FVIII:C	pdVWF/pdFVIII was administered in combination. The average ratio of VWF:RCo per IU FVIII was 2.5 (range 2.1–2.7) IU in the study medication batches.	pdVWF/pdFVIII was administered in combination. The average ratio of VWF:RCo to FVIII:C activity was 0.9 ± 0.14 in the study medication batches.
Dosing schedule	Bleeding episodes were to be treated with an initial infusion of 40 to 60 IU/kg VWF:RCo rVWF for minor to moderate bleeds and up to 80 IU/kg VWF:RCo for major bleeds The initial dose of rVWF was to be administered together with rFVIII at a ratio of 1.3:1 6 0.2 VWF:RCo/FVIII:C and subsequently without rFVIII as long as therapeutic FVIII:C levels were maintained. See bleed definitions below	Dosing recommendations included a loading dose of 60 to 80 IU VWF:RCo (27–36 IU FVIII:C) per kilogram (kg) body weight, followed by maintenance doses of 40–60 IU VWF:RCo (18–27 IU FVIII:C) per kg every 8–12 h for 3 days. If further treatment was necessary, infusions of 40–60 IU VWF:RCo (18–27 IU FVIII:C) per kg were given daily for up to 7 days.	A general dosing recommendation of 20–50 IU Wilate® per kilogram bodyweight was given for the treatment or prevention of spontaneous or trauma induced haemorrhages. Actual dose and duration of treatment depended on the individual clinical situation (e.g. severity and location of bleeding, VWD type) and were at the discretion of the treating physician. Study drug was administered intravenously as a bolus infusion.
Bleed classification	*Major bleeds:* severe or refractory epistaxis or menorrhagia, gastrointestinal bleeding, central nervous system trauma, hemarthrosis, or posttraumatic haemorrhage *Minor to moderate bleeds:* epistaxis, oral bleeding, or menorrhagia	*Severe bleeds:* refractory epistaxis, gastrointestinal (GI) haemorrhage, central nervous system trauma, other traumatic haemorrhage. *Moderate bleeds:* (moderate epistaxis, oral bleeding, menorrhagia), *Mild bleeds:* All other.	Not reported
Haemostatic effect	24 h after initial infusion. [Study protocol]	Patients were scheduled to complete the study 3	Timing not reported

Timing of efficacy rating		days after the last infusion. A patient's study participation was completed if, in the opinion of the investigator, he or she would not benefit	
Haemostatic effect rating	Defined as the number of treated bleeding episodes with a rating of excellent or good. Haemostatic effect was evaluated by a 4 point score defined as Excellent=1 Good=2 Moderate=3 None=4 The definition of each category was very elaborate – see Table 12 below.	Defined as: the proportion of subjects with an excellent or good overall haemostatic efficacy Haemostatic efficacy was measured by the investigator's daily rating according to a 3-point scale (excellent/good, fair/poor, or none) for each treatment event as well as an overall rating, following completion of the study treatment. The categories were defined as *Excellent/Good:* Similar haemostasis to that expected for persons without known bleeding disorders *Fair/poor:* Less haemostasis than expected for persons without known bleeding disorders *None:* Severe bleeding judged to be due to VWD despite Humate-P therapy. If the patient had daily efficacy ratings of fair/poor or none for three consecutive ratings, treatment was considered to be temporarily ineffective.	Investigators and/or patients had to rate the efficacy of the treatment using a 4-point verbal scale (excellent, good, moderate or none) No further description of the categories is reported.
# infusions	Defined as the number of infusions required to control a bleed. Control of a bleed was defined as a haemostatic efficacy rating of < 2.5 based on the numeric value of the 4-point scale (see above)	Defined as "Number of study infusions required".	Not prespecified [Not reported]

Table 12 Efficacy rating scale applied in the phase III study for Veyvondi. [9]

	Efficacy rating criterion	
Rating	**Minor and moderate bleeding events**	**Major bleeding events**
Excellent (=1)	Actual number of infusions ≤ estimated number of infusions required to treat that bleeding episode No additional VWF-containing/coagulation factor-containing product required	Actual number of infusions ≤ estimated number of infusions required to treat that bleeding episode No additional VWF-containing/coagulation factor-containing product required
Good (=2)	1-2 infusions greater than estimated required to control that bleeding episode No additional VWF-containing/coagulation factor-containing product required	<1.5× infusions greater than estimated required to control that bleeding episode No additional VWF-containing/coagulation factor-containing product required
Moderate (=3)	3 or more infusions greater than estimated used to control that bleeding event No additional VWF-containing/coagulation factor-containing product required	≥1.5× more infusions greater than estimated used to control that bleeding event No additional VWF-containing/coagulation factor-containing product required
None (=4)	Severe uncontrolled bleeding or intensity of bleeding not changed Additional VWF-containing/coagulation factor-containing product required	Severe uncontrolled bleeding or intensity of bleeding not changed Additional VWF-containing/coagulation factor-containing product required

5.2.2 Results per study

The results per study are tabulated and commented in the section on comparative analysis below

5.2.3 Comparative analyses

Haemostatic efficacy

Table 13 Outcome: Haemostatic effect for on demand treatment

On demand studies **Outcomes**	**Veyvondi** **[4]**	**Haemate** *[11]*	**Wilnativ** ***[2]***
Safety population	37	33	44
No treated patients	22	33	44
No. bleeds	192	53	1095
No. bleeds rated Excellent/good	188	52	Number not reported
Haemostatic effect **Percentage of bleeds rated Excellent/Good**	**97.9%** [95% CI 93.4-100.0]	**98%** [95% CI 88.1-100.0]	**96%**

The discrepancy between the reported haemostatic effect of 100% in Gill 2015 and the 97.9% in the EPAR is caused by the fact that EMA requested an additional evaluation of the investigator assessment of the haemostatic effect. The re-evaluation led to a reclassification of four investigator efficacy assessments lowering the percentage from 100% to 97.9%. [4]

A sub-analysis of the 130 bleeds that were evaluated *prospectively* by the investigator showed that the proportion of bleeds rated excellent/good was 97.7% (127/130; 95% CI: 93.4-99.5), emphasizing the robustness of the data. This result is consistent with the results for all evaluated bleeds (N=192). [4]

Number of infusions

Table 14 Outcome: Number of infusions per bleed for on demand treatment

	Veyvondi *[9]*; [4]	**Haemate** *[11]*	**Wilnativ** *[2]*
# Infusions, median (range)	1.0 (1-4)	2 (1-36)	NR - See narrative
Minor; median (range)	1 (1-3)	1	NR
Moderate; **median (range)**	1 (1-4)	2	NR
Major; median (range)	2 (1-3)	4	NR

For Wilnativ the number of infusions required is not reported per se. *[2]*

However, in the publication the following is stated:

> *The mean dose per treatment day was 29 IU/kg bodyweight, and a mean of 1.93 treatment days was required to stop the bleeding. In the majority of bleeding episodes that required more than one infusion, only one infusion per treatment day was administered. [2]*

In addition, the median (range) number of treatment days is reported to be 1 (1-29). *[2]*

Summary

For Veyvondi 188 of 192 (97.9%) bleed treatments were rated as either excellent (95.8%) or good (2.1%). *[4]* For Haemate 52 of 53 (98 %) evaluable bleed treatments were rated excellent/good, and for Wilnativ 96% (of 1095 bleed treatments) were rated excellent/good. *[11] [2]*

The efficacy rating for Veyvondi by bleed location showed that 98.3% ratings of excellent/good for joint bleeds, 83.4% for gastrointestinal bleeds, and 97.4% for mucosal bleeds [4], whilst the efficacy rate for Wilnativ varied from 99% in joint and oral bleeds to 82 % in gastrointestinal bleeds. *[2]* Data for Haemate by anatomical site is not reported. *[11]*

The median number of infusions with Veyvondi was 1.0 (1-4) *[9] [4],* which is lower than the 2.0 (1-36) reported for Haemate. *[11]* Data for number of infusions per bleed is not reported for Wilnativ. However, the median number of infusion days was 1 (1-29) with at least one infusion per day. *[2]*

The number of infusions required for Veyvondi is thus 1 lower than for Haemate. In addition, the range of infusions needed is apparently much narrower for Veyvondi than for Haemate [2.0 (1-36)] and Wilnativ [1 (1-29)].

Overall it seems as if the haemostatic efficacy is similar for Veyvondi and the two comparators while the required numbers of infusions with Veyvondi is lower and with a much narrower range.

Serious thromboembolic events, anaphylaxis and inhibitor

The data and comparative analysis for the outcomes “serious thromboembolic events”, “anaphylaxis” and “inhibitor” are separately presented in section 5.5.

5.3 What is the clinical added value of vonicog alfa compared to plasma derived vWF in prevention and treatment of bleeding in minor surgery in patients with vWD?

The studies (Peyvandi 2018 for Veyvondi and Borel-Derlon for Willfact) relevant for the response to this question have very different definitions of surgery types, which limits the possibilities of providing a response that only addresses minor surgery. *[10, 12]*

Therefore, a comprehensive overview of data reported in the publications will be provided according to the definitions in the publications to allow for a relevant evaluation of the respective outcomes.

Important study characteristics and differences between studies are described in the following sections.

5.3.1 Presentation of relevant studies

The following studies are included in the response to this clinical question.

Veyvondi: Peyvandi F, et al. A. Phase 3 Study of Recombinant von Willebrand Factor in Patients with Severe von Willebrand Disease Who Are Undergoing Elective Surgery. J Thromb Haemost. 2018 Oct 25. doi: 10.1111/jth.14313. [Epub ahead of print] PubMed PMID: 30362288. *[12]*

Data for the phase III study for rVWF (Veyvondi) for prevention of bleeds in elective minor and major surgery is reported in Peyvandi 2018 and the EPAR. *[4, 12]*

Important characteristics of the study is tabulated in study characteristics Table 15 below, and in Table 41 in the appendix.

Willfact: Borel-Derlon A, et al. Treatment of severe von Willebrand disease with a high-purity von Willebrand factor concentrate (Wilfactin): a prospective study of 50 patients. J Thromb Haemost. 2007 Jun;5(6):1115-24. *[10]*

No EPAR is available for Willfact. The SmPC does not contain any clinical efficacy data.

Data for Willfact for prevention of bleeds in surgery is reported in Borel-Derlon 2007, which is a publication reporting from two separate studies on 4 separate study populations: on demand, surgery, short term prophylaxis and long-term prophylaxis. *[10]*

General information on this study is described in detail in the response to clinical question #1 on p. 15 and in Table 38 in the appendix.

Differences between studies

Important study characteristics for the evaluation of the reported data are tabulated in Table 15.

There are two characteristics of high importance for the interpretation of the reported data, particularly of the outcomes measure “number of infusions”.

Definition and reporting of surgery types is very different between the studies as Peyvandi reports outcomes according to major, minor and oral surgery, whilst Borel-Derlon reports according to surgery type (e.g. orthopaedic, gynaecological etc). *[12] [10]*

The actual number of infusions needed per surgery is reported by Peyvandi including the 12-24h pre-operative infusion and by Borel-Derlon excluding the 12-24 h pre-operative infusion. *[12] [10]*

The different definitions can be seen in Table 15 below and will be addressed in detail in the narrative comparison of the outcome “number of infusions” on p. 32.

Table 15 Overview of Study Characteristics related to Clinical Question #3		
	Veyvondi ***[12]*; [4]**	**Willfact** ***[10]***
VWD type; n (%)	1: 3 (20) 2M: 1 (6.7) 2A: 2 (13.3) 3: 8 (53.3) 2B: 1 (6.7)	1: 5 (11) 2M: 1 (2) 2A: 14 (32) 2N: 1 (2) 2B: 9 (20) 3: 14 (32)
Surgery, total (N)	N = 15	N=108
Types of surgery	Described in section 5.3.3	Described in section 5.3.3
Dosing schedule	At 12–24 hours before surgery, rVWF 40–60 IU/kg VWF:RCo was given intravenously to allow endogenous FVIII:C levels to rise to ≥30 IU/dL (minor/oral surgery) or ≥60 IU/dL (major surgery), which were to be assessed within 3 hours of initiation of the surgery. If target FVIII:C levels were achieved, rVWF alone was administered within 1–2 hours before surgery to achieve predefined peak levels. Intraoperative and postoperative dosing were individualized to maintain target trough levels according to PK/PD results, as well as the intensity and duration of the haemostatic challenge. Post-surgery, patients were monitored for 14 days and target trough plasma levels of VWF:RCo and FVIII:C were maintained according to the type of surgery the patient received	For elective surgery all patients received an infusion of VWF (50 or 60 IU/kg)) One hour prior to surgery, all patients received Willfact at a dose of 50 IU/kg in the French study and 60 IU/kg in the European study according to local clinical practices. Intraoperative and postoperative dosing were individualized to maintain target trough levels according to PK/PD results, as well as the intensity and duration of the haemostatic challenge.
Loading dose VWF 12-24 h before	All patients were to receive a loading dose of rVWF 40–60 IU/kg VWF:RCo 12- 24 hours pre-operatively	Patients undergoing elective surgery with baseline FVIII levels below 60 IU/dL received a VWF concentrate infusion (50 or 60 IU/kg).
Co administration of FVIII 1-2 h pre-operatively	If target FVIII:C levels were not achieved, rVWF was co-administered with rFVIII (ADVATE®, Antihemophilic Factor [Recombinant]) within 1–2 hours before surgery to meet recommended peak levels.	Co-administration of FVIII preoperatively in elective patients was not reported to be predefined.
Surgery classification	Three severity classifications *Major* surgeries were defined as those that carried a significant risk of large volume blood loss or blood loss into a confined anatomical space, such as major orthopaedic-, abdominal-, gynaecologic-, head and neck-, intracranial-, cardiovascular- or spinal-surgery, and extraction of impacted third molars. *Minor* surgical procedures included placement of intravenous access devices, removal of small skin lesions, arthroscopy, gastroscopy, colonoscopy, or conization. *Oral* surgeries included extractions of <3 non-molar teeth with no bony involvement.	Surgery type is not prespecified in the methodology section except for this wording: "Invasive procedures (such as gastrointestinal endoscopies, hysteroscopies, coronary angiography, i.m. injections, intra-articular infiltrations and dental scaling) were considered minor procedures." Data is reported with the following categorization: The 65 surgical procedures were orthopaedic (n = 14), gynaecological/obstetrical (n = 10), general (n = 7), dental (n = 14) and gastrointestinal (n=12), including transjugular liver needle biopsies (n = 20). In addition, data for 43 invasive procedures are reported.
Timing of efficacy	The primary outcome measure was the overall haemostatic efficacy of rVWF	For surgical procedures, the efficacy was reported by the haematologist at

Table 15 Overview of Study Characteristics related to Clinical Question #3		
	Veyvondi ***[12]*; [4]**	**Willfact** ***[10]***
rating reported	with or without Advate 24 hours after last perioperative infusion of Veyvondi or at Completion Visit Day 14 (whichever occurred first)	the time of hospital discharge.
Haemostatic effect rating	The rating scale used was the haemostatic efficacy rating scale ("excellent", "good", "moderate", or "none") using a 4-point scale. *Excellent:* Haemostasis achieved with rVWF with or without rFVIII was as good or better than that expected for the type of surgical procedure performed in a haemostatically normal subject *Good:* Haemostasis achieved with rVWF with or without rFVIII was probably as good as that expected for the type of surgical procedure performed in a haemostatically normal subject *Moderate:* Haemostasis with rVWF with or without rFVIII was clearly less than optimal for the type of procedure performed but was maintained without the need to change the rVWF concentrate. *None:* Patient experienced uncontrolled bleeding that was the result of inadequate therapeutic response despite proper dosing, necessitating a change of rVWF concentrate	Haemostasis was evaluated using a 4-point scale: *Excellent:* bleeding during surgery and the postoperative period similar to that expected for normal individuals; *Good:* slightly excessive bleeding; *Moderate:* moderately excessive bleeding; *None:* severe bleeding
Number of infusions reported	Reports median number of infusions including the 12-24-hour pre-operative infusions	Reports only peri- and postoperative infusions.

5.3.2 Results per study

The results per study are tabulated in the comparison section below.

5.3.3 Comparative analyses

Due to the differences and the inconsistency of reporting between the two studies, a precise comparison between the study data is complicated.

The major reason for potential bias is the difference between surgery types, where the Peyvandi study includes a majority (66%) of major surgeries as compared to the lower number (~33%) of major surgeries in the Borel-Derlon study. *[12] [10]*

In the Veyvondi study all patients by protocol received a loading dose of Veyvondi 12-24 hours before the surgery. *[12]* In the Willfact study 49.5 % (47 of 95) received a loading dose. For the remainder of patients, the preoperative level of FVIII was considered sufficiently high to ensure haemostasis. *[10]*

Co-administration of FVIII occurred by mistake in 20% (3 of 15) of the patients in the Veyvondi study*[12]*, while data for Willfact includes for 12 % (13 of 108) patients who received FVIII pre-operatively. *[10]* However infusion of FVIII to the patients in the Veyvondi study was a mistake by the study staff as all three patients had levels of FVIII IU/dL before the infusion, and thus should not have received FVIII. *[12]*

Haemostatic efficacy

Both studies report a haemostatic efficacy of 100 % across the subtypes of surgeries and bleeds. *[10] [12]*

Table 16 Outcome: Haemostatic effect in surgery

Surgery outcomes	Veyvondi *[12]*; [4]	Willfact *[10]*
Safety population	15	50
No patients with surgery	15	45
No surgeries	15	108
Haemostatic effect (%) (excellent or good)	**100 %**	**100%**
No of effective treatment/total surgeries	15/15	108/108

The high success rate can partly be attributed to the fact that the evaluation of haemostatic efficacy was performed at the day of discharge of patients in the Borel-Derlon study *[10]*, whilst the evaluation in the Peyvandi study was performed 24 hours after the last perioperative infusion of Veyvondi or at Completion Visit Day 14 (whichever occurred first). *[12]*

The data for haemostatic effect should also be evaluated in the light of the skewed distribution of major and minor surgeries between the two studies as explained in detail in the section below on number of infusions needed.

Number of infusions

The differences in the type of surgery plays an important role in the evaluation of the number of infusions needed to obtain haemostatic effect.

Distinction between major and minor surgery

As described above a large number of surgeries reported in the Borel-Derlon study were minor or invasive procedures with limited risk of major bleeds, while the Peyvandi study reported on two thirds major surgeries and one third minor surgeries. *[10], [12]*

The narrative will therefore address not only the overall number of infusions needed but also provide a narrative comparison of the number of infusions needed for major and minor bleeds separately.

While comparison of the overall numbers of infusions needed apparently indicate that more infusions are needed for Veyvondi, the more detailed comparison clearly highlight the influence of the substantial number of minor and invasive surgeries included in the data for Willfact.

The comparison divided by major and minor surgeries indicate the number of infusions needed for Veyvondi for major surgeries is somewhat lower than for Willfact, whilst the number of infusions needed for minor procedures seems comparable between the two products.

Reporting differences

An additional confounder is the fact that number of infusions reported for Veyvondi includes the preoperative given 12-24 hours pre-operatively, while the number for infusions for Willfact is reported not including any 12-24 hours pre-operative infusion. *[10, 12]* This creates a difference in the numbers of one infusion for all parameters in disfavour of Veyvondi.

Table 17 Outcome: Number of infusions per surgery

Surgery outcomes	**Veyvondi** *[12]*; [4]	**Willfact** *[10]*
Safety population	**15**	**50**
No patients with surgery	15	45
No surgeries	15	108
Infusions	Data reported for all infusions preop 12-24h, pre-op 1-2 h, intraoperative and postoperative	Only for perioperative and postoperative doses, but not for the doses 12-24 h before surgery
Infusions, total (median)	**6 (2-15)**	**3 (1-65)**
Infusions, total median excl. 24 pre-surgery infusions	5 (1-14)	3 (1-65)
By procedure type **Type (number of procedures)**		
Oral (n=1)	5	NR
Minor (n=4)	3 (2-4)	NR
Major (n=10)	7.5 (4-15)	NR
Orthopedic (n=14)	NR	22 (3-65)
Gyn/obs (n=10)	NR	15.0 (1-29)
General (n=7)	NR	9.0 (1-18)
Dental (n=14)	NR	2.5 (3-21)
Gastrointestinal (n=12)	NR	5.5 (3-21)
Needle liver biopsy (n=8)	NR	4.0 (3-8)
Invasive procedures (n=8)	NR	2.0 (1-4)

Major surgeries – infusions needed

Procedures at high risk of bleeding – and thus major surgery - can considered to be the orthopaedic, gynaecological/obstetric and gastrointestinal surgeries.

The median number of infusions needed to compare in major surgeries would then be 7.5 (4-15) infusions for Veyvondi with 22 (3-65), 15 (1-29) and 5.5 (3-21) infusions for Willfact in similar types of major surgeries. *[10, 12]*

This comparison highlights two important points; a) the median number of infusions required in major surgery seems lower with Veyvondi than with Willfact and b) the range of infusions needed with Veyvondi is much narrower than for Willfact.

Minor surgeries – infusions needed

Procedures at lower risk of bleeds (minor surgeries) would include the types not included in the comparison above.

The median number of infusions needed to compare in minor surgeries would then be 3-5 infusions (minor/oral surgery) with a range of 2-5 for Veyvondi and in the between 2-9 (general, dental, biopsy, invasive procedures) with a range of 1.21 infusions for Willfact in similar types of minor surgeries. *[12] [10]*

This comparison seems to indicate that the number of infusions needed in minor surgery is comparable between Veyvondi and Willfact, but with a narrower range for infusions needed with Veyvondi.

Summary of need for number of infusions

The comparison highlights the need for separating the data into major and minor surgery respectively.

In major surgery the comparison indicates that the number of infusions needed for Veyvondi is lower with a narrower range than for Willfact. *[12] [10]*

In minor surgery the comparison indicates that the number of infusions needed is comparable, but with a narrower range for Veyvondi. *[12] [10]*

The narrower range for infusions with Veyvondi may lead to a higher predictability for the need for infusions as well as shorter treatment time.

Serious thromboembolic events, anaphylaxis and inhibitor

The data and comparative analysis for the outcomes “serious thromboembolic events”, “anaphylaxis” and “inhibitor” are separately presented in section 5.5.

5.4 What is the clinical added value of vonicog alfa compared to plasma derived vWF in prevention and treatment of bleeding in major surgery in patients with vWD?

5.4.1 Presentation of relevant studies

Willfact

Data for Willfact in major surgery is presented in section 5.3 above in connection with the narrative on clinical question # 3.

Veyvondi

Data for Veyvondi for prevention of bleeds in surgery is reported in the following study:

Peyvandi F, et al. Phase 3 Study of Recombinant von Willebrand Factor in Patients with Severe von Willebrand Disease Who Are Undergoing Elective Surgery. J Thromb Haemost. 2018 Oct 25. doi: 10.1111/jth.14313. [Epub ahead of print] PubMed PMID: 30362288. *[12]*

Peyvandi 2018 was a phase III, prospective, open-label, uncontrolled, nonrandomized study with the objective of evaluating the haemostatic efficacy/safety profile of rVWF, with/without recombinant factor VIII (rFVIII), in patients with severe VWD undergoing surgery. *[12]*

Data from the surgery study is also available in the EPAR. [4]

Important characteristics of the study are tabulated in study characteristics Table 18 below, and in Table 41 in the appendix.

Haemate

Data for Haemate for prevention of bleeds in surgery is reported in the following two studies:

Gill JC, Shapiro A, Valentino LA, Bernstein J, Friedman C, Nichols WL, Manco-Johnson M. von Willebrand factor/factor VIII concentrate (Humate-P) for management of elective surgery in adults and children with von Willebrand disease. Haemophilia. 2011 Nov;17(6):895-905.

Lethagen S, et al. HAEMATE P Surgical Study Group. von Willebrand factor/factor VIII concentrate (Haemate P) dosing based on pharmacokinetics: a prospective multicentre trial in elective surgery. J Thromb Haemost. 2007 Jul;5(7):1420-30. Epub 2007 Apr 16. PubMed PMID: 17439628. *[15]*

Gill 2007 was a prospective, open-label, multinational phase IV study with the objective of evaluating the safety, efficacy and optimal dosing of a VWF/FVIII concentrate (Humate-P) in subjects with VWD undergoing elective surgery.

Lethagen 2007 was a prospective multicentre open-label cohort study with the objective of determining the feasibility of dosing Haemate P VWF/factor VIII (FVIII) concentrate based on pharmacokinetics (PK) in the management of surgical subjects with VWD. *[15]*

Important characteristics of these studies are tabulated in study characteristics Table 15, and in Table 41 in the appendix.

Wilnativ

Data for Wilnativ for prevention of bleeds in surgery is reported in the following two studies:

Srivastava A, et al; Wonders Study Investigators. Efficacy and safety of a VWF/FVIII concentrate (Wilate®) in inherited von Willebrand disease patients undergoing surgical procedures. Haemophilia. 2017 Mar;23(2):264-272. *[13]*

Windyga J, et al.; European Wilate® Study Group. Efficacy and safety of a new generation von Willebrand factor/factor VIII concentrate (Wilate®) in the management of perioperative haemostasis in von Willebrand disease patients undergoing surgery. Thromb Haemost. 2011 Jun;105(6):1072-9. *[3]*

Srivastava 2017 was a prospective, open-label, multinational, multi-centre phase III clinical study with the objective of evaluating the haemostatic efficacy and safety of Wilnativ in maintaining intra- and postoperative haemostasis in surgical procedures. *[13]*

Windyga 2011 reports on a clinical study program consisting of 4 individual studies designed with objective to evaluate clinical efficacy, safety and tolerability of Wilnativ in patients with inherited VWD of all disease types, in the prevention and treatment of bleeding episodes as well as in prevention of bleedings in surgeries. In this section, only data for prevention of bleeding in surgery is considered. *[3]* Data from these 4 studies are also used in the section on on-demand treatment, reported by Berntorp 2009. *[2]*

Differences between studies

Important study characteristics for the evaluation of the reported data are tabulated in Table 15.

The main difference between the studies is the extent of co-administration of FVIII.

As both Haemate and Wilnativ are combination products containing both pdVWF and pdFVIII, all patients in these studies had FVIII co-administered for all infusions. *[13]*

In contrast Veyvondi is administered as rVWF monotherapy unless pre-operative values of FVIII necessitates co-administration of FVIII, thereby eliminating any unnecessary administration of FVIII. *[12]*

In the study all patients had a FVIII:C-level above ≥60 IU/dL after having received the initial dose of Veyvondi, but by a mistake by the study staff 3 of 15 patients had FVIII infusions unnecessarily. *[12]*

While co-administration of FVIII with Haemate and Wilnativ may eliminate the need for early (24h) pre-operative infusions of VWF, the administration of FVIII may result in supra-physiological levels of FVIII increasing the risk of thromboembolic complications. [21]

In order to ensure the presence of a sufficient pre-operative level of FVIII, an infusion with rVWF was administered to all patients in the Veyvondi study, while no such infusion was necessary in the studies with Haemate and Wilnativ due to the unavoidable co-administration of FVIII in these combination products. *[12] [13] [[14] [3, 15]*

Overview of differences and similarities between the surgery studies

Table 18 Overview of Study Characteristics related to Clinical Question #4

	Veyvondi *[12]*; **[4]**	**Haemate** *[14]*	**Haemate** *[15]*	**Wilnativ** *[13]*	**Wilnativ** *[3]*
Patient population	Patients aged ≥18 years with severe VWD of all types who had planned elective surgery were eligible for the study.	Adults and children with of VWD with a family scheduled for elective surgery and expected to require at least two consecutive days of perioperative treatment with a VWF/FVIII concentrate,	Males and females > 5 years old with hereditary VWD were eligible. Enrolment was restricted to subjects scheduled for elective surgery requiring a hospital stay of at least 24 h.	6 years or older; diagnosed with congenital VWD (von Willebrand Disease); require therapy with a VWF product to treat any major surgical procedure	Patients with inherited VWD of any type. Three studies enrolled patients >12 years of age and one study included patients aged ≤12 years.
Age; median (range) unless otherwise stated	40 (20-70)	21 (1-75)	Per age group 5–16 yrs: 2; 17–64 yrs: 22; ≥65 yrs: 5	36.0 (12-74)	50 (6-77)
VWD type; **n (%)**	1: 3 (20) 2A: 2 (13.3) 2B: 1 (6.7) 2M: 1 (6.7) 3: 8 (53.3)	1: 17 (40.5) 2A: 2 (4.8) 2B: 4 (9.5) 2M: 6 (14.3) 3: 13 (31.0)	1: 10 (34.5) 2A: 10 (34.5) 2M: 1 (3) 3: 8 (28)	Type 1: 7 (23.3) Type 2: 2 (6.7) Type 3: 21 (70.0)	1: 4 (12.5) 2: 9 (28.1) 3: 19 (59.4)
Dosing schedule	At 12–24 hours before surgery, rVWF 40–60 IU/kg VWF:RCo was given intravenously to allow endogenous FVIII:C levels to rise to ≥30 IU/dL (minor/oral surgery) or ≥60 IU/dL (major surgery), which were to be assessed within 3 hours of initiation of the surgery. If target FVIII:C levels were achieved, rVWF alone was administered within 1–2 hours before surgery to achieve the peak levels described defined in the	Based on PK evaluation following a dose of Humate-P 60 IU/kg 15 subjects, the in vivo recovery (IVR) value obtained in the PK study was used to determine the 'full dose' of VWF/FVIII expected to achieve target VWF:RCo and FVIII plasma levels of at least 100 IU dL)1. The actual surgical loading dose was then calculated as 1.5 times the 'full dose' to compensate for the potential for increased factor consumption during	Plasma derived FVIII/vWF (Haemate-P) was administered to a total of 28 patients. General recommendations for target levels of VWF:RCo and FVIII:C to be attained after the loading dose and therapeutic/maintenance infusions were provided to the investigators. The loading dose required to achieve a target VWF:RCo concentration increment (ΔVWF:RCo) in IU/dL was calculated based on	Plasma derived FVIII/vWF was administered to a total of 30 patients. All patients received 60 IU/kg of Wilate® for the in vivo recovery (IVR) investigation at study start to calculate the recommended dosing for surgeries; additionally, the following guidelines were given: *Major surgery* A loading dose of 40–60 VWF:RCo IU/kg1 within 3 h of start of procedure was	Dosing was calculated according to the investigator's discretion in one study and according to the following recommendations in three studies: major surgery; dosing once daily or every other day with the objective to maintain a FVIII:C level of >50 IU/dl until healing is complete; minor surgery: dosing once daily or every other day with the objective to maintain a FVIII:C level of >30 IU/ dl until healing is

	protocol. Intraoperative and postoperative dosing were individualized to maintain target trough levels according to PK/PD results, as well as the intensity and duration of the haemostatic challenge. Post-surgery, patients were monitored for 14 days and target trough plasma levels of VWF:RCo and FVIII:C were maintained according to the type of surgery the patient received	surgery and postoperatively as seen in haemophilia [24]. In the absence of evidence of increased factor consumption, a protocol amendment was subsequently adopted such that surgical loading doses were designed to achieve plasma vWF:RCo levels of 50–60 IU dL)1 for oral/minor surgeries, and 80–100 IU dL)1 for major surgeries. Doses were rounded to include the entire final vial of VWF/FVIII concentrate with a deviation from calculated dose of ≤10%. The initial maintenance infusion dose was based on individual terminal half-life value for VWF:RCo: half the 'full dose' of VWF/FVIII concentrate was given every 12 h for those with a VWF:RCo half-life >10 h and every 8 h for those with a half-life of 6–10 h.	individual subject PK results as dose = ΔVWF:RCo-bw/$IVR_{observed}$. The initial loading infusion was administered 1–2 h before the start of the elective procedure. Postoperative doses were given at the discretion of the investigator. It was recommended that required postoperative infusions be administered at least once every 24 h	given to achieve peak plasma VWF:RCo level of 100%. A maintenance dose of 20–40 VWF:RCo IU/kg or half of the loading dose was given every 12–24 h. Trough levels of VWF:RCo were to be maintained at >50% for at least 6 days. At least two maintenance doses were to be administered within the first 24 h after the start of surgery. *Minor surgery.* A loading dose of 30–60 VWF:RCo IU/kg within 3 h of start of procedure was given to achieve peak plasma VWF: RCo level of 50%. A maintenance dose of 20–40 VWF: RCo IU kg/1 or half of the loading dose was given every 12–24 h.	complete; dental surgery: single dose with the objective to maintain a FVIII:C level of >30 IU/dl for up to six hours.
Loading dose VWF 12-24 h before	Yes – all patients were to receive a loading dose of rVWF 40–60 IU/kg VWF:RCo 12- 24 hours pre-operatively	n/a	n/a	n/a	n/a
Co administration of FVIII 1-2 h pre-operatively	If target FVIII:C levels were not achieved, rVWF was administered with rFVIII (ADVATE®, Antihemophilic Factor [Recombinant]) within 1–2 hours before surgery to meet recommended peak levels.	n/a	n/a	n/a	n/a

Surgery **Loading dose 1-2h pre-operative**	rVWF alone was administered	PdVWF/FVIII was administered	pdVWF/FVIII was administered	pdVWF/FVIII was administered	pdVWF/FVIII was administered
Surgery classification	Three severity classifications *Oral* surgeries included extractions of <3 non-molar teeth with no bony involvement. *Minor* surgical procedures included placement of intravenous access devices, removal of small skin lesions, arthroscopy, gastroscopy, colonoscopy, or conization. *Major* surgeries were defined as those that carried a significant risk of large volume blood loss or blood loss into a confined anatomical space, such as major orthopaedic-, abdominal-, gynaecologic-, head and neck-, intracranial-, cardiovascular- or spinal-surgery, and extraction of impacted third molars.	Three severity classifications *Oral:* (simple tooth extraction); *Minor:* simple operations not considered a risk to life that could be performed in an outpatient setting with or without sedation); or *Major:* operation involving considerable hazard or risk to life or limb, frequently involving general anaesthesia, multiple (>2) tooth extractions and removal of >1 impacted wisdom tooth	Surgery type is not prespecified in the methodology section. Data is reported with the following categorization: *Minor:* Hand surgery, Arthroscopic synovectomy, meniscus resection, extraction of less than four teeth, haemorrhoid resection, circumcision *Major:* Arthroscopic removal of osteosynthesis material, total knee replacement, hysterectomy, Hysterectomy-adnexectomy, adnexectomy, extraction of greater than or equal to four teeth, laparoscopic cholecystectomy, removal of basalioma, mandibular osteotomy	Surgery type is not prespecified in the methodology section. Data is reported with the following categorization *Minor:* dental, orthopaedic, ophthalmologic and ear, nose and throat surgeries. *Major:* orthopaedic, obstetric/gynaecological, gastrointestinal, dental and ear, nose and throat surgeries.	*Minor:* All surgery not included in the definition of major. *Major surgery:* requirement for general or spinal anaesthesia, surgical opening into the great body cavities, procedures where severe haemorrhage was possible, orthopaedic interventions involving joints (ankle, knee, hip, wrist, elbow, shoulder), 3rd molar extraction, surgeries or conditions in which the subject's life was considered at risk.

Definitions of efficacy outcomes reporting in the surgery studies

	Veyvondi ***[12]*; [4]**	**Haemate** ***[14]***	**Haemate** ***[15]***	**Wilnativ** ***[13]***	**Wilnativ** ***[3]***
Haemostatic effect **Timing of efficacy rating**	The primary outcome measure was the overall haemostatic efficacy of rVWF with or without rFVIII (Advate) 24 hours after last perioperative infusion of IP or at Completion Visit Day 14 (whichever occurred first)	Haemostatic efficacy was rated directly after the end of the surgical procedure, 24 h after the last VWF/FVIII concentrate infusion (defined as the primary endpoint), and 14 days after surgery.	A pre-defined timing of haemostasis endpoints is not reported. However, in the publication results are presented for Day 0 (surgery), Day 1 after surgery and Day 14 after surgery.	Efficacy of Wilate® was assessed by the surgeon at the end of each surgical procedure and postoperatively by the investigator based on postoperative bleeding and oozing, covering the time period from the end of the procedure up to 24 h following the last Wilate® infusion.	The assessment of efficacy was made after complete recovery from the surgical procedure (at the Investigator's discretion).
Haemostatic efficacy rating	The rating scale used was the haemostatic efficacy rating scale ("excellent", "good", "moderate", or "none") using a 4-point scale *Excellent:* Hemostasis achieved with rVWF with or without rFVIII was as good or better than that expected for the type of surgical procedure performed in a haemostatically normal subject *Good:* Hemostasis achieved with rVWF with or without rFVIII was probably as good as that expected for the type of surgical procedure performed in a haemostatically normal subject *Moderate:* Hemostasis with rVWF with or without rFVIII was clearly less than optimal for the type of procedure performed but was maintained without the need to change the rVWF concentrate	**Effective** was defined as "Excellent" and "Good" and **Ineffective** for Moderate/poor or None using a 4-point scale: *Excellent*: Haemostasis not significantly different from normal; *Good*: Mildly abnormal haemostasis, such as mild oozing; *Moderate/Poor*: Moderately abnormal haemostasis in terms of quantity or quality; *None*: Severely abnormal haemostasis, such as severe, uncontrollable haemorrhage).	Haemostatic efficacy was rated daily by the treating physician on a four-point scale of excellent, good, moderate, or none. *Excellent*: Clinical haemostasis was within normal limits *Good*: Slight oozing *Moderate*: Moderate, controllable bleeding *None*: Haemorrhage that was difficult to control	Efficacy of Wilate® was assessed by the surgeon at the end of each surgical procedure (last suture) using a stringent and objective 4-point efficacy scale (excellent, good, moderate or none) based on blood loss and transfusion requirements during surgery, and postoperatively by the investigator based on postoperative bleeding and oozing, covering the time period from the end of the procedure up to 24 h following the last Wilate® infusion. The precise definitions of Excellent, Good, Moderate and None are not reported.	Haemostatic efficacy was rated by the investigator using a four-point scale (excellent, good, moderate or none). Three studies used the following definitions: *Excellent:* haemostasis achieved, cessation of bleeding episode. *Good:* slight oozing and adequate control of bleeding episode; did not require additional product; *Moderate:* moderate bleeding, or control of bleeding required additional product; *None*: severe uncontrolled bleeding or intensity of bleeding not changed (in case of non-severe bleeding episodes); *In one study*, efficacy was rated excellent, good, moderate or none according to the Investigator's discretion (two

	None: Patient experienced uncontrolled bleeding that was the result of inadequate therapeutic response despite proper dosing, necessitating a change of rVWF concentrate				surgeries were performed in this study, one major and one minor).
# infusions	# of infusions were not predefined as an outcome but has been reported as median number of infusions per day both overall and split by oral, minor and major surgery.	# of infusions were not predefined as an outcome, but has been reported for minor and major surgery, respectively, but not the overall number.	# of infusions were not predefined as an outcome, but has been reported for minor and major surgery, respectively, but not the overall number.	# of infusions were not predefined as an outcome, and is not reported	# of infusions were not predefined as an outcome but has been reported as median number of infusions per day both overall and split by minor and major surgery.

5.4.2 Results per study

The definitions of outcomes measures and results per study are tabulated in the comparison section below.

Data for Willfact in major surgery is presented in section 5.3 above in connection with the narrative on clinical question # 3.

5.4.3 Comparative analyses

The studies varied with regard to types of surgery as the proportion of major surgery ranged from 71.4 % to as low as 47.4 %. In addition, the reporting differed regarding categorization into oral, minor and major. An overview is provided Table 19 below.

Demographics of surgery subtypes

Table 19 Surgery subtype demographics

	Veyvondi ***[12]*; [4]**	**Haemate** ***[14]***	**Haemate** ***[15]***	**Wilnativ** ***[13]***	**Wilnativ** ***[3]***
Safety population	**15**	**42**	**29**	**39**	**32**
No. patients with surgery	15	35	27	28	32
No. surgeries	15	35	27	30	57
Type of surgeries (no.)					
Oral	1 (6.7%)	3 (8.6)	NR†	NR†	NR†
Minor	4 (26.7%)	7 (20.0%)	11 (40.7%)	9 (30.0%)	30 (52.6%)
Major	10 (66.6%)	25 (71.4%)	16 (59.3%)	21 (70.0%)	27 (47.4%)
† Included in minor/major depending on severity					

Haemostatic efficacy

Data for haemostatic efficacy is tabulated below.

The percentages reaching a rating of excellent/good ranges from 100% for Veyvondi to 94.3% for Wilnativ.

Table 20 Outcome: Haemostatic effect in surgery

Outcomes: Haemostatic effect	**Veyvondi** ***[12]*; [4]**	**Haemate** ***[14]***	**Haemate** ***[15]***	**Wilnativ** ***[13]***	**Wilnativ** ***[3]***
Safety population	15	42	29	39	32
No. patients with surgery	15	35	27	28	32
No. surgeries	15	35	27	30	57
Haemostatic effect Percentage surgeries w/ Excellent/Good rating	**100 %**	**91.4%** (Immediate post op) **94,3%** (Beyond post op)	**96.3 %** (Day of surgery) **100 %** (post-op day 1)	**96.7 %**	**96%**
No. of successful treatments/no. surgeries	15/15	32/35 33/35	26/27† 27/27†	29/30	51/53
†calculated by Shire from the n and the percentage					

Data for haemostatic effect in prevention of surgery seems comparable.

Number of infusions

The number of infusions needed are tabulated below.

Table 21 Outcome: Number of infusions per surgery

Surgery outcomes Number of infusions	**Veyvondi** ***[12]*; [4]**	**Haemate** ***[14]***	**Haemate** ***[15]***	**Wilnativ** ***[13]***	**Wilnativ** ***[3]***
Explanatory comments	Data reported for *all infusions* preop 12-24h, pre-op 1-2 h, intraoperative and postoperative†		All patients received one loading dose. The data below show the reported data for number of infusions *excluding the mandatory* loading dose.	Not reported	All patients received one loading dose
No. total infusions, median (range)	6 (2-15)	Not reported	Not reported	Not reported	2 (1-29)
No. total infusions by surgery type					
Oral	5 (1 patient only)	2 (2-4)	Not reported	Not reported	Not reported
Minor	3 (2-4) median, (range)	9.5 (5-15) median, (range)	3 (2-7 IQR) *4 (including the loading dose)*	Not reported	1.0 (1-3) median, (range)
Major	7,5 (4-15) median, (range)	10 (4-55) median, (range)	7 (4.5-11.5 IQR) *8 (incl. loading dose)*	Not reported	25 (10-79) median, (range)

† all patients had a FVIII:C-level above ≥60 IU/dL after having received the initial dose of Veyvondi, but by a mistake by the study staff 3 of 15 patients had FVIII infusions unnecessarily

Major surgeries – infusions needed

The median number of infusions needed to compare in major surgeries would then be 7.5 (4-15) infusions for Veyvondi compared to 10 (4-55) and 7 (4.5-11.5 IQR) for Haemate and with 25 (10-79) for Wilnativ in similar types of major surgeries. *[12]*

This comparison highlights two important points; a) the median number of infusions required in major surgery seems on par or lower with Veyvondi than with the comparators and b) the range of infusions needed with Veyvondi is narrower than for the comparators.

Minor surgeries – infusions needed

The median number of infusions needed to compare in minor surgeries would then be 3-5 infusions (minor/oral surgery) with a range of 2-5 for Veyvondi and between 1-9.5 with a range of 1-15 infusions for the comparators in minor surgeries. *[12]*

This comparison seems to indicate that the number of infusions needed in minor surgery is at least comparable between Veyvondi and the comparators, but with a narrower range for infusions needed with Veyvondi.

Summary of need for number of infusions

The comparison highlights the need for separating the data into major and minor surgery respectively.

In major surgery the comparison indicates that the number of infusions needed for Veyvondi is at least on par or lower with a narrower range than for the comparators.

In minor surgery the comparison indicate that the number of infusions needed is comparable, but with a narrower range for Veyvondi.

The narrower range for infusions with Veyvondi may lead to a higher predictability for the need for infusions as well as shorter treatment time.

Serious thromboembolic events, anaphylaxis and inhibitor

The data and comparative analysis for the outcomes “serious thromboembolic events”, “anaphylaxis” and “inhibitor” are separately presented in section 5.5.

5.5 Data and comparative analysis for the outcomes serious thromboembolic events, anaphylaxis and inhibitor

General comment

Please observe:

- the data reported for the 50 patients for Willfact in the section on on-demand and surgery refers to the same patient population as these patients overlapped. *[10]*
- The data reported for Wilnativ in the on-demand part of 4 studies [Berntorp 2009] may be overlapping with data reported from the surgery part of the same studies *[3]* The split in number of patients below does however reflect the number of patients in each of the reported populations.

Anaphylaxis

Data on development of anaphylaxis was reported inconsistently or not at all. The available data are presented in the tables below.

On demand indication

For the on-demand indication the incidence of development of anaphylaxis was only reported for Veyvondi. *[9]* [4] The remaining studies did not report this outcome.

Table 22 Outcome: Anaphylaxis in on demand treatment

On demand studies **Outcomes**	**Veyvondi**	**Haemate**	**Wilnativ**	**Willfact**
Reference	*[9]*; [4]	*[11]*	*[2]*	*[10]*
Safety population	37	33	44	50
Anaphylaxis	0 (none)	Not reported.	Not reported	Not reported

Surgery indication

For the surgery indication the incidence of development of anaphylaxis was only reported for Veyvondi *[9]* EPAR]. The remaining studies did not report this outcome.

Table 23 Outcome: Anaphylaxis in surgery

Surgery studies **Outcomes**	**Veyvondi**	**Haemate**	**Haemate**	**Wilnativ**	**Wilnativ**	**Willfact**
Reference	*[12]*; [4]	*[14]*	*[15]*	*[13]*	*[3]*	*[10]*
Safety population	N = 15	N= 42	N=29	N=28	N=32	50
Anaphylaxis	0 (none)	Not reported	Not reported	Not reported	Not reported	Not reported‡

Summary

The scarce and inconsistent reporting does not allow for a proper comparison of the incidence of anaphylaxis across the products. In addition, the normal incidence of anaphylaxis is low why a real difference would not be expected to show up in studies with this limited number of patients.

A review of the summaries of product characteristics for the intervention and the comparators did not identify any significant difference in wording regarding incidence and prevalence of anaphylaxis of importance as these texts are all based on the standard wordings provided in the CHMP Guideline for Core SPC for Human Derived von Willebrand Factor (CPMP/BPWG/278/02). [1, 5-8]

In this context it should be noted that Veyvondi – in contrast to the plasma derived comparators – is a *recombinant* von Willebrand Factor, which may impact the incidence of anaphylaxis.[1]

Inhibitor

Data on development of inhibitor was reported inconsistently or not at all. The available data are presented in the tables below.

Not all publications defined if a formal laboratory test had been performed or if the presence of inhibitors was evaluated by clinical signs.

On demand indication

The reported information is provided in the table below.

Table 24 Outcome: Inhibitor development in on demand treatment

On demand studies	**Veyvondi**	**Haemate**	**Wilnativ**	**Willfact**
Reference	*[9]*; [4]	*[11]*	*[2]*	Borel-Derlon 2007, *[10]*
Inhibitor FVIII	0 (none)	Not reported	Not reported	0 (none)
Comment			*"No clinical signs of antibodies were seen"*	*only type 3 VWD patients (n=18) screened*

Surgery indication

The reported information is provided in the table below.

Table 25 Outcome: Anaphylaxis in surgery

	Veyvondi	**Haemate**	**Haemate**	**Wilnativ**	**Wilnativ**	**Willfact**
Reference	*[12]*; [4]	*[14]*	*[15]*	*[13]*	*[3]*	Borel-Derlon 2007, *[10]*
Safety population)	N = 15	N= 42	N=29	N=28	N=32	50
Inhibitor vs VWF	0 (none)	Not reported	0 (none)	0 (none)	0 (none)	0 (none)
Inhibitor vs FVII	0 (none)	Not reported	0 (none)	0 (none)	0 (none)	0 (none)
Comment						*only type 3 VWD patients (n=18) screened*

Summary

The inconsistent reporting does not allow for a proper comparison of the incidence of development of inhibitors across the products. However, across all publications, there is no instances of development of inhibitor reported.

A review of the summaries of product characteristics for the intervention and the comparators did not identify any significant difference in wording regarding incidence and prevalence of inhibitors of importance as these texts are all based on the standard wordings provided in the CHMP Guideline for Core SPC for Human Derived von Willebrand Factor (CPMP/BPWG/278/02). [1, 5-8]

Serious thromboembolic events

The reported information is provided in the table below.

Table 26 Outcome: Serious venous thromboembolic events in on demand treatment

On demand studies	Veyvondi	Haemate	Wilnativ	Willfact
Outcomes				
Reference	*[9]*; [4]	*[11]*	*[2]*	*[10]*
Safety population	37	33	44	50
Serious thromboembolic events	**0 (none)**	**0 (none)**	**0 (none)**	**0 (none)**

Surgery indication

The reported information is provided in the table below.

Table 27 Outcome: Serious venous thromboembolic events in surgery

Surgery studies	Veyvondi	Haemate	Haemate	Wilnativ	Wilnativ	Willfact
Outcomes						
Reference	*[12]*; [4]	*[14]*	*[15]*	*[13]*	*[3]*	*[10]*
Safety population)	N = 15	N= 42	N=29	N=28	N=32	50
Serious thromboembolic events	**1 (one) DVT,**	**0 (none)**	**1 (one)**	**0 (none)**	**0 (none)**	**0 (none)**
Type	Deep venous thrombosis		Pulmonary embolism			
Relation to study drug	Unlikely related		Possibly related			

A total of two serious thromboembolic events have been reported across the participants in the included studies. In both cases the patient had a disease profile with high risk for thromboembolic events, especially in connection with surgery.

- Veyvondi - one case of a serious deep venous thrombosis, which was rated as not related by the investigator and defined as unlikely related in the EPAR. *[12] [4]*
- Haemate - one case of pulmonary embolism, which was rated probably related by the investigator.

The case stories are provided below.

Veyvondi -Case description – thromboembolic event during treatment

One subject (43-year-old female) experienced 2 thrombotic AEs (non-serious deep vein thrombosis 4 days after the surgery followed by serious deep vein thrombosis 8 days after surgery). [4]

The subject was hospitalised for total hip replacement surgery, received Veyvondi and rFVIII treatment (baseline for PK assessment, loading dose of rFVIII, last infusion of Veyvondi on Day 7 after surgery) and dabigatran for thrombosis prevention which was later switched to enoxaparin. [4]

3 days after surgery, a non-occlusive thrombosis of the left common and deep femoral veins, which did not meet the criteria for a SAE, was diagnosed. The event was considered life-threatening 7 days after surgery because a floating thrombus of left common femoral vein was reported. [4]

The investigator judged these thrombotic AEs as unlikely related to rVWF, not related to Advate, and not related to study procedures. [4]

The patient's ADAMTS13 level was below the normal range (37%; normal range 50 to 160%). Laboratory data and assessment of thrombophilic polymorphism did not show abnormalities. A caval filter was placed on the same day and the event was considered resolved when the subject was rehospitalised for removal of the vena cava filter 2 months later. [4]

The event was rated with moderate severity, unlikely related to Veyvondi treatment and probably related to orthopaedic surgery. [4]

Haemate - Case description – thromboembolic event during treatment

The pulmonary embolism developed 10 days after bilateral knee replacement in an 81-year-old female subject with type 1 VWD. *[15]*

Several thromboembolic risk factors were present in this subject: advanced age, recent major orthopaedic surgery and thrombocytosis ($769x10^9$ pr. L); she did not receive any antithrombotic prophylaxis treatment. The embolism was detected by scintigraphy after the development of dyspnoea and resolved under heparin treatment 6 days later without sequelae. *[15]*

The subject had a FVIII:C level of 70 IU/dL prior to the loading dose on the day of surgery, and dosage was not adjusted according to FVIII levels during the treatment course, so that the plasma FVIII:C reached levels as high as 450 IU dL)1 on the day before the diagnosis of a pulmonary embolism. *[15]*

Three days after the embolism was diagnosed the subject received a half dose of VWF/FVIII without any complications. *[15]*

Warnings and precautions in the SmPC

A review of the summaries of product characteristics for the intervention and the comparators did not identify any significant difference in wording regarding incidence and prevalence of thromboembolic events of importance as these texts are all based on the standard wordings provided in the CHMP Guideline for Core SPC for Human Derived von Willebrand Factor (CPMP/BPWG/278/02). [1, 5-8]

The warnings all include requirements for special attention to the patient's level of FVIII as a high level of FVIII increase the risk of thromboembolic events. In addition, the use of combination products containing FVIII and VWF in a fixed ratio necessitates a higher level of monitoring of the FVIII level.

Risks connected to high levels of FVIII

The plasma derived combination products have different ratios of VWF/FVIII; Haemate 2.4:1 and Wilnativ 1:1.[5, 7]

Risk of thrombotic events

Studies have shown an association between elevated plasma VWF/FVIII levels and an increased tendency towards postoperative thrombotic events in VWD patients undergoing VWF/FVIII supplementation.[22] [23].

A systematic review of prospective studies (1990–2011) reporting safety data of factor concentrates in patients with haemophilia A (HA), haemophilia B (HB) and von Willebrand disease (VWD) was conducted to identify the incidence and type of thrombotic AEs [24]. In 71 studies (45 in HA, 15 HB, 11 VWD) enrolling 5528 patients treated with 27 different concentrates (20 plasma derived, 7 recombinant), 20 thrombotic AEs (2 HA, 11 HB, 7 VWD) were reported, including two major venous thromboembolic episodes (both in VWD patients on prolonged replacement for surgery) The overall prevalence was 3.6 per 103 patients (3.6 per 104 for severe AEs) and 1.13 per 105 infusions, with higher figures in VWD than in haemophilia. [24]

A study in VWD patients with the objective to elucidate the roles of the ABO blood group, VWF, and clotting factor VIII in the process of deep-vein thrombosis has been performed. Koster et al undertook a population-based patient-control study in which 301 consecutive patients younger than 70 with a first, objectively diagnosed episode of venous thrombosis and without an underlying malignant disorder were compared with 301 healthy controls matched for age and sex. [25]

In univariate analysis, blood group, VWF concentration, and factor VIII concentrations were all related to deep-vein thrombosis. The risk of thrombosis increased with increasing VWF or factor VIII concentration

and was higher in subjects of non-O blood groups than in those of group 0. In multivariate analysis, only factor VIII remained as a risk factor, and the dose-response relation between factor VIII concentration and risk of thrombosis persisted (subjects with factor VIII concentrations above 1500 IU/L had an adjusted odds ratio of 4.8 [95% Cl 2.3-10.0]). By contrast, the adjusted odds ratio for each VWF stratum did not differ from 1. [25]

Overall, this data supports the relationship between FVIII levels and thrombosis, and that the risk of thrombosis is higher in VWD compared to haemophilia patients, likely due to a FVIII accumulation. Furthermore, the risk of TEs in major surgical procedures (e.g. hip replacement) within the normal population is well established. Without prophylactic anticoagulation, the frequency of deep-vein thrombosis after total hip replacement is high, in the range of 50 to 60 percent. [26, 27]

Changes in VWD and FVIII during surgery

At present, VWD patients undergoing major surgery are prophylactically treated to promote haemostasis. There is variability in perioperative clinical practice; however, most guidelines suggest replacing the deficient factor to a level of 1.0 IU/mL (or 100%). As mentioned above, studies have shown an association between elevated plasma VWF/FVIII levels and an increased tendency towards postoperative thrombotic events in patients undergoing such supplementation. [22] [23] Studies have also demonstrated that VWF/FVIII behave as acute phase reactants and plasma VWF/FVIII levels rise under stress conditions, such as surgery and inflammatory states. [28] [29-31] Despite the above-mentioned thrombotic risk, a significant bleeding risk of 2–9% has been documented in VWD patients undergoing surgery.[32] To further understand how to balance these risks in VWD patients, Kahlon et al studied the physiological response of VWF and FVIII to surgery in normal individuals.[33]

In the study by Kahlon et al, eligible subjects >18 years of age undergoing total hip or knee replacement were recruited. Blood samples were drawn at five time points: baseline, preoperatively, 30 min after surgical incision, 30 min postoperatively and postoperative day 1. All VWF variables were seen to significantly decrease intraoperatively and increase postoperatively. [33]

In summary, VWF multimers showed a statistically significant decrease in high molecular weight multimers intraoperatively and an increase postoperatively. Data presented in the Kahlon study establish a physiological baseline for VWF parameters in the normal population and demonstrate mean VWF/factor VIII levels greater than 1.0 IU/mL intraoperatively. As such, current management in VWD patients does not appear to mimic the normal physiological response to surgery. [33]

In VWD patients receiving VWF/FVIII concentrates during surgery FVIII levels can increase above normal whilst maintaining target VWF levels close to 100%. In addition, VWF levels can decrease below normal whilst maintaining target FVIII close to 100%. VWF/FVIII levels in a patient with VWD type 3 is illustrated in Figure 3 [1]. Thus, this non-physiological response in clotting factors may both increase risk of thrombosis and risk of bleeding. Replacement with only VWF to type 3 VWD would have a greater possibility to mimic the normal physiological response. Virtually all reported cases of thromboembolism in VWD have been associated with supra-normal FVIII levels usually with additional risk factors including surgery.

Summary

Even though risk of thromboembolic events is well-known in these patient populations the incidence reported in the included studies is low. In addition, the two reported cases both occurred in circumstances with several different risk factors for development of thromboembolic complications.

It is therefore difficult to draw any firm conclusions on the potential difference between the included drugs in general clinical practice.

It is however well documented that increased levels of FVIII increases the risk of thromboembolic events, why co-administration of FVIII should be kept at a minimal level.

Veyvondi contains recombinant von Willebrand factor only, while FVIII, if needed, is administered separately. This facilitates the possibility of individualizing the patient's treatment based on FVIII levels.

The risk of excessive levels of FVIII and consequently the risk of thromboembolic events can thus be considered to be minimized with the use of Veyvondi.

6 Other considerations

6.1 Use of combination products vs separate administration of vWF and FVIII

The need for the availability of home infusion for patients with von Willebrand disease depends on several factors.

In Denmark approx. 250 patients have been diagnosed with von Willebrand Disease, the absolute majority of which are treated on demand with DDAVP. Only few patients are treated with infusion of VWF products. [21]

While no formal data have been identified, the Bleeders' Association (Bløderforeningen) reports a total of 13 patients receiving home infusions at their web site.

Identifying the patient for home infusion

The FVIII levels of VWD patients are quite stable over time. The need for co-infusion of FVIII differ significantly between patients based on the type of VWD and the severity of the individual patient's disease.

A recent publication by Favorolo et al summarizes the expected need for treatment types for the different types and severities of VWD. Co-administration of FVIII will most frequently be needed in patients with VWD type III as this type is the most severe. In addition, patients with severe type I may also need FVIII co-administration.[34]

Based on the baseline value of FVIII and VWF, the type of VWD and the clinical profile of the patient, the clinician may evaluate the extent to which the patient will be in need of FVIII co-infusion in case of bleeds.

However, even in the case of need for FVIII co-administration only one infusion of FVIII will be needed in order to establish the relevant therapeutic level of FVIII to ensure the full efficacy of the infused VWF.[1] The patients will therefore only have very limited amounts of FVIII at home limiting the risk of waste.

With only 13 patients receiving home infusions, and only patients with severe disease in need of FVIII co-administration the overall number of patients with a need for supply of FVIII at home will be very limited.. However, for those with known very low levels of FVIII, the FVIII infusion must be mandatory. For the latter the risk of waste of FVIII would thus be close to non-existent.

Safety aspects of home infusion with separate FVIII and VWF

As previously described no data are available for Veyvondi as on demand monotherapy. However, data for Willfact as reported in Borel-Derlon indicate that treatment with pdVWF monotherapy even in severe bleeds was successful without patient safety being jeopardized. [10] These data are described in detail in section 5.1.

Administering a fixed combination of FVIII and VWF, not only as the initial infusion, but also subsequently if more than one infusion must be included in the assessment of patient safety. As described in section 5.5 it is well-documented that increased levels of FVIII can be problematic for patients both in on demand treatment and in prevention of surgery due to the increased risk of thromboembolic events..

Though the need for two separate administration of FVIII and Veyvondi respectively may have a slight disadvantage for practical purposes, this may very well be counterbalanced by lowering the risk of thromboembolic events due supraphysiological FVIII levels as a result of use of combination products.

Handling of infusions

The need for two separate infusions will be limited due to the low number of patients. Patients will however need to be trained in the use of the mixing devices relevant for the products to be administered. Whilst preparation of infusion earlier was somewhat cumbersome, the new generations of mixing and administration devices have high level of user friendliness.

Veyvondi is provided in the Mix2Vial device which is already in use also with Haemate, Wilnativ and Willfact.[1, 5-7] Patients currently in treatment are thus already familiar with this device.

FVIII products are provided with different devices of which some seem more user friendly than others.[21]

In order to minimize the risk for errors during reconstitution and administration, the clinician must evaluate the feasibility of the available devices in the light of the patient capability and preference and ensure the proper level of training for the patient/caregiver.

Currently available FVIII products have a shelf life of up to 36 months at 2-8 degrees centigrade.[21] For the few patients with severe disease and therefore need for immediate availability of FVIII, the FVIII product supplied should be the one with the longest shelf-life to minimize the potential for waste due to expiry.

Summary

In summary it is difficult to quantify the exact need for the use of FVIII co-administration in case of home infusions. The need must be evaluated by the treating physician based on the individual patient's disease profile and the clinicians personal experience.

Data from the use of the existing pdVWF product Willfact indicate that patient safety does not seem to be jeopardized by allowing the patients managing home infusions. [10]

Separate administration of Veyvondi and FVIII can be expected to minimize the risk of supraphysiological levels of FVIII resulting from administration of FVIII/VWF combination products, thereby reducing the risk of thromboembolic complications.

6.2 Overview of manufacturing details

Table 28 Manufacturing details

ATC	B02BD10
Product	Veyvondi®
Active substance	Vonicog alfa (recombinant von Willebrand Factor)
Manufacturer	Baxter AG, Industriestrasse 67, 1221 Vienna, Austria
Production	Recombinant DNA (rDNA) technology in the Chinese Hamster Ovary (CHO) cell line without the addition of any exogenous human-or animal-derived protein in the cell culture process, purification or final formulation. The product contains only trace amounts of human recombinant coagulation factor VIII.
Human or animal protein in cell culture	No
Human albumin as a stabilizer	No
Plasma source	n/a
Purification and virus inactivation	No
Pathogens as theoretically can be found in the product despite inactivation	n/a
Ref.: [1]	

6.3 Product strengths and storage

Table 29 Product strength and storage

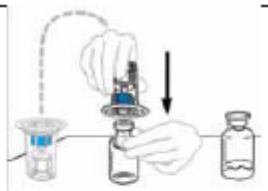
ATC	B02BD10
Product	Veyvondi®
Strength (IU)/Package size	Veyvondi 650 IU powder and solvent for solution for injection Each pack contains: - powder in a vial (type I glass), with a butyl rubber stopper - 5mL of solvent in a vial (type I glass), with a rubber stopper (chlorobutyl) - one reconstitution device (Mix2Vial) VEYVONDI 1300 IUpowder and solvent for solution for injection Each pack contains: - powder in a vial (type I glass), with a butyl rubber stopper - 10 mL of solvent in a vial (type I glass), with a rubber stopper (bromobutyl)

	- one reconstitution device (Mix2Vial)
Storage	Shelf life 3 years *Powder* Do not store above 30°C. Do not freeze. Store in the original package in order to protect from light.
After reconstitution	Chemical and physical in-use stability has been demonstrated for 3 hours at 25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24hours at 2 to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

Ref.: [1]

6.4 Reconstitution system (device)

The device for reconstitution is the Mix2Vial device, which is also the device supplied with Haemate, Wilnativ and Willfact. [1, 5-8]
This will reduce the need for training of patients when shifting between products.

4	Turn the package with the Mix2Vial device upside down and place it over the top of the solvent vial. Firmly insert the blue plastic spike of the device into the center of the solvent vial stopper by pushing straight down. Grip the package at its edge and lift it off the Mix2Vial device. Be careful not to touch the clear plastic spike. The solvent vial now has the Mix2Vial device connected to it and is ready to be connected to the VEYVONDI vial.	
5	To connect the solvent vial to the VEYVONDI vial, turn the solvent vial over and place it on top of the vial containing VEYVONDI concentrate. Fully insert the clear plastic spike into the VEYVONDI vial stopper by firmly pushing straight down. This should be done right away to keep the liquid free of germs. The solvent will flow into the VEYVONDI vial by vacuum. Check that all the solvent has transferred. Do not use if vacuum has been lost and the solvent does not flow into the VEYVONDI vial.	

6.5 Assay methods

Table 30 Assay methods

Product	Active substance	FVIII potency is determined by	Need for product-specific standard for analysis in one-stage clotting assay?
VEYVONDI®	Vonicog alfa (recombinant von Willebrand factor)	The potency of VWF (IU) is measured using the European Pharmacopeia ristocetin	No

cofactor activity assay (VWF: RCo). The ristocetin cofactor activity of recombinant human von Willebrand factor was determined against the International Standard for von Willebrand factor concentrate (WHO).

6.6 Infusion rate

VEYVONDI is for intravenous use.
The rate of administration should be slow enough to ensure the comfort of the patient, up to a maximum of 4mL/min. After constitution each ml contains 130 IU.[1]
An injection of 50 IU of VEYVONDI® per kg bodyweight on a patient with a bodyweight of 70 kg (3500 IU) will be able to be infused in less than 7 minutes.[1]

6.7 Packsizes

The pack sizes for Veyvondi are:

	Dimensions	Volume	Weight
Veyvondi 650 IU	107 x 61 x 57 mm	0.372 l	69 g
Veyvondi 1300 IU	123 x 61 x 72 mm	0.540 l	97 g

6.8 Utensils in package

The administration set contains:

- Each pack contains:
  - powder in a vial (type I glass), with a butyl rubber stopper
  - 5 or 10 mL of solvent in a vial (type I glass), with a rubber stopper (bromobutyl)
  - one reconstitution device (Mix2Vial)

6.9 Comparison of dose relationship

The requested information is provided in the tables below.

Table 31 In vivo recovery and T½

Parameter	Veyvondi [1]	Haemate[7]	Wilnativ[5]	Willfact[6]
In vivo recovery (IVR) (IU/dl per IU/kg)	1.7-2.0 see detailed data below	1.9 (median) (0.6-4.5)	1.56 (mean) ±0.48 (SD) (Range 0.90-2.93)	2.1 (mean) (NR)
T½; hours	17.8-22.6 See detailed data below	9.9 h (median) (2.8-51.1)	23.3 (mean) ±12.6 (SD) (Range 7.4-58.4)	12 h (mean) (8-14)

Table 32 In vivo recovery and T½ for Veyvondi per study

	Phase 1 PK50 VEYVONDI with octocog alfa (Study 070701) Mean (95% CI) SD	**Phase 3 PK50 VEYVONDI** (Study 071001) Mean (95% CI) SD	**Phase 3 PK80 VEYVONDI** (Study 071001) Mean (95% CI) SD	**Surgery PK50 VEYVONDI** (Study 071101) Mean (95% CI) SD
T1/2	19.3 (14.3; 24.3) 10.99	22.6 (19.5; 25.7) 5.34	19.1 (16.7; 21.5) 4.32	17.8 (12.9; 22.8) 7.34
IR at Cmax	1.7 (1.4; 2.0) 0.62	1.9 (1.6; 2.1) 0.41	2.0 (1.7; 2.2) 0.39	2.0 (1.7; 2.3) 0.45

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8 Appendices

8.1 Literature search – Eligibility criteria

Inclusion and exclusion criteria were the same for abstract and full text screening. Any study of unclear relevance from the abstract was retrieved and screened as the full text.

The following sources were searched for relevant documents on January 14, 2019.

- BIOSIS Previews®, Embase®, MEDLINE® (via ProQuest).
- CENTRAL via Cochrane (http://cochranelibrary-wiley.com/cochranelibrary/search?searchRow.searchOptions.searchProducts=clinicalTrialsDoi).

The criteria are presented in the table below.

Table 33 Literature search – eligibility criteria	
Studies to include	
Study designs	Inclusion criteria • Prospective trials • Interventional trials Exclusion criteria: • Retrospective
Population	Inclusion criteria • Von Willebrand Disease, inherited Exclusion criteria • Studies with other populations than patients diagnosed with RMS
Indication	Von Willebrand disease
Interventions	Veyvondi (vonicog alfa)
Comparator	Plasma derived VWF (Willfact) Plasma derived VWF/FVIII (Haemate, Wilnativ)
Outcome	• Hemostatic efficacy (in bleeding and surgery) • Number of infusions • Serious venous thromboembolic events • Inhibitor • Anaphylaxis
Data sources	
Databases	**Databases:** BIOSIS Previews®, Embase®, MEDLINE® through ProQuest CENTRAL through COCHRANE library
Other sources	EPAR, SPC
Selection criteria	
	1. Exclusion by title and abstract 2. Exclusion by full text
Time Period covered	
	No time limits applied
Search Date	
	ProQuest and CENTRAL 05NOV2018

8.1.1 PRISMA 2009 Flow Diagram

BIOSIS Previews®, Embase®, MEDLINE® were searched via ProQuest. The output consisted of 3000 records according to the search string shown in Table 36

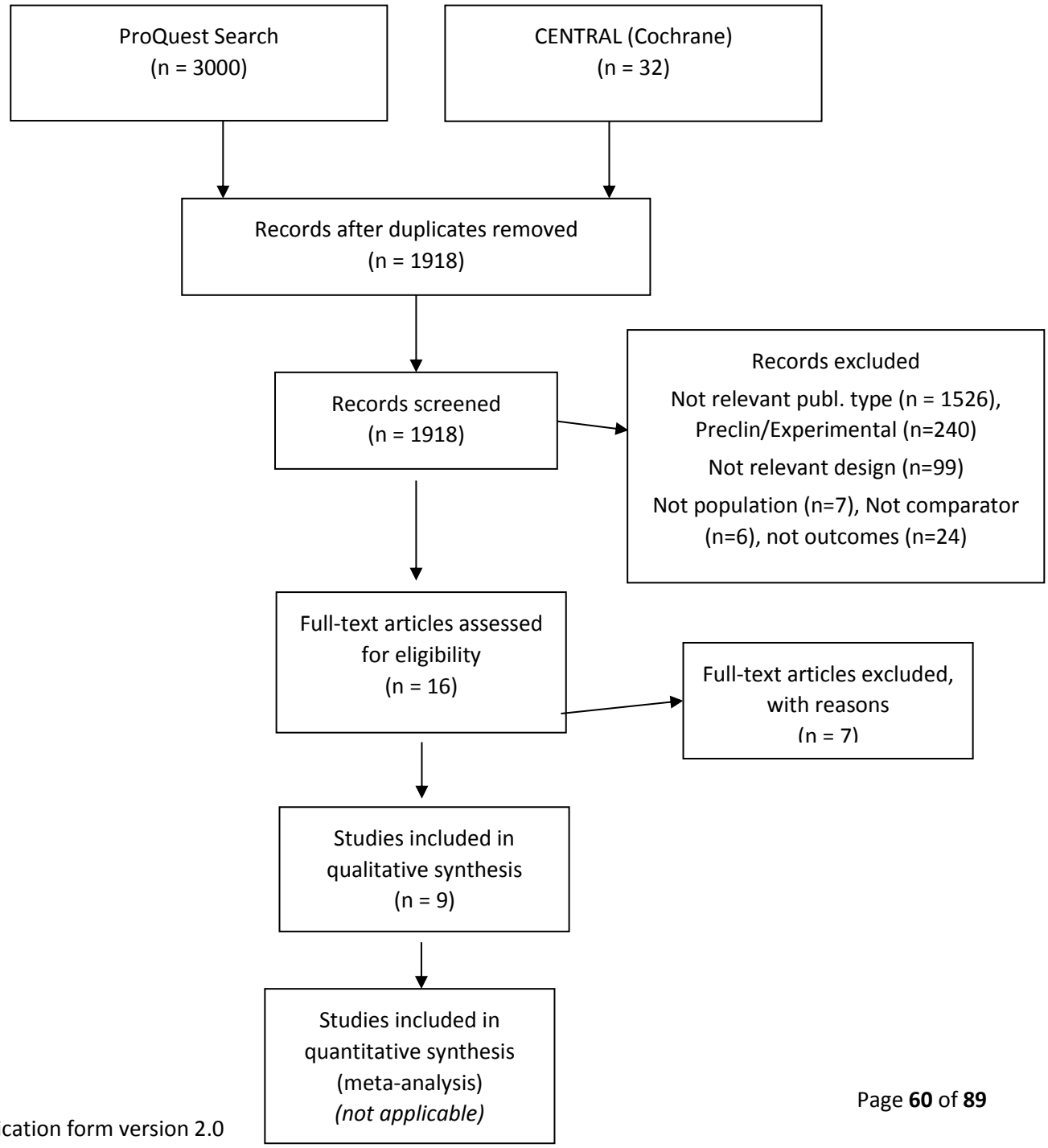
After automated deduplication using the ProQuest deduplication function, the remaining output was 1964 records. After a manual deduplication the final number of records identified was 1918. The flow is shown in the PRISMA chart below

1.1 Identification

1.4 Screening

1.2 Eligibility

1.3 Included



8.1.2 Full text review – Excluded studies

Seven studies were excluded after full text review.

Table 34 Literature search – Excluded publications after full text review		
	Publication	**Reason for exclusion**
1	Batty P, Chen YH, Bowles L, Hart DP, Platton S, and Pasi KJ. **Safety and efficacy of a von Willebrand factor/factor VIII concentrate (Wilate®): A single centre experience.** *Haemophilia; 2014, 20(6): 846-853*	Reports on retrospective data
2	Castaman G, Coppola A, Zanon E, Boeri E, Musso M, Siragusa S, Federici AB, Mancuso G, Barillari G, Biasoli C, Feola G, Franchini M, Moratelli S, Gamba G, Schinco P, Valdrè L, Dragani A, Mazzucconi G, Tagliaferri A, and Morfini M. **Efficacy and safety during formulation switch of a pasteurized VWF/FVIII concentrate: Results from an Italian prospective observational study in patients with von Willebrand disease.** *Haemophilia; 2013, 19(1): 82-88*	Non-interventional, observational design
3	Lethagen S, Berntorp E, and Nilsson IM. **Pharmacokinetics and hemostatic effect of different factor VIII/von Willebrand factor concentrates in von Willebrand's disease type III.** *Annals of hematology; 1992, 65(6): 253-9*	Does not report relevant outcomes for the PICO.
4	Lubetsky A, Schulman S, Varon D, Martinowitz U, Kenet G, Gitel S, and Inbal A. **Safety and efficacy of continuous infusion of a combined factor VIII-von Willebrand factor (vWF) concentrate (Haemate-P) in patients with von Willebrand disease.** *Thrombosis and haemostasis; 1999, 81(2): 229-33*	Reports on case series, treated with continuous infusion. Outcomes per PICO not reported.
5	Mannucci PM, Chediak J, Hanna W, Byrnes J, Ledford M, Ewenstein BM, Retzios AD, Kapelan BA, Schwartz RS, and Kessler C. **Treatment of von Willebrand disease with a high-purity factor VIII/von Willebrand factor concentrate: a prospective, multicenter study.** *Blood; 2002, 99(2): 450-6*	The investigated drug is Alphanate – not relevant for the current PICO.
6	Mannucci PM, Tenconi PM, Castaman G, and Rodeghiero F. **Comparison of four virus-inactivated plasma concentrates for treatment of severe von Willebrand disease: a cross-over randomized trial.** *Blood; 1992, 79(12): 3130-7*	Outcomes not relevant – reports PK data
7	Mannuccio Mannucci P, Kyrle PA, Schulman S, Di Paola J, Schneppenheim R, Cox Gill J. **Prophylactic efficacy and pharmacokinetically guided dosing of a von Willebrand factor/factor VIII concentrate in adults and children with von Willebrand's disease undergoing elective surgery: a pooled and comparative analysis of data from USA and European Union clinical trials**. *Blood transfusion = Trasfusione del sangue.* 2013;11(4):533-540	Describes pooled data from the separate studies reported in Lethagen 2007 and Gill 2011 – studies that are included in the application as separate entries. *[14] [15]*

8.1.3 Literature search – search strings

The search strings applied in ProQuest and CENTRAL respectively are tabulated below.

CENTRAL search string

- CENTRAL via Cochrane

Table 35 Literature search – Search strategy CENTRAL

#1: MeSH descriptor: [Von Willebrand Disease] explode all trees

#2: VWD OR Von-Willebrand-Disease OR Von-Willebrands-Disease OR Von-Willebrand-Syndrome OR Von-Willebrands-Syndrome OR Von-Willebrand-Disorder OR Von-Willebrands-Disorder

#3: #1 OR #2

#4: Vonvendi OR Veyvondi OR vonicog-alfa OR vonicog-alpha OR Bax111 OR Bax-111 OR SHP677 OR SHP-677 OR Rvwf OR recvwf OR von-Willebrand-factor-recombinant OR VWF-recombinant OR recombinant-von-Willebrand-Factor OR rec-von-Willebrand-Factor

#5: Haemate OR Haemate-P OR Humate OR Humate-P OR Wilnativ OR Wilate OR Willfact OR Wilfactin

#6: Pdfviii-vwf OR pdfviii-fvw OR pdvwf-fviii OR pdfvw-fviii OR pdfviii-pdvwf OR pdfviii-pdfvw OR pdvwf-pdFVIII OR pdfvw-pdfviii OR pdHfviii-vwf OR pdhfviii-fvw OR pdHvwf-fviii OR pdhfvw-fviii OR pdHfviii-pdvwf OR pdhfviii-pdfvw OR pdHvwf-pdFVIII OR pdhfvw-pdfviii OR HFVIII-VWF OR hfviii-fvw OR hvwf-fviii OR hfvw-fviii OR pdahf-vwf OR pdahf-fvw OR pdVWF-ahf OR pdfvw-ahf OR pdahf-pdVWF OR pdahf-pdfvw OR pdVWF-pdahf OR pdfvw-pdahf

#7: von-Willebrand-Factor-Factor-VIII OR Factor-VIII-von-Willebrand-Factor OR von-Willebrand-Factor-concentrate OR von-Willebrand-Factor-complex OR vwf-concentrate OR vwf-complex OR

Von-Willebrand-factor-in-factor-viii-concentrate OR plasma-derived-Factor-VIII-concentrates-containing-adequate-von-Willebrand-factor OR plasma-derived-FVIII-pdFVIII-von-Willebrand OR FVIII-concentrate-containing-high-levels-of-VWF

#8: #4 OR #5 OR #6 OR #7

#9: #3 AND #8

ProQuest search string

BIOSIS Previews®, Embase®, MEDLINE® were searched via ProQuest according to the search string shown in Table 36.

Table 36 Literature search – Search strategy ProQuest (Biosis, Embase, MEDLINE)

Set#	Searched for	With duplicates	After automated deduplication
S5	S4 AND S3	3000	1964
S4	(Ti,ab,subst,if(Vwd* OR *vwd) OR ti,ab,subst((“von Willebrand” OR “von willibrand” OR “van willebrand” OR “van willibrand” OR vonwillebrand OR vonwillibrand OR vanwillebrand OR vanwillibrand) P/0 (disease or diseases OR disorder or disorders OR syndrome or syndromes OR patient or patients OR subject or subjects OR volunteer or volunteers)) OR ti,ab,subst((“von Willebrands” OR “von willibrands” OR “van willebrands” OR “van willibrands” OR vonwillebrands OR vonwillibrands OR vanwillebrands OR vanwillibrands) P/0 (disease or diseases OR disorder or disorders OR syndrome or syndromes OR patient or patients OR subject or subjects OR volunteer or volunteers)) OR ti,ab,subst((“von Willebrand’s” OR “von willibrand’s” OR “van willebrand’s” OR “van willibrand’s” OR vonwillebrand’s OR vonwillibrand’s OR vanwillebrand’s OR vanwillibrand’s) P/0 (disease or diseases OR disorder or disorders OR syndrome or syndromes OR patient or patients OR subject or subjects OR volunteer or volunteers)) OR ti,ab,subst((deficient or “deficiency of” or “deficiency including”) P/1 (VWF OR FVW OR “Von willebrand factor” OR “Von willibrand factor” OR “Van willebrand factor” OR “Van willibrand factor” OR “Vonwillebrand factor” OR “Vonwillibrand factor” OR “Vanwillebrand factor” OR “Vanwillibrand factor” OR “Von willebrands factor” OR “Von willibrands factor” OR “Van willebrands factor” OR “Van willibrands factor” OR “Vonwillebrands factor” OR “Vonwillibrands factor” OR “Vanwillebrands factor” OR “Vanwillibrands factor” OR “Von willebrand’s factor” OR “Von willibrand’s factor” OR “Van willebrand’s factor” OR “Van willibrand’s factor” OR “Vonwillebrand’s factor” OR “Vonwillibrand’s factor” OR “Vanwillebrand’s factor” OR “Vanwillibrand’s factor”)) OR ti,ab,subst((VWF OR FVW OR “Von willebrand factor” OR “Von willibrand factor” OR “Van willebrand factor” OR “Van willibrand factor” OR “Vonwillebrand factor” OR “Vonwillibrand factor” OR “Vanwillebrand factor” OR “Vanwillibrand factor” OR “Von willebrands factor” OR “Von willibrands factor” OR “Van willebrands factor” OR “Van willibrands factor” OR “Vonwillebrands factor” OR “Vonwillibrands factor” OR	18477	

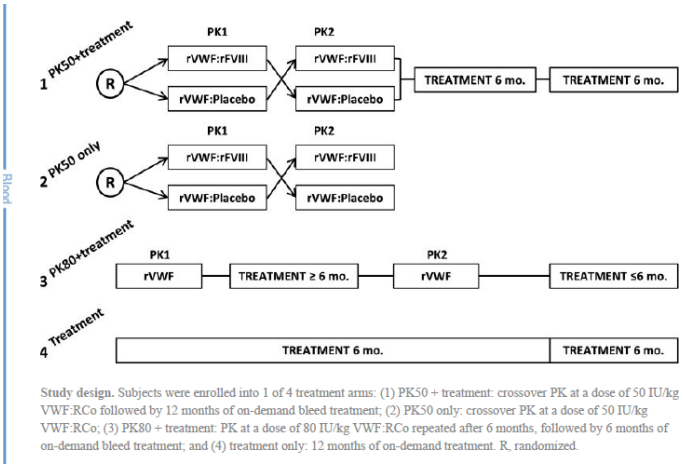
	“Vanwillebrands factor” OR “Vanwillibrands factor” OR “Von willebrand’s factor” OR “Von willibrand’s factor” OR “Van willebrand’s factor” OR “Van willibrand’s factor” OR “Vonwillebrand’s factor” OR “Vonwillibrand’s factor” OR “Vanwillebrand’s factor” OR “Vanwillibrand’s factor”) P/1 (deficient) p/1 (patient or patients OR subject or subjects OR volunteer or volunteers)) OR EMB.EXACT("von Willebrand disease") OR MESH.EXACT.EXPLODE("von Willebrand Diseases"))		
S3	S1 OR S2	9302	
S2	Ti,ab,subst(Haemate* OR HaemateP OR Humate* OR HumateP) OR ti,ab,subst((((("Factor viii" OR fviii OR "f viii" or f8 or "factor 8" or "f 8" OR ahf or “Factor eight” OR factoreight OR feight OR f-eight) N/1 (VWF OR FVW OR “Von willebrand” OR “Von willibrand” OR “Van willebrand” OR “Van willibrand” OR Vonwillebrand OR Vonwillibrand OR Vanwillebrand OR Vanwillibrand OR “Von willebrand’s” OR “Von willibrand’s” OR “Van willebrand’s” OR “Van willibrand’s” OR “Vonwillebrand’s” OR “Vonwillibrand’s” OR “Vanwillebrand’s” OR “Vanwillibrand’s” OR “Von willebrands” OR “Von willibrands” OR “Van willebrands” OR “Van willibrands” OR “Vonwillebrands” OR “Vonwillibrands” OR “Vanwillebrands” OR “Vanwillibrands”)) N/2 (concentrate OR concentrates or product or products OR complex OR complexes))) OR Ti,ab,subst((VWF OR FVW OR “Von willebrand” OR “Von willibrand” OR “Van willebrand” OR “Van willibrand” OR Vonwillebrand OR Vonwillibrand OR Vanwillebrand OR Vanwillibrand OR “Von willebrand’s” OR “Von willibrand’s” OR “Van willebrand’s” OR “Van willibrand’s” OR “Vonwillebrand’s” OR “Vonwillibrand’s” OR “Vanwillebrand’s” OR “Vanwillibrand’s” OR “Von willebrands” OR “Von willibrands” OR “Van willebrands” OR “Van willibrands” OR “Vonwillebrands” OR “Vonwillibrands” OR “Vanwillebrands” OR “Vanwillibrands”) N/1 ("Factor viii" OR fviii OR "f viii" or f8 or "factor 8" or "f 8" OR ahf or “Factor eight” OR factoreight OR feight OR f-eight) N/2 (concentrate OR concentrates or product or products OR complex OR complexes)) OR Ti,ab,subst(("von willebrand factor" OR vwf OR fvw) P/1 (concentrate OR concentrates or product or products OR complex OR complexes)) OR ti,ab,subst(pdfviii/vwf OR pdfviii/fvw or pdvwf/fviii or pdfvw/fviii or pdfviii/pdvwf or pdfviii/pdfvw or	6165	

	pdvwf/pdFVIII or pdfvw/pdfviii OR pdHfviii/vwf or pdhfviii/fvw or pdHvwf/fviii or pdhfvw/fviii or pdHfviii/pdvwf or pdhfviii/pdfvw or pdHvwf/pdFVIII or pdhfvw/pdfviii OR HFVIII/VWF or hfviii/fvw OR hvwf/fviii or hfvw/fviii OR pdf8/vwf or pdf8/fvw or pdvwf/f8 or pdfvw/f8 or pdf8/pdvwf or pdf8/pdfvw or pdvwf/pdF8 or pdfvw/pdf8 OR HF8/VWF or hf8/fvw OR pdhf8/vwf or pdhf8/fvw or pdhvwf/f8 or pdhfvw/f8 or pdhf8/pdvwf or pdhf8/pdfvw or pdhvwf/pdF8 OR pdhfvw/pdf8 OR VWF/HF8 OR fvw/hf8 OR pdahf/vwf or pdahf/fvw or pdVWF/ahf or pdfvw/ahf OR pdahf/pdVWF or pdahf/pdfvw or pdVWF/pdahf or pdfvw/pdahf) OR Ti,ab,subst("plasma derived FVIII/VWF" OR "plasma derived FVIII/FVW" OR "von Willebrand factor in factor viii concentrate" OR "von Willebrand factor in factor viii concentrates" OR "plasma-derived Factor VIII concentrates containing adequate von Willebrand factor" or "plasma-derived FVIII (pdFVIII)/von Willebrand factor (VWF)" OR "plasma-derived factor VIII and vonWillebrand factor (VWF) complex" OR "Plasma derived fVIII (pdfVIII) products that contain varying amounts of von Willebrand Factor (VWF)" OR "plasma-derived AHF/VWF" or "PD-AHF/VWF" or "plasma-derived factor VIII and von Willebrand factor (VWF) complex" OR "FVIII concentrate containing high levels of VWF" OR "concentrate of von Willebrand factor (VWF) and factor VIII") OR EMB.EXACT("blood clotting factor 8 plus von Willebrand factor")		
S1	Ti,ab,subst,if(Vonvendi* OR Veyvondi* OR "vonicog alfa" OR "vonicog alpha" OR Bax111 OR Bax-111 OR SHP677 OR SHP-677 OR Rvwf) OR Ti,ab,subst((Recombinant OR rec) P/3 (VWF OR FVW OR "Von willebrand" OR "Von willibrand" OR "Van willebrand" OR "Van willibrand" OR Vonwillebrand OR Vonwillibrand OR Vanwillebrand OR Vanwillibrand OR "Von willebrand's" OR "Von willibrand's" OR "Van willebrand's" OR "Van willibrand's" OR "Vonwillebrand's" OR "Vonwillibrand's" OR "Vanwillebrand's" OR "Vanwillibrand's" OR "Von willebrands" OR "Von willibrands" OR "Van willebrands" OR "Van willibrands" OR "Vonwillebrands" OR "Vonwillibrands" OR "Vanwillebrands" OR "Vanwillibrands")) OR EMB.EXACT("recombinant von Willebrand factor") OR Ti,ab,subst(Willfact* OR Wilfactin*) OR TI,AB(("efficacy of" or "use of" or used or given or replacing OR replace OR replacement or "replaced with" or "replacements of"	5542	

	or "replaces with" or "replacement of" or "usage of" or administ* or "administ* of" or infus* or "infus* of" or inject* or "inject* of" or deliver* or "deliver of" or "treat* with" or exogenous* or receiv* or substitut* or "substitut* of" or "substitut* with" or purified or intravenous* or subcutaneous* or IV or "i.v." or endovenous* or sc or "s.c." or dosing or dosage or “dose of” or concentrate* or product or products or "plasma derived" or plasmatic or pd or complex* OR therapy OR therapies OR “efficacy with” OR “efficacy of” OR “benefit with” OR “benefit of” OR “usefulness of” OR supplement*) N/1 (VWF OR FVW OR “Von willebrand factor” OR “Von willibrand factor” OR “Van willebrand factor” OR “Van willibrand factor” OR “Vonwillebrand factor” OR “Vonwillibrand factor” OR “Vanwillebrand factor” OR “Vanwillibrand factor” OR “Von willebrands factor” OR “Von willibrands factor” OR “Van willebrands factor” OR “Van willibrands factor” OR “Vonwillebrands factor” OR “Vonwillibrands factor” OR “Vanwillebrands factor” OR “Vanwillibrands factor” OR “Von willebrand’s factor” OR “Von willibrand’s factor” OR “Van willebrand’s factor” OR “Van willibrand’s factor” OR “Vonwillebrand’s factor” OR “Vonwillibrand’s factor” OR “Vanwillebrand’s factor” OR “Vanwillibrand’s factor”))		

8.2 On demand - Main characteristics of included studies

8.2.1 Veyvondi -Studies reporting on on-demand treatment of bleeding episodes

Table 37 Study characteristics [9]	
Trial name	*Gill 2015*
NCT number	*NCT01410227*
Objective	*This phase 3 prospective clinical trial was designed to assess the PK, safety, and haemostatic efficacy of rVWF in the treatment of bleeding episodes in adults with severe VWD.*
Publications – title, author, journal, year	*Gill JC, et al. Haemostatic efficacy, safety, and pharmacokinetics of a recombinant von Willebrand factor in severe von Willebrand disease. Blood. 2015 Oct 22;126(17):2038-46*
Study type and design	*Phase III, non-randomized, cross-over assignment, open label study.* *Subjects were enrolled into 1 of 4 arms to receive rVWF for PK assessment and/or 6 months of on-demand bleed treatment. Enrolment was conducted across all 4 treatment arms in parallel.*  **Study design.** Subjects were enrolled into 1 of 4 treatment arms: (1) PK50 + treatment: crossover PK at a dose of 50 IU/kg VWF:RCo followed by 12 months of on-demand bleed treatment; (2) PK50 only: crossover PK at a dose of 50 IU/kg VWF:RCo; (3) PK80 + treatment: PK at a dose of 80 IU/kg VWF:RCo repeated after 6 months, followed by 6 months of on-demand bleed treatment; and (4) treatment only: 12 months of on-demand treatment. R, randomized.
Follow-up time	*The study period was 12 months in which the patients were treated in case of bleeds.*
Population (inclusion and exclusion criteria)	***Inclusion Criteria:*** *Participant has been diagnosed with:* • *Type 1 (Von Willebrand factor: Ristocetin cofactor activity (VWF:RCo) < 20 IU/dL) or,* • *Type 2A (VWF:RCo < 20 IU/dL), Type 2B (as diagnosed by genotype), Type 2N (Factor VIII activity (FVIII:C) <10% and historically documented genetics), Type 2M or,* • *Type 3 (Von Willebrand factor antigen (VWF:Ag) ≤ 3 IU/dL) or,* • *Severe Von Willebrand disease (VWD) with a history of requiring substitution therapy with von Willebrand factor concentrate to control bleeding* *Ages 18-65 years, all genders. Participant, who participates in the treatment for bleeding episodes, has had a minimum of 1 documented bleed (medical history) requiring VWF coagulation factor replacement therapy during the previous 12 months prior to enrolment.* *Participant has a Karnofsky score ≥ 60%* *Participant is at least 18 and not older than 65 years of age at enrolment* *If female of childbearing potential, participant presents with a negative pregnancy test* *Participant agrees to employ adequate birth control measures for the duration of the study* *Participant is willing and able to comply with the requirements of the protocol* *Exclusion Criteria:*

	• *Participant has been diagnosed with pseudo VWD or another hereditary or acquired coagulation disorder other than VWD (eg qualitative and quantitative platelet disorders or elevated PT/international normalized ratio [INR] >1.4).* • *Participant has a documented history of a VWF:RCo half-life of <6 hours.* • *Participant has a history or presence of a VWF inhibitor at screening.* • *Participant has a history or presence of a factor VIII (FVIII) inhibitor with a titer ≥0.4 BU (by Nijmegen assay) or ≥ 0.6 BU (by Bethesda assay).* • *Participant has a known hypersensitivity to any of the components of the study drugs, such as mouse or hamster proteins.* • *Participant has a medical history of immunological disorders, excluding seasonal allergic rhinitis/conjunctivitis, mild asthma, food allergies or animal allergies.* • *Participant has a medical history of a thromboembolic event.* • *Participant is HIV positive with an absolute CD4 count <200/mm3.* • *Participant has been diagnosed with cardiovascular disease (New York Heart Association [NYHA] classes 1-4.* • *Participant has an acute illness (eg, influenza, flu-like syndrome, allergic rhinitis/conjunctivitis, non-seasonal asthma) at screening.* • *Participant has been diagnosed with significant liver disease as evidenced by any of the following: serum alanine aminotransferase (ALT) 5 times the upper limit of normal; hypoalbuminemia; portal vein hypertension (e.g. presence of otherwise unexplained splenomegaly, history of oesophageal varices).* • *Participant has been diagnosed with renal disease, with a serum creatinine level ≥2 mg/dL.* • *In the judgment of the investigator, the participant has another clinically significant concomitant disease (e.g. uncontrolled hypertension) that may pose additional risks for the participant.* • *Participant has been treated with an immunomodulatory drug, excluding topical treatment (eg, ointments, nasal sprays), within 30 days prior to enrolment* • *Participant is pregnant or lactating at the time of enrolment.* • *Participant has participated in another clinical study involving an IP or investigational device within 30 days prior to enrolment or is scheduled to participate in another clinical study involving an investigational product or investigational device during the course of this study.* • *Participant has a history of drug or alcohol abuse within the 2 years prior to enrolment.* • *Participant has a progressive fatal disease and/or life expectancy of less than 3 months.* • *Participant is identified by the investigator as being unable or unwilling to cooperate with study procedures.* • *Participant suffers from a mental condition rendering him/her unable to understand the nature, scope and possible consequences of the study and/or evidence of an uncooperative attitude.* • *Participant is in prison or compulsory detention by regulatory and/or juridical order*
Intervention	*For the PK part of the study, please refer to NCT01410227.* *For the main part of the study the intervention for bleeding episodes (37 patients with a total of 192 bleeding episodes), was as follows:* • *An initial infusion of 40 to 60 IU/kg VWF:RCo rVWF for minor to moderate bleeds and up to 80 IU/kg VWF:RCo for major bleeds* • *To ensure an immediate haemostatic level of FVIII:C, the initial dose of rVWF was to be administered together with rFVIII (Advate) at a ratio of 1.3:1 ± 0.2 VWF:RCo/FVIII:C and subsequently without rFVIII as long as therapeutic FVIII:C levels were maintained*

<table>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><th>Parameter</th><th>Value*</th></tr>
<tr><td>Sex, N (%)</td><td></td></tr>
<tr><td>Male</td><td>17 (45.9)</td></tr>
<tr><td>Female</td><td>20 (54.1)</td></tr>
<tr><td>VWD type, N (%)</td><td></td></tr>
<tr><td>1</td><td>2 (5.4)</td></tr>
<tr><td>2A</td><td>5 (13.5)</td></tr>
<tr><td>2N</td><td>1 (2.7)</td></tr>
<tr><td>3</td><td>29 (78.4)</td></tr>
<tr><td>Age, years [median (range)]</td><td>37 (18-64)</td></tr>
<tr><td>Weight, kg [median (range)]</td><td>73.0 (44.0-142.7)</td></tr>
<tr><td>Previous treatment,† N (%)</td><td></td></tr>
<tr><td>On-demand</td><td>27 (73.0)</td></tr>
<tr><td>Prophylaxis</td><td>3 (8.1)</td></tr>
<tr><td>Combination of on-demand and prophylaxis</td><td>7 (18.9)</td></tr>
<tr><td>Number of bleeding episodes per year prior to study (N = 36) [median (range)]</td><td>0.7 (0.0-6.0)</td></tr>
</table>
*Total number of subjects exposed was 37.
†Treatment within 24 months prior to enrollment.
</td></tr>
<tr><td>Primary and secondary endpoints</td><td>
Primary endpoint:
Percentage of Participants With Treatment Success for Treated Bleeding Episodes
Secondary endpoints included:

Percentage of Treated Bleeding Episodes With an Efficacy Rating of "Excellent" or "Good"
Percentage of Treated Bleeding Episodes With an Efficacy Rating of "Excellent" or "Good", Excluding Gastrointestinal Bleeds
Number of Infusions of rVWF:rFVIII and/or rVWF Per Bleeding Episode
Number of Units of rVWF:rFVIII and/or rVWF Per Bleeding Episode
Percentage of Participants Who Develop Inhibitory Antibodies to FVIII
Percentage of Participants Who Develop Inhibitory Antibodies to VWF
Percentage of Participants Who Develop Binding Antibodies to VWF
Percentage of Participants Who Develop Binding Antibodies to CHO
Percentage of Participants Who Develop Binding Antibodies to rFurin
Percentage of Participants Who Develop Binding Antibodies to Mouse Immunoglobulin
Percentage of Participants Who Had an Occurrence of Thrombotic Events
Number of Adverse Events Related to Study Product Including Clinically Significant Changes in Laboratory Parameters and Vital Signs
Number of Participants with Adverse Events Related to Study Product Including Clinically Significant Changes in Laboratory Parameters and Vital Signs
(VAS).
Number of Adverse Events by Infusion Related to Study Product Including Clinically Significant Changes in Laboratory Parameters and Vital Signs

[ct.gov]
For endpoint related to the PK part of the study please refer to clinicaltrials.gov (NCT01410227).
</td></tr>
<tr><td>Method of analysis</td><td>For the primary efficacy analysis of the rate of subjects with treatment success, which was defined as a mean efficacy rating score <2.5 (Table 1), the null hypothesis of a rate of ≤0.65 was tested on a 5% 1-sided level implicitly, by computing the Clopper-Pearson interval of proportions at the 90% confidence level.
Similarly, for the secondary efficacy analysis, the rate of all treated bleeds with excellent or good treatment outcome was tested against the null hypothesis of ≤0.60 on a 5% 1-sided level implicitly, by computing the Clopper-Pearson 90% confidence</td></tr>
</table>

	interval (CI) of the proportions. *Safety (adverse events) was evaluated descriptively.*
Subgroup analyses	*n/a*

8.2.2 Willfact/Willfactin -Studies reporting on on-demand treatment of bleedings episodes

Table 38 Study characteristics Borel-Derlon 2007 [10]	
Trial name	Treatment of severe von Willebrand disease with a high-purity von Willebrand factor concentrate (Wilfactin): a prospective study of 50 patients.
NCT number	Not reported
Objective	To assess the efficacy and safety of the concentrate in different clinical situations: (i) treatment of spontaneous bleeding episodes (managed at home or requiring hospitalization); (ii) prevention of bleeding during scheduled or unscheduled surgical or invasive procedures; (iii) short-term prophylaxis in non-surgical situations with an increased risk of bleeding and (iv) secondary long-term prophylaxis in patients with frequently recurring bleeding episodes
Publications – title, author, journal, year	*Borel-Derlon A, et al.* Treatment of severe von Willebrand disease with a high-purity von Willebrand factor concentrate (Wilfactin): a prospective study of 50 patients. J Thromb Haemost. 2007 Jun;5(6):1115-24. PubMed PMID: 17403090. *Goudemand J, et al* Pharmacokinetic studies on Wilfactin, a von Willebrand factor concentrate with a low factor VIII content treated with three virus inactivation/ removal methods. J Thromb Haemost 2005; 3: 2219–27. [17] [PK outcomes only, but includes more details on the study design than Borel-Derlon 2007]
Study type and design	This prospective trial was conducted in two parts. The first part (called the French study) was conducted at six French centers in the form of a crossover PK study comparing for bioequivalence the study product (Wilfactin) and the earlier one (Facteur Willebrand-LFB_) in patients with type 3 VWD. [17] The second part (called the European study) was conducted at five European centers as a crossover PK study comparing Wilfactin with FVIII/VWF concentrates currently licensed for treatment of VWD in patients with severe VWD (see definition below). The French study was not randomized, open label, while the European study was randomized open label.
Follow-up time	In the on demand part of the study 26 patients received a total of 733 infusions over 565 exposure days for 139 bleeding episodes.
Population (inclusion and exclusion criteria)	[Information sourced from the publication as the study has not been registered at www.clinicaltrials.gov.] For each study, patients were eligible if they had an inherited form of VWD shown to not respond adequately to a standardized test infusion of desmopressin [10] and if they had previously needed treatment with plasma-derived products or red blood cells (RBC). For the **European study**, patients with severe VWD were enrolled if they had: (i) a clinically significant history of bleeding (more than one lifetime bleeding episode and (ii) at least one of the following laboratory abnormalities: skin bleeding time longer than 15 min, VWF ristocetin cofactor activity (VWF:RCo) less than 10 IU dL^{-1} or FVIII coagulant activity less than 20 IU dL^{-1}. For the **French study**, patients were enrolled if VWF:RCo was less than 30 IU dL^{-1} or FVIII was less than 30 IU dL^{-1} for type 2 N VWD.

	In both studies, the presence of anti-VWF or anti-FVIII alloantibodies was an exclusion criterion. The VWD types were categorized according to the revised classification of Sadler et al. [Sadler JE, Budde U, Eikenboom JC, Favaloro EJ, Hill FG, Holmberg L, Ingerslev J, Lee CA, LillicrapD,MannucciPM,Mazurier C,Meyer D, NicholsWL, NishinoM, Peake IR, Rodeghiero F, Schneppenheim R, Ruggeri ZM, Srivastava A, Montgomery RR, et al. Working Party on von Willebrand Disease Classification. Update on the pathophysiology and classification of von Willebrand disease: a report of the Subcommittee on von Willebrand Factor. J Thromb Haemost 2006; 4: 2103–14]
Intervention	Patients received Wilfactin at an initial dose of 50 IU/kg in the French study and 60 IU/kg in the European study, depending on the current practice of the participating clinicians. Investigators were allowed to give a concomitant priming dose of FVIII concentrate (30 to 40 IU/kg) to patients with severe bleeding episodes and to those with baseline plasma FVIII levels below 20 IU/dL. Subsequent infusions of the VWF concentrate, if required by the clinical situation, were also standardized (two daily infusions of 60 IU kg–1 for the first 48 h in the European study and 30–50 IU kg–1 in the French study).
Baseline characteristics	Demographic data has only been reported for the full study population participating in the four different arms. Fifty patients (32 females and 18 males) were originally enrolled: 5 had type 1, 16 type 2A, 9 type 2B, 1 type 2 M, 1 type 2 N, and 18 type 3 VWD. Of these 26 patients (15 type 3, 1 type 1, 7 type 2A and 3 type 2B) received in the spontaneous bleed part of the study. For the overall study population, the median age was 37 years (range 5–81) and body weight ranged from 24 to 102 kg (median: 62). Three children were less than 15 years old. The median plasma levels of VWF:RCo was < 10 (10-33), and FVIII 27 (< 1-63). The baseline levels of VWF:RCo were less than 10 IU/dL in 36 patients (72%) and those of FVIII were less than 20 IU/dL in 23 patients (46%).
Primary and secondary endpoints	The publication does not include specific information on pre-defined endpoints. The main reported outcomes are <u>Treatment of spontaneous episodes</u> • Number of infusions • Number of bleeding episodes • Total no. of infusions • Median infusion dosage VWF:RCo IU/kg • Median number of infusions per bleeding episode • No. of FVIII infusions with first VWF infusion • Excellent/Good efficacy responses (%) <u>Prevention of bleeding during surgery/invasive procedures</u> • No patients • No procedures • No infusions administered • Median infusion dosage VWF:RCo IU/kg • Median no infusions • Median exposure days • Excellent/good response at hospital discharge • Median consumption during hospitalization (VWF:RCo IU/kg))
Method of analysis	[Information on the statistical methods is very limited in the publication] All the patients enrolled in the study who received at least one dose of VWF concentrate were included in the per protocol analysis. Descriptive statistics (mean and standard deviations or median and ranges) were used.

	In order to evaluate the impact of secondary long-term prophylaxis on the frequency of breakthrough bleeding episodes, the data were normalized to reflect a comparable time of prophylaxis (e.g. 1 year).
Subgroup analyses	Not reported

8.2.3 Haemate/Humate - Studies reporting on on-demand treatment of bleedings episodes

Table 39 Study characteristics Gill 2003 [11]	
Trial name	Successful treatment of urgent bleeding in von Willebrand disease with factor VIII/VWF concentrate (Humate-P®): use of the ristocetin cofactor assay (VWF:RCo) to measure potency and to guide therapy
NCT number	Not reported.
Objective	The study was designed to evaluate the safety and efficacy of Humate-P® (Aventis Behring, King of Prussia, PA, USA) in patients with VWD in (i) urgent bleeding episodes; and (ii) in patients undergoing urgent and necessary surgery. In this application only data for the urgent bleeding episodes will be included as the PICOin the protocol is focused on elective surgery.
Publications – title, author, journal, year	Gill JC, et al. Successful treatment of urgent bleeding in von Willebrand disease with factor VIII/VWF concentrate (Humate-P): use of the ristocetin cofactor assay (VWF:RCo) to measure potency and to guide therapy. Haemophilia. 2003 Nov;9(6):688-95. PubMed PMID: 14750934.
Study type and design	This was a prospective, multicentre, open-label, nonrandomized study.
Follow-up time	Patients were followed until 3 days after the last infusion with study drug, and if the investigator concluded that the patient would not benefit from further infusions. A total of 53 serious bleeding events were evaluated; 48 (91%) had complete follow-up; five (9%) discontinued prior to completion [consent withdrawn, lost to follow-up (two events), doctor's decision, and scheduling conflicts].
Population (inclusion and exclusion criteria)	The study is not registered at clinicaltrials.gov. The following information has been sourced from the publication (Gill 2003). Patients were males or females of any age with a diagnosis of congenital VWD in whom desmopressin was known or suspected to be inadequate. They were expected to respond to exogenously administered VWF and to have a serious, life- or limb-threatening haemorrhage. Patients known to have inhibitors to VWF were excluded.
Intervention	The intervention was factor VIII/VWF concentrate (Humate-P/Haemate). Each investigator was asked to follow the study dosing guidelines, but the final decisions on dosing were based on the investigators_ clinical judgment. Dosing recommendations included a loading dose of 60 to 80 IU VWF:RCo (27–36 IU FVIII:C) per kilogram (kg) body weight, followed by maintenance doses of 40–60 IU VWF:RCo (18–27 IU FVIII:C) per kg every 8–12 h for 3 days. If further treatment was necessary, infusions of 40–60 IU VWF:RCo (18–27 IU FVIII:C) per kg were given daily for up to 7 days. Maintenance doses could be extended longer than 7 days in unusual circumstances. During the first 3 days of therapy, the nadir level of VWF:RCo activity was to be maintained above 50 IU dL)1 (50%).
Baseline characteristics	A total of 33 patients from 19 centres were enrolled between November 1998 and August 1999 for serious bleeding events. Of these, nine patients were enrolled more than once (two to eight times) for multiple events. Thirty-one patients (94%) were Caucasian; one (3%) was African-American; and one (3%) was native Alaskan. Eighteen (55%) were female. The median age was 31.0 years, and the median weight was 67.0 kg.

	Twenty-six patients (79%) were over the age of 16 years. Nine patients (27%) had type 1 VWD; four (12%), type 2A; four (12%), type 2B; 12 (36%), type 3; and four (12%), unspecified.
Primary and secondary endpoints	Haemostatic efficacy was measured by the investigator's daily rating (excellent/good, fair/poor, or none) for each treatment event as well as an overall rating, following completion of the study treatment. If the patient had daily efficacy ratings of fair/poor or none for three consecutive ratings, treatment was considered temporarily ineffective. Additional efficacy assessments included the number of study medication infusions required, the number of days treated, and the occurrence of visible haemorrhages. The safety of FVIII/VWF concentrate was assessed by analysing the incidence of unexpected and treatment- related adverse events (AEs).
Method of analysis	All statistical analyses were descriptive. Two-sided confidence intervals (CI) according to Clopper-Pearson were calculated for the proportion of subjects with an excellent or good overall haemostatic efficacy and for the proportion of subjects with a temporarily ineffective treatment regimen. The safety analysis included data from treatment events in which patients received at least one dose of study medication. The efficacy analysis included data from patient treatment events in which there was one postbaseline-efficacy assessment and the study subject received at least one dose of the study medication. For purposes of this analysis, bleeding episodes were categorized as severe [refractory epistaxis, gastrointestinal (GI) haemorrhage, central nervous system trauma, other traumatic haemorrhage], moderate (moderate epistaxis, oral bleeding, menorrhagia), or mild.
Subgroup analyses	n/a

8.2.4 Wilnativ/Wilate - Studies reporting on on-demand treatment of bleedings episodes

Table 40 Study characteristics Berntorp 2009[2]	
Trial name	Treatment and prevention of acute bleedings in von Willebrand disease--efficacy and safety of Wilate, a new generation von Willebrand factor/factor VIII concentrate. Haemophilia. In the application this study will be referred to as "Berntorp 2009"
NCT number	This study has not been recorded in www.clinicaltrials.gov.
Objective	The publication reports on a clinical study program consisting of 4 individual studies* designed with objective to evaluate clinical efficacy, safety and tolerability of Wilate®, an albumin-free VWF/FVIII concentrate with a ratio of the two haemostatic moieties of approximately 1 to 1 in patients with inherited VWD of all disease types, in the prevention and treatment of bleeding episodes as well as in prevention of bleedings in surgeries. *It has not been possible to identify separate publications or descriptions for these studies individually. The results for results for prevention of bleedings in surgery are reported in Windyga 2011 described elsewhere in this application. *[3]*
Publications – title, author, journal, year	Berntorp E, Windyga J; European Wilate Study Group. Treatment and prevention of acute bleedings in von Willebrand disease--efficacy and safety of Wilate, a new generation von Willebrand factor/factor VIII concentrate. Haemophilia. 2009 Jan;15(1):122-30. doi: 10.1111/j.1365-2516.2008.01901.x. PubMed PMID: 19149848.
Study type and design	The studies were prospective, open, noncontrolled, non-randomized, multicentre phase II- or phase III-trials.
Follow-up time	No specific follow up time has been reported.
Population (inclusion and exclusion criteria)	The study is not registered at clinicaltrials.gov. The following information has been sourced from the publication (Berntorp 2009). <u>Inclusion:</u> Inherited VWD of all types. Only HIV negative patients not sufficiently responding to DDAVP treatment were eligible to participate. Moreover, in all but one study only patients older than 12 years were included. <u>Exclusion</u> criteria were amongst others: Pregnant or lactating women, patients with present or past inhibitor activity against FVIII or VWF, known history of intolerance vs. plasma derived or blood products, and severe illnesses such as liver or kidney diseases, were excluded from participation in the studies.
Intervention	A general dosing recommendation of 20–50 IU Wilate® per kilogram bodyweight was given for the treatment or prevention of spontaneous or trauma induced haemorrhages. Actual dose and duration of treatment depended on the individual clinical situation (e.g. severity and location of bleeding, VWD type) and were at the discretion of the treating physician. Study drug was administered intravenously as a bolus infusion. In the on-demand part of the studies 44 patients received a total of 1095 infusions.
Baseline characteristics	Demographic characteristics and bleeding frequency before study entry of the 44 patients included in the European Wilate® trials.

		VWD type 2				
	VWD type 1	2A	2B	2N	VWD type 3	Total
Number of individuals (n)	8	6	4	2	24	44
Male/female (n)	4/4	1/5	2/2	1/1	12/12	20/24
Mean age, years (range)	34.9 (5–63)	43 (10–73)	54 (35–65)	25 (25–25)	24.9 (6–56)	31.9 (5–73)

	Mean body weight, kg (range)	58 (19–70)	67 (26–80)	78 (63–88)	64 (63–65)	60 (23–104)	62 (19–104)
	Mean number of BEs per month before study entry (range)	1.5 (0.1–8)	1.9 (0.25–4)	4.6 (1–8)	0.17 (0.08–0.25)	4.2 (0.2–28)	3.2 (0.1–28)
	Mean VWF:RCo baseline, % (range)	50 (12–95)	35 (14–63)	27 (12–42)	80 (63–97)	4 (1–14)	–
	Mean VWF:Ag baseline, % (range)	49 (12–108)	80 (22–183)	58 (30–116)	90 (84–96)	<5*	–
	Mean FVIII:C baseline, % (range)	46 (5–78)	68 (35–135)	59 (36–117)	4 (3–5)	3 (0–16)	–
Primary and secondary endpoints	The publication does not specifically report endpoints in a formalized manner. The following is an excerpt of the relevant sections in the publication. Response to treatment was rated by the investigator, or by the patients or their parents in case of home treatment, using a 4-point verbal scale (excellent, good, moderate, none). This is reported as no of treated bleeds, dose per treatment day (mean/median), no of treatment days (mean/median), percentage efficacy (excellent/good) per bleeding site. Other outcomes reported per type of VWD include: No. (mean/median) treatment days per bleeding episode, mean and median dose per kg per day, mean and median loading dose per kg per day, man and median maintenance dose per kg per day All adverse events (AEs) occurred during the trials were reported, including events present at baseline which worsened during the study. Adverse events were classified using MedDRA primary system organ class preferred terms. AEs were reported by patients or their parents and recorded by the investigators. Tolerability was assessed by investigators and patients using a 4-point verbal rating scale (very good, good, satisfactory and unsatisfactory).						
Method of analysis	Statistical analyses were performed on a dataset pooled from four separate good clinical practice prospective trials. Descriptive statistics (mean, median, range and SD) were employed for the data analysis of the study variables. Several subgroup analyses were performed, e.g. patients of 12 or less years of age, patients with GI bleeds, or patients with extended periods of prophylactic treatment. All treated patients were included in the efficacy and safety analyses.						
Subgroup analyses	See above.						

8.3 Surgery - Studies reporting on prevention of bleeding in surgery

8.3.1 Willfact/Willfactin - Studies reporting on prevention of bleeds during surgery

For studies reporting on Willfact/Willfactin in surgery, please refer to the description of Borel-Derlon in section 8.2.4.

8.3.2 Veyvondi - Studies reporting on prevention of bleeds during surgery

Table 41 Study characteristics Peyvandi 2018 [12]	
Trial name	"Peyvandi 2018" A Phase 3, Prospective, Multicentre Study to Evaluate Efficacy and Safety of Recombinant Von Willebrand Factor (rVWF) With or Without ADVATE in Elective Surgical Procedures in Subjects With Severe Von Willebrand Disease
NCT number	NCT02283268
Objective	This study evaluated the haemostatic efficacy/safety profile of rVWF, with/without recombinant factor VIII (rFVIII), in patients with severe VWD undergoing surgery
Publications – title, author, journal, year	Peyvandi F, et al. Phase 3 Study of Recombinant von Willebrand Factor in Patients With Severe von Willebrand Disease Who Are Undergoing Elective Surgery. J Thromb Haemost. 2018 Oct 25. doi: 10.1111/jth.14313. [Epub ahead of print] PubMed PMID: 30362288
Study type and design	This was a phase 3, prospective, open-label, uncontrolled, nonrandomized study.
Follow-up time	Patients were followed for 14 days post-surgery.
Population (inclusion and exclusion criteria) [CT.gov]	Inclusion Criteria: • Diagnosis of severe von Willebrand disease (VWD) as listed below and elective surgical procedure planned 1. Type 1 (Von Willebrand factor : Ristocetin cofactor activity (VWF:RCo) <20 IU/dL), or 2. Type 2A (as verified by multimer pattern), Type 2B (as diagnosed by genotype), Type 2N (FVIII:C<10% and historically documented genetics), Type 2M, or 3. Type 3 (Von Willebrand factor antigen (VWF:Ag) ≤ 3 IU/dL) • VWD with a history of requiring substitution therapy with von Willebrand factor (VWF) concentrate to control bleeding • If type 3 VWD (VWF Antigen /VWF:Ag ≤ 3 IU/dL), participant has a medical history of at least 20 exposure days to VWF/FVIII coagulation factor concentrates (including cryoprecipitate or fresh frozen plasma) • If type 1 or type 2 VWD, participant has a medical history of 5 exposure days or a past major surgery requiring VWF/FVIII coagulation factor concentrates (including cryoprecipitate or fresh frozen plasma) • Participant is at least 18 years of age • If female of childbearing potential, participant presents with a negative pregnancy test • If applicable, participant agrees to employ adequate birth control measures for the duration of the study • Participant is willing and able to comply with the requirements of the protocol Exclusion Criteria:

	• Diagnosis of pseudo VWD or another hereditary or acquired coagulation disorder (eg, qualitative and quantitative platelet disorders or elevated prothrombin time [PT] / international normalized ratio [INR] > 1.4) • History or presence of a VWF inhibitor at screening • History or presence of a factor VIII (FVIII) inhibitor with a titer ≥ 0.4 BU (Nijmegen-modified Bethesda assay) or ≥ 0.6 BU (by Bethesda assay) • Known hypersensitivity to any of the components of the study drugs, such as to mouse or hamster proteins • Medical history of immunological disorders, excluding seasonal allergic rhinitis/conjunctivitis, mild asthma, food allergies or animal allergies • Medical history of a thromboembolic event • HIV positive with an absolute CD4 count < 200/mm3 • Platelet count < 100,000/mL • Diagnosis of significant liver disease, as evidenced by, but not limited to, any of the following: serum alanine aminotransferase (ALT) 5 times the upper limit of normal; hypoalbuminemia; portal vein hypertension (e.g. presence of otherwise unexplained splenomegaly, history of oesophageal varices) or liver cirrhosis classified as Child B or C • Diagnosis of renal disease, with a serum creatinine level ≥ 2 .5mg/dL • Participant has been treated with an immunomodulatory drug, excluding topical treatment (eg, ointments, nasal sprays), within 30 days prior to signing the informed consent • Participant is pregnant or lactating at the time informed content is obtained • Participant has participated in another clinical study involving an investigational product (IP), other than rVWF with or without ADVATE, or investigational device within 30 days prior to enrolment or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study. However, eligible patients participating in the rVWF Prophylaxis Study (071301) may be enrolled. • Progressive fatal disease and/or life expectancy of less than 3 months • Participant is identified by the investigator as being unable or unwilling to cooperate with study procedures • Participant suffers from a mental condition rendering him/her unable to understand the nature, scope and possible consequences of the study and/or evidence of an uncooperative attitude • Participant is in prison or compulsory detention by regulatory and/or juridical order • Participant is a member of the study team conducting this study or in a dependent relationship with one of the study team members. Dependent relationships include close relatives (ie, children, partner/spouse, siblings, parents) as well as employees.
Intervention	Patients scheduled for major surgery had an initial PK/PD evaluation over a 72-hour period within 42 days of surgery, and results were used to guide preoperative dosing. The intervention was rVWF (vonicog alfa, Veyvondi®), and depending on FVIII levels rFVIII (Advate®). At 12-24 hours before surgery, rVWF 40–60 IU/kg VWF:RCo was given intravenously to allow endogenous FVIII:C levels to rise to ≥30 IU/dL (minor/oral surgery) or ≥60 IU/dL (major surgery), which were to be assessed within 3 hours of initiation of the surgery. If target FVIII:C levels were achieved, rVWF alone was administered within 1–2 hours before surgery to achieve the predefined peak levels described in the publication. If target FVIII:C levels were not achieved, rVWF was co-administered with rFVIII (ADVATE®, Antihemophilic Factor [Recombinant]) within 1–2 hours before surgery to

	meet recommended peak levels. Intraoperative and postoperative dosing were individualized to maintain target trough levels according to PK/PD results, as well as the intensity and duration of the haemostatic challenge. Post-surgery, patients were monitored for 14 days and target trough plasma levels of VWF:RCo and FVIII:C were maintained according to the type of surgery the patient received
Baseline characteristics	**Characteristic** — **Total (N=15)** Sex, n (%) Male — 7 (46.7) Female — 8 (53.3) Age, median (range), y — 40 (20–70) Weight, median (range), kg — 73.5 (52–127.2) BMI, median (range), kg/m2 — 25.6 (17.1–38) VWD type, n (%) 1 — 3 (20) 2A — 2 (13.3) 2B — 1 (6.7) 2M — 1 (6.7) 3 — 8 (53.3) FVIII:C, mean (SD), IU/dL All VWD types (n=15) — 16.4 (19.9) Type 1 VWD (n=3) — 17 (4) Type 2A VWD (n=2) — 34.5 (23.3) Type 2B VWD (n=1) — 36 Type 2M VWD (n=1) — 66 Type 3 VWD (n=8)* — 3.0 (1.5) Mean (SD) VWF:RCo, IU/dL All VWD types (n=14) — 10.6 (13.3) Type 1 VWD (n=3) — 14.3 (3.1) Type 2A VWD (n=2) — 29.0 (26.9) Type 2B VWD (n=1) — 23 Type 2M VWD (n=1) — 13 Type 3 VWD (n=7) — 1.7 (4.5)
Primary and secondary endpoints	**Primary endpoint:** <u>Overall Haemostatic Efficacy as Assessed by the Investigator (Hemophilia Physician)</u> *[Time Frame: 24 hours after last peri-operative infusion or at completion of Day 14 (± 2 days) visit, whichever occurs earlier]* Haemostatic efficacy was rated on a scale of excellent - good - moderate – none, defined as follows: • Excellent: Intra-, and postoperative haemostasis achieved with rVWF with or without ADVATE was as good or better than that expected for the type of surgical procedure performed in a haemostatically normal subject. • Good: Intra-, and postoperative haemostasis achieved with rVWF with or without ADVATE was probably as good as that expected for the type of surgical procedure performed in a haemostatically normal subject. • Moderate: Intra-, and postoperative haemostasis with rVWF with or without ADVATE was clearly less than optimal for the type of procedure performed but was maintained without the need to change the rVWF concentrate. • None: Participant experienced uncontrolled bleeding that was the result of inadequate therapeutic response despite proper dosing, necessitating a change of rVWF concentrate. **Secondary endpoints**

	• Intraoperative Actual Versus Predicted Blood Loss as Assessed by the Operating Surgeon • Intraoperative Actual Blood Loss Relative to Predicted Blood Loss • Intraoperative Actual Versus Predicted Blood Loss Score as Assessed by the Operating Surgeon • Intraoperative Haemostatic Efficacy Score as Assessed by the Operating Surgeon • Daily Intra- and Postoperative Weight-adjusted Dose of rVWF With or Without ADVATE • Occurrence of Adverse Events • Occurrence of Thrombotic Events • Occurrence of Severe Allergic Reactions (e.g. Anaphylaxis) • Number of Participants Who Developed Inhibitory and Total Binding Antibodies to Von Willebrand Factor (VWF) and Inhibitory Antibodies to Factor VIII (FVIII) • Number of Participants Who Developed Antibodies to Chinese Hamster Ovary (CHO) Proteins, Mouse Immunoglobulin G (IgG) or Recombinant Furin (rFurin) For endpoint related to the PK parts of the study, please refer to clinicaltrials.gov (NCT02283268)
Method of analysis	A minimum of 15 patients with severe VWD who were undergoing surgery were planned, with ≥10 major surgical procedures evaluated. Descriptive statistical analyses included point estimates and 90% confidence intervals for the incidence of individuals with haemostatic efficacy rated “excellent/good” and were determined using a Clopper Pearson test and SAS v9.4. PK/PD and safety were summarized using descriptive statistics.
Subgroup analyses	n/a

8.3.3 Haemate/Humate - Studies reporting on prevention of bleeds during surgery

Table 42 Study characteristics Gill 2011 [14]	
Trial name	Study of Safety and Efficacy of Antihemophilic Factor/Von Willebrand Factor Complex (Humate-P®) Using Individualized Dosing in Pediatric and Adult Surgical Subjects With Von Willebrand's Disease
NCT number	NCT00168090
Objective	The objective of the study was to evaluate the safety, efficacy and optimal dosing of a VWF/FVIII concentrate (Humate-P) in subjects with VWD undergoing elective surgery.
Publications – title, author, journal, year	Gill JC, Shapiro A, et al. von Willebrand factor/factor VIII concentrate (Humate-P) for management of elective surgery in adults and children with von Willebrand Disease. Haemophilia. 2011 Nov;17(6):895-905.
Study type and design	This was a prospective, open-label, multinational phase IV study.
Follow-up time	Follow-up time after surgery was defined as 24 h after the last infusion or on Day 14 which ever was earlier.
Population (inclusion and exclusion criteria) [ct.gov]	Key Inclusion Criteria: • Subjects of any age • Clinical and laboratory diagnosis of vWD that can be expected to show no haemostatic response to DDAVP • Require substitution with vWF/FVIII complex due to a surgery Key Exclusion Criteria: • Known significant haemostatic disorder other than vWD • Acquired vWD • Known antibodies to FVIII or vWF • Known platelet type vWD • Emergency surgery or any surgery with a degree of urgency not permitting completion of a pharmacokinetic assessment required by the study protocol • History of allergic reaction to Humate-P® • Treatment with any other investigational drug in the last four weeks before the entry into the study (with exception of trials concerning anti-HIV agents) • Progressive fatal disease/life expectancy of less than 6 months • Treatment with DDAVP, cryoprecipitate, whole blood, plasma and plasma derivatives containing substantial quantities of FVIII and/or vWF within 5 days of the pre-surgical pharmacokinetic assessment • Paediatric patients of insufficient body weight to permit PK sampling • Woman in the first 20 weeks of pregnancy
Intervention	Plasma derived FVIII/VWF (Humate-P/Haemate). The dosing was individualized as each subject underwent a PK analysis in the steady state before surgery, with the results used to determine the initial preoperative loading and maintenance dosing. For the first 15 patients the in vivo recovery (IVR) value obtained in the PK study was used to determine the 'full dose' of VWF/FVIII expected to achieve target VWF:RCo and FVIII plasma levels of at least 100 IU dL)1. The actual surgical loading dose was then calculated as 1.5 times the 'full dose' to compensate for the potential for increased factor consumption during surgery and postoperatively as seen in haemophilia. In the absence of evidence of increased factor consumption, a protocol amendment was subsequently adopted such that surgical loading doses were designed to achieve

	plasma VWF:RCo levels of 50–60 IU dL)1 for oral/minor surgeries, and 80–100 IU dL)1 for major surgeries
Baseline characteristics	Total, N: 42 ‡16 years, n (%): 33 (78.6) <16 years, n (%): 9 (21.4) Median age, years (range): 21 (1–75) Gender, n (%) Female: 28 (66.7) Ethnicity, n (%) White: 31 (73.8) African American: 2 (4.8) Hispanic: 7 (16.7) Oriental/Asian: 1 (2.4) Other: 1 (2.4) Mean body mass index, kg m)2 (range): 24.9 (13.3–63.6) VWD type, n (%) 1: 17 (40.5) 1 severe*: 2 (4.8) 2A: 2 (4.8) 2A severe*: 1 (2.4) 2B: 4 (9.5) 2B severe*: 1 (2.4) 2M: 6 (14.3) 2M severe*: 2 (4.8) 3: 13 (31.0) 3 severe*: 12 (28.6) Median baseline VWF:RCo (range): 13 IU dL)1 (6–124 IU dL)1) Median baseline FVIII (range): 39 IU dL)1 (0.5–96 IU dL)1)
Primary and secondary endpoints	The primary efficacy endpoint was overall haemostatic efficacy, defined as the investigator's assessment of haemostatic efficacy 24 h after the last VWF/FVIII concentrate infusion, or on day 14, whichever was earlier, using the 4-point scale. Efficacy was assessed as 'effective' for excellent or good haemostasis and 'ineffective' for moderate/poor or no haemostasis. Other clinical endpoints included estimated blood loss and transfusion requirements. Safety outcomes included clinical evidence of thromboembolic complications, viral testing for parvovirus B19 and hepatitis C. All adverse events (AEs), including new intercurrent illness or worsening of existing illness, were reported and documented
Method of analysis	The study consisted of three phases: a preoperative PK phase, a surgery phase (from the preoperative loading dose of VWF/FVIII concentrate to day 14) and a viral safety follow-up phase (baseline to 4 weeks after final infusion). The intent-to-treat (ITT) population was defined as all enrolled subjects who underwent surgery. The preoperative PK population included all subjects who had sufficient laboratory values to determine a reliable PK profile. The safety population comprised all subjects who received at least one dose of study drug. Primary efficacy analysis. The primary efficacy endpoint was overall haemostatic efficacy, defined as the investigator's assessment of haemostatic efficacy 24 h after the last VWF/FVIII concentrate infusion, or on day 14, whichever was earlier, using the 4-point scale. Efficacy was assessed as 'effective' for excellent or good haemostasis and 'ineffective' for moderate/poor or no haemostasis. A two-sided, 95% Blyth–Still–Casella confidence interval (CI) was utilized for calculation of the proportion of subjects with effective treatment using StatXact (Cytel, Inc., Cambridge, MA, USA) for Windows.

Subgroup analyses	Not reported

Table 43 Study characteristics Lethagen 2007 [15]	
Trial name	von Willebrand factor/factor VIII concentrate (Haemate P) dosing based on pharmacokinetics: a prospective multicenter trial in elective surgery.
NCT number	Not reported
Objective	To determine the feasibility of dosing Haemate P_ VWF/factor VIII (FVIII) concentrate based on pharmacokinetics (PK) in the management of surgical subjects with VWD.
Publications – title, author, journal, year	Lethagen S, Kyrle PA, Castaman G, Haertel S, Mannucci PM; HAEMATE P Surgical Study Group. von Willebrand factor/factor VIII concentrate (Haemate P) dosing based on pharmacokinetics: a prospective multicenter trial in elective surgery. J Thromb Haemost. 2007 Jul;5(7):1420-30. Epub 2007 Apr 16. PubMed PMID: 17439628.
Study type and design	Prospective multicentre open-label cohort study.
Follow-up time	Final evaluation was performed on Day 14 after surgery.
Population (inclusion and exclusion criteria)	The study is not recorded at www.clinicaltrials.gov. The following information is from the publication. Inclusion • a clinical and laboratory diagnosis of VWD • a history of abnormal bleeding • males and females > 5 years old with hereditary VWD Enrolment was restricted to subjects scheduled for elective surgery requiring a hospital stay of at least 24 h. Exclusion criteria were • acquired VWD, known antibodies to FVIII or VWF, platelet type VWD, and exposure to DDAVP, FVIII inhibitor bypass activity (FEIBA), cryoprecipitate or blood or plasma derivatives containing FVIII or VWF within 10 days prior to PK infusion or surgery.
Intervention	Plasma derived FVIII/vWF (Haemate-P) was administered to a total of 28 patients. General recommendations for target levels of VWF:RCo and FVIII:C to be attained after the loading dose and therapeutic/maintenance infusions were provided to the investigators. The loading dose required to achieve a target VWF:RCo concentration increment (ΔVWF:RCo) in IU/dL was calculated based on individual subject PK results as dose = ΔVWF:RCo-bw/$IVR_{observed}$. The initial loading infusion was administered 1–2 h before the start of the elective procedure. Postoperative doses were given at the discretion of the investigator. It was recommended that required postoperative infusions be administered at least once every 24 h
Baseline characteristics	**Characteristic** **n** **%** Gender Female 20 69 Male 9 31 Ethnic group Caucasian 26 90 Oriental 3 10 Age (years) 5–16 2 7 17–64 22 76

	‡65	5	17
	Type of von Willebrand disease		
	1	10	34.5
	2A	10	34.5
	2M	1	3
	3	8	28
	Type of surgery		
	Minor	11	41
	Major	16	59
Primary and secondary endpoints	Endpoints are not reported in a hierarchical manner but included both pharmacokinetic and clinical endpoints. Of relevance for this application is • assessment of haemostatic efficacy according to a 4-point scale at the day of surgery, day 1 after surgery and day 14 after surgery		
Method of analysis	The method of analysis is reported for the pharmacokinetic evaluations only, but not for the clinical endpoint. Results for haemostasis efficacy are provided as percentage (CI) of patients with a given haemostasis rating.		
Subgroup analyses	n/a		

8.3.4 Wilnativ/Wilate - Studies reporting on prevention of bleeds during surgery

<table>
<tr><td colspan="2">Table 44 Study characteristics Srivastava 2017 [13]</td></tr>
<tr><td>Trial name</td><td>Prospective, Open-Label, Multi-Centre, Phase III Clinical Study to Investigate the Efficacy and Safety of Human Factor VWF/FVIII Concentrate (Wilate) in Subjects With Inherited Von Willebrand Disease Who Undergo Surgical Procedures (WONDERS)</td></tr>
<tr><td>NCT number</td><td>NCT01365546</td></tr>
<tr><td>Objective</td><td>To evaluate the haemostatic efficacy and safety of Wilate® in maintaining intra- and postoperative haemostasis in surgical procedures</td></tr>
<tr><td>Publications – title, author, journal, year</td><td>Srivastava A, et al. Efficacy and safety of a VWF/FVIII concentrate (Wilate®) in inherited von Willebrand disease patients undergoing surgical procedures. Haemophilia. 2017 Mar;23(2):264-272.</td></tr>
<tr><td>Study type and design</td><td>Prospective, open-label, multinational, multicentre phase III clinical study.</td></tr>
<tr><td>Follow-up time</td><td>For the efficacy parameter the patient was followed until 24h after the last infusion with Wilate.</td></tr>
<tr><td>Population (inclusion and exclusion criteria)</td><td>Inclusion Criteria:
6 years or older
Diagnosed with congenital VWD (von Willebrand Disease)
Require therapy with a VWF (von Willebrand Factor) product to treat any major surgical procedure
Exclusion Criteria:
Known coagulation disorder other than VWD
Known history of, or suspected VWF or FVIII inhibitors
Subjects with hepatic liver disease
Known or suspected hypersensitivity or previous evidence of severe side effects to Wilate or other VWF/FVIII concentrates
Pregnant women in the first 20 weeks of gestation</td></tr>
<tr><td>Intervention</td><td>Human VWF/FVIII concentrate (Wilate®) intravenous infusion. Dose based on subject's individual in vivo-recovery.
Dosing
All doses were administered as a bolus intravenous infusion. All patients received 60 IU/kg of Wilate® for the in vivo recovery (IVR) investigation at study start to calculate the recommended dosing for surgeries; additionally, the following guidelines were given:
Major surgery. A loading dose of 40–60 VWF:RCo IU/kg1 within 3 h of start of procedure was given to achieve peak plasma VWF:RCo level of 100%. A maintenance dose of 20–40 VWF:RCo IU/kg or half of the loading dose was given every 12–24 h. Trough levels of VWF:RCo were to be maintained at >50% for at least 6 days. At least two maintenance doses were to be administered within the first 24 h after the start of surgery.
Minor surgery. A loading dose of 30–60 VWF:RCo IU/kg within 3 h of start of procedure was given to achieve peak plasma VWF: RCo level of 50%. A maintenance dose of 20–40 VWF: RCo IU kg/1 or half of the loading dose was given every 12–24 h.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td>Parameters</td><td>ITT population (N=30)</td></tr>
<tr><td>Age at screening</td><td></td></tr>
<tr><td>Mean (SD)</td><td>38.3 (16.8)</td></tr>
<tr><td>Median (range)</td><td>36.0 (12-74)</td></tr>
</table>
</td></tr>
</table>

Height (cm)	
Mean (SD)	161.9 (11.2)
Median (range)	162.0 (141-187)
Weight	
Mean (SD)	69.4 (23.6)
Median (range)	63.7 (39-126)
Gender, N (%)	
Male	9 (30.0)
Female	21 (70.0)
Race, N (%)	
White	18 (60.0)
Asian	12 (40.0)
VWD type, N (%)	
Type 1	7 (23.3)
Type 2	2 (6.7)
Type 3	21 (70.0)
Family history of VWD, N (%)	
Yes	11 (36.7)
No	16 (53.3)
Unknown	3 (10.0)
VWF inhibitor activity, N (%)	
Yes	0 (0)
No	30 (100)

Primary and secondary endpoints

Primary Outcome Measures :

- Overall Haemostatic Efficacy (Success or Failure) of Wilate, Based on the Intra-operative Assessment of the Surgeon and the Post-operative Assessment by the Investigator Using a 4-point Ordinal Efficacy Scale. [Time Frame: 30 Days]

Efficacy of Wilate in surgical procedures was assessed intra-operatively by the surgeon and post-operatively by the investigator. The IDMC additionally conducted an independent adjudication of all haemostatic efficacy results ('secondary adjudication') and adjudicated the surgeons'/investigators' assessments of the intra- and post-operative assessments where there were discrepancies between the two assessments ('primary adjudication').
It was specified in the SAP that the study will be terminated early and success claimed if the two-sided 98.75% confidence interval (CI) for the overall success rate excludes and is greater than 0.60 (equivalent to 25 or more successes out of the 30 procedures).

Secondary Outcome Measures:
1. Assessment of Intra-operative Haemostatic Efficacy [Time Frame: 1 Day]
The efficacy of Wilate during surgical procedures was assessed by a 4-point ordinal efficacy scale by the surgeon at the end of the surgical procedure and took the predicted versus actual blood loss and transfusion requirements into consideration. Outcome measure 1 takes the results of outcome measure 2 and 3 into consideration and is an overall assessment covering intra- and post-operative efficacy.

2. Post-operative Efficacy Assessment [Time Frame: up to 30 days]
Post-operative efficacy was assessed by the investigator, covering the time period from the end of the procedure up to 24 hours following the last infusion of study

	medication. This assessment took the post-operative bleeding and oozing into consideration Clinical tolerability was assessed by monitoring vital signs, laboratory parameters (including VWF inhibitors and virus markers) and adverse events.
Method of analysis	The primary analysis focused on the overall proportion of surgeries rated as successful (Table 1). For the overall efficacy assessment, a CI of 98.75% was used, and for the intra- and postoperative assessment, a CI of 95% was used.
Subgroup analyses	n/a

Table 45 Study characteristics Windyga 2011[3]	
Trial name	*Efficacy and safety of a new generation von Willebrand factor/factor VIII concentrate (Wilate®) in the management of perioperative haemostasis in von Willebrand disease patients undergoing surgery*
NCT number	Not reported.
Objective	The aim of this study was to assess the efficacy of Wilate®, a new generation, plasma-derived, high-purity, double virus-inactivated von Willebrand factor (VWF) and factor VIII (FVIII) concentrate (ratio close to physiological 1:1) in the perioperative management of haemostasis in von Willebrand disease (VWD). The publication reports on a clinical study program consisting of 4 individual studies* designed with objective to evaluate clinical efficacy, safety and tolerability of Wilate®, an albumin-free VWF/FVIII concentrate with a ratio of the two haemostatic moieties of approximately 1 to 1 in patients with inherited VWD of all disease types, in the prevention and treatment of bleeding episodes as well as in prevention of bleedings in surgeries. *It has not been possible to identify separate publications or descriptions for these studies individually. The results for results for prevention of bleedings in surgery are reported in Berntorp 2009 2011 described elsewhere in this application
Publications – title, author, journal, year	*Windyga J, von Depka-Prondzinski M; European Wilate® Study Group. Efficacy and safety of a new generation von Willebrand factor/factor VIII concentrate (Wilate®) in the management of perioperative haemostasis in von Willebrand disease patients undergoing surgery. Thromb Haemost. 2011 Jun;105(6):1072-9. doi: 10.1160/TH10-10-0631. Epub 2011 Mar 24. PubMed PMID: 21437358.*
Study type and design	The publication reports pooled data from four European, prospective, open-label, non-controlled, non-randomised, multicentre phase II or III clinical trials.
Follow-up time	The assessment of efficacy was made after complete recovery from the surgical procedure (at the Investigator's discretion).
Population (inclusion and exclusion criteria)	Inclusion: Patients with inherited VWD of any type who did not respond adequately to DDAVP (confirmed by a test if appropriate) and were HIV-negative were eligible for inclusion. Three studies enrolled patients >12 years of age and one study included patients aged ≤12 years. Exclusion: Pregnant or lactating women, patients with current or past history of inhibitor activity against FVIII or VWF, patients with known intolerance to plasma- derived or blood products, and patients with severe illness (e.g. liver or kidney disease) were excluded.

<table>
<tr><td></td><td>This publication reports data for perioperative management of hemostasis on 33 patients from a total of 84 patients enrolled in the four studies.</td></tr>
<tr><td>Intervention</td><td>The intervention was plasma derived FVIII/VWF (Wilate®, Wilnativ®).

Dosing was calculated according to the investigator's discretion in one study and according to the following recommendations in three studies: major surgery; dosing once daily or every other day with the objective to maintain a FVIII:C level of >50 IU/dl until healing is complete; minor surgery: dosing once daily or every other day with the objective to maintain a FVIII:C level of >30 IU/ dl until healing is complete; dental surgery: single dose with the objective to maintain a FVIII:C level of >30 IU/dl for up to six hours.
Wilate® was administered intravenously as a bolus or continuous infusion.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td></td><td colspan="3">VWD Subtype</td><td>Total</td></tr>
<tr><td></td><td>1</td><td>2</td><td>3</td><td></td></tr>
<tr><td>Number of patients</td><td>4</td><td>9</td><td>19</td><td>32</td></tr>
<tr><td>Male/female, n</td><td>0/4</td><td>6/3</td><td>9/10</td><td>15/17</td></tr>
<tr><td>Age at entry, years
median (range)</td><td>56 (50-65)</td><td>55 (25-77)</td><td>40 (6-70)</td><td>50 (6-77)</td></tr>
<tr><td>Body weight, kg
median (range)</td><td>65 (60-67)</td><td>75 (53-95)</td><td>66 (28-104)</td><td>67 (28-104)</td></tr>
<tr><td>Mean VWF:RCo,
% median (range)</td><td>57.5 (15-59)</td><td>31 (10-86)</td><td>5* (0-10)</td><td>10* (0-86)</td></tr>
<tr><td>Mean FVIII:C,
% median (range)</td><td>51.5 (6-125)</td><td>50* (10-105)</td><td>7 (2-39)</td><td>10* (2-125)</td></tr>
<tr><td colspan="5">*Data were not available for one patient.</td></tr>
</table>
</td></tr>
<tr><td>Primary and secondary endpoints</td><td>Haemostatic efficacy was rated by the investigator using a four-point scale (excellent, good, moderate or none).
Three studies used the following definitions: none: severe uncontrolled bleeding or intensity of bleeding not changed (in case of non-severe bleeding episodes); moderate: moderate bleeding, or control of bleeding required additional product; good: slight oozing and adequate control of bleeding episode; did not require additional product; excellent: haemostasis achieved, cessation of bleeding episode. In one study, efficacy was rated excellent, good, moderate or none according to the Investigator's discretion (two surgeries were performed in this study, one major and one minor). The assessment of efficacy was made after complete recovery from the surgical procedure (at the Investigator's discretion).
All adverse events (AEs) that occurred during the trials and baseline AEs that worsened during the trials were recorded. AEs were classified using the standard MedDRA coding dictionary. Tolerability was also assessed by investigators and patients using a four-point rating scale (very good, good, satisfactory and unsatisfactory).</td></tr>
<tr><td>Method of analysis</td><td>Statistical analyses were performed on a dataset pooled from four separate prospective trials. Descriptive statistics (mean, median, range and SD) were employed for the data analysis of the study variables.</td></tr>
<tr><td>Subgroup analyses</td><td>Subgroup analyses were performed according to surgery type (major or minor) and in children aged 12 years or younger. Methodology not reported.</td></tr>
</table>

Medicinrådets protokol for vurdering af klinisk merværdi for vonicog alfa til behandling af von Willebrand sygdom

Handelsnavn	Veyvondi
Generisk navn	Vonicog alfa
Firma	Shire
ATC-kode	B02BD10
Virkningsmekanisme	Rekombinant von Willebrand faktor (rvWf)
Administration/dosis	Infusion af 40-80 IE/kg hver 8.-24. time i henhold til det ønskede faktorniveau og den opnåede effekt.
Forventet EMA-indikation	Voksne (≥ 18 år) med von Willebrand sygdom (vWD) når behandling med desmopressin (DDAVP) alene er ineffektiv eller ikke er indiceret til behandling af hæmorrhagi og kirurgisk blødning samt forebyggelse af kirurgisk blødning.
Godkendelsesdato Offentliggørelsesdato Dokumentnummer Versionsnummer	09.10.2018 30.10.2018 28812 1.1

Ændringslog

Version	Dato	Rettelser
1.1	30.10.2018	Effektmålet ”Alvorlig venøs tromboemboli” er konsekvensrettet og angivet som værende ”vigtigt”, både i tabel 2 på side 8 og i beskrivelsen af effektmålet. De søgetermer, som skal anvendes ved litteratursøgningen, er rettet, fordi søgningen alene skal baseres på indikationen ”von Willebrand disease”.

Fagudvalgets sammensætning og sekretariatets arbejdsgruppe se bilag 1

Indhold

Forkortelser

DDAVP:	Desmopressin
EMA:	*European Medicines Agency*
EPAR:	European public assessment report
FVIII:	Koagulationsfaktor VIII
GRADE:	System til vurdering af evidens (*Grading of Recommendations Assessment, Development and Evaluation*)
IVR:	*In vivo recovery*
RCo:	Ristocetin co-faktor
rFVIII	Rekombinant koagulationsfaktor VIII
rvWf	Rekombinant von Willebrand faktor
ULM:	*Ultra large multimers*
vWD:	von Willebrand sygdom
vWf:	von Willebrand factor

1 Formål

Protokollen har til formål at definere de kliniske spørgsmål, der ønskes belyst i vurderingen af vonicog alfa som mulig standardbehandling af patienter (≥ 18 år) med von Willebrand sygdom (vWD). I protokollen angives en definition af populationer, komparatorer og effektmål, der skal præsenteres i den endelige ansøgning, samt de metoder, der ønskes anvendt til den komparative analyse. Arbejdet med protokollen er igangsat på baggrund af den foreløbige ansøgning vedrørende vonicog alfa modtaget den 3. september 2018.

Protokollen danner grundlaget for den endelige ansøgning for vurderingen af den kliniske merværdi af vonicog alfa sammenlignet med dansk standardbehandling. Alle effektmål, der er opgivet i denne protokol, skal besvares med en sammenlignende analyse mellem vonicog alfa og de tre komparatorer Haemate, Wilnativ og Willfact af både absolutte og relative værdier for de udspecificerede populationer i de angivne måleenheder (se tabel 1). Litteratursøgning og databehandling udføres som beskrevet i protokollen.

2 Baggrund

Von Willebrand sygdom er den hyppigste blødersygdom i Danmark. Incidens og prævalens er ikke fuldstændig kendt, da mange milde tilfælde ikke diagnosticeres. Der er registreret i alt ca. 250 patienter med vWD ved de højt specialiserede hæmofilicentre i København og Aarhus [1].

vWD skyldes mangel på virksom von Willebrand faktor (vWf). Von Willebrand faktor er et glykoprotein, der medierer blodpladeaggregation og -adhæsion ved karskade som led i den primære hæmostase, og dermed blodets evne til at størkne og standse blødninger. Von Willebrand faktor (vWF) er bærerprotein for koagulationsfaktor VIII (FVIII), og vWf-mangel er derfor ofte associeret med nedsat FVIII. Svær vWD vil også medføre svær FVIII-mangel og sekundær hæmostasedefekt som ved hæmofili A.

vWD klassificeres ift. vWf-aktivitet og -niveau [2], og vWD inddeles i 3 typer: vWD type 1 er defineret ved nedsat vWf-mængde, vWD type 2 ved nedsat funktion af vWf, mens vWD type 3 defineres ved fuldstændig mangel på vWf. For at stille diagnosen vWD, skal der foruden nedsat vWf være en familiehistorie med blødning og klinisk betydende blødningstendens.

2.1 Nuværende behandling

Behandlingen af vWD omfatter infusion af et vWf-præparat. Udfordringerne ved det nuværende behandlingsregime er at opnå en god hæmostase, dvs. at standse spontan blødning samt sikre, at patienter som gennemgår kirurgi, ikke oplever større blødning under det kirurgisk indgreb ift. patienter uden vWD.

De aktuelt tilgængelige vWF er alle plasmaderiverede. Rekombinante præparater er generelt at foretrække fremfor plasmaderiverede præparater. Dette skyldes, at der i plasmaderiverede præparater er risiko for patogener, som ikke nødvendigvis inaktiveres ved virusinaktivering. Udviklingen af virusinaktiverende metoder har minimeret risikoen for smitte med HIV og hepatitis C, men udbruddet af variant Creutzfeldt-Jakob sygdom i Storbritannien i 1997, som skyldtes prioner, der ikke destrueres ved virusinaktiverende behandling, var en påmindelse om, at det kun er muligt at screene for og inaktivere kendte patogener [1].

De forskellige plasmaderiverede vWf-præparater varierer med hensyn til FVIII-indhold. I henhold til den gældende behandlingsvejledning [3] tilbydes danske patienter med vWD som 1. valg behandling med Haemate, som indeholder vWf og FVIII i forholdet 2,4:1. Som 2. og 3. valg tilbydes patienter med vWD henholdsvis Wilnativ, der indeholder vWf og FVIII i forholdet 1:1 eller Willfact, der indeholder vWf og FVIII i forholdet ≥ 10:1.

Behandling af vWD i henhold til type 1, 2 og 3 er listet i tabel 1:

Tabel 1: Behandling af vWD inddelt efter type vW

Type vWD	Årsag	Sværhedsgrad	Behandling
Type 1	Nedsat mængde vWf	Svær, moderat eller mild	On-demand behandling med desmopressin (DDAVP) eller vWf ved behov for gentagne doser
Type 2	Nedsat funktion af vWf	Svær, moderat eller mild	Enkelte i profylakse, de fleste i on-demand behandling med DDAVP eller vWf
Type 3	Fuldstændig mangel på vWf	Altid svær	Profylakse eller on-demand behandling med vWf

2.2 Vonicog alfa

Vonicog alfa er et rekombinant vWf (rvWf)-præparat, der virker som endogen vWf. Vonicog alfa er fremstillet i chinese hamster ovarieceller uden brug af humant protein.

Vonicog alfa forventes, jf. firmaets foreløbige ansøgning, godkendt til behandling af voksne (≥ 18 år) med vWD til behandling af hæmorrhagi og kirurgisk blødning samt forebyggelse af blødning i forbindelse med kirurgiske indgreb, når behandling med DDAVP alene er ineffektiv eller ikke er indiceret.

Vonicog alfa kan doseres som monoterapi eller i kombination med FVIII, og dosering bestemmes individuelt efter personens vægt, blødningstype og sværhedsgrad samt ud fra monitorering af relevante kliniske og klinisk biokemiske parametre. Ved behandling af blødninger bør den initiale dosis af vonicog alfa være på 40 til 80 IE/kg. Ifm. kirurgi bør FVIII-niveauet vurderes inden for 3 timer forud for indledning af kirurgisk procedure.

3 Kliniske spørgsmål

3.1 Klinisk spørgsmål 1

1. *Hvad er den kliniske merværdi af vonicog alfa, i forhold til plasmaderiveret vWf, ved behandling af blødning hos patienter med vWD og med normalt eller let nedsat FVIII-niveau (> 30 %)?*

Population
Patienter på 18 år eller derover med vWD og et FVIII-niveau > 30 %.

Intervention
Vonicog alfa.

Komparator
Plasmaderiveret vWf.

Effektmål
Se tabel 2.

3.2 Klinisk spørgsmål 2

2. *Hvad er den kliniske merværdi af vonicog alfa, i forhold til plasmaderiveret vWf, ved behandling af blødning hos patienter med vWD og lavt FVIII-niveau (< 30 %)?*

Population
Patienter på ≥ 18 år med vWD og et FVIII-niveau < 30 %.

Intervention
Vonicog alfa + rFVIII.

Komparator
Plasmaderiveret vWf + FVIII i kombination.

Effektmål
Se tabel 2.

3.3 Klinisk spørgsmål 3

3. *Hvad er den kliniske merværdi af vonicog alfa, i forhold til plasmaderiveret vWf, ved forebyggelse og behandling af blødninger ved mindre kirurgiske indgreb hos patienter med vWD?*

Population
Patienter på ≥ 18 år med vWD, som gennemgår et mindre kirurgisk indgreb.

Intervention
Vonicog alfa.

Komparator
Plasmaderiveret vWf.

Effektmål
Se tabel 2.

3.4 Klinisk spørgsmål 4

4. *Hvad er den kliniske merværdi af vonicog alfa, i forhold til plasmaderiverede vWf, ved forebyggelse og behandling af blødning ved større kirurgiske indgreb hos patienter med vWD?*

Population
Patienter på ≥ 18 år med vWD, som gennemgår et større kirurgisk indgreb.

Intervention
Vonicog alfa + evt. FVIII.

Komparator
Plasmaderiveret vWf.
Plasmaderiveret vWf + FVIII i kombination.

Effektmål
Se tabel 2.

3.5 Valg af effektmål

Tabel 2 summerer de valgte effektmål, deres vigtighed, mindste klinisk relevante forskel og kategori.
For alle effektmål ønskes både absolutte og relative værdier. For de relative værdier vurderes den kliniske relevans (merværdi), jævnfør væsentlighedskriterierne beskrevet i Medicinrådets metodehåndbog for vurdering af nye lægemidler. De relative effektestimater kan angives i relativ risiko (RR), odds ratio (OR) eller hazard ratio (HR). Det skal begrundes i ansøgningen, hvis der afviges fra de ønskede effektmål.

Tabel 2. Oversigt over valgte effektmål.
For hvert effektmål er angivet deres vigtighed. For kritiske og vigtige effektmål er desuden angivet den mindste klinisk relevante forskel samt indplacering i de fire kategorier (overlevelse, alvorlige symptomer og bivirkninger, livskvalitet og ikke-alvorlige symptomer og bivirkninger).

Effektmål*	**Vigtighed**	**Kategori**	**Måleenhed**	**Mindste klinisk relevante forskelle (absolutte værdier)**
Hæmostatisk effekt (ved blødning og kirurgi)	Kritisk	Alvorlige symptomer og bivirkninger	Antal blødninger	10 procentpoint forskel i antal blødninger, hvor patienten opnår ”meget god” eller ”god” hæmostatisk effekt
Antal infusioner per blødning	Kritisk	Alvorlige symptomer og bivirkninger	Mediane antal infusioner	En infusion
Inhibitor mod vWf	Kritisk	Alvorlige symptomer og bivirkninger	Antal hændelser	To hændelser i hvert af de aktuelle studier
Anafylaksi	Vigtig	Alvorlige symptomer og bivirkninger	Antal hændelser	To hændelser i hvert af de aktuelle studier
Alvorlig venøs tromboemboli	Vigtig	Alvorlige symptomer og bivirkninger	Antal hændelser	To hændelser i hvert af de aktuelle studier

* For alle effektmål ønskes data med længst mulig opfølgningstid.

Kritiske effektmål

Hæmostatisk effekt (antal blødninger)
Målet med lægemiddelbehandlingen er, at opnå hæmostase og derved standse blødningen på stedet for den vaskulære skade. Fagudvalget vurderer derfor hæmostatisk effekt som et kritisk effektmål.

I kliniske studier scorer patienten eller klinkeren den hæmostatiske effekt vha. de følgende kategorier:

1: Meget god
2: God
3: Moderat
4: Ingen

Der findes forskellige definitioner af de enkelte kategorier, hvilket der skal tages højde for ved sammenligning af data fra forskellige studier.

Hæmostatisk effekt ved kirurgi vurderes af kirurgen og scores i fire tilsvarende kategorier. Herudover vurderer kirurgen almindeligvis blodtabet og angiver, om det er mindre, normalt eller større end forventet.

Der er således tale om hhv. patientens eller kirurgens subjektive vurdering, hvorfor fagudvalget vurderer, at effektmålet er forbundet med en vis usikkerhed. Andelen af patienter, som opnår god eller meget god hæmostase, ligger almindeligvis omkring 85-90 %. Fagudvalget vurderer derfor, at den mindste kliniske relevante forskel i antal behandlede blødninger med god eller meget god hæmostatisk effekt er 10 %.

Antal infusioner per blødning (median antal infusioner)
Antallet af nødvendige infusioner til behandling af en blødning er et kritisk effektmål, da umiddelbar behandlingseffekt skaber klinisk bedring, og da et lavere antal infusioner forventes at minimere den praktiske ulempe. Da de fleste blødninger normalt kan behandles tilfredsstillende med 1-2 infusioner, vurderer fagudvalget, at den mindste klinisk relevante forskel er en infusion per blødning.

Inhibitor for vWf (antal hændelser)
Patienter med vWD kan ved behandling med et vWf-præparat udvikle neutraliserende antistoffer (inhibitor) mod vWf, hvorved vWf-præparatet gøres uvirksomt. Ved vWD type 3 er der beskrevet udvikling af inhibitor, enten mod vWF eller FVIII. Det vides ikke, om behandling med rVWF sammen med rFVIII fremfor plasmaderiverede kombinationspræparater medfører ændret risiko for forekomst af inhibitor hos denne population. Patientgruppen i aktuelle studier er typisk lille, og observationstiden kort, hvorfor fund af ét tilfælde i aktuelle studier vil vække stor bekymring. Det kan dog være en tilfældig forskel, at man finder en hændelse med inhibitor i det ene studie og ikke i det andet. Ved to tilfælde i ét studie og ingen i et andet studie af samme størrelse vil det næppe være tilfældigt. Fagudvalget vurderer derfor, at en forskel på to hændelser med inhibitor imellem studierne er klinisk relevant.

Vigtige effektmål

Anafylaksi som alvorlig bivirkning
Patienter med vWD, som udvikler inhibitor mod vWf, kan foruden en større risiko for blødningsepisoder have en risiko for at udvikle livstruende anafylaksi ifm. behandling med et vWf-præparat, og anafylaksi udgør dermed en alvorlig bivirkning. Studier af vWD er som oftest baseret på relativt få patienter og af kort varighed, hvorfor fund af ét tilfælde i aktuelle studier vil vække stor bekymring, men det kan være et tilfældigt fund. To tilfælde vil være kritisk. Fagudvalget finder derfor, at den mindste klinisk relevante forskel er to tilfælde af anafylaksi per studie.

Alvorlig venøs tromboemboli (antal hændelser)
Der er beskrevet forekomst af trombose ved suprafysiologisk FVIII-niveau hos patienter i Haemate behandling. Dette ser ikke ud til at være tilfældet i observationelle studier ved behandling med Wilnativ [4]. Det anbefales derfor, at FVIII-niveauet monitoreres ved gentagen dosering af Haemate, og ved høje værdier skiftes til Willfact eller Wilnativ [1].

Fagudvalget ønsker på den baggrund, at udvikling af venøs tromboemboli rapporteres udelukkende ift. alvorlige episoder, hvilket omfatter proksimal dyb venetrombose, lungeemboli, trombose i centralnervesystemet eller andre vitale organer. Risikoen skal opvejes imod, at der er tale om en patientgruppe med en meget høj blødningsrisiko. Patientgruppen i aktuelle studier er typisk lille og observationstiden kort. Fagudvalget vurderer derfor, at to tilfælde af alvorlig venøs tromboemboli i hvert aktuelt studie er klinisk relevant.

Mindre vigtige effektmål

Livskvalitet
Livskvalitet er vurderet til at være et mindre kritisk effektmål i denne vurdering. Det skyldes, at vonicog alfa aktuelt ikke er godkendt til profylakse og anvendes derfor kun, når der opstår en blødning, eller hvis

patienten skal have foretaget et kirurgisk indgreb. Fagudvalget mener ikke, at det er realistisk at forvente, at en evt. forskel i effekt ved at behandle 1-2 blødninger per måned vil påvirke patientens daglige livskvalitet.

Andre bivirkninger
Den hyppigste alvorlige bivirkning af vonicog alfa er tromboemboli og udvikling af antistoffer, som fagudvalget har valgt at vurdere særskilt som kritiske effektmål. For behandling med vWf er bivirkninger såsom overfølsomhed og udslæt almindelige men sjældent alvorlige, hvorfor fagudvalget vurderer disse bivirkninger som et mindre vigtigt effektmål.

4 Litteratursøgning

Databaser for søgningen
Relevant litteratur søges i databaserne MEDLINE (via PubMed eller Ovid) og CENTRAL (via Cochrane Library).

Derudover skal EMAs European public assessment reports (EPAR) konsulteres for både det aktuelle lægemiddel og dets komparator(er).

Søgetermer
Søgningen skal inkludere det generiske navn og handelsnavnet for både det aktuelle lægemiddel og dets komparator(er), som kombineres med termer for indikationen.

Søgningen skal som minimum indeholde termer, som er beskrivende for de områder, der er angivet i tabellen herunder. Både indekseret (f.eks. Medical Subject Headings, MeSH) og fritekstsøgning skal anvendes.

Lægemiddel/komparator(er)	**Indikation**
Veyvondi, vonicog alfa Haemate, Wilnativ, Willfact, von Willebrand factor	Von Willebrand disease

De anvendte søgetermer, og hvordan de er blevet kombineret, dokumenteres separat for hver af de to databaser.

Kriterier for udvælgelse af litteratur
Der ekskluderes først på titel- og abstractniveau, dernæst ved gennemlæsning af fuldtekstartikler. Artikler, der ekskluderes ved fuldtekstlæsning, skal fremgå med forfatter, årstal og titel i en eksklusionsliste, hvor eksklusionen begrundes kort. Den samlede udvælgelsesproces skal afrapporteres ved brug af et PRISMA-flowdiagram (http://prisma-statement.org/PRISMAStatement/FlowDiagram.aspx).

Ved usikkerheder, om hvorvidt en artikel på titel- og abstractniveau lever op til inklusions- og eksklusionskriterierne, skal der anvendes et forsigtighedsprincip til fordel for artiklen, hvorved fuldtekstartiklen vurderes.

Inklusions- og eksklusionskriterier: Alle prospektive interventionsstudier af intervention og komparator publiceret min. 25 år tilbage skal inkluderes, såfremt de er gennemført hos den i protokollen specificerede population og rapporterer mindst ét af de præspecificerede effekt- eller bivirkningsmål.

Vurderingen af klinisk merværdi baseres på data fra publicerede fuldtekstartikler og data fra EMAs EPAR – Public assessment reports. Data skal derudover stemme overens med protokollens beskrivelser. Upublicerede data og data fra f.eks. abstracts kan fremsendes og vil indgå i vurderingen, såfremt Medicinrådet finder, at de er nødvendige for at sikre en fair sammenligning. Data skal i så fald stamme fra de forsøg,

hovedpublikationerne rapporterer fra, og ansøger skal acceptere, at Medicinrådet offentliggør dem i ansøgningsskemaet og i rapporten vedr. klinisk merværdi.

5 Databehandling/analyse

De inkluderede studier og baselinekarakteristikken af studiepopulationerne beskrives i Medicinrådets ansøgningsskema. Det skal angives, hvilke studier der benyttes til at besvare hvilke kliniske spørgsmål.

Al relevant data skal som udgangspunkt ekstraheres ved brug af Medicinrådets ansøgningsskema. Der skal udføres en komparativ analyse for hvert enkelt effektmål på baggrund af relevant data fra inkluderede studier. For hvert effektmål og studie angives analysepopulation (f.eks. intention-to-treat (ITT), per-protocol) samt metode. Resultater for ITT-populationen skal angives, hvis muligt, hvis komparative analyser ikke i udgangspunktet er baseret på denne population. Alle ekstraherede data skal krydstjekkes med de resultater, der beskrives i EPAR'en. Findes uoverensstemmelser, gives en mulig grund herfor.

Hvis ekstraherede data afviger fra de forhåndsdefinerede PICO-beskrivelser, specielt i forhold til præspecificeret population og effektmål, begrundes dette.

Hvis data for et effektmål ikke er tilgængelig for alle deltagere i et studie, vil der ikke blive gjort forsøg på at erstatte manglende data med en meningsfuld værdi. Det vil sige, at alle analyser udelukkende baseres på tilgængelige data på individniveau.

For effektmål (ORR, SAE, behandlingsstop pga. bivirkninger og ikkealvorlige bivirkninger), hvor det er naturligt at beregne både absolut og relativ forskel, vil den relative forskel være basis for statistiske analyser. Den absolutte forskel vil derefter blive beregnet, baseret på den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen. Det antagne niveau vil afspejle det forventede niveau i Danmark ved behandling med komparator (hvis relativ risiko (RR) = 0,5 og antaget andel med hændelse i komparatorgruppen er 30 %, da er den absolutte risiko reduktion (ARR) = 30 – 30 x 0,5 = 15 %-point).

Hvis der er mere end et sammenlignende studie, foretages en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt. Hvis der ikke foreligger sammenlignende studier, kan data eventuelt syntetiseres indirekte (evt. i form af formelle netværksmetaanalyser eller ved brug af Buchers metode), hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Medicinrådet forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans.

For effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, vil eventuelle metaanalyser blive baseret på standardized mean difference (SMD). Den estimerede SMD vil blive omregnet til den foretrukne skala for effektmålet. Til dette formål anvendes medianen af de observerede standardafvigelser i de inkluderede studier.

Hvis det ikke er en mulighed at udarbejde metaanalyser (herunder netværksmetaanalyser), syntetiseres data narrativt. Studie- og patientkarakteristika samt resultater fra de inkluderede studier beskrives narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er). Forskelle i patientkarakteristika og studiekontekst (f.eks. geografi og årstal) mellem studier skal beskrives og vurderes for at afgøre, hvorvidt resultaterne er sammenlignelige.

Valget af syntesemetode (metaanalyse eller narrativ beskrivelse) begrundes, og specifikke analysevalg truffet i forhold til metoden skal fremgå tydeligt.

6 Andre overvejelser

Anvendelse af kombinationspræparater vs. separat administration af vWf og FVIII
I svære tilfælde af vWD med sekundær FVIII-mangel vil det være nødvendigt med behandling med et FVIII-præparat sideløbende med behandling med vonicog alfa. Det betyder i praksis, at patienten skal have to forskellige præparater i hjemmet fremfor ét kombinationspræparat, samt at der skal administreres to infusioner i stedet for én. For patienter med et lavt faktorforbrug, som ikke når at bruge deres hjemmelager inden udløbsdato, betyder det, at to pakninger må kasseres i stedet for én med deraf øget medicinspild.

For patienter med et lavt FVIII-niveau finder fagudvalget derfor, at de patientsikkerhedsmæssige overvejelser, ved at patienten skal anvende to præparater i stedet for ét, skal medtages i vurderingen.

Sammenligning af dosisforhold
Fagudvalget finder det relevant at belyse, hvorvidt en enhed vonicog alfa svarer til en enhed plasmaderiveret vWf, da dette kan have betydning for sammenligningen af de økonomiske omkostninger ved behandlingen. Det samlede faktorforbrug afhænger af det antal enheder (IE), der skal indgives for at opnå det ønskede faktorniveau (*in vivo* recovery (IVR)) og den terminale halveringstid.

Ansøger bedes derfor – i tabelform – oplyse IVR og den terminale halveringstid for både vonicog alfa og de tre plasmaderiverede vWf-komparatorer

Lægemiddelhåndtering
I RADS' baggrundsnotat for behandling af hæmofili [1] er der foretaget en struktureret gennemgang af aspekter vedrørende lægemiddelhåndtering, som potentielt kan have betydning for patientsikkerheden og -præferencer. Fagudvalget vil gerne have oplyst følgende forhold for vonicog alfa, som potentielt kan få betydning for valget mellem vonicog alfa og de plasmaderiverede præparater:

- Virusinaktiveringsmetoder
- Opbevaringsbetingelser og holdbarhed
- Rekonstitutionssystem (device)
- Tilgængelighed af forskellige styrker
- Monitoreringsmetoder (laboratorieanalyser)
- Pakningens størrelse (mål og samlede rumfang)
- Medfølgende utensilier (spritswap, kanyler og plaster).

7 Referencer

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8 Bilag 1: Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende bløddersygdom

Forvaltningslovens § 4, stk. 2 har været anvendt i forbindelse med udpegning af medlemmer til dette fagudvalg.

Formand	***Indstillet af***
Eva Funding Overlæge	Lægevidenskabelige Selskaber og Region Hovedstaden
Medlemmer	***Udpeget af***
Har ikke en relevant specialist til fagudvalget	Region Nordjylland
Anne-Mette Hvas Professor, overlæge, ph.d.	Region Midtjylland
Lone Hvitfeldt Poulsen Overlæge	Region Midtjylland
Jesper Farup Revsholm Afdelingslæge	Region Syddanmark
Rune Larsen Overlæge	Region Sjælland
Marie Louise Schougaard Christiansen Afdelingslæge, klinisk farmakolog, ph.d.	Dansk Selskab for Klinisk Farmakologi (DSKF)
Afventer ny udpegning	Dansk Selskab for Sygehusapoteksledelse (DSS)
Kan ikke udpege en kandidat	Dansk Selskab for Klinisk Biokemi
Marianne Hutchings Hoffmann Overlæge	Dansk Pædiatrisk Selskab
Finder det ikke længere relevant at have en kandidat i fagudvalget	Dansk Selskab for Anæstesiologi og Intensiv Medicin
Peter Kampmann Overlæge, lægefaglig teamleder	Dansk Selskab for Trombose og Hæmostase
2 patienter	Danske Patienter

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