

# The potential correlation between patient-reported symptoms and the use of additional haemostatic medication for joint bleeding in haemophilia patients with inhibitors: a post hoc exploratory analysis of recombinant activated factor VII data from the ADEPT2 trial

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Haemophilia treatment guidelines advocate early home-based treatment of acute bleeds. In the ADEPT2 trial, data were collected on the home treatment of bleeds with recombinant activated factor VII (rFVIIa) in haemophilia patients with inhibitors and self-reported bleeding-related symptoms. A total of 93% of all bleeds, and 91.5% of joint bleeds, were treated successfully with one to three doses of 90 µg/kg rFVIIa. However, some patients self-administered additional haemostatic medication (AHM) up to 48 h after the first rFVIIa treatment. The aim of this trial was to investigate the relationship between patient-reported symptoms, time to treatment initiation, and the use of AHM. A post hoc analysis was conducted on 177 joint bleeds and the patient-reported categorical symptoms of pain, swelling, mobility, tingling, and warmth, and the pain visual analogue scale (VAS) score. Analyses were descriptive and used logistic regression modelling. Complete symptom data were available for 141, 136, and 129 joint bleeds at 0 or 1, 3, and 6 h, respectively. Pain and pain VAS assessments were the best predictors of AHM use. Patients who self-administered AHM had higher mean pain VAS scores at each time point; both pain and pain VAS scores declined over time. Time to treatment initiation was an independent

predictor for AHM use. Higher initial pain scores and longer time to treatment were the best predictors for administration of AHM. The observation that some patients chose to self-infuse in the face of declining levels of pain warrants further study to better understand the reasons behind patient decision-making. *Blood Coagul Fibrinolysis* 28:224–229 Copyright © 2017 The Author(s). Published by Wolters Kluwer Health, Inc.

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## Introduction

In patients with haemophilia and inhibitors, prompt treatment of acute bleeds with bypassing agents is essential to reduce the risk of severe and life-threatening bleeding [1]. Treatment guidelines advocate early on-demand treatment of acute bleeds in all patients with haemophilia to optimise outcomes [1]; patients are encouraged to treat their bleeds at home, as soon as they think one has occurred, as indicated by their symptoms. By allowing immediate access to treatment, home therapy enables fast initiation of haemostatic treatment and substantially decreases the risk for bleeding complications, including reduced pain and disability [2,3].

Recombinant activated factor VII (rFVIIa; NovoSeven RT, Novo Nordisk A/S, Bagsværd, Denmark) is a bypassing therapy indicated for the treatment of bleeds (including home therapy), and the prevention of bleeding in those undergoing surgery or invasive procedures, in patients with congenital haemophilia A or B with

inhibitors [4]. The haemostatic efficacy and safety of rFVIIa is well established [5–12].

The ADEPT2 trial was a randomized, double-blind, active-controlled, phase III trial that collected detailed information on self-reported bleeding-related symptoms and other bleeding-related data for the home treatment of acute bleeds in patients with haemophilia A and B with inhibitors, with either rFVIIa or vatreptacog alfa (a rFVIIa analogue) [13]. For bleeds treated with rFVIIa, one to three doses of 90 µg/kg were effective [defined as no additional haemostatic medication (AHM)] in 93% (211/227) of all acute bleeds, and 91.5% (162/177) of all joint bleeds, 12 h after the first dose [13], with the use of AHM reported for 8.5% (15/177) of joint bleeds. However, when evaluated at 12–24 and 24–48 h after rFVIIa treatment initiation, AHM use for joint bleeds was slightly higher (13% at 12–24 h and 21% at 24–48 h). These data provided an opportunity to better understand the relationship between patient-reported bleeding-related

symptoms and the decision to use AHM. This knowledge may assist physicians in anticipating which bleeds may require AHM in patients with haemophilia A and B with inhibitors, enabling earlier and/or improved rFVIIa treatment and better outcomes.

This study presents a post hoc exploratory analysis of data on joint bleeds treated with rFVIIa from the ADEPT2 trial. It was designed to investigate the potential relationship between patient-reported bleeding-related symptoms and the subsequent decision by patients to use AHM. In addition, it was explored how frequently patients reported their bleeding-associated symptoms, to inform future patient-reported symptom collection strategies in clinical trials of haemophilia patients with inhibitors.

## Methods

The design of the ADEPT2 trial has been published previously [13]. Patients with haemophilia A or B and inhibitors were randomized 3:2 to treatment with vatreptacog alfa (one to three doses at 80 µg/kg) or rFVIIa (one to three doses at 90 µg/kg). Patients were included if they were male, at least 12 years old, and had experienced at least five bleeds requiring haemostatic drug treatment within the previous 12 months. Only those patients who received treatment with rFVIIa for joint bleeds are presented here.

Acute bleeds were primarily treated in a home setting. Patients reported details of bleeds and treatment outcomes using an electronic diary. The initial rFVIIa dose was to be administered as soon as the patient recognized the symptoms of a bleed, preferably within 2 h of onset. If there was no improvement or worsening of bleeding-related symptoms at 3 or 6 h after the first administration, a second or third dose of rFVIIa could be administered at the patient's discretion. If the bleed could not be controlled with up to three doses of rFVIIa, patients could be given AHM according to the local standard of care. Treatment failure was defined as the use of AHM within 12 h after the first dose.

## Statistical analyses

In this post hoc investigation, statistical analyses were performed to investigate the potential association between six patient-reported bleeding-related symptoms at 0 or 1, 3, 6, and 9 h after the first dose of rFVIIa for the treatment of a joint bleed, and the subsequent use of AHM up to 48 h (according to the local standard of care). The six symptoms examined were: pain as evaluated using the visual analogue scale (VAS; reported on a 0–100 scale) at 1, 3, 6, and 9 h after the first dose of rFVIIa, and the presence or absence (i.e. binary response) of pain, swelling, tingling, warmth, and movement difficulties, immediately after the first dose of rFVIIa (0 h) and at 3, 6, and 9 h. Information was gathered on how many patients reported the presence of a symptom. In addition, for each

patient and time point, the proportion of bleeds for which a symptom was reported was calculated for bleeds subsequently treated with AHM versus those that were not, and the group mean and SD were calculated.

The empirical association between each bleeding-related symptom and the use of AHM was explored using the presence of a symptom as a predictor for the use of AHM and vice versa for the absence of a symptom. For each symptom examined, the error rate was calculated as the number of patients with a positive report of a symptom who decided not to administer AHM (false positives), plus the number of patients who decided to use AHM but without a positive report of a symptom (false negatives), divided by the total number of bleeds.

A logistic regression analysis was also performed to estimate the probability that a bleed would be treated with AHM; use of AHM up to 48 h was included as a binary response (yes/no) with the six patient-reported symptoms as explanatory variables, and time from bleed onset to treatment initiation added as a basic variable (if this was found to be a significant, separate covariate). To compare the utility of the six symptoms in predicting subsequent AHM use, separate logistic regression analyses were conducted for each symptom.

Initially, a simple logistic regression model accounting for patient variability via a random intercept was extended to include time to treatment, to determine its significance as a basic explanatory variable. Comparison of the six different symptoms was subsequently conducted by adding the 0 or 1, 3, and 6-h symptom data to the basic model, and quantifying the resulting prediction capabilities via the Akaike Information Criterion (AIC) and the observed classification error (the observed percentage of bleeds with an incorrect AHM prediction). The relative importance of the different symptoms was then ranked using the AIC and classification error. The ranking of symptoms was made at each of the first three time points, using all symptoms up to the given time point. Only bleeds for which a complete set of the reported symptoms were available up to a given time point were included in the analyses (at that time point). Owing to the exploratory nature of the investigation, no adjustment for multiple testing was conducted. All statistical analyses were performed using SAS (version 9.3; SAS Institute Inc., Cary, North Carolina, USA).

## Results

### Patients and bleeds

In ADEPT2, 227 acute bleeds were treated with rFVIIa in 57 patients (range one to 16 bleeds per patient); 177 of the rFVIIa-treated bleeds were joint bleeds. Of these, 131 joint bleeds did not report AHM use and 35 bleeds reported that AHM was used within 48 h. For 11 bleeds, new bleeds were reported to occur at a different anatomical location within the first 48 h after treatment initiation;

data from these 11 bleeds were therefore not included in the predictive analyses.

### Reporting of symptoms

Data for all five bleeding-related binary symptoms were provided for all 177 joint bleeds at treatment initiation (0 h). For pain VAS scores, data for fewer bleeds were reported; at the first time point at which data were recorded for pain VAS (1 h after treatment initiation), scores were reported for 152 joint bleeds (Table 1). The lowest adherence to symptom reporting for all symptoms was observed 9 h after treatment initiation. The number of joint bleeds for which symptom reporting was complete and AHM status was available was 141 at the first symptom-reporting time point (0 or 1 h after treatment initiation), 136 at 3 h, 129 at 6 h, and 105 at 9 h (Table 1). Owing to the substantial amount of symptom data not reported at 9 h after treatment initiation, and the possibility that AHM may already have been administered before the collection of the 9 h symptom data, the subsequent analyses are focussed on the 0 or 1, 3, and 6 h time points.

### Symptom prevalence by additional haemostatic medication status

Pain VAS score declined over time, from a mean (SD) of 21.6 (22.9) 1 h after treatment initiation to 18.1 (19.7) and 13.1 (17.2) at 3 and 6 h, respectively. For binary symptoms, the observed proportion of bleeds for which patients reported that a symptom was present declined over time for all symptoms examined (Fig. 1).

In general, a higher proportion of bleeds for which patients subsequently used AHM up to 48 h after treatment initiation had symptoms reported compared with bleeds for which AHM was not used (Fig. 1). For movement difficulties, pain, and tingling, the observed proportion of bleeds for which these symptoms were reported immediately after the first dose appeared to be similar for those bleeds where patients did or did

not subsequently use AHM (Fig. 1); however, there appeared to be a greater decline over time in the proportion of bleeds associated with these symptoms for those bleeds not subsequently treated with AHM than for those that were.

For swelling and warmth, parallel decreases over time in the proportion of bleeds associated with these symptoms was observed for bleeds subsequently treated, or not treated, with AHM; however, for bleeds subsequently treated with AHM, the presence of these symptoms was reported for a higher proportion of bleeds at each time point (Fig. 1). Similarly, parallel declines in pain VAS score were observed in both groups of patients, but higher pain VAS scores were recorded by patients at 1, 3, and 6 h for joint bleeds subsequently treated with AHM compared with those that were not. Of note, for 17 bleeds where patients reported that pain and movement restriction were not present, only one of these was subsequently treated with AHM compared with 16 bleeds for which patients decided not to use AHM.

### Empirical association between each symptom assessed and the use of additional haemostatic medication

When using individual binary symptoms as predictors for the use of AHM up to 48 h, a time-dependent improvement in the error rate was observed for all of the bleeding-related symptoms examined (Fig. 2). Pain appeared to show the best improvement in predictive ability over time, whereas warmth had the lowest error rate up to 6 h.

### Logistic regression analysis

In a logistic regression analysis with AHM use as response (and subject variation modelled as a random effect), time from bleeding onset to treatment initiation was a significant covariate ( $P = 0.044$ ) (Table 2). The odds ratio for an increase of 1 h in the time to treatment was ( $e^{0.5570} = 1.75$ ). When including symptoms for 0 or 1 h, or up to 3 h after treatment initiation, the continuous pain VAS score had the highest degree of predictability according to the AIC, whereas tingling and swelling generally displayed the poorest degree of predictability (Table 3). However, when symptoms up to 6 h were included in the logistic regression, the binary pain score provided the best AIC value. The coefficients for the best models according to AIC are presented in Table 2. When using the classification error to evaluate the models as an alternative to AIC, pain VAS had the lowest classification error at 1, 3, and 6-h time points (Table 3).

### Discussion

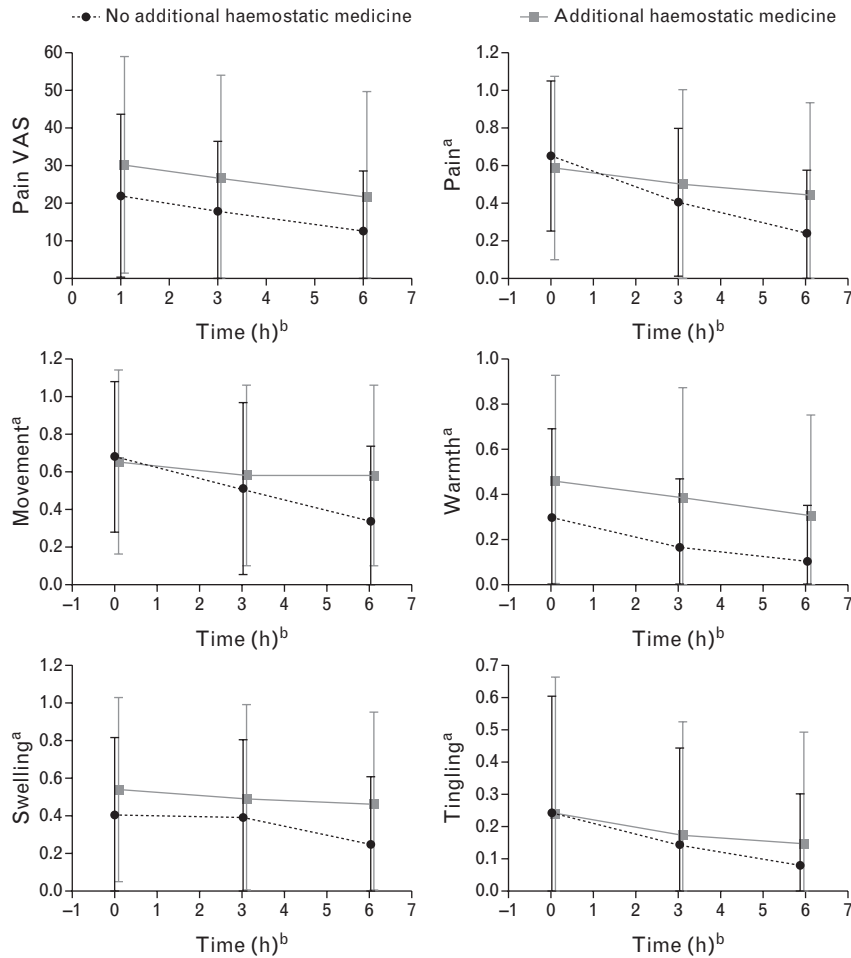
Joint bleeds are the hallmark of haemophilia, and the occurrence of only a few bleeds in the same joint triggers irreversible, progressive joint damage [14]. Prophylaxis, which aims to prevent the occurrence of haemarthroses and thereby any ensuing arthropathy is considered the gold standard of treatment for patients with haemophilia

**Table 1** Frequency of patient-reported responses

Symptom	Assessment time point			
	0/1 h	3 h	6 h	9 h <sup>a</sup>
Pain, <i>n</i> (%)	177 (100.0)	176 (99.4)	176 (99.4)	128 (72.3)
Movement, <i>n</i> (%)	177 (100.0)	176 (99.4)	176 (99.4)	128 (72.3)
Swelling, <i>n</i> (%)	177 (100.0)	176 (99.4)	176 (99.4)	128 (72.3)
Tingling, <i>n</i> (%)	177 (100.0)	176 (99.4)	176 (99.4)	128 (72.3)
Warmth, <i>n</i> (%)	177 (100.0)	176 (99.4)	176 (99.4)	128 (72.3)
Pain VAS, <i>n</i> (%)	152 (85.9)	157 (88.7)	149 (84.2)	128 (72.3)
Complete data set <sup>b</sup>	141 (79.7)	136 (76.8)	129 (72.9)	105 (59.3)

VAS, visual analogue scale. <sup>a</sup>As trial medication was only administered at 0, 3, and 6 h, the questions posted at 9 h in the patient diary differed at this time point, and follow-up measures in relation to missing data were different as well. Consequently, the 9 h time point data have a different answering pattern, including a larger fraction of missing records. <sup>b</sup>Joint bleeds for which all symptoms were reported and data on the use of additional haemostatic medication were available. Data for 11 bleeds were not included as new bleeds were reported to occur at a different location within the first 48 h after treatment initiation.

Fig. 1

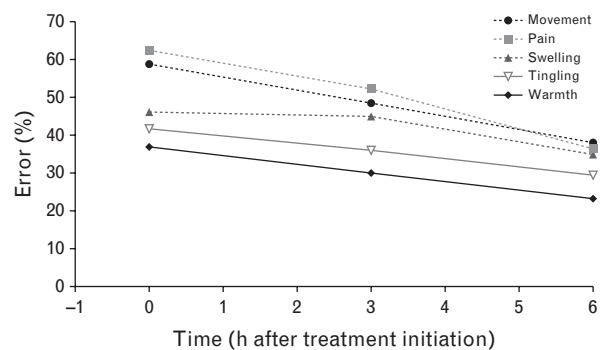


Patient-reported bleeding-related symptoms at 0 or 1, 3, and 6 h after the first dose of rFVIIa. Values are the mean  $\pm$  SD for patients who reported that additional haemostatic medication was used at 48 h vs. those who did not (please note that the scales used for the Y-axis of each graph are not all the same). <sup>a</sup>Mean proportion of bleeds for which patients reported this symptom; <sup>b</sup>Time after treatment initiation.

[15]. For many patients worldwide, on-demand treatment of bleeds is the only option available. In addition, for haemophilia patients with inhibitors, while bypassing agents are available for the treatment and prevention of bleeds, prophylaxis with bypassing agents is not licenced in all countries. Furthermore, the bleeding prevention achieved with bypassing agents is lower than that observed for factor VIII and IX replacement products (and require more frequent injections). Hence, most haemophilia patients with inhibitors treat on demand rather than prophylactically, and the on-demand treatment of bleeds remains an important component of the management of haemophilia.

Although many clinical trials and registries have explored the effectiveness of rFVIIa for the on-demand treatment of bleeds, and data have been collected on bleeding-related symptoms, to our knowledge, the potential relationship between the patient-perceived effectiveness

Fig. 2



The presence or absence of a symptom as a predictor of additional haemostatic medication use and vice versa.

**Table 2** Logistic regression – best predictive models for all time points using observations where all symptoms were available

Parameter	N	Coefficient (P value)				
		Intercept	Time to treat	0/1 h	3 h	6 h
None	141	–2.71 (0.001)	0.56 (0.044)			
Pain VAS	141	–3.98 (0.006)	0.64 (0.057)	0.04 (0.144)		
Pain VAS	136	–3.81 (0.007)	0.85 (0.022)	–0.10 (0.082)	0.14 (0.030)	
Pain VAS	129	–3.558 (0.009)	0.69 (0.061)	–0.08 (0.195)	0.08 (0.357)	0.03 (0.547)
Pain	129	–2.92 (0.012)	0.68 (0.062)	–1.48 (0.219)	–2.68 (0.204)	4.44 (0.027)

VAS, visual analogue scale.

of on-demand treatment and bleeding-related symptoms has not been explored. The results from the ADEPT2 trial, in which the efficacy of rFVIIa treatment, time to treatment initiation, and patient-reported bleeding-related symptoms were recorded for 177 joint bleeds, provided an opportunity to better understand the course of symptoms, how symptoms may change over time following rFVIIa treatment, and the factors and/or symptoms that may be important to consider when optimising the on-demand treatment of joint bleeds. Higher initial pain and longer time to treatment initiation were found to be the best predictors for the patient decision to self-administer AHM for joint bleeds treated on demand with rFVIIa.

For those bleeds for which patients did not decide to self-administer AHM up to 48 h, the data suggest that there may be faster symptom resolution and/or lower symptom prevalence over the first 6 h; according to the AIC, pain provided the best generalizable predictor of bleeds for which patients subsequently self-infused AHM. At 3 h after treatment initiation, the pain VAS score provided the best model fit whereas binary pain reporting had a better model fit at 6 h. When evaluating the symptom importance according to the classification error, the pain VAS score produced the lowest classification error at all three time points. The higher model fit of pain VAS at 1 and 3 h, together with the overall low error rate, suggests

that collection of symptom responses on an ordinal scale is more informative than binary responses and may improve analytical value. In this respect, the findings of a recent investigation suggest that the use of mechanical pain thresholds may be a promising objective tool for pain perception [16], although further validation is required.

Of note, the data also showed a parallel decline in pain VAS between those patients who did and did not decide to self-administer AHM, but that those who had greater pain VAS scores at the outset were the ones who tended to use AHM. This finding suggests that bleeds perceived to be more serious or severe, based on the higher pain levels over the first 6 h after treatment initiation, were more likely to be treated for longer periods; in this context it may be that the patient decided to use AHM after bleeding was controlled in an attempt to consolidate the haemostatic effect [17]. It could also be hypothesized that it may be more difficult for patients to determine if active bleeding has stopped when it is associated with more severe symptoms, such that patients decide to use AHM despite an improvement in their symptoms.

Traditionally, a tingling sensation (or ‘aura’) has been considered to be an important symptom indicative that a joint bleed may have occurred before the manifestation of physical symptoms [1]. Here, the number of joint bleeds for which tingling was reported was less than for all of the other symptoms, and tingling did not appear to be useful as a predictive factor for the subsequent AHM use. Instead, the results presented here showed that, at treatment initiation, movement restriction and pain were the most commonly reported symptoms, had predictive value for the subsequent use of AHM, and appear to be the most informative symptoms to report for future studies. However, it is of note that while it is widely assumed that bleeding is the cause of joint pain, in keeping with the findings of Ceponis and colleagues [18], not all patients reported pain to be present when rFVIIa treatment was initiated. For joints bleeds for which pain was not reported, it will be interesting to determine which bleeding-related symptoms were reported instead and further studies on the hierarchy of bleeding-related symptom precedence and the subsequent use of AHM are warranted.

**Table 3** Ranking of the predictive ability of each bleeding-related symptom on the subsequent use of additional haemostatic medication according to Akaike Information Criterion and classification error (logistic regression with random intercept)

Symptom	Assessment time points					
	0/1 h; N = 141 <sup>a</sup>		0/1 to 3 h; N = 136 <sup>a</sup>		0/1 to 6 h; N = 129 <sup>a</sup>	
	Rank (AIC)	Rank (class)	Rank (AIC)	Rank (class)	Rank (AIC)	Rank (class)
Pain VAS	1 (127.6)	1 (10.6%)	1 (118.6)	1 (8.8%)	3 (117.0)	1 (7.8%)
Pain	2 (129.3)	2 (12.1%)	2 (123.8)	3 (13.2%)	1 (109.7)	2 (9.3%)
Movement	4 (130.5)	3 (12.8%)	4 (125.1)	3 (13.2%)	2 (110.9)	4 (12.4%)
Warmth	2 (129.3)	2 (12.1%)	3 (123.9)	2 (12.5%)	4 (120.1)	4 (12.4%)
Swelling	4 (130.5)	4 (14.2%)	5 (125.7)	2 (12.5%)	4 (120.1)	5 (14.7%)
Tingling	3 (130.4)	3 (12.8%)	6 (125.9)	2 (12.5%)	5 (121.6)	3 (10.1%)

AIC, Akaike Information Criterion; class, classification error in percentage; the classification is based on a dichotomization at 0.5; VAS, visual analogue scale.

<sup>a</sup> For each time point, the model includes all symptom variables. Only bleeds with all symptoms reported up to the given time point are included.

Rapid bleeding control is thought to be the key to reduce bleeding complications in haemophilia patients with inhibitors [19]. Here, while the majority of patients were treated within 2 h after the start of a joint bleed [13], it is of note that the results of the regression analysis demonstrated that the time from bleeding onset to treatment initiation was a significant independent predictor of the decision by patients to use AHM. The importance of early treatment initiation to optimize the on-demand use of rFVIIa was highlighted by findings of Salaj and colleagues [11,20] who reported that early treatment was associated with faster pain resolution and fewer rebleeds. Our findings showed that patients who decided to use AHM tended to have higher symptom prevalence or pain scores and/or slower symptom resolution; it may be that, for patients exhibiting this pattern of symptomatology, further individualized treatment and rFVIIa dosing could be needed. Regardless, it is important to note that standard rFVIIa treatment was effective at 12 h after treatment initiation for nearly all joint bleeds (91.5%); even at 48 h after treatment, for the majority of joint bleeds in ADEPT2 (142/177), including those associated with high pain and mobility impairment, patients decided not to use AHM and rFVIIa treatment was effective.

### Conclusion

Using data obtained from the ADEPT2 trial on rFVIIa treatment and patient-reported bleeding-related symptoms recorded for 177 joint bleeds, higher initial pain scores and longer time to treatment were found to be the best predictors for administration of AHM. The observation that some patients chose to self-infuse in the face of declining levels of pain warrants further study to better understand the reasons behind patient decision-making.

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P.D.A. performed the initial statistical analysis. The manuscript was written and edited by all of the contributing authors; all authors reviewed and approved the final submitted version.

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### Conflicts of interest

P.D.A. and G.R. are Novo Nordisk employees. P.A. was a Novo Nordisk A/S employee during the development of this manuscript. J.M. has received research grants from

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