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Cost-Effectiveness of Voncento Prophylaxis Versus On-Demand Treatment in von Willebrand Disease in the United Kingdom

Tracking no: ADV-2024-014376R1

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Abstract:
von Willebrand factor (VWF) concentrates may be required for on-demand treatment (ODT) or long-term prophylaxis (LTP) in von Willebrand disease (VWD). This study assesses the cost-effectiveness of LTP compared with ODT in VWD patients treated with Voncento in the United Kingdom (UK). A Markov structure was developed to estimate quality-adjusted life years (QALYs) and costs of VWD treatment over a lifetime horizon. Treatment options included ODT or LTP. For both options, we assumed plasma-derived VWF/factor VIII (pdVWF/FVIII) 2.4:1 (Voncento) as the VWF product used. Clinical parameters were obtained from published literature and Voncento's summary characteristics. Utility weights were obtained from published literature. Costs (in 2021 GBP) and outcomes were discounted annually by 3.5%. Sensitivity analyses were conducted. Three baseline annual bleed rate (ABR) scenarios (11, 26.5 and 39.6) were considered. In the base-case analyses, Voncento LTP resulted in lower costs (-£831,206) and greater QALY (6.14) versus ODT. Savings were primarily due to reductions in product use required (-£529,571) and bleed-related other medical costs (-£301,352). Compared with ODT, LTP also resulted in 322.52 fewer major bleeds and 515.68 fewer minor bleeds over a lifetime horizon. Probabilistic sensitivity analyses showed dominance in 96.12% of simulations and cost-effectiveness in 97.68% of simulations. For the 39.6 ABR scenario, LTP was also dominant compared with ODT. Results suggest that Voncento LTP is more effective and cost-saving compared with ODT in the UK for VWD patients with higher ABR. Prophylaxis for patients with frequent bleeds is likely to be a cost-saving and effective strategy.

Conflict of interest: COI declared - see note

COI notes: MW and CMc are employees of RTI Health Solutions, which received funding from CSL Behring for the development of the model and manuscript. GC has served on advisory committees/speaker for Baxalta, Bayer, CSL Behring, Pfizer, SOBI, Novo Nordisk, UniQure, Roche and Kedrion, and received research support from Pfizer, SOBI and CSL Behring. WT has received speaker fees from AstraZeneca, Alexion, Bayer, CSL Behring, NovoNordisk, Portola, Pfizer, Sobi Sanofi and Takeda, and has participated in advisory boards for Sanofi, Takeda, Pfizer, LFB Biopharmaceuticals, Grifols and Ablynx. CMi has received research support from Baxter/Takeda, CSL Behring and Grifols and honoraria or consultation fees from CSL Behring, LFB, Octapharma and Takeda. GE has received honoraria/consultant fees from Bayer, Bristol Myers Squibb, Boehringer Ingelheim, CSL Behring, Novo Nordisk and Pfizer. WM has received consultant and personal fees from Bayer, Biotest, CSL Behring, Pfizer, Octapharma, LFB, SOBI, Biogen, and BPL. RT and SY are employees of CSL Behring.

Preprint server: No;

Author contributions and disclosures: MW contributed to the model conceptualization and development, data collection, running of analyses, and manuscript development. CMc contributed to the data collection, model programming, running of analyses, and drafting of the manuscript. SY contributed to the study concept, model conceptualization and development, data collection, and drafting of the manuscript. WM, GE, and GC contributed to the model conceptualization and critical revision of the manuscript. WT, CMi and RT contributed critical review of the project scope with respect to the UK perspective and critical revision of the manuscript. All authors agreed on manuscript content and provided critical review and revisions to the manuscript during its development. All authors read and approved the final manuscript.

Non-author contributions and disclosures: Yes; We would like to acknowledge the following individuals for their helpful input during the development of this model: Andrew Davies (University of Glasgow, Glasgow, UK); Jaime Garcia-Chavez (La Raza National Medical Center, Mexico City, Mexico); Paula James (Queens University, Kingston, Ontario, Canada); Jose Luis Lamas (Sotero Del Rio Hospital, Puente Alto, Chile); Sandra Santos (formerly at CSL Behring, Hattersheim am Main, Germany); Pavel Zarkhov (Dmitriy Rogachev National Medical Research Centre of Pediatric Hematology, Oncology and Immunology, Moscow, Russia). All named attended an advisory board to discuss the model, which was funded by CSL Behring.

Agreement to Share Publication-Related Data and Data Sharing Statement: Email to the corresponding author

Clinical trial registration information (if any):

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Running Title: von Willebrand Disease Cost-Effectiveness Model

Word Count: 2477 [Limit: 4,000 words]

Abstract Word Count: 249 [Limit: 250 words]

Number of Tables and Figures: 6 (3 tables; 3 figures)

Key Point Summaries: [1-2 bullets summarizing most relevant outcomes]

- The cost-effectiveness of Voncento prophylaxis versus on-demand treatment for von Willebrand disease in the United Kingdom was studied
- Results suggest that prophylaxis with Voncento is more effective and cost-saving compared with on-demand treatment in the United Kingdom

ABSTRACT

von Willebrand factor (VWF) concentrates may be required for on-demand treatment (ODT) or long-term prophylaxis (LTP) in von Willebrand disease (VWD). This study assesses the cost-effectiveness of LTP compared with ODT in VWD patients treated with Voncento in the United Kingdom (UK). A Markov structure was developed to estimate quality-adjusted life years (QALYs) and costs of VWD treatment over a lifetime horizon. Treatment options included ODT or LTP. For both options, we assumed plasma-derived VWF/factor VIII (pdVWF/FVIII) 2.4:1 (Voncento) as the VWF product used. Clinical parameters were obtained from published literature and Voncento's summary characteristics. Utility weights were obtained from published literature. Costs (in 2021 GBP) and outcomes were discounted annually by 3.5%. Sensitivity analyses were conducted. Three baseline annual bleed rate (ABR) scenarios (11, 26.5 and 39.6) were considered. In the base-case analyses, Voncento LTP resulted in lower costs (-£831,206) and greater QALY (6.14) versus ODT. Savings were primarily due to reductions in product use required (-£529,571) and bleed-related other medical costs (-£301,352). Compared with ODT, LTP also resulted in 322.52 fewer major bleeds and 515.68 fewer minor bleeds over a lifetime horizon. Probabilistic sensitivity analyses showed dominance in 96.12% of simulations and cost-effectiveness in 97.68% of simulations. For the 39.6 ABR scenario, LTP was also dominant compared with ODT. Results suggest that Voncento LTP is more effective and cost-saving compared with ODT in the UK for VWD patients with higher ABR. Prophylaxis for patients with frequent bleeds is likely to be a cost-saving and effective strategy.

Key words: prophylaxis; cost effectiveness; von Willebrand; economic evaluation

INTRODUCTION

Von Willebrand disease (VWD) is the most common inherited bleeding disorder, affecting approximately 1 in 1000 individuals.[1] The disease is classified in different categories, ranging from type 1 (partial quantitative deficiency of von Willebrand factor [VWF]) to type 3 (virtually complete deficiency of VWF).[2] Patients with VWD may experience excessive bleeding events resulting in morbidity and reduced quality of life; in addition, VWD presents a substantial economic burden to the healthcare system and patients.[3-6]

Approaches to the management of VWD include VWF replacement therapy, delivered either as on-demand treatment (ODT) at the time of bleeds or as long-term prophylaxis (LTP) for their prevention. Several studies have suggested that LTP leads to a reduction in bleeds compared with ODT management of bleed events.[7-10] According to recent treatment guidelines, LTP is recommended in individuals with severe and/or frequent bleeds.[11]

While some clinical data for ODT and LTP are available, economic analyses of VWD treatment strategies are sparse. Recent data suggest LTP to be cost-effective compared with ODT in the United States.[12] However, to our knowledge, no published studies have estimated the cost-effectiveness of treatment strategies from a United Kingdom (UK) population. As such, the objective of this study was to assess the cost effectiveness of LTP versus ODT treatment strategies in VWD patients with different baseline annual bleed rate (ABR). We conduct the analysis considering a plasma-derived VWF/factor VIII (pdVWF/FVIII) 2.4:1 product (Voncento) in the UK.

METHODS

Model structure

We developed a Markov structure with 6-monthly cycles to estimate the cost-effectiveness of treatment strategies in patients ≥12 years of age diagnosed with VWD and eligible for LTP or ODT with Voncento. Within this model structure, patients incur risk of bleed events (major or minor bleeds) during each cycle, depending on treatment strategy. Because joint bleeds can lead to progressive joint damage in patients with VWD, the model also considered the development and treatment of arthropathy with joint surgery (Figure 1). The risk of requiring joint surgery was estimated based on patient's Pettersson score over time; those with a Pettersson score of 28 would require joint surgery, based on a previous study in hemophilia A.[13,14] Patients over the age of 80 years were assumed to forgo surgery even if their Pettersson score reached 28.

[INSERT FIGURE 1 HERE]

Each model health state was associated with a cost and quality-of-life impact. Costs are presented in 2021 GBP (£). The model time horizon was that of a patient's lifetime with 6-month cycle length, and a national payer perspective was taken. Costs and outcomes were discounted at 3.5%.[15]

Comparators

The comparison modeled was LTP vs ODT. For the VWF product, we selected Voncento as it represents the majority share of VWD product use in the UK.[16] Dosing details for each strategy are presented in Table 1.

Model inputs

All model inputs can be found in Table 1. We describe these inputs in the following subsections.

General inputs

The model population assumed a 43.98-year-old average patient age, and 51.95% male, with VWD and eligible for prophylaxis. Each of these assumptions were estimated from a systematic literature review of clinical studies in VWD.[17] Patient weight was based on age.[18]

There is substantial heterogeneity within the VWD population, and the decision to treat with LTP is not necessarily uniform. As such, we did not model the cost-effectiveness of treatment within a particular subgroup of the VWD population (e.g., type 1, type 2, type 3). Instead, we modeled based on the baseline ABR within the population to determine the potential cost-effectiveness of LTP vs ODT among individuals who may be eligible for LTP. We assume that the distribution of the modeled VWD population is similar to the populations eligible for prophylaxis clinical trials.[7-9]

Bleed risk inputs

The modeled ABR for patients on ODT and the relative risk of bleeds for LTP compared with ODT were derived from published clinical studies.[7-9] Due to variability in the risk of bleeds within the VWD population and the expected impact of bleed risk on results, three different baseline bleed risk scenarios were considered: lower ABR (11); base-case ABR (26.5); and higher ABR (39.6). Based on a previous study, major bleeding events (non-surgical) included any bleeding into a joint or muscle or in the brain, or a mucosal bleeding of the gastrointestinal tract (excluding nasal or oral bleeding). All other bleeding events were classified as ‘minor’

unless the investigator assessment noted otherwise.[8] Based on this study, we estimated that 62% of bleeds experienced by individuals on ODT were minor, and 70% of bleeds for those on LTP were minor.[8]

Joint surgery risk inputs

The joint surgery health state represents the treatment for arthropathy within the model. The per-cycle risk of joint surgery was assumed to be a function of joint bleed events. Due to limited data in a VWD population we applied an approach similar to previous studies in hemophilia based on the Pettersson score. The Pettersson score is a radiological scoring system to classify the degree of joint damage to the elbows, knees, and ankles.[19] In the model, we assume that with every 12.6 joint bleeds a patient's Pettersson score increases by 1 point.[13,14] The model assumed the baseline Pettersson score to be 14 and that joint surgery occurs when Pettersson score reaches 28.[14,20] To estimate the number of joint bleeds incurred, we assumed that 24% of bleeds in VWD are joint bleeds, based on a published study of bleeding patterns in individuals with VWD.[21] Thus, the increase in Pettersson score each six-month cycle was calculated as (ABR*6 months/12 months)*24%/12.6.

Efficacy inputs

Relative risks of bleeds for LTP regimens compared with ODT were estimated by dividing the ABR for LTP by the ABR for ODT using a published LTP study for Voncento.[7,8] Specifically, we divided the observed ABR for LTP by the ABR for ODT to estimate the relative risk reduction for LTP. We then used this relative risk applied to the baseline ABR for the modeled population, assuming the relative risk to be constant regardless of baseline ABR.

Cost inputs

Because net prices are not publicly available, list prices per VWF international unit (IU) were obtained from a standard published source[22] in order to illustrate the potential cost impact. Prophylaxis dose level and frequency were obtained from the Summary of Product Characteristics (SmPC).[23] ODT costs were estimated using recommended dose per IU, number of daily doses, and duration of treatment obtained from the SmPC.[23] Early hemarthrosis and more extensive hemarthrosis were used as proxy for minor and major bleeds, respectively. Cost to treat minor and major bleeds were obtained from a standard costing source.[24] We conservatively assumed no difference in VWF product dosage per bleed between patients on LTP and ODT.

Quality of life inputs

Due to the lack of data in patients with VWD, we used patients with hemophilia as a proxy for age specific and joint surgery utilities from previous hemophilia studies.[20,25-27] Quality-adjusted life year (QALY) decrements by major and minor bleed were obtained from a published utility study of antiplatelet therapy.[28]

Mortality inputs

The model considered all-cause mortality based on age and sex.[29] To be conservative with respect to the benefits of LTP, no disease-specific mortality risk adjustments associated with bleed risk were included.

Model calculations

For the cost-effectiveness analysis, the incremental cost-effectiveness ratio (ICER) was estimated as ICER = $(C_L - C_o) / (E_L - E_o)$ where: C_L is the cost accrued over the chosen time horizon for LTP; C_o is the cost accrued over the chosen time horizon for ODT; E_L is the effectiveness (QALY) accrued over the chosen time horizon for LTP; and E_o is the effectiveness accrued over the chosen time horizon for ODT.

Sensitivity analyses

To test the robustness of the model assumptions and specific parameters, we examined the effect on the ICER of changing one parameter at a time in one-way sensitivity analyses (OWSA). Individual parameters were varied within plausible ranges of values from the literature, standard errors, 95% confidence intervals, or ±20% change (when data on ranges are not available). Sensitivity results for each input were ranked from most sensitive to least sensitive and plotted on a tornado diagram. Drug price was excluded from the sensitivity analyses as prices are assumed to be known with certainty.

In addition to OWSA, we also performed probabilistic sensitivity analyses (PSA) (second-order Monte Carlo simulation) in which all included parameters were varied simultaneously. Analyses were run 5,000 times to evaluate the stability of the results. Results of PSA are presented in the form of a scatter plot. Both the OWSA and PSA were run using the base-case ABR population.

Finally, scenario analyses were conducted on the baseline ABR and on the resource use (hospitalizations, outpatient visits) required to treat bleed events. Specifically, for the ABR scenarios we considered a lower ABR and a higher ABR scenario in line with the baseline ABR

from two other published clinical studies in VWD.[7,9] For the resource use scenarios, we assumed a lower bound and upper bound of resource use. Details on each can be seen in the results.

RESULTS

Results of the base-case analyses for each treatment regimen can be seen in Table 2. LTP was both less costly and more effective than ODT, i.e. LTP was more effective and cost-saving compared with ODT. Specifically, LTP was expected to result in a QALY gain of 6.14 QALY compared with ODT, driven by a reduction in major bleeds (-323), minor bleeds (-516), and joint surgeries (-0.62). LTP was also expected to result in substantial cost savings (-£831,206) compared with ODT. Notably, these cost savings included 23.7% reductions (-£529,571) in product costs: Prophylaxis costs (£1,636,822) were more than offset by savings in incremental bleed-related product costs (£2,166,393). LTP was also expected to reduce bleed-related other medical costs (-£301,352) and joint surgery costs (-£283).

[INSERT TABLE 2 HERE]

Scenario analyses results can be seen in Table 3. Baseline bleed risk was a substantial determinant in the cost-effectiveness results, whereas hospital and outpatient resource use per bleed did not have a significant effect on results. In all but the lower baseline ABR scenario, LTP remained the dominant strategy in all scenarios.

[INSERT TABLE 3 HERE]

Results of the base-case OWSA can be seen in Figure 2, because many parameters were examined in the OWSA, we have plotted the top 10 most sensitive parameters in the tornado diagram for easy viewing. Results were most sensitive to the estimates of baseline annual

number of bleeds; dose strength, duration, and number of daily doses for treatment of major bleeds; LTP dosing and dose frequency; and severity of bleeds with ODT. However, LTP remained more effective and cost-saving in all individual parameter variation.

[INSERT FIGURE 2 HERE]

The PSA results for the base-case analyses can be seen in Figure 3. When compared with ODT, LTP was found to be cost-saving in 96.12% of simulations and cost-effective in 97.68% of simulations at willingness-to-pay thresholds of £20,000 per QALY.

[INSERT FIGURE 3 HERE]

DISCUSSION

This analysis evaluated the potential economic impact of treatments for patients with VWD from a UK perspective. Specifically, we examined the cost-effectiveness (i.e. value for money) of prophylaxis treatment with Voncento versus using only ODT. This is, to our knowledge, the first published cost-effectiveness modeling analysis of VWD prophylaxis from a UK perspective.

In the base-case analysis comparing LTP versus ODT in patients treated with Voncento in the UK, LTP was found to reduce VWF product costs (including LTP and bleed-related product costs) by 23.7% in addition to reducing costs for other medical resource use (hospitalizations, outpatient visits, and joint surgeries). Patients on LTP were also expected to incur fewer bleeds and joint surgeries while gaining more QALYs compared to those on ODT.

The scenario analyses conducted suggest that, despite substantial heterogeneity in the population and parameter uncertainty, LTP with Voncento is likely to be cost-effective. In OWSA, no

parameters resulted in LTP not being cost saving. In scenario analyses comparing LTP to ODT, all scenarios showed LTP to be cost saving and more effective except when considering a baseline ABR of 11. In probabilistic sensitivity analyses, Voncento LTP was dominant over ODT in over 95% of simulations.

There are a few limitations of this analysis. First, studies used to obtain efficacy measurements had small sample sizes, which may be problematic in a VWD population as bleed risk is highly variable. Second, limited data on the long-term risk of arthropathy in a VWD population made it challenging to assess the risk and impact of developing arthropathy in these patients. However, any underestimate of the risk of joint surgery in a VWD population would only underestimate the value of LTP, and thus our findings are likely conservative. Furthermore, the use of data from a hemophilia population for arthropathy risk introduces uncertainty. Though as seen in the OWSA, the risk of arthropathy was not found a major driver of cost-effectiveness in this study. Additionally, the price of VWF product is based on published list prices and, as such, may not reflect locally agreed prices. Thus, while these results are approximations and illustrative, they importantly demonstrate relative cost savings irrespective of product price. This study shows that there are important cost savings to the healthcare system with prophylaxis; the exact amount is dependent on confidential price agreements VWD products have in place. Lastly, substantial heterogeneity exists among the baseline bleed risks observed in VWD.[8] Thus, we explored the scenarios with different baseline bleed risks. Despite these limitations, the results were fairly robust to parameter variation.

Although this study was conducted assuming a UK VWD population, the results themselves may be illustrative for other countries. As the majority of the VWD care costs modeled were found to be VWF product related, the applicability of these results to other country settings would depend

VWF product costs and the baseline ABR within that country. For countries where patients tend to have a higher ABR, LTP will likely be more cost-effective. Conversely, countries where patients typically have a lower ABR, LTP will be less cost-effective. The price of VWF and the acceptable cost-effectiveness ratio will also have an impact on the cost-effectiveness of LTP within a given country.

As there is substantial heterogeneity within the VWD population, we would not interpret the cost-effectiveness of LTP to be applicable to all patients with VWD; for those with a low ABR, we would not expect LTP to be cost-effective. However, the results of this analysis suggest that LTP is cost-effective compared with ODT in medium to high ABR populations. Despite the product costs associated with LTP, the reduction in bleed events with LTP compared with ODT and their associated direct medical costs (product costs, hospitalization, outpatient visits) more than offset the incremental product costs of LTP. LTP can also improve the patients' quality of life, by reducing the risk of bleeds and the associated morbidity from experiencing these bleeds. As such, LTP should be the recommended strategy for patients with medium to high ABRs.

Acknowledgments

We would like to acknowledge the following individuals for their helpful input during the development of this model: Andrew Davies (University of Glasgow, Glasgow, UK); Jaime Garcia-Chavez (La Raza National Medical Center, Mexico City, Mexico); Paula James (Queens University, Kingston, Ontario, Canada); Jose Luis Lamas (Sotero Del Rio Hospital, Puente Alto, Chile); Sandra Santos (formerly at CSL Behring, Hattersheim am Main, Germany); Pavel Zarkhov (Dmitriy Rogachev National Medical Research Centre of Pediatric Hematology, Oncology and Immunology, Moscow, Russia).

Author contributions

MW contributed to the model conceptualization and development, data collection, running of analyses, and manuscript development. CMc contributed to the data collection, model programming, running of analyses, and drafting of the manuscript. SY contributed to the study concept, model conceptualization and development, data collection, and drafting of the manuscript. WM, GE, and GC contributed to the model conceptualization and critical revision of the manuscript. WT, CMi and RT contributed critical review of the project scope with respect to the UK perspective and critical revision of the manuscript.

All authors agreed on manuscript content and provided critical review and revisions to the manuscript during its development. All authors read and approved the final manuscript.

Conflicts of interest

MW and CMc are employees of RTI Health Solutions, which received funding from CSL Behring for the development of the model and manuscript. GC has served on advisory committees/speaker for Baxalta, Bayer, CSL Behring, Pfizer, SOBI, Novo Nordisk, UniQure, Roche and Kedrion, and received research support from Pfizer, SOBI and CSL Behring. WT has received speaker fees from AstraZeneca, Alexion, Bayer, CSL Behring, NovoNordisk, Portola, Pfizer, SOBI, Sanofi and Takeda, and has participated in advisory boards for Sanofi, Takeda, Pfizer, LFB Biopharmaceuticals, Grifols and Ablynx. CMi has received research support from Baxter/Takeda, CSL Behring and Grifols and honoraria or consultation fees from CSL Behring, LFB, Octapharma and Takeda. GE has received honoraria/consultant fees from Bayer, Bristol Myers Squibb, Boehringer Ingelheim, CSL Behring, Novo Nordisk and Pfizer. WM has received

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TABLES

Table 1. Model parameters

Parameter		Estimate
Baseline ABR		
Baseline annual number of bleeds		
Low[9]		11.0
Medium (base case)[8]		26.5
High[7]		39.6
LTP treatment-specific inputs		**Estimate**
LTP dosing (VWF IU/kg)		
Dose strength (VWF IU/kg)		32.5
Dose frequency (doses per week)		2
Derived relative risk of bleed for LTP[8]		0.04
Bleed-related inputs	**Minor bleed**	**Major bleed**
Dosing for bleeds (VWF IU/kg)		
Dose strength (VWF IU/kg)	30.0	45.0
Daily doses	2	2
Duration of treatment (days)	1	4
Probability of medical resource use		
Outpatient visit	25.0%	50.0%
Inpatient stay for hospitalization	0.0%	50.0%
Percentage of bleeds that are joint bleeds[21]	24.0%	24.0%
Severity of bleeds while receiving ODT[8]	61.84%	38.16%
Severity of bleeds while receiving prophylaxis	70.00%	30.00%

treatment[8]

Cost inputs		**Unit cost**	
Voncento list price per IU of VWF[22]		£0.32	
Other costs[24]			
Outpatient visit		£166.51	
Inpatient stay for hospitalization		£2,992.13	
Joint surgery costs		£1,383.50	
Weight inputs		**Males**	**Females**
Average patient weight (kg)[18]			
11-12 years		46.90	47.06
13-15 years		60.99	58.29
16-24 years		77.54	65.80
25-34 years		85.65	72.56
35-44 years		86.82	74.47
45-54 years		88.84	75.69
55-64 years		87.98	73.86
65-74 years		87.45	71.73
75+ years		79.98	67.34
Utility inputs	**PS 0**	**PS 1-27**	**Surgery**
Health state utility weights[20,25-27]			
Ages 0-30 years	0.94	0.82	0.72
Ages 31-40 years	0.84	0.74	0.65
Ages 41-50 years	0.86	0.69	0.61
Ages 51-60 years	0.83	0.63	0.56
Ages 61-100 years	0.73	0.54	0.48

ABR, annual bleed rate; IU, international unit; kg, kilogram; LTP, long-term prophylaxis; ODT, on-demand treatment; PS, Pettersson score; VWF, von Willebrand factor.

Table 2. Base case results: Costs and outcomes in a medium baseline ABR scenario

Parameter	Voncento LTP	Voncento ODT
Costs		
Total costs	£1,718,847	£2,550,053
Drug costs	£1,709,462	£2,239,033
Prophylaxis	£1,636,822	£0
Bleed-related	£72,640	£2,239,033
Other medical costs		
Outpatient visit	£1,010	£28,440
Hospitalization	£8,375	£282,297
Joint surgeries	£0	£283
Outcomes		
QALYs	11.30	5.16
Life years	32.63	32.63
Joint bleeds	7.32	192.00
Joint surgeries	0.00	0.62
Minor bleeds	23.01	538.69
Major bleeds	9.86	332.38
Incremental cost per QALY gained		
Voncento LTP vs Voncento ODT	-£135,311/QALY gained (Voncento LTP dominates)	

ABR, annual bleed rate; LTP, long-term prophylaxis; ODT, on-demand treatment; QALY, quality-adjusted life year.

Table 3. Scenario analysis results

Scenario	Total cost		Total QALY		ICER
	LTP	ODT	LTP	ODT	
Base case	£1,718,847	£2,550,053	11.30	5.16	-£135,311
Baseline ABR: low (11)	£1,670,870	£1,058,395	11.42	8.86	£239,150
Baseline ABR: high (39.6)	£1,759,395	£3,810,809	11.20	2.04	-£223,864
Lower bound bleed resources used[a]	£1,709,928	£2,255,026	11.30	5.16	-£88,736
Upper bound bleed resources used[b]	£1,730,338	£2,900,505	11.30	5.16	-£190,490

ABR, annual bleed rate; ICER, incremental cost-effectiveness ratio; LTP, long-term prophylaxis; ODT, on-demand treatment; QALY, quality-adjusted life year.

[a]Lower bound = Minor bleeds: outpatient 0%, inpatient 0%; Major bleeds: outpatient 50%, inpatient 0%.

[b]Upper bound = Minor bleeds: outpatient 10%, inpatient 10%; Major bleeds: outpatient 0%, inpatient 100%.

FIGURE CAPTIONS

Figure 1. Markov structure: The Markov structure includes three health states: “No Joint Surgery”, “Joint Surgery”, and “Death.” Within these health states, patients incur a risk of major and minor bleed events each cycle. The risk of joint surgery is dependent on the number of joint bleeds incurred. Risk of death is a function of age and sex.

Figure 2: Tornado diagram for one-way sensitivity analysis: The OWSA is presented as a tornado diagram, which illustrates the impact of individual parameter variation on incremental cost-effectiveness results. The 10 most sensitive parameters are presented.

Figure 3. Probabilistic cost-effectiveness scatter plot: The probabilistic sensitivity analyses are presented as a scatter plot of the 5,000-iteration, second-order Monte Carlo simulation.

Figure 1

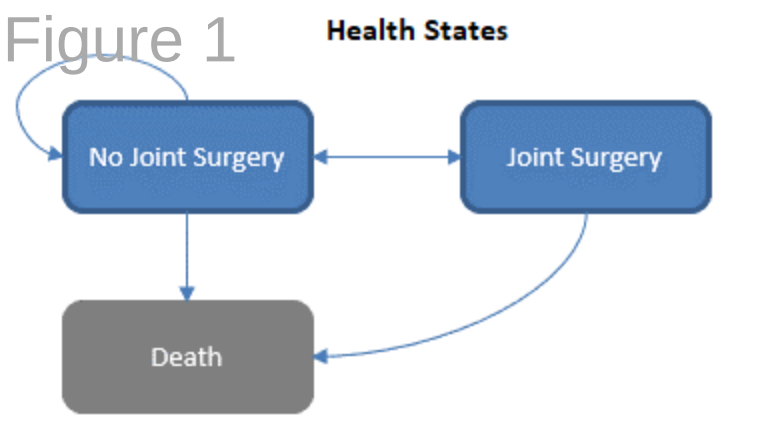

Figure 2

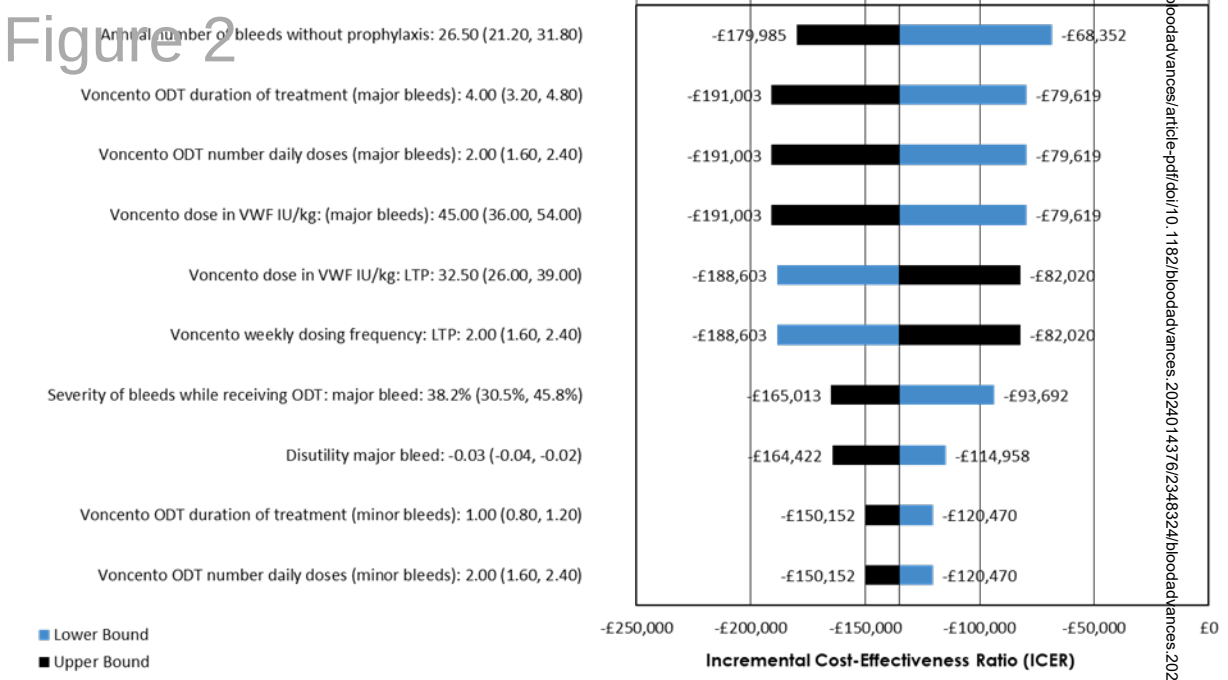

Figure 3