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ORIGINAL ARTICLE

Clinical outcomes after joint surgery in patients on turoctocog alfa pegol (N8-GP) prophylaxis: A *post hoc* analysis

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Visual summary: [A storyboard for a video summary is provided separately]

Abstract

Introduction: Joint damage in haemophilia often requires surgical correction. However, the surgery effect on bleeding rates and other clinical joint outcomes can be unclear.

Aim: To investigate the effects of joint surgery on joint annualized bleeding rates (JABRs) and physical health outcomes in patients with haemophilia A undergoing N8-GP prophylaxis.

Methods: Patients in the pathfinder 2 trial received N8-GP prophylaxis, enrolling in the pathfinder 3 trial for indicated surgery. Patients returned to pathfinder two post-surgery, continuing N8-GP prophylaxis until end-of-trial. JABRs were calculated from bleeding across all joints for pre-surgery (immediately before surgery) and post-surgery (to pathfinder 2 study end) periods. Joint-health-related outcomes were derived from patient records.

Results: Data (41 joint surgeries; $n = 30$) were analysed statistically using datamining and descriptively. Pre-surgery mean JABR was higher in patients who later were operated than in 146 non-operated patients ($p = .004$). In operated patients, mean JABR decreased from 1.33 pre-surgery to .37 post-surgery ($p = .011$). In all but three patients, JABR improved or remained the same post-surgery. In the three patients whose JABR remained at one (all with multiple joint arthropathy), post-surgery bleeds were mostly at non-operated sites. Two of the three patients whose JABR increased post-surgery had undergone surgery for reasons unlikely to improve JABR. Mobility parameters often improved in patients whose JABR remained at zero.

Conclusion: Patients with haemophilia treated with N8-GP prophylaxis benefit from surgeries. However, this analysis could not differentiate the relative contributions of surgical interventions and prophylactic treatment to the improvement of JABR.

KEYWORDS
hemarthrosis, haemophilia A, joint diseases, orthopaedic procedures, patient reported outcome

1 | INTRODUCTION

Patients with haemophilia A often experience recurrent joint bleeding; as a result, haemophilic arthropathy can develop,[1] which may require surgery. For patients with haemophilia A requiring orthopaedic surgery, the World Federation for Haemophilia recommends, in addition to factor replacement therapy, close monitoring and careful pain management in the post-operative period.[1] The aim of surgery is to improve wellbeing and quality of life of patients with haemophilia A[1]; however, it is important that patients and their haemophilia care team have realistic expectations about post-surgery outcomes.[2] Understanding the effects of surgery on bleeding rates, pain and mobility helps facilitate these discussions.

Turoctocog alfa pegol (N8-GP; Novo Nordisk A/S, Bagsvaerd, Denmark) is an extended half-life human recombinant factor VIII (FVIII) product[3]; its efficacy and safety were extensively studied in the pathfinder clinical trial programme.[4] The pivotal pathfinder 2 trial ($N = 186$) investigated the efficacy and safety of N8-GP prophylaxis in adults and adolescents (≥12 years of age) with severe haemophilia A previously treated with ≥150 exposure days of any FVIII product. It found that patients treated with a prophylaxis regimen of N8-GP every fourth day achieved an observed median annualized bleeding rate (ABR) of .84. During the sixth year of pathfinder 2, 64% of patients experienced no bleeds.[5]

Pathfinder 3 ($N = 36$; 35 underwent 49 major surgeries) specifically investigated the efficacy and safety of N8-GP in a subgroup of patients from pathfinder 2 who required major surgery and had received at least five doses of N8-GP, and has been described previously.[4,6,7] During surgery, haemostasis was rated excellent or good in 96% of surgeries; there were four joint bleeds in the post-operative period, all were managed successfully with N8-GP (except in one case where haemostasis efficacy post-bleed was not evaluated).[4,7] After pathfinder 3 treatment completion, patients returned to pathfinder 2 and continued N8-GP prophylaxis until end-of-trial.[6]

The aim of this *post hoc* analysis was to evaluate the effect of joint surgery followed by N8-GP prophylaxis on clinical outcomes restricted to joints (joint ABR [JABR]) and patient-reported outcomes (PROs) in patients with haemophilia A. This evaluation was performed by applying datamining techniques retrospectively to the final results of the pathfinder 2 and 3 clinical trials and analysing the resulting data descriptively.

2 | MATERIALS AND METHODS

2.1 | Research questions and analyses undertaken

Three analyses were performed to elucidate the outcomes of elective orthopaedic surgery followed by N8-GP prophylaxis in patients with haemophilia A. JABR and physical health outcomes were assessed to address the following exploratory scientific questions:

- Question 1: How does the JABR in patients who did not require surgery on their joints compare with the pre-surgery JABR in the operated patients? (Addressed using a datamining analysis),
- Question 2: Does JABR in patients whose joints were operated on change from pre-surgery to post-surgery, with N8-GP prophylaxis throughout? (Addressed using a datamining analysis),
- Question 3: Why, in some patients, does JABR either not improve or worsen from pre-surgery to post-surgery? (Addressed using a descriptive analysis).

Where datamining was used, we conducted retrospective, exploratory interrogation of multiple pre-existing data sources, applying statistical analysis to answer specific scientific questions.

2.2 | Data source

Data from adult and adolescent patients enrolled in the multinational pathfinder 2 trial (NCT01480180), who subsequently joined the pathfinder 3 trial (NCT01489111) to undergo their elective orthopaedic surgery and then rejoined pathfinder 2, were considered for this *post hoc* datamining analysis. The design of the pathfinder 3 trial (including N8-GP surgical protocol and assessment details) has been described elsewhere.[6,7] The multinational pathfinder 3 trial produced a cohort of patients who were operated for major surgery and whose JABR outcomes were known. This cohort was used in this *post hoc* analysis. The analysis only concerned the period during which the patients received prophylaxis with N8-GP every fourth day – periods when patients received on-demand treatment were excluded. Non-joint surgeries were also excluded.

2.3 | Statistical analyses

The statistical analyses described below were developed to compare bleed rates across strata of clinical relevance (e.g., bleed location) and across various time points (e.g., pre- and post-surgery). Unless already available in the trial data collected, bleed rates per strata were computed based on the number of bleeds during the defined relevant time periods.

Analytical assessments were undertaken to determine the JABR of operated and non-operated patients. Pathfinder 2 and pathfinder 3 data were combined in a single dataset structure that would allow a statistical analysis of the chosen clinical outcome of interest, ABRs and, in particular, JABR. ABRs and JABRs were calculated at different time points relative to the surgery. JABRs were calculated collectively across all reported joint locations; therefore, JABRs are not specific to the location of joint surgery.

The datamining model calculated ABRs and JABRs based on the number of bleeds reported between the relevant time point and 365 days prior; where a full 365 days of prior data were not available or would overlap with an earlier surgery period, the period of available qualifying bleed count data was used and scaled to yield an ABR that could be fairly compared with other calculated ABRs. To evaluate the impact of surgery on individual patients in pathfinder 3, ABRs and

TABLE 1 Baseline characteristics and bleed frequency in operated patients

Baseline characteristics[a]	Prophylaxis[b] ($n = 22$)	On-demand[c] ($n = 8$)	Total ($N = 30$)
Age, mean (SD)	35.5 (13.5)	43.2 (11.1)	37.6 (13.2)
BMI, mean (SD)	25.2 (4.6)	26.3 (4.9)	25.5 (4.7)
ABR			
Mean (SD)	4.6 (5.7)	30.5 (31.2)	11.5 (19.8)
Median (IQR)	2.5 (1.0–5.8)	19.5 (11.2–34.8)	3.5 (2.0–12.0)
Pre-surgery JABR range[b]			
0 to < 1, *n* (%)	12 (54.5)	3 (37.5)	15 (50.0)
1 to < 3, *n* (%)	7 (33.3)	4 (50.0)	11 (36.7)
3 to < 20, *n* (%)	3 (13.6)	1 (12.5)	4 (13.3)

Abbreviations: ABR, annualized bleeding rate; BMI, body mass index; IQR, interquartile range; JABR, joint annualized bleeding rate; SD, standard deviation.
[a]One patient counted in the calculations for the baseline characteristics had no surgery information in their patient records, but PRO outcomes were recorded.
[b]The 'prophylaxis' and 'on-demand' subgroups refer to treatment regimens before entry into pathfinder 2; after study entry, all 30 patients were on prophylaxis (28 patients started the pathfinder 2 study on prophylaxis while two patients started on-demand but switched to prophylaxis during the study).
[c]Counts presented based on JABR status before first surgery (some patients underwent multiple surgeries).

JABRs were calculated at three specific time points: (1) baseline ABR as the self-reported historical ABRs collected at the start of pathfinder 2; (2) pre-surgery JABR as imputed from the pre-surgery period; (3) post-surgery JABR as the outcome JABR at the end of pathfinder 2. For each joint surgery, the number of days of prophylactic N8-GP treatment before (since treatment initiation) and after (until trial completion) surgery were calculated. Pre-surgery JABR ranges (0– < 1, 1– < 3 and 3– < 20) were established and patients stratified according to prophylactic or on-demand treatment. The ranges were chosen to provide clinical context to the data. Pre-surgery JABR of operated patients was computed from the number of days of N8-GP prophylaxis exposure for each of the 41 applicable surgeries (i.e., exposure in the 365 days prior, if available, as described above). For comparison purposes, median JABRs were calculated for corresponding treatment durations from the non-operated patient cohort who started pathfinder 2 on a prophylaxis regimen of N8-GP every fourth day ($n = 146$) at equivalent N8-GP exposure durations to the 41 surgeries among the operated cohort.

Pre-surgery versus post-surgery JABRs in operated patients were compared with non-parametric Mann-Whiney U testing (pre-surgery JABRs based on number of surgeries; post-surgery JABRs based on number of patients). Pre-surgery JABRs in non-operated versus operated patients were compared using non-parametric Wilcoxon signed-rank testing (pairwise comparison between non-operated vs. operated group); pre-surgery JABR of the non-operated cohort was calculated by averaging the JABRs of this cohort at the 41 surgery time points.

2.4 | Descriptive analysis

A qualitative assessment of the clinical characteristics of patients who underwent surgeries in pathfinder 3 was undertaken and a descriptive analysis generated. Patients were classified according to whether their JABR improved, did not change, or worsened when comparing pre-surgery with study outcome values. Records of individual patients were examined to evaluate their medical history, identifying specific events and circumstances contributing to bleeding patterns. Individual patient responses to three questions relevant to physical health from the Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) AU1.0 were assessed before and after surgery, and responses to these questions ('In the past 4 weeks, I had pain in my joints', 'In the past 4 weeks, it was painful for me to move', 'In the past 4 weeks, I had difficulty walking as far as I wanted to') extracted. Pre-surgery, responses were collected at pathfinder 3 screening; post-surgery responses were collected at the first visit after return into pathfinder 2.

3 | RESULTS

3.1 | Baseline characteristics

Data from 41 joint surgeries in 30 patients were analysed statistically and descriptively. Patients received N8-GP prophylaxis for a mean of 702.0 days pre-surgery (standard deviation [SD], 547.5 days; range: 17–2017 days) and 1180 days post-surgery (SD, 572.5 days; range: 54–1938 days). The baseline characteristics and bleed frequency for operated patients included in the analysis are shown in Table 1. Twenty-two patients were on a prophylactic regimen before entering pathfinder 2; eight received on-demand treatment before pathfinder 2. In the present analysis, prophylactic treatment with N8-GP was undertaken for < 365 days in 14 patients (14 surgeries); of these 14 patients, seven (seven surgeries) had a JABR of 0 both pre-surgery and post-surgery. A pre-surgery JABR of 0– < 1 was common for patients treated with prophylaxis ($n = 12$, 54.5%), whereas only 37.5% of patients ($n = 3$) treated on-demand had a JABR of 0– < 1.

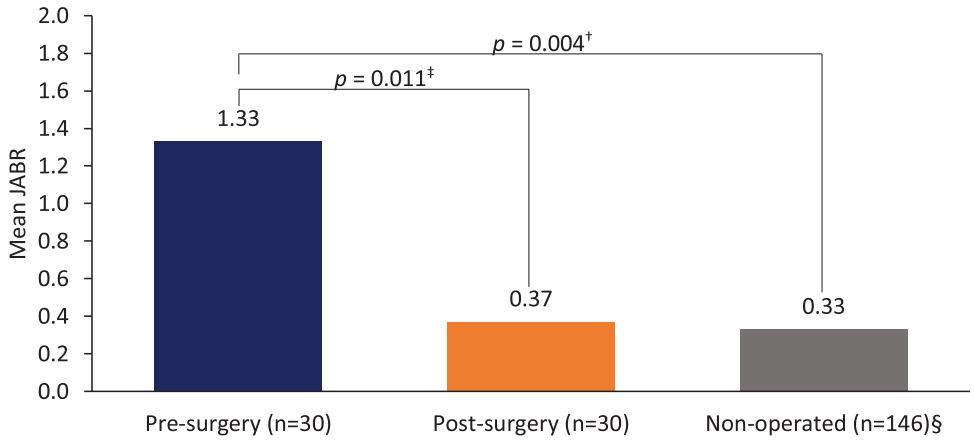

FIGURE 1 Mean JABR in pre-surgery and post-surgery periods and in non-operated patients in a pre-surgery-equivalent period. Figure shows mean JABR, to give context to the data and the differences found by the statistical analyses; median JABR for all three groups was 0. All 30 patients in the operated cohort (pre-surgery and post-surgery data) were on prophylaxis with N8-GP every 4 days (28 patients started the pathfinder 2 study on prophylaxis, while two patients started on-demand but switched to prophylaxis during the study). Data regarding surgery was not available in the records of one patient; however, PRO data were recorded and therefore this patient has been counted in the operated cohort. All 146 patients in the non-operated cohort started the main phase of pathfinder 2 on N8-GP prophylaxis every 4 days. †Wilcoxon signed-rank test. ‡Mann-Whitney U test. §Mean JABR of the non-operated cohort was calculated from periods of N8-GP exposure equivalent to the 41 surgeries. Median JABR was calculated using the same periods. JABR, joint annualized bleeding rate; N8-GP, turoctocog alfa pegol

TABLE 2 Numbers of patients and surgeries in each JABR outcome group

	Post-surgery versus pre-surgery JABR				
	Improved	Remained at 0	Remained at 1	Worsened[a]	Total
Number of patients	13	13[bc]	3[b]	3	30
Pre-surgery JABR ranges[d]					
0	N/A	12	N/A	3	15
1 to < 3	9	N/A	2	0	11
3 to < 20	4	N/A	N/A	0	4
Number of surgeries	17	18	3	3	41

[a]Of the three patients whose JABR worsened, all had long-standing arthropathy/chronic pain; one patient was operated for implant pain and another patient was operated for bilateral trigger thumbs.
[b]One patient in this group was not counted in the stratification by pre-surgery JABR ranges, as they had a previous surgery where JABR improved.
[c]One patient in this group had no surgery information in their patient records, but PRO outcomes were recorded.
[d]Counts presented based on JABR status after first surgery (some patients underwent multiple surgeries).
Abbreviations: JABR, joint annualized bleeding rate; N/A, not applicable.

3.2 | Datamining analysis of JABR in operated patients

In patients who were operated, there was a significant decrease in JABR between pre-surgery and post-surgery (mean JABR 1.33 vs. .37; $p = .011$; median JABR 0 vs. 0; Figure 1). Pre-surgery JABR was significantly higher in operated than in non-operated patients over an equivalent period (mean JABR 1.33 vs. .33; $p = .004$; median JABR 0 vs. 0; Figure 1). Data regarding surgery was not available in one patient's records; however, PRO data were recorded and therefore this patient has been counted in the operated cohort.

3.3 | Descriptive analysis of JABR post-surgery

3.3.1 | Patients whose JABR improved or remained the same

In most operated patients, post-surgery JABR improved or stayed the same versus pre-surgery ($n = 27$; Table 2). Most of these patients had a pre-surgery JABR of < 3, but four patients who improved had a pre-surgery JABR of ≥3. Patients whose JABR improved from pre-surgery to post-surgery (17 surgeries; $n = 13$) were operated on for the following reasons: arthropathy and/or pain in joint (15 surgeries;

TABLE 3 Patient profiles for patients whose JABR remained at 1 or worsened post-surgery

	JABR remained at 1			JABR worsened		
Patient profile	**1**	**2**	**3**	**4**	**5**	**6**
Age, years	37	66	25	20	15	63
Indication for surgery	Elective total right knee replacement	Total knee replacement	Bilateral trigger thumbs	Elective removal of right hip prosthesis[a]	Bilateral trigger thumbs	Elective total right knee replacement
Relevant history	Chronic history of multiple joint arthropathy and pain	Haemophilic arthropathy in the right knee and chronic history of multiple joint arthropathy	Chronic history of multiple joint arthropathy	Implant pain	In addition to bilateral trigger thumbs, had pain and limited movement range in left knee	Haemophilic arthropathy
Change in PRO 6 months after surgery	Not available	At 1 year: worsened scores in pain in the joints and difficulty to move	Less difficulty to walk; other scores were the same	Remained the same (score 1, never)	At 1.5 years: worsened scores; difficulty to walk remained the same (score 1, never)	Improved in all questions
Historical versus post-surgery ABR	24 versus 1	8 versus 1	3 versus 1	3 versus 3	2 versus 4	1 versus 2
Pre-surgery versus post-surgery JABR	1 versus 1	1 versus 1	1 versus 1	0 versus 2	0 versus 3	0 versus 2

Abbreviations: ABR, annualized bleeding rate; JABR, joint annualized bleeding rate; PRO, patient-reported outcome.
[a]This prosthesis was removed due to implant pain; new prosthesis was not added.

$n = 12$) and bone problems (fracture of femoral neck, left ankle talocalcaneal posterior coalition and in situ calcaneo-talar fixation for left ankle talocalcaneal posterior coalition; two surgeries; $n = 2$). One patient was operated for two different indications: chronic pain and a bone anomaly (patient 2 in Supplementary Appendix Table 1). In 15 out of these 17 surgeries, JABR decreased to zero; in the remaining two surgeries, JABR decreased to one (Supplementary Appendix Table 1).

The majority of patients whose JABR was zero both pre-surgery and post-surgery were operated on for arthropathy (11 surgeries; $n = 9$). Other indications for surgery in this group included prosthesis issues (five surgeries; $n = 3$) and Charcot ankle (one surgery; $n = 1$). One patient in this group was not operated on. One patient was counted twice due to two surgeries for different indications.

In the subgroup of patients who were operated for arthropathy and whose JABR remained at zero, all had long-standing haemophilic arthropathy. There were only three bleeding episodes at the operated site; in all other instances, any bleeding was at non-operated sites.

All patients whose JABR was stable at one had multiple joint arthropathy, and post-surgery bleeds were mostly at non-operated sites.

3.3.2 | Patients whose JABR worsened

In patients whose JABR worsened from pre-surgery to post-surgery ($n = 3$), JABR increased from 0 (pre-surgery) to 2–3 (post-surgery). All patients in this group had a pre-surgery JABR of 0. Two of the three patients whose JABR increased were operated for prosthetic pain and bilateral trigger thumbs (patient profiles 4 and 5 in Table 3). The patient who was operated for arthropathy (patient profile 6, Table 3) experienced joint or muscle bleeding in the right leg (knee, calf and thigh) 23 days after surgery; this was likely due to insufficient FVIII substitution, and FVIII dose was subsequently increased; mobility-related outcomes improved in this patient.

3.4 | PRO outcomes, post-surgery

Joint pain (from the Haem-A-QoL PRO questionnaire) most often remained the same, while mobility and pain during movement most often improved, in patients whose JABR was 0 pre-surgery and post-surgery (Table 4). A similar pattern was found when Haem-A-QoL PRO scores were analysed in patients whose JABR did not improve post-surgery (i.e., remained at 0, remained at 1, or worsened) (Supplementary Appendix Table 2). In this set of patients, following seven surgeries the PRO score associated with pain in joints improved, following four surgeries the PRO score worsened and following 11 surgeries the PRO score stayed the same. Following 14 surgeries, the PRO score associated with movement-related pain improved, following five surgeries it worsened and following three surgeries it stayed the same. Following 12 surgeries the PRO score associated with difficulty walking improved, following five surgeries it worsened and following six surgeries it stayed the same.

TABLE 4 Effect of surgery on PRO scores in patients whose JABR was 0 before and after surgery (13 patients; 18 surgeries)

Change in PRO parameter from baseline assessment	Count of surgeries			
	Parameter improved	Parameter remained the same	Parameter worsened	N/A
PRO parameter				
Pain in the joints	6	9	2	1
Painful to move	13	1	4	–
Difficulty to walk as far as wanted	10	4	4	–

Joint-health-related PROs were based on responses to the Haem-A-QoL AU1.0 before (at the pathfinder 3 screening visit) and after (first visit after return into pathfinder 2) surgery, as recorded in patient records. Questions in the Haem-A-QoL AU1.0: 'In the past 4 weeks, I had pain in my joints', 'In the past 4 weeks, it was painful for me to move', 'In the past 4 weeks, I had difficulty walking as far as I wanted to'. Haem-A-QoL scoring: 1 = never experience this, 2 = seldom experience this, 3 = sometimes experience this, 4 = often experience this, 5 = experience this all of the time.

Abbreviations: Haem-A-QoL, Haemophilia Quality of Life Questionnaire for Adults; JABR, joint annualized bleeding rate; N/A, not applicable; PRO, patient-reported outcome.

4 | DISCUSSION

This combined analysis of pathfinder 2 and 3 data permitted assessment of joint bleeding and PROs after joint surgery in patients receiving continued N8-GP prophylaxis. JABR was significantly higher in patients who had major joint surgery compared with a cohort from pathfinder 2 not operated. The results from the pre- to post-surgery analysis are reassuring, because JABR significantly declined following surgery. Importantly, most patients included in this study had a relatively low pre-surgery JABR. Furthermore, the descriptive analyses provided insights into patients whose JABR did not improve. Most patients whose JABR worsened were operated for indications such as prosthetic pain and bilateral trigger thumbs, resolution of which may not be expected to necessarily lead to improvement in long-standing arthropathy and hence JABR. In patients whose JABR remained at 1, post-surgery bleeds were mostly at non-operated locations, which indicates that surgery may have improved joint pathology and decreased bleeding in the affected joint. In all patients whose JABR did not improve, particularly in those whose JABR remained at 0, Haem-A-QoL PRO parameters indicated improvements in pain and mobility.

The main result of this study was the significant mean JABR decrease between the pre-surgery and post-surgery periods in patients receiving N8-GP prophylaxis. This is important because repeated joint bleeds lead to synovitis and hyperplasia, ultimately resulting in haemophilic arthropathy[8]; tertiary prophylaxis with a recombinant FVIII, when compared with on-demand treatment, has been shown to reduce bleeding and have positive effects on patients' lives.[9] In our analysis, reduced bleeding post-surgery may occur for various reasons: improved joint function, better physiotherapy as part of haemophilia management optimization, a temporary more sedentary lifestyle, or, in patients with total joint replacement, complete removal of synovia from the joint. Regardless of the cause, decreased post-surgery bleeding may prevent the inflammatory milieu characteristic of haemophilic joints, thereby precluding further joint damage.

In this study, pre-surgery JABR was higher in operated patients versus non-operated patients. Chronic pain and functional impairment due to severe joint damage is a main reason to undergo major orthopaedic surgery,[1] hence a higher JABR would be expected in operated patients.

In addition to JABR, post-surgery outcomes may be measured through parameters such as changes in mobility impairment, current health status and pain, which impact patients' lives and have great clinical relevance.[10] The qualitative analysis of the clinical narratives and patient profiles presented here, in combination with the JABR analyses, elucidated whether our findings reflected clinical experience. These results should be considered in the broader context for patients with haemophilia A, who face challenges in their day-to-day lives due to the musculoskeletal complications secondary to haemophilia.[11] Our study showed that in patients whose JABR improved post-surgery, most had no post-surgery bleeds, and the rest had a JABR of 1. In the context of important outcomes for patients' lives, reductions in bleeds and improvements in quality of life could be highly beneficial. This study may indicate that, even in patients whose JABR remained the same (at 0 or 1 pre- and post-surgery), other factors (e.g., decrease in pain, improvements in mobility) could be contributing to a beneficial effect of surgery and N8-GP prophylaxis. Our finding of improvements in mobility-related scores is consistent with a PRO analysis of pathfinder 2 data,[12] in which adults showed improvements in the Physical Health domain of the Haem-A-QoL and parents of adolescents showed improvements in the Haemophilia Quality of Life Questionnaire (although adolescents themselves did not).[12] However, not all patients whose JABR remained the same experienced improvements in these clinically relevant factors. This is supported by a previous study showing that a higher degree of haemophilic arthropathy may be associated with decreased quality of life (particularly in physical aspects).[13]

All patients whose JABR remained at 0 post-surgery had long-standing arthropathy; therefore, examining mobility PRO outcomes and pain was particularly relevant. The findings on these outcomes in these patients were reassuring; however, an important caveat is the small number of patients included, meaning generalizations should be minimized. Studies with more patients are necessary to confirm our findings.

All patients included in this analysis were being treated with N8-GP; therefore, our results were due to a combination of surgery and N8-GP prophylaxis. However, this analysis was not designed to evaluate the individual effects of surgery and N8-GP prophylaxis, or the relative contribution of each to the beneficial effects observed in this study.

The first major limitation to these analyses was that it was not possible to determine the root cause for the reported outcomes, because the effects of surgery were supplemented by the effects of N8-GP prophylaxis. The second was that the sample size available was too small for statistical comparisons in most cases. Some of the presented analyses use averaged calculations (e.g., mean ABR), which may give an inaccurate representation of the cohort because the mean is likely to be

heavily influenced by magnitude and number of outliers, which disproportionally affect it. Also, as this study was not designed to investigate the causative factors for the improvements in JABR and PROs, these findings should be interpreted with caution. Finally, pathfinder 3 was a multicentre trial – there may have been some differences in surgical techniques/practices between sites and surgeons, but these differences were not systematically assessed.

5 | CONCLUSION

Our results provide evidence that JABR significantly declined post-surgery and, most often, pain and mobility parameters improved in patients whose pre- and post-surgery JABR was zero. It is likely that the beneficial effects observed in our study are a result of both surgery and concurrent treatment with N8-GP prophylaxis. Our results therefore support the notion that patients with haemophilia A being treated with N8-GP prophylaxis benefit from surgeries, as do those with low pre-surgery JABRs.

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AUTHOR CONTRIBUTIONS

All authors provided substantial contribution to the concept and design, analysis and/or interpretation of data; critical writing or revising the intellectual content; and final approval of the version to be published.

DATA AVAILABILITY STATEMENT

Novo Nordisk is the proprietary owner of all raw data analysed. Transformed data used for the analytical and descriptive analyses are available from the corresponding author, KH, upon reasonable request and subject to approval by Novo Nordisk. Underlying data from the pathfinder 2 and pathfinder 3 trials, which formed the data source for this analysis, will be shared with bona fide researchers submitting a research proposal requesting access to data. The access request proposal form and the access criteria can be found at novonordisk-trials.com. Data will be available permanently after research completion and approval of product and product use in both the EU and USA on a specialised Statistical Analysis System data platform. The analyses available for use will be those as approved by the Independent Review Board according to the IRB Charter (see novonordisk-trials.com). Individual participant data will be shared in data sets in a de-identified/-anonymized format. In addition, the study protocol and redacted Clinical Study Report will be available according to Novo Nordisk data sharing commitments.

CONFLICTS OF INTEREST

KH has received fees for speaking and research support from Novo Nordisk. AT has received funding for research or honoraria for lectures / consultancy from Bayer, Biotest, Chugai, CSL Behring, Novo Nordisk, Octapharma, Pfizer, Roche, SOBI, Takeda. SS is an employee of Novo Nordisk. PC has received grant/research support from Bayer, CSL Behring, Freeline Therapeutics, Novo Nordisk, Pfizer, Sobi and Takeda (Shire); and consultancy fees from Alnylam, Bayer, Biogen, Cangene, CSL Behring, Chugai, Freeline Therapeutics, Novo Nordisk, Pfizer, Roche, Spark Therapeutics, Sanofi, Sobi and Takeda (Shire).

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REFERENCES

1. Srivastava A, Santagostino E, Dougall A, et al. WFH guidelines for the management of hemophilia. *Haemophilia*. 2020;26(Suppl 6):1-158.
2. Escobar MA, Brewer A, Caviglia H, et al. Recommendations on multidisciplinary management of elective surgery in people with haemophilia. *Haemophilia*. 2018;24(5):693-702.
3. Giangrande P, Andreeva T, Chowdary P, et al. Clinical evaluation of glycoPEGylated recombinant FVIII: efficacy and safety in severe haemophilia A. *Thromb Haemost*. 2017;117(2):252-261.
4. Matsushita T, Mangles S. An overview of the pathfinder clinical trials program: long-term efficacy and safety of N8-GP in patients with hemophilia A. *J Thrombosis Haemost*. 2020;18 Suppl 1(Suppl 1):26-33.
5. Giangrande P, Abdul Karim F, Nemes L, et al. Long-term safety and efficacy of N8-GP in previously treated adults and adolescents with hemophilia A: final results from pathfinder2. *J Thromb Haemost*. 2020;18 Suppl 1(S1):5-14.
6. Hampton K, Chowdary P, Dunkley S, et al. First report on the safety and efficacy of an extended half-life glycoPEGylated recombinant FVIII for major surgery in severe haemophilia A. *Haemophilia*. 2017;23(5):689-696.
7. Tosetto A, Neff A, Lentz SR, et al. Turoctocog alfa pegol provides effective management for major and minor surgical procedures in patients across all age groups with severe haemophilia A: full data set from the pathfinder 3 and 5 phase III trials. *Haemophilia*. 2020;26(3):450-458.
8. Pulles AE, Mastbergen SC, Schutgens REG, Lafeber FPJG, van Vulpen LFD. Pathophysiology of hemophilic arthropathy and potential targets for therapy. *Pharmacol Res*. 2017;115:192-199.
9. Manco-Johnson MJ, Lundin B, Funk S, et al. Effect of late prophylaxis in hemophilia on joint status: a randomized trial. *J Thromb Haemost*. 2017;15(11):2115-2124.
10. Konkle BA, Skinner M, Iorio A. Hemophilia trials in the twenty-first century: defining patient important outcomes. *Res Pract Thromb Haemost*. 2019;3(2):184-192.
11. Bauer KA. Current challenges in the management of hemophilia. *Am J Manag Care*. 2015;21(6 Suppl):S112-S122.
12. Kearney S, Raffini LJ, Pham TP, et al. Health-related quality-of-life and treatment satisfaction of individuals with hemophilia A treated with turoctocog alfa pegol (N8-GP): a new recombinant extended half-life FVIII. *Patient Prefer Adherence*. 2019;13:497-513.

13. Fischer K, Bom JG, Mauser-Bunschoten EP, Roosendaal G, Berg HM. Effects of haemophilic arthropathy on health-related quality of life and socio-economic parameters. *Haemophilia*. 2005;11(1):43-48.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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