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# Safety and efficacy of turoctocog alfa (NovoEight®) during surgery in patients with haemophilia A: results from the multinational guardian™ clinical trials

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**Summary.** Recombinant factor VIII (rFVIII) products provide a safe and efficacious replacement therapy for prevention and treatment of bleeding episodes in patients with haemophilia A. The present investigations from the multinational, open-label guardian™ clinical trials assessed the haemostatic response of turoctocog alfa (NovoEight®), a rFVIII product, in patients with severe haemophilia A (FVIII ≤ 1%) undergoing surgery. All patients had a minimum of 50 exposure days to any FVIII product prior to surgery and no history of inhibitors. A total of 41 procedures (13 orthopaedic, 19 dental and 9 general) were performed in 33 patients aged 4–59 years. Of the 41 procedures, 15 were major surgeries in 13 patients and 26 were minor surgeries in 21 patients. The success rate for haemostatic response was 100% (success was defined as 'excellent' or 'good' haemostatic outcome). Turoctocog alfa consumption on the day of surgery ranged from 27 to 153 IU $kg^{-1}$. The mean daily dose declined over time, while retaining adequate FVIII coverage as measured by trough levels. Overall, no safety issues were identified. No thrombotic events were observed and none of the patients developed FVIII inhibitors. In conclusion, the present results show that turoctocog alfa was effective in controlling blood loss by obtaining a sufficient haemostatic response in patients with severe haemophilia A undergoing surgery.

**Keywords:** clinical trial, haemophilia A, NovoEight®, recombinant factor VIII, surgery, turoctocog alfa

## Introduction

Haemophilia A is a recessive X-linked congenital bleeding disorder, caused by mutation in the coagulation factor VIII (FVIII) gene on the long arm of the X-chromosome. With a deficiency or absence of FVIII, the activation of coagulation factor X (FX) becomes severely impaired, and consequently, the thrombin burst is delayed and insufficient for normal haemostasis. Recurrent joint bleeds, most commonly in weight-bearing joints, lead to chronic arthropathy, muscular atrophy and deformities [1,2]. Major surgeries, such as orthopaedic procedures, are often required by patients with haemophilia A. Such surgeries carry the risk of substantial blood loss and require haemostatic control to be maintained for extended periods of time. Despite the use of FVIII therapy, surgery in patients

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with haemophilia A remains challenging [3], and clinical guidance on treatment during surgery procedures in this patient population is still required.

The aim of this publication is to present the results from three clinical trials assessing the safety and efficacy of turoctocog alfa (NovoEight®), a human recombinant factor VIII (rFVIII) product [4,5], during surgery in patients with severe haemophilia A.

## Materials and methods

### *Patients*

The present report includes information on surgeries performed in the completed phase 3 guardian™ programme (the guardian™ 1 trial in adolescent and adult patients [6] and the guardian™ 3 trial in paediatric patients [7]). In addition, information on surgeries performed in the ongoing extension to these two trials (guardian™ 2) is included as of 1 September 2012.

Minor surgery could be performed in all 3 trials, while major surgery could be performed only in the guardian™ 1 and 2 trials that were designed with surgery sub-trials (definitions of minor and major surgeries are provided in Table 1). Major surgery was not allowed in the paediatric trial (guardian™ 3); the necessity of major surgery in this trial led to withdrawal.

All patients had severe haemophilia A (FVIII ≤ 1%) and were previously treated with at least 150 exposure days (adolescents and adults) or at least 50 exposure days (paediatric patients) to any FVIII product and had no history of inhibitors. Patients with previous significant thromboembolic events and immune-deficient patients (defined by a CD4 + lymphocyte count below 200 $\mu L^{-1}$), were excluded from the trial.

The guardian™ trials were approved by all relevant independent ethics committees and institutional review boards. All patients or their legally authorized representatives provided written informed consent before any trial-related activities. The trials were conducted in accordance with the declaration of Helsinki [8] and Good Clinical Practice [9], and are registered at www.clinicaltrials.gov (NCT00840086, NCT00984126 and NCT01138501).

### *Treatment*

Peri-operative turoctocog alfa treatment could be administered as bolus injections or continuous infusion (Table 1). Dosing was determined by the investigator based on the local practice. All patients received a preoperative loading dose of turoctocog alfa immediately prior to the surgical procedure. Following the last surgically related turoctocog alfa dose, patients reverted to preventive treatment with turoctocog alfa under the guardian™ programme, in which safety was monitored continuously.

**Table 1.** Definitions for major and minor surgeries*.

| | Major surgery† | Minor surgery |
|---|---|---|
| Definition | An invasive operative procedure where one or more of the following occurred:<br>• A body cavity was entered<br>• A mesenchymal barrier was crossed<br>• A fascial plane was opened<br>• An organ was removed<br>• Normal anatomy was operatively altered | An invasive operative procedure in which only skin, mucous membranes, or superficial connective tissue was manipulated |
| Expected duration of surgery-related FVIII treatment | At least 7 days including the day of surgery‡ | Less than 7 days including the day of surgery |
| Treatment | Bolus injection or continuous infusion | Bolus injection |
| Dose level | Dosing was determined by the investigator based on the local practice. The protocols recommended to aim for FVIII trough levels above 0.50 IU $mL^{-1}$ from the day of surgery through day 7 post surgery | Dosing determined by the investigator based on the local practice |

*The decision on whether a surgery was a minor or a major surgery was taken before the surgery was performed. Thus, in a few examples the criteria for treatment duration of major surgeries (at least 7 days) and minor surgeries (less than 7 days) do not apply. More details were collected for major surgeries, and the surgeries were therefore not reclassified based on the duration.
†Major surgery was not allowed in the paediatric trial (guardian™ 3).
‡Patients receiving bolus injections could be discharged before day 7 post surgery, but were to have daily assessments at least until that day.

**Table 2.** Definition and evaluation of haemostatic response during and after surgery.

| Evaluation | During surgery | After surgery |
|---|---|---|
| Excellent | Blood loss less than expected | Better than expected in this type of patient and procedure |
| Good | Blood loss as expected | As expected in this type of patient and procedure |
| Moderate | Blood loss more than expected | Less than optimal for the type of procedure, maintained without change of treatment regimen |
| None | Uncontrolled bleeding | Bleeding due to inadequate therapeutic response with adequate dosing; change of regimen required |

Success was defined as 'excellent' or 'good' haemostatic outcome.

### *Assessments and analysis*

The primary objective of the clinical trial programme was to evaluate the safety of turoctocog alfa, while surgery-related efficacy and safety were assessed as part of the secondary objectives.

Patient age and body mass index were recorded prior to surgery. Efficacy assessments were performed during and after the surgical procedures. For all surgeries, these assessments included haemostatic response (Table 2) and turoctocog alfa consumption on the day of surgery and in total. In addition, information on duration of surgery, blood loss and number of blood transfusions was collected for major surgeries. The haemostatic response was evaluated at the end of the surgical procedure.

During the surgical period the following safety assessments were performed: adverse events (daily), vital signs, ECG, physical examination and safety laboratory parameters. FVIII trough levels were measured daily. Inhibitor assessment was performed both in the surgical period as well as when preventive treatment was resumed.

All evaluations were based on descriptive statistics.

**Table 3.** Patient demographics and types of surgical procedures.

| | Type of surgery | | |
|---|---|---|---|
| | Major | Minor | Total |
| Number of patients | 13 | 21 | 33 |
| Age group | | | |
| Children (≤11 years) | 0 | 7 | 7 |
| Adolescents (12–17 years) | 1 | 0 | 1 |
| Adults (≥ 18 years) | 12 | 14 | 25 |
| Race | | | |
| Caucasian/White | 12 | 13 | 24 |
| Asian | 1 | 8 | 9 |
| Number of surgeries | 15 | 26 | 41 |
| Orthopaedic | 13 | 0 | 13 |
| Synovectomy | 5 | 0 | 5 |
| Arthroplasty* | 8 | 0 | 8 |
| Dental | 0 | 19 | 19 |
| General | 2 | 7 | 9 |
| Abdominal surgery† | 1 | 0 | 1 |
| Other‡,§ | 1‡ | 7§ | 8 |

One patient had both major and minor surgery. This patient is counted only once in the total column.
*Knee replacement (3), total hip (2), ankle arthroscopy (1), reduction of finger fracture (1), elbow radial head excision (1).
†Pan-proctocolectomy, ileo-anal pouch.
‡Circumcision.
§Nail extirpation (2), central venous access device procedures (2), incision of periumbilical abscess (1), closure of fistula (1) and debridement and pus drainage (1).

**Table 4.** Details and outcomes of 15 major surgeries in 13 patients.

| | Surgery | | | | Turoctocog alfa exposure | | | | Haemostatic response | |
|---|---|---|---|---|---|---|---|---|---|---|
| Major surgeries | Procedure | Duration h:mm | Blood loss mL | No. of blood transfusions | Days in treatment* | Daily dose (min–max) IU kg$^{-1}$ | Consumption† on day of surgery IU kg$^{-1}$ | Total consumption† IU kg$^{-1}$ | During surgery | After surgery |
| | | | | | | | | | Score (1–4) | |
| 1 | Arthroprosthesis, knee | 1:30 | 200 | 1 | 7 | 45 – 141 | 45 | 768 | Good | Good |
| 2 | Arthroscopy and synovectomy, partial meniscectomy | 1:33 | 750 | 0 | 32 | 0 – 103 | 103 | 1468 | Good | Excellent |
| 3 | Arthroscopy, ankle | 0:40 | ND | 0 | 7 | 27 – 55 | 27 | 219 | Excellent | Excellent |
| 4 | Circumcision | 0:30 | 5 | 0 | 12 | 0 – 100 | 100 | 331 | Excellent | Excellent |
| 5‡ | Knee replacement | 1:50 | 100 | 0 | 9 | 50 – 117 | 61 | 693§ | Good | Good |
| 6‡ | Elbow radial head excision | | | | | | | | | |
| 7 | Knee replacement | 1:30 | ND | 0 | 44 | 0 – 61 | 61 | 1030 | Excellent | Excellent |
| 8 | Pan-proctocolectomy, ileo-anal pouch | 3:23 | 30 | 0 | 7 | 0 – 138 | 103 | 586 | Excellent | Good |
| 9 | Synovectomy, ankle | 1:21 | 50 | 0 | 13 | 50 – 76 | 76 | 684 | Excellent | Good |
| 10 | Synovectomy, ankle | 1:05 | 10 | 0 | 15 | 0 – 75 | 75 | 454 | Excellent | Good |
| 11 | Synovectomy, ankle | 1:19 | 50 | 0 | 13 | 0 – 75 | 75 | 423 | Excellent | Excellent |
| 12 | Synovectomy, knee. Extirpation of osteosynthetic graft | 1:00 | 200 | 0 | 24 | 0 – 98 | 98 | 1502 | Good | Good |
| 13 | Total hip arthroplasty | 1:40 | 1000 | 3 | 21 | 0 – 153 | 153 | 1200 | Excellent | Excellent |
| 14‡ | Total hip arthroprosthesis | 3:25 | 1000 | 1 | 7 | 37 – 56 | 56 | 306 | Good | Excellent |
| 15‡ | Reduction of finger fracture | | | | | | | | | |

Each shaded or white row represents one patient.
*A more frequent dosing regimen or higher doses could be given after return to preventive treatment.
†Dose administered as bolus injection, unless specified otherwise.
‡These surgeries were two simultaneous (but independent) operations performed in each patient, i.e. four operations in two patients. In these two patients only the combined outcome was recorded.
§Combination of 28 IU kg$^{-1}$ administered as bolus injection and 665 IU kg$^{-1}$ administered as continuous infusion.

 

### *Drug product*

Turoctocog alfa is produced by expression in CHO cells without any serum- or animal-derived components. The turoctocog alfa drug product is a B-domain truncated rFVIII molecule that consists of a heavy chain, including a 21 amino acid sequence of the natural B domain, and a light chain. Upon thrombin activation, the B domain is removed, thereby rendering the activated turoctocog alfa to be identical to native activated FVIII. Turoctocog alfa can be monitored by standard FVIII one-stage or chromogenic assays.

Turoctocog alfa was supplied as a sterile, freeze-dried powder in single-use vials of 250 or 2000 IU per vial to be reconstituted with 4.3 mL 0.9% sodium chloride for injection.

## Results and discussion

### *Patient demography and type of surgeries*

A total of 15 major and 26 minor surgical procedures were performed in 33 male patients (7 children, 1 adolescent and 25 adults). The patients had a median (range) age of 24 (4–59) years and a median (range) body mass index of 22.5 (14.8–32.6). The majority of the surgeries were performed in Caucasians (24 patients) while the remaining 9 patients were Asians (Table 3).

The performed surgeries included a wide spectrum of procedures from uncomplicated dental procedures to joint replacements and other orthopaedic surgeries, to major abdominal surgery (Tables 4 and 5). In line with the nature of the haemophilic condition, most (13 of 15) of the major surgeries performed in the trials were orthopaedic procedures related to haemophilic arthropathy (Table 4). In two patients, two independent major surgeries were performed simultaneously (Table 4). For these two patients, only one combined outcome of their surgeries was recorded. A total of 19 of the 26 minor surgeries were dental procedures (Table 5). This is consistent with the known challenges connected with preventive dental care and treatment in patients with haemophilia and the consequent need for planned dental surgical intervention [10]. The dental procedures covered a range of procedures from uncomplicated extractions of deciduous teeth to multiple extractions of molars. Two extractions were due to periodontitis.

**Table 5.** Details and outcomes of 26 minor surgeries in 21 patients.

| | | Turoctocog alfa exposure | | | Haemostatic response |
|---|---|---|---|---|---|
| | Surgery procedure | Days in treatment days | Daily dose (min–max) IU kg$^{-1}$ | Total consumption* IU kg$^{-1}$ | During surgery Score (1–4) |
| 1 | Catheter implementation | 6 | 115–172 | 746 | Good |
| 2 | Closure of fistula | 6 | 36–71 | 304 | Good |
| 3 | Debridement and pus drainage | 1 | 50–50 | 50 | Good |
| 4 | Dental extraction | 1 | 22–22 | 22 | Good |
| 5 | Dental extraction | 1 | 52–52 | 52 | Excellent |
| 6 | Dental extraction | 1 | 24–24 | 24 | Good |
| 7 | Dental extraction (impacted wisdom tooth) | 1 | 25–25 | 25 | Excellent |
| 8 | Dental extraction (impacted wisdom tooth) | 1 | 25–25 | 25 | Excellent |
| 9 | Dental extraction (2 premolars) | 1 | 29–29 | 29 | Excellent |
| 10 | Dental extraction (1 premolar) | 1 | 28–28 | 28 | Good |
| 11 | Dental extraction (2 deciduous teeth) | 1 | 27–27 | 27 | Excellent |
| 12 | Dental extraction (2 teeth due to caries) | 1 | 87–87 | 87 | Good |
| 13 | Dental extraction (1 tooth due to caries) | 1 | 44–44 | 44 | Good |
| 14 | Dental extraction (impacted wisdom tooth) | 1 | 49–49 | 49 | Good |
| 15 | Dental extraction (molar) | 2 | 28–48 | 76 | Good |
| 16 | Dental extraction (molar) and scaling | 1 | 25–25 | 25 | Good |
| 17 | Dental extraction due to caries | 1 | 37–37 | 37 | Excellent |
| 18 | Removal of ingrown nail | 1 | 27–27 | 27 | Excellent |
| 19 | Dental extraction due to periodontitis | 5 | 79–158 | 606 | Excellent |
| 20 | Dental extraction due to periodontitis | 5 | 50–150 | 550 | Excellent |
| 21 | Dental extraction due to periodontitis | 2 | 100–100 | 200 | Excellent |
| 22 | Dental root treatment | 1 | 60–60 | 60 | Excellent |
| 23 | Incision of periumbilical abscess | 1 | 60–60 | 60 | ND† |
| 24 | Ingrown nail extraction | 1 | 34–34 | 34 | Good |
| 25 | Removal of MediPort left subclavicular area | 1 | 57–57 | 57 | Excellent |
| 26 | Surgical extraction of tooth and radix of tooth | 13‡ | 0–60 | 513 | Excellent |

Each shaded or white row represents one patient. For dental extractions, the diagnosis, tooth type(s) and number of teeth are included in those cases where the investigator had described this.

*All doses were administered as bolus injection.

†ND, not determined.

‡Due to the surgery type (surgical extraction of tooth and radix of tooth) this surgery was recorded as a minor surgery even though surgery-related turoctocog alfa treatment was more than 7 days.

### *Treatment*

For major surgeries, doses were recorded daily following surgery (Fig. 1). Four of the 13 patients undergoing major surgery reverted to preventive treatment after 7 days (Fig. 1 and Table 4). However, for three of these four patients more frequent dosing or higher doses were administered during preventive treatment in the weeks after surgery than during their preventive regimen before surgery at the discretion of the investigator to aid postoperative healing. The extended surgery-related treatment received by many patients might be due to the practice of dosing turoctocog alfa prior to physical therapy.

Turoctocog alfa consumption on the day of surgery ranged from 27 to 153 IU $kg^{-1}$ (Table 4). The mean daily dose declined over time (Fig. 1), while providing adequate FVIII coverage as measured by trough levels (Fig. 2). The increase in mean dose for those patients still in surgery-related treatment observed after day 10 (Fig. 1) might be explained by some patients having days without treatment followed by days on treatment or be due to the decrease in the number of patients remaining in surgery-related treatment, since those remaining were likely using more factor than those not remaining. The total median (range) consumption of turoctocog alfa was 684 (219–1502) IU $kg^{-1}$ for major surgeries and 49.5 (22–746) IU $kg^{-1}$ for minor surgeries.

Antithrombotic prophylaxis was allowed but was not administered to any patients. An antifibrinolytic agent (tranexamic acid) was used in several cases during and after surgery.

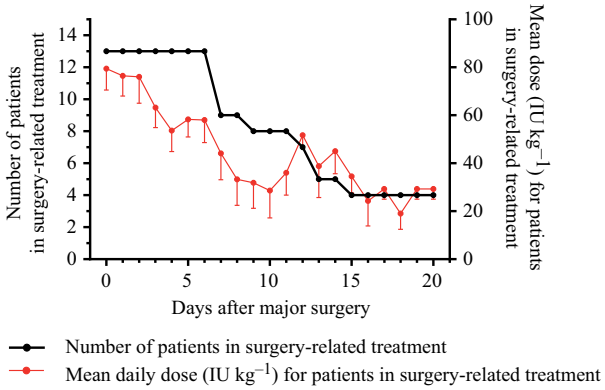


**Fig. 1.** Duration of surgery-related treatment and mean daily doses of turoctocog alfa (major surgeries, $N = 13$). For the mean daily doses, the number of patients at each time point corresponds to number of patients who were still in surgery-related treatment at that time point. Data points show mean dose (IU $kg^{-1}$) and error bars represent ± standard error of the mean.

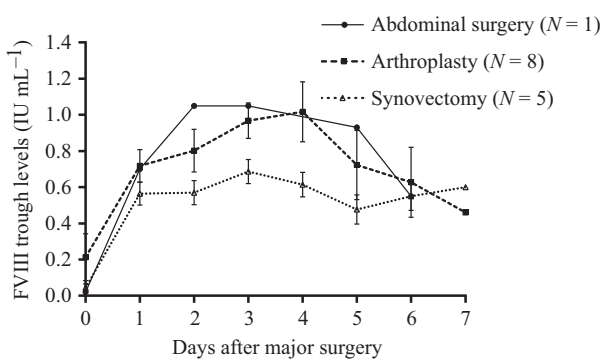


**Fig. 2.** Trough levels during the first 7 days after surgery in patients undergoing major surgery. Data points show mean FVIII trough levels (IU $mL^{-1}$) and error bars represent ± standard error of the mean. *N* represents number of surgeries.

### *Clinical efficacy*

The success rate for haemostatic response during and after surgery was 100%. For all major surgeries, the haemostatic response was rated 'excellent' (8 of 13 during surgery and 7 of 13 after surgery) or 'good' (5 of 13 during surgery and 6 of 13 after surgery). For minor surgeries (which were rated only during surgery), half (13 of 26) were rated as 'excellent'. The remaining surgeries were rated as 'good', except one clinical assessment that was not determined (Fig. 3). Similar haemostatic results have been reported for other commercially available FVIII products [11–13]. A known limitation of comparisons of reported haemostatic responses is that the definition given to each of the treatment outcomes often differs between trials and is largely subjective [14]. In the guardian™ programme, the 4-point scale used to assess haemostatic response during and after surgery was similar to the assessment scales used in surgery trials with other FVIII products, allowing comparisons between treatment outcomes.

A notable result in this study was a 23-year-old patient who underwent complex gastro-intestinal surgery of more than 3 h duration with only minor blood loss and with 'excellent' and 'good' haemostatic outcome during and after surgery, respectively.

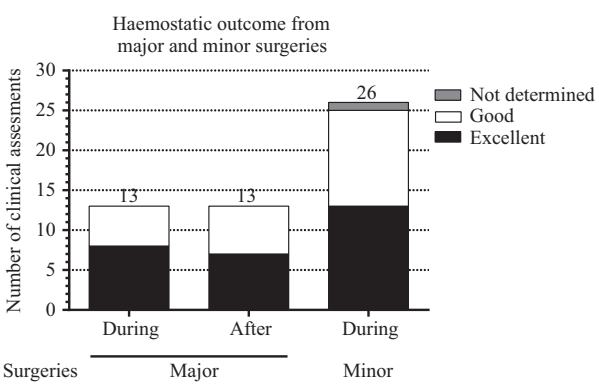


**Fig. 3.** Summary data of haemostatic outcome from major and minor surgeries.

Two patients had a blood loss of 1000 mL: one 55-year-old polytrauma patient undergoing two combined procedures of total hip arthroprosthesis and reduction of finger fracture and a 25-year-old patient undergoing total hip arthroplasty. These two patients accounted for 4 of 5 blood transfusions given for all major surgery patients.

### *Clinical safety*

Safety was assessed in all 33 treated patients. No safety issues were identified. All patients undergoing major surgery continued preventive treatment after their surgery. Except from two patients with less than 2 months of preventive treatment after their surgery, all other patients received preventive treatment for more than 6 months after their surgery. None of the patients developed FVIII inhibitors during the surgery period or when preventive treatment was resumed [6,7]. Furthermore, no postoperative bleeding complications were reported. A total of 5 adverse events were recorded in 5 patients during major surgery (paraesthesia, haemorrhage, allergy to chemicals, arthralgia and vomiting). All events were mild or moderate in severity and all events were evaluated by the investigator as unlikely to be related to the trial product. All patients, except the patient with allergy, recovered fully from these adverse events. No thrombotic events were recorded.

One death occurred during the guardian™ 2 trial. This patient underwent emergency surgery due to a traumatic injury, but due to emergency circumstances, no information about the haemostatic response was collected and this patient is therefore not included in the 33 patients described in this paper. This patient received turoctocog alfa treatment pre- and postoperatively, until he died 2 days after arrival at the hospital. His death was assessed as unrelated to the trial drug. No other fatal events occurred during the guardian™ trials.

## Conclusion

The guardian™ trials investigated the safety and efficacy of turoctocog alfa in more than 200 patients. In the present paper we describe the safety and efficacy of turoctocog alfa during 41 surgeries, including 15 major surgeries in 13 patients. Although limited in number, the procedures cover a wide surgical spectrum ranging from dental procedures to major abdominal surgery. The results from the present study show that turoctocog alfa is effective and well-tolerated when used across a wide range of surgical procedures.

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## Author contributions

Elena Santagostino, Steven Lentz, Mudi Misgav, Brigitte Brand, Pratima Chowdary, Aleksandar Savic, Yurdanur Kilinc, Yehuda Amit, Annunziato Amendola and Luigi Solimeno enrolled and cared for patients. Irina Matytsina contributed to the interpretation of data and assisted with the manuscript outline. Trine Saugstrup was responsible for handling and presentation of the data. All authors gave input, reviewed and approved the manuscript.

## Disclosures

Elena Santagostino has received fees as a speaker in meetings organized by Bayer, Baxter, Pfizer, CSL Behring, Novo Nordisk, Biotest, Kedrium, Octaphamra and Grifols, acted as a paid consultant for Bayer, Pfizer, CSL Behring, Novo Nordisk and Grifols and received unrestricted research grants from Novo Nordisk and Pfizer. Steven Lentz has received consultancy fees and research funding from Novo Nordisk. Mudi Misgav has received fees as a speaker in meetings organized by Novo Nordisk. Brigitte Brand has received fees for speaking and was an advisory board member for Novo Nordisk. Pratima Chowdary has received honoraria from Bayer, Baxter, Biogen Idec, CSL Behring, Novo Nordisk and Pfizer, served on advisory boards for Baxter, Biogen Idec, CSL Behring and Pfizer, and received funding from CSL Behring, Novo Nordisk and Pfizer. Aleksandar Savic has served as an investigator in studies sponsored by Novo Nordisk. Luigi Solimeno received fees for speaking from Novo Nordisk, Baxter, Pfizer and Bayer. Trine Saugstrup and Irina Matytsina are full time employees of Novo Nordisk A/S. Trine Saugstrup has stocks for Novo Nordisk A/S. Yurdanur Kilinc, Yehuda Amit and Annunziato Amendola declared no interests that might be perceived as posing a conflict or bias.

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