22 April 2022
EMA/CHMP/2055442022
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: NovoSeven

International non-proprietary name: eptacog alfa (activated)

Procedure No. EMEA/H/C/000074/II/0116

Marketing authorisation holder (MAH) Novo Nordisk A/S

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	adverse event
AIP	abnormally invasive placenta
ANSM	Agence nationale de sécurité du médicament et des produits de santé (France)
ANZHR	Australian and New Zealand Haemostasis Registry
ATE	arterial thromboembolic event
BMI	body mass index
CI	confidence interval
CTR	clinical trial report
CZ	Czech Republic
DIC	disseminated intravascular coagulation
DK	Denmark
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FAS	full analysis set
FFP	fresh frozen plasma
FVII	coagulation factor VII
GCP	Good Clinical Practice
GVP	Good Pharmacovigilance Practices
Hb	haemoglobin
HELLP	haemolysis, elevated liver enzymes, low platelet count
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	intensive care unit
IQR	interquartile range
IV	intravenous
MEB	Medicines Evaluation Board (The Netherlands)
MODS	multiple organ dysfunction syndrome
MOF	multiple organ failure
NL	Netherlands
NSR	non-interventional study report
PI	prediction interval
PP	per protocol
PPH	postpartum haemorrhage
PPHc	PPH consortium
PS	propensity score
PSAS	propensity score matched analysis set
RBC	red blood cells
RCOG	Royal College of Obstetricians and gynaecologists
RCT	randomised controlled trial
RMP	risk management plan
rFVIIa	recombinant coagulation factor VIIa
SAP	statistical analysis plan
SIRS	systemic inflammatory response syndrome
SmPC	Summary of Product Characteristics
TE	thromboembolic event
T0	at inclusion for trial 4816
TXA	tranexamic acid

UK	United Kingdom
US	United States
VTE	venous thromboembolic event
WHO	World Health Organization

Definition of terms

NN7711 = clinical trial and non-interventional studies for NovoSeven in severe postpartum haemorrhage.

The clinical trial/studies are referred to by their unique 4-digit number followed by a short name identifying the data source in parentheses as below:

- NN7711-4816 is referred to as trial 4816 (RCT)
- NN7711-4729 is referred to as study 4729 (Bern)
- NN7711-4733 is referred to as study 4733 (PPH consortium)
- NN7711-4731 is referred to as study 4731 (UniSeven)
- NN7711-4732 is referred to as study 4732 (ANZHR)

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novo Nordisk A/S submitted to the European Medicines Agency on 8 October 2021 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of severe postpartum haemorrhage for NovoSeven. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet is also updated in accordance. Version 8.0 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

Timetable	Actual dates
Submission date	8 October 2021
Start of procedure:	30 October 2021
CHMP Rapporteur Assessment Report	24 December 2021
PRAC Rapporteur Assessment Report	24 December 2021
PRAC members comments	5 January 2022
CHMP Co-Rapporteur Critique	7 January 2022

Timetable	Actual dates
Updated PRAC Rapporteur Assessment Report	6 January 2022
PRAC Outcome	13 January 2022
CHMP members comments	17 January 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	21 January 2022
Request for supplementary information (RSI)	27 January 2022
CHMP Rapporteur Assessment Report	24 March 2022
PRAC Rapporteur Assessment Report	24 February 2022
PRAC Outcome	7 April 2022
CHMP members comments	11 April 2022
Updated CHMP Rapporteur Assessment Report	13 April 2022
Opinion	22 April 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Postpartum haemorrhage

Physiological mechanisms are in place to limit postpartum blood loss after placental separation. In normal situations, haemostasis is initiated when uterine bleeding occurs from spiral arteries after placental separation, occurring after delivery of the baby. This is controlled by a combination of two mechanisms:

- Contractions of the myometrium, which compress the blood vessels supplying the placental bed and causes mechanical haemostasis.
- Local haemostatic factors in the decidual cells of the endometrium (tissue factor, type-1 plasminogen activator inhibitor, systemic coagulation factors [e.g., platelets, increased circulating clotting factors]), will initiate endometrial haemostasis.

The pathogenesis of most cases of post-partum haemorrhage (PPH) is uterine atony, i.e. failure of uterine contractions. The potential for massive haemorrhage due to failure of normal physiologic mechanisms at delivery is high, as in late pregnancy uterine artery blood flow is 500 to 700 mL/min and accounts for approximately 15 percent of cardiac output.

In this application, the MAH proposes to add the following new indication:

"Severe postpartum haemorrhage

NovoSeven is indicated for the treatment of severe postpartum haemorrhage."

The following indication has been agreed by CHMP:

"Severe postpartum haemorrhage

NovoSeven is indicated for the treatment of severe postpartum haemorrhage when uterotonics are insufficient to achieve haemostasis."

The following separate posology is proposed for this new indication:

Severe postpartum haemorrhage

"Dose range and dose interval

The recommended dose range for the treatment of bleeding is 60 – 90 µg per kg body weight administered by intravenous bolus injection. Peak coagulant activity can be expected at 10 minutes. A second dose can be administered based on clinical response of the individual patient.
It is recommended that in case of insufficient haemostatic response, a second dose can be administered after 30 minutes."

Epidemiology

The global incidences of PPH and severe PPH are estimated to be 6−11% and 1−3% of all births, respectively, but with substantial variations across regions. PPH continues to be the leading preventable cause of maternal illness and death globally. Worldwide, postpartum haemorrhage accounts for 8% of maternal deaths in developed regions of the world and 20% of maternal deaths in developing regions (WHO syst. Analys., Lancet 2014).

Risk factors PPH

A personal or family history of previous PPH, advanced age, obesity, high parity. Despite efforts to identify patients who are at increased risk for PPH, this life-threatening complication often occurs in women who have no identifiable risk factors.

Biologic features

Primary postpartum haemorrhage (PPH) is an obstetric emergency and the most common form of major obstetric haemorrhage. The traditional definition of primary PPH is the loss of 500 ml or more of blood from the genital tract within 24 hours of the birth of a baby. PPH can be minor (500–1000 ml) or major (more than 1000 ml). Major can be further subdivided into moderate (1001–2000 ml) and severe (more than 2000 ml). In women with lower body mass (e.g. less than 60 kg), a lower level of blood loss may already be clinically significant (Guideline Royal College of Obstetricians and Gynaecologists (RCOG)).

Aetiology and pathogenesis

Causes of PPH

The causes of PPH can be summarised by the four "T's": tone (uterine atony), trauma (lacerations or uterine rupture), tissue (abnormal or retained placenta or clots), and thrombin (pre-existing or acquired coagulopathy). The most common cause is uterine atony (accounting for approximately 70% of cases), followed by obstetrical lacerations (approximately 20%), retained placental tissue (approximately 10%), and clotting-factor deficiencies (<1%). (American College of Obstetricians and Gynaecologists (AGOG) 2017, Bienstock et al, NEJM 2021).

Focal or diffuse atony

Uterine atony (i.e., lack of effective uterus contractions after delivery), is the most common cause of PPH (>80 percent of cases). Placental disorders (e.g. abnormal implantation of the placenta, placenta previa, abruptio placentae), retained products of conception, and uterine inversion may result in PPH because these inhibit effective uterine contraction. With diffuse atony, blood loss can be much greater than observed because a flaccid and dilated uterus may contain a significant amount of blood. With focal localised atony, the fundal region may be well contracted while the lower uterine segment is dilated (ballooning) and atonic. Although diffuse uterine atony is the most common cause of PPH, it is often responsive to administration of additional uterotonic drugs; thus, it is not the most common reason for massive transfusion at delivery.

Trauma

Trauma-related bleeding can be due to lacerations (including uterine rupture) or surgical incisions.

Coagulopathy

Coagulopathy or platelet dysfunction can contribute to PPH in women with an inherited or acquired bleeding disorder. Women with von Willebrand disease are especially at risk for PPH because von Willebrand factor levels, which typically increase during pregnancy, decline rapidly after delivery. Acute acquired coagulopathies can be caused by amniotic fluid embolism, placental abruption, preeclampsia with severe features, or HELLP syndrome (Haemolysis, Elevated Liver enzymes, Low Platelets). Coagulopathy can also be a result of PPH when there is a severe reduction of clotting factors due to persistent heavy bleeding and haemodilution of the remaining clotting factors.

Postpartum haemorrhage can lead to severe anaemia requiring blood transfusion, disseminated intravascular coagulopathy, hysterectomy, multisystem organ failure and death (Royal College of Obstetricians and Gynaecologists (RCOG)).

Clinical presentation, diagnosis

The typical clinical signs and symptoms of hypovolemia due to PPH include hypotension and tachycardia. However, signs and symptoms of hypovolemia due to PPH may not appear until blood loss exceeds 25% of total blood volume (>1500 ml during late pregnancy).

The traditional definition of postpartum hemorrhage is blood loss of more than 500 ml after a vaginal delivery or more than 1000 ml after a caesarean delivery. More recently, postpartum hemorrhage has been redefined as a cumulative blood loss of 1000 ml or more or blood loss associated with signs or symptoms of hypovolemia, irrespective of the route of delivery, see table 1 of main definitions PPH below (UptoDate2021).

Table 1 Examples of definitions for postpartum haemorrhage

Organisation	Definition of PPH
World Health Organization 2012[1]	Blood loss ≥500 mL within 24 hours after birth. Severe PPH: Blood loss ≥1000 mL within the same time frame.
American College of Obstetricians and Gynaecologists (ACOG 2017)[2]	Cumulative blood loss ≥1000 mL or blood loss accompanied by signs or symptoms of hypovolemia within 24 hours after the birth process (includes intrapartum loss) regardless of route of delivery.

Royal College of Obstetricians and Gynaecologists (RCOG 2016)[3]	Minor PPH (500 to 1000 mL) and major PPH (>1000 mL). Subdivisions of major PPH include moderate (1001 to 2000 mL) or severe (>2000 mL).
International expert panel[4]	Active bleeding >1000 mL within the 24 hours following birth that continues despite the use of initial measures, including first-line uterotonic agents and uterine massage.

[1]WHO recommendations for the prevention and treatment of postpartum haemorrhage: WHO; 2012.
[2]ACOG Practice Bulletin Number 183, October 2017: Postpartum hemorrhage. Obstet Gynecol 2017; 130:e168.
[3]Prevention and management of postpartum haemorrhage: Green-top guideline No. 52. BJOG 2017; 124:e106.
[4]Abdul-Kadir R, McLintock C, Ducloy AS, et al. Evaluation and management of postpartum hemorrhage: Consensus from an international expert panel. Transfusion 2014; 54:1756.

Management

Prophylactic measurements of PPH

In women without risk factors for PPH and delivering vaginally, oxytocin is administered for prophylaxis of PPH in the third stage of labour (period after delivery of the infant up to delivery of the placenta).

Treatment of PPH

The treatment options for PPH relate to the underlying cause of haemorrhage.

A combination of pharmacological, blood products, mechanical and surgical interventions are used presently; additionally, clinicians can consider the use of haemostatic agents.

First line treatments

Several medical products are approved for treatment of PPH due to uterine atony, of which oxytocin is considered first choice. Additional medicinal products include methergine, prostaglandin E2 agonists (dinoprost, sulprostone). Misoprostol, a prostaglandin E1 agonist, is used off-label, but has less efficacy than oxytocin. Additionally, also intravenous tranexamic acid, an antifibrinolytic agent, is used off-label, since the WOMAN trial (Shakur *et al,* Lancet), at the time of uterotonic treatment, has been included in many PPH management protocols.

Second line therapies

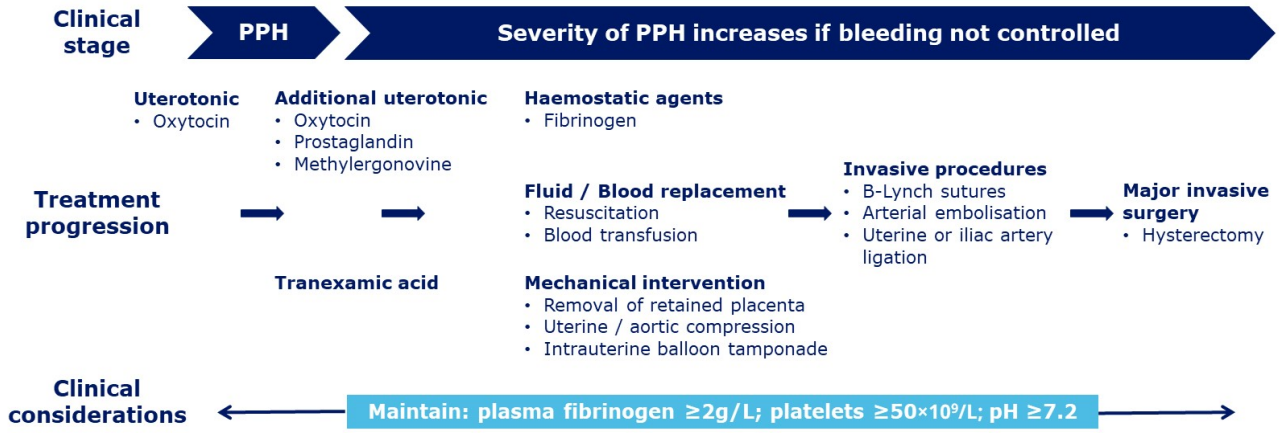
If bleeding persists after uterotonics, clinicians can use a combination of haemostatic agents (fibrinogen), transfusion of blood products (RBC, FFP, platelets, cryoprecipitate), fluid replacement and minimally invasive mechanical interventions (removal of retained placenta, intrauterine balloon tamponade, etc) (RCOG 2016). Non-invasive mechanical methods such as uterine compression and aortic compression may be applied concomitantly as needed.

There are no firm criteria for the timing of initiation of blood product transfusion or haemostatic agents; consequently, the decision is based primarily on clinical, but also laboratory assessments including blood count and coagulation/haemostasis parameters. First-line invasive procedures in the form of uterine compression sutures are also considered appropriate if bleeding continues. In cases where uterine compression sutures are inadequate to control bleeding, selective arterial embolisation or uterine/iliac artery ligation may be performed as second-line interventions. In the event of uncontrolled haemorrhage that becomes life-threatening, emergency hysterectomy may be implemented as a life-saving measure.

Various international and national guidelines have been developed for the management of PPH, based on collective experience and results from registry studies. Protocols for the management of PPH have developed over many years and there are variations across guidelines. A simplified overview is given of

the principles of treatment in recent guidelines, illustrated in Figure 1. The various treatments (including off-label use of NovoSeven) are often applied in parallel.

Figure 1 Principles of treatment for postpartum haemorrhage



A plasma fibrinogen level of greater than 2 g/l should be maintained during ongoing PPH (RCOG 2016).

2.1.2. About the product

NovoSeven is an activated recombinant coagulation factor VII produced in baby hamster kidney cells by recombinant DNA technology. NovoSeven is structurally similar to human plasma factor VIIa except for a difference in glycosylation. NovoSeven was authorised in the EU in February 1996 and was approved in the US in March 1999.

Mechanism of action

The biological activity of NovoSeven is identical to plasma-derived FVIIa. The mechanism of action includes the binding of NovoSeven to exposed tissue factor (TF) at the site of vessel injury or tissue damage. This complex activates factor IX into factor IXa, and factor X into factor Xa, leading to the initial conversion of small amounts of prothrombin into thrombin. Thrombin leads to the activation of platelets and factor V and VIII at the site of injury, and to the formation of the haemostatic plug by converting fibrinogen into fibrin. Pharmacological doses of NovoSeven activate factor X directly on the surface of activated platelets, localised to the site of injury, independent of tissue factor. This results in the conversion of prothrombin into large amounts of thrombin, thereby aiding coagulation and the arrest of bleeding. Accordingly, the pharmacodynamic effect of NovoSeven gives rise to an increased local formation of factor Xa, thrombin and fibrin. As the haemostatic effect of NovoSeven is localised to the site of vascular injury where tissue factor is exposed, and platelets are activated, NovoSeven does not induce systemic activation of coagulation.

Current off-label use of NovoSeven in severe postpartum haemorrhage

NovoSeven is not currently approved for use in severe PPH. Nevertheless, there is a growing body of evidence from off-label use, including patient registries and literature reports, describing the use of NovoSeven for the treatment of women with severe PPH. Reviews of published clinical studies and case reports suggest a beneficial role for NovoSeven in the management of severe PPH (Francini 2007, 2010). When used earlier in the treatment cascade, as shown by a RCT (trial 4816; included in this submission) where NovoSeven was used after uterotonics failure. (Lavigne-Lissalde, J Throm Haemost 2015). The control of bleeding may prevent progression to more invasive interventions such as uterine or iliac artery

ligation, radiological arterial embolisation, uterine compression sutures and/or hysterectomy. Coagulopathy in PPH may arise due to dilutional coagulopathy (replacement of blood loss with crystalloids and colloids leading to dilution of coagulation factors and platelets), localised consumption, disseminated consumption and/or increased fibrinolysis. (Collins et al, J Thromb Haemost 2016).

Thus, in addition to optimising obstetric management, correction of coagulopathy by replacement of coagulation factors and treatment with haemostatic drugs such as NovoSeven may improve outcomes in women with severe PPH. An analysis of individual patient data from women requiring massive transfusion for major obstetric haemorrhage, prospectively collected across population-based studies from Europe and Australia, found that NovoSeven use was variable, ranging from 8-16%. (McCall et al, PLoS One 2021).

Recommendations for the use of NovoSeven for treatment of severe PPH are included in some national guidelines based on professional consensus and results from registry studies. Those guidelines that describe off-label use of NovoSeven for management of severe PPH often recommend its use rather late in the treatment cascade, in order to avoid a hysterectomy or for life-saving situations. Recommendations in current guidelines also differ regarding dosage and number of doses of NovoSeven, but generally recommend 60 µg/kg, 90 µg/kg or 60−90 µg/kg and between 1 and 3 doses, see table 2 below.

Table 2 PPH Treatment Guidelines

Issuer of the Guideline (year) (country)	Guideline title	Dose of fFVIIa	No. of dosages	When to use NovoSeven
Europe				
Feduniw et al (2020) (***Poland***)	Epidemiology, prevention and management of early postpartum haemorrhage — a systematic review-	90	NA	Should be considered when severe bleeding is present.
DGGG, OEGGG and SGGG (2018) (***Germany, Austria and Switzerland***)	Peripartum Haemorrhage, Diagnosis and Therapy. Guideline of the DGGG, OEGGG and SGGG (S2k Level, AWMF Registry No. 015/063, March 2016) Geburtsh Frauenheilk 2018; 78: 382–399[36]	90	1-2	After other options fail (before hysterectomy if the patient wishes for more children). Plasma factor concentrations and platelet numbers should be optimised before NovoSeven® is administered.
Bern university hospital (2018)[3] (***Switzerland***)	Standardized Management Protocol in sPPH: A Single-centre study	60	Up to 3	If bleeding persisted after transfusion of 4 RBCs, 4 FFP units, and 2 g of fibrinogen
Czech-Slovak interdisciplinary consensus (2018) (***Czech Republic and Slovakia***)	Diagnostics and treatment peripartal life threatening bleeding (Source CZ affiliate)	NA	NA	NovoSeven should be considered in patients with life threatening bleeding after failure of standard procedures and before hysterectomy. The optimal conditions for efficacious rFVIIa administration include: fibrinogen> 1 g / l, concentration of haemoglobin> 60 g / l, platelets> 50 × 109 / l, pH> 7.2.
Research protocol: Italian association of hospital obstetricians and gynaecologists (AOGOI) and more (2017)[37] (***Italy***)	The daily-practiced post-partum haemorrhage management: an Italian multidisciplinary attended protocol	60-90	2 (15-30 min.)	If there is no response to the previous measures, the administration of NovoSeven can be suggested; this may be repeated as a last resort before hysterectomy

CNGOF/SFAR (2015) (***France***)	Postpartum haemorrhage: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF) in collaboration with the French Society of Anaesthesiology and Intensive Care (SFAR)	NA	NA	NovoSeven is recommended to be used before and after hysterectomy only for an uncontrolled hemorrhage after the failure of conventional treatment and after having undertaken the correction of platelet levels and other hemostasis parameters.
Dutch Society for Obstetrics and Gynaecology (NVOG) (2013) (***The Netherlands***)	NVOG guideline: Postpartum Haemorrhage	NA	NA	Used only in situations of uncontrolled blood loss and always in multidisciplinary consultation with anaesthesiologist/intensivist and haematologist
Royal College of Obstetricians and Gynecologists (RCOG) (2016) (***United Kingdom***)[29]	Prevention and Management of Postpartum Haemorrhage[29]	NA	NA	The use of NovoSeven may be considered as a treatment for life-threatening PPH but should not delay or be considered a substitute for a life-saving procedure, such as embolization or surgery, or transfer to a referral centre.
Share Network Group (2016) ***(Portugal)***	Interventional Algorithms for the Control of Coagulopathic Bleeding in Surgical, Trauma, and Postpartum Settings: Recommendations from the Share Network Group8	90-120	NA	Last-line nonsurgical intervention, if bleeding persists after correction of fibrinogen concentration and other physiological parameters (acidosis, hypocalcaemia, hypothermia, thrombocytopenia, and hyperfibrinolysis).
Spanish journal of anaesthesiology and resuscitation (2015) Morillas-Ramírez et al (2014) (***Spain***)	Update of the treatment protocol of the obstetric haemorrhage	90	2	Compassionate use. Before proceeding to hysterectomy, NovoSeven use must be considered 2 dosages with 20 min interval if no response
United States				
Higgins et al (2019) ***(US)***	Postpartum hemorrhage revisited: new challenges and solutions11	NA	NA	Not recommended for routine treatment of PPH.
Pacheco et al (2019) ***(US)***	Medical management of postpartum hemorrhage: An update.12	NA	NA	In very selected cases. Use of lower doses (<25 µg/kg) could decrease the risk of thrombotic events.
American College of Obstetricians and Gynecologists (2017***) (US)***	ACOG Practice Bulletin No. 183. Clinical Practice Guidelines for Obstetrician-Gynecologists: Postpartum Hemorrhage13	NA	NA	NovoSeven® use is not considered first-line therapy and should be reserved for extenuating circumstances after multiple rounds of the standard massive transfusion agents and in consultation with a local or regional expert in massive haemorrhage.
Schorn and Phillippi (2014) (US)	Volume replacement following severe postpartum hemorrhage14	90	2 (20 min)	During or following severe PPH
Pacheco et al (2013) (US)	The role of massive transfusion protocols in obstetrics15	40	NA	If bleeding persists after blood products are administered. NovoSeven® incorporated in a massive transfusion protocol, as 40 µg/kg every 3rd round. (Round 1 = RBC + FFP + platelets + cryoprecipitate. Round 2 = RBC + FFP + cryoprecipitate)
Rest of the World				

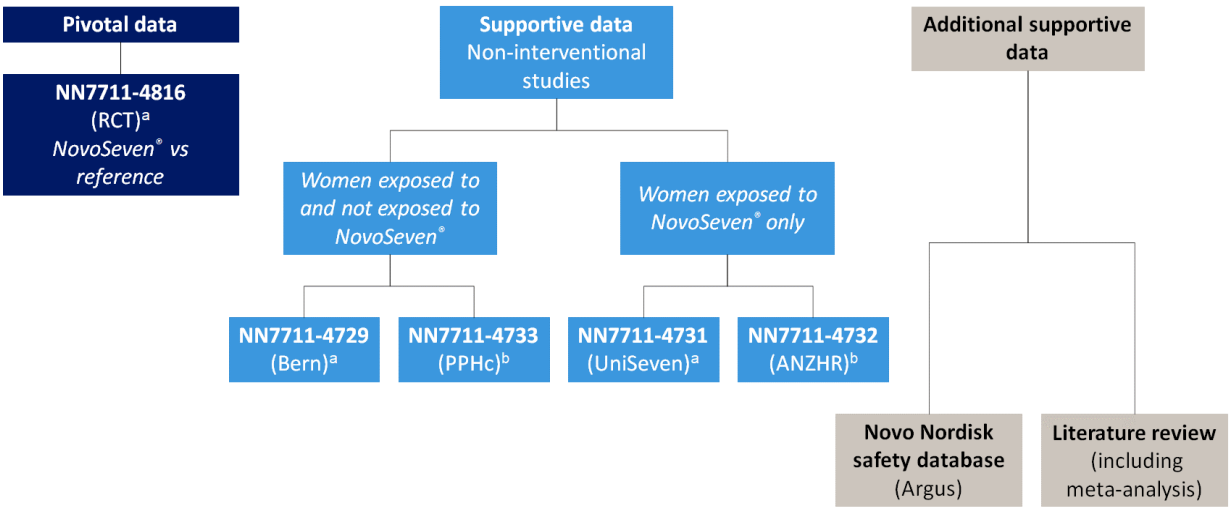
Auckland District Health Board (2015) ***(New Zealand***)	Postpartum Haemorrhage (PPH) Prevention and Management[38]	90	NA	NovoSeven can be used after other options fail
International guidelines				
NATA with FIGO, EBCOG and ESA (2019) (International)	Patient blood management in obstetrics: prevention and treatment of postpartum haemorrhage. A NATA consensus statement17	NA	NA	The use of NovoSeven® may be considered alongside acidosis correction, only as a last resort in massive ongoing PPH.
Expert panel (2014) (International)	Evaluation and management of postpartum hemorrhage: consensus from an international expert panel18	90	up to 2 (15-30 mins)	In life-threatening PPH, NovoSeven® may be used as an adjunct to other surgical treatments. Platelets (>50x109/L) and fibrinogen (>2 g/L) should be checked and corrected before administration of NovoSeven®.

Abbreviations: NA: not available; DGGG: German Society of Gynaecology and Obstetrics; OEGGG: Austrian Society of Gynaecology and Obstetrics; SGGG: Swiss Society of Gynaecology and Obstetrics; CNGOF: French College of Gynaecologists and Obstetricians, SFAR: French Society of Anesthesiology and Intensive Care.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

This application presents data on the clinical efficacy and safety of NovoSeven, when used for the treatment of women with severe PPH. Pivotal data are provided from 1 open-label RCT (trial 4816), published in 2015 https://onlinelibrary.wiley.com/doi/10.1111/jth.12844. Together with observational evidence from 4 non-interventional studies. The non-interventional studies were based on patient-level data from a single hospital centre (study 4729), partly published by Colluci *et al,* 2018, national-level data from 3 countries (study 4733) and data from 2 registries covering 3 countries describing off-label use of NovoSeven (studies 4731 and 4732). Data are also provided from the Novo Nordisk safety database (Argus) and from a literature review of published clinical studies (including a meta-analysis) and case-reports of women with severe PPH treated with NovoSeven, depicted in figure 2.

Figure 2 Overview of clinical data sources



a Analyses of patient-level data were performed by Novo Nordisk.

b Analyses of patient-level data were performed by external academic institutions.

Abbreviations: ANZHR = Australian and New Zealand Haemostasis Registry; PPHc = PPH consortium; RCT = randomised controlled trial

2.1.4. General comments on compliance with GCP

As stated by the MAH, the randomised controlled trial was conducted in accordance with ICH GCP. The 2 epidemiological studies and the 2 registries are stated to have been conducted in accordance with the Guidelines for Good Pharmacoepidemiology Practices, and claimed to include elements of the EMA draft guideline on registry-based studies were retrospectively implemented when the draft guideline was published in September 2020.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

According to the guideline "Guideline on the environmental risk assessment of medical products for human use", an environmental risk assessment is not required for substances like amino acids, peptides, proteins, carbohydrates, and lipids since they are unlikely to result in significant risk to the environment. Therefore, no ERA is required for this extension of indication for NovoSeven.

2.2.2. Introduction

GCP

The Clinical phase 3 trial was performed in accordance with GCP as claimed by the authors.

The 2 epidemiological studies and the 2 registries are stated to have been conducted in accordance with the Guidelines for Good Pharmacoepidemiology Practices.

- Tabular overview of clinical studies

Table 3 Key features of the clinical data sources

Trial or study ID / Countries / Location	Trial or study design / Study period / Final data cut-off date	Number of women with severe PPH		NovoSeven dose regimen
		NovoSeven	No NovoSeven / Control[a]	
Randomised controlled trial				
4816 (RCT) / FR, CH / Module 5.3.5.1	Prospective, multicentre, randomised, open label, parallel-group comparative trial to assess efficacy and safety of NovoSeven in women with severe PPH after sulprostone (uterotonic) failure / 04-Apr-2007 to 05-Nov-2010 / 14-Apr-2021	42[b] (FAS)	42 (FAS)	Single intravenous dose of 60 µg/kg NovoSeven

Trial or study ID / Countries / Location	Trial or study design / Study period / Final data cut-off date	Number of women with severe PPH		NovoSeven dose regimen
		NovoSeven	No NovoSeven / Control[a]	
Non-interventional studies				
4729 (Bern) / CH / Module 5.3.5.2	Retrospective, single-centre, non-interventional cohort study to evaluate clinical outcomes of NovoSeven in women with severe PPH/ 01-Jan-2006 to 30-Apr-2016 / 13-Jan-2021	52 (FAS) 18 (PSAS)	113 (FAS) 43 (PSAS)	At the discretion of the physician and as per the local clinical practice
4733 (PPHc) / DK, NL, UK[c] / Module 5.3.5.2	Retrospective, multi-country, non-interventional, cohort study to evaluate clinical outcomes of NovoSeven in women with severe PPH / DK: 2001 to 2009; NL: Jan-2011 to Jan-2013; UK: Jul-2012 to Jun-2013 / 08-Jan-2021	40 (DK FAS) 16 (DK PSAS) 37 (NL FAS) 24 (NL PSAS) 13 (UK FAS)	199 (DK FAS) 44 (DK PSAS) 1223 (NL FAS) 71 (NL PSAS) 149 (UK FAS)	At the discretion of the physician and as per the local clinical practice
4731 (UniSeven) / CZ / Module 5.3.5.2	Retrospective, non-interventional cohort study using data from UniSeven registry to describe clinical outcomes in women with severe PPH treated with NovoSeven / Jul-2003 to Apr-2014 / 31-Jul-2020	87 (FAS)[d]	NA	At the discretion of the physician and as per the local clinical practice
4732 (ANZHR) / AU, NZ / Module 5.3.5.2	Retrospective, non-interventional cohort study using data from the ANZHR to describe clinical outcomes in women with severe PPH treated with NovoSeven / 2000 to 2009 / 20-Apr-2021	166 (FAS)	NA	At the discretion of the physician and as per the local clinical practice
Other data sources				
Literature review / Module 5.3.5.4	A literature review of **safety** and other clinical outcomes in women with severe PPH who were treated with NovoSeven or other therapies based on published clinical studies and case reports / 01-Jan-1996 to 01-Jul-2020	672 (meta-analysis) 100 (case reports)	2181 (meta-analysis)	Dose and number of doses varied across published studies and case reports

Trial or study ID / Countries / Location	Trial or study design / Study period / Final data cut-off date	Number of women with severe PPH		NovoSeven dose regimen
		NovoSeven	No NovoSeven / Control[a]	
Novo Nordisk safety database (Argus report) / Module 5.3.5.4	Review of all cases of women with PPH reported cumulatively in the NovoSeven Argus database until 30-Jun-2020 with a focus on TEs and cases with a fatal outcome. Subgroups of women treated with NovoSeven with or without TEs were analysed. / 1995 to 30-Jun-2020	123 (39 with TEs; 84 without TEs)	NA	At the discretion of the physician and as per the local clinical practice

Note: Trial 4816 (RCT) was sponsored and conducted by Nîmes University Hospital. Novo Nordisk performed reanalysis of patient-level data for trial 4816 and analysis of patient-level data for studies 4729 (Bern) and 4731 (UniSeven). Department of Clinical Epidemiology, Leiden University Medical Center performed analysis of patient-level data for study 4733 (PPHc). Department of Epidemiology and Preventive Medicine, Monash University performed analysis of patient-level data for study 4732 (ANZHR).

[a] For the FAS, "No NovoSeven" refers to women in the reference group (trial 4816) or those who did not receive NovoSeven (studies 4729, 4733 and literature review); For the PSAS, "Control" refers to the matched controls from the propensity score matching (studies 4729 and 4733).

[b] A total of 51 women were exposed to NovoSeven in trial 4816: 42 women randomised to NovoSeven, 8 women in reference group that received NovoSeven on compassionate basis after the treating physician had decided to proceed with hysterectomy (after assessment of the primary endpoint) and 1 woman in reference group that received NovoSeven at randomisation in error.

[c] It was planned to also include data from France. However, these data could not be collected primarily due to the burden on hospital staff due to the COVID-19 pandemic at the time.

[d] A total of 111 women with PPH were exposed to NovoSeven but this includes 24 women for whom severe PPH was not confirmed (blood loss <1500 mL or missing information on blood loss).

Abbreviations: ANZHR = Australian and New Zealand Haemostasis Registry; AU = Australia; CH=Switzerland; CZ = Czech Republic; DK = Denmark; FAS = full analysis set; FR = France; NA=not applicable; NL = Netherlands; NZ = New Zealand; PPH = postpartum haemorrhage; PPHc = PPH consortium; PSAS = propensity score analysis set; RCT = randomised clinical trial; TE = thromboembolic event; UK = United Kingdom

2.2.3. Pharmacokinetics

Pharmacokinetics of NovoSeven in women with severe postpartum haemorrhage has not been investigated.

2.2.4. Pharmacodynamics

Mechanism of action

The biological activity of NovoSeven is identical to plasma-derived FVIIa. The mechanism of action includes the binding of NovoSeven to exposed tissue factor. This complex activates factor IX into factor IXa, and factor X into factor Xa, leading to the initial conversion of small amounts of prothrombin into thrombin. Thrombin leads to the activation of platelets and factor V and VIII at the site of injury, and to the formation of the haemostatic plug by converting fibrinogen into fibrin. Pharmacological doses of NovoSeven activate factor X directly on the surface of activated platelets, localised to the site of injury, independent of tissue factor. This results in the conversion of prothrombin into large amounts of thrombin, thereby aiding coagulation and the arrest of bleeding. Accordingly, the pharmacodynamic effect

of NovoSeven gives rise to an increased local formation of factor Xa, thrombin and fibrin. As the haemostatic effect of NovoSeven is localised to the site of vascular injury where tissue factor is exposed, and platelets are activated, NovoSeven does not induce systemic activation of coagulation.

Primary and secondary pharmacology

No new pharmacodynamic data have been submitted within the dossier. However, although the PD profile of NovoSeven in women with severe PPH has not been investigated, time to peak coagulant activity has been studied in healthy subjects and haemophilia patients.

A PK/PD study in 22 healthy subjects (n=22), who received a single intravenous dose of NovoSeven (90 µg/kg), showed maximal FVIIa activity at 5-10 minutes after dosing.

Two PK/PD studies have evaluated the time to peak coagulant activity after NovoSeven administration in haemophilia patients. The first study, which evaluated single (270 µg/kg) and multiple (90 µg/kg × 3) intravenous doses of NovoSeven in haemophilia A and B patients (n=6), showed that time to clot formation, velocity of clot formation, maximum clot strength and peak thrombin generation were maximal at 10 minutes after NovoSeven administration (for both single and multiple doses). The second study in haemophilia A and B patients with inhibitors (n=13) showed that the time to peak coagulant activity occurred 10 minutes after a single intravenous injection (35-70 µg/kg) of NovoSeven.

Based on the available PD data, the time to peak coagulant activity of NovoSeven is approximately 10 minutes.

The proposed 30 minute dose-interval was based on available PD data of NovoSeven, PPH guidelines recommending a second dose 15-30 minutes after the first dose of NovoSeven[1,2] as well as the RCT where clinical response was evaluated within 30 minutes of NovoSeven administration.

2.2.5. Discussion on clinical pharmacology

Pharmacokinetics of NovoSeven in women with severe postpartum haemorrhage has not been investigated. No new pharmacodynamic studies have been presented for this new indication. However, based on the available PD data in healthy volunteers and haemophilia patients, the time to peak coagulant activity of NovoSeven is approximately 10 minutes.

Considering the different dose recommendations proposed for this indication, i.e. a different dose interval of 30 minutes in case of insufficient response, this information is reflected in section 4.2 and section 5.1 of the SmPC.

The recommended dose range for the treatment of bleeding is 60 – 90 µg per kg body weight administered by intravenous bolus injection. Peak coagulant activity can be expected at 10 minutes. A second dose can be administered based on clinical response of the individual patient.

It is recommended that in case of insufficient haemostatic response, a second dose can be administered after 30 minutes.

The SmPC reflects that the Pharmacokinetics of NovoSeven in patients with severe postpartum haemorrhage have not been investigated.

[1] Affronti G, Agostini V, Brizzi A, Bucci L, De Blasio E, Frigo MG, et al. The daily-practiced post-partum hemorrhage management: an Italian multidisciplinary attended protocol. Clin Ter. 2017;168(5):e307-e16.
[2] Abdul-Kadir R, McLintock C, Ducloy AS, El-Refaey H, England A, Federici AB, et al. Evaluation and management of postpartum hemorrhage: consensus from an international expert panel. Transfusion. 2014;54(7):1756-68.

2.2.6. Conclusions on clinical pharmacology

Pharmacokinetics of NovoSeven in women with severe postpartum haemorrhage has not been investigated. No new pharmacodynamic studies have been presented for this new indication. However, based on the available PD data in healthy volunteers and haemophilia patients, the time to peak coagulant activity of NovoSeven is approximately 10 minutes, which is important considering the different dose recommendations proposed for this indication.

Considering the different dose recommendations proposed for this indication, i.e. a different dose interval of 30 minutes in case of insufficient response, this information is reflected in section 4.2 and section 5.1 of the SmPC.

2.3. Clinical efficacy

2.3.1. Dose response study

No formal studies were performed for the evaluation of dose-response in the currently applied indication.

Regarding the dose selected in the pivotal randomised trial (study 4816), patients received one early single intravenous dose of 60 µg/kg rhuFVIIa. This rhuFVIIa dose was, according to literature data, the lowest dose with clinical effect in the setting of severe PPH and was chosen to reduce, as far as possible, the thrombotic risk associated with Novoseven. This dose is lower than the minimum dose of 90 µg/kg that is approved for NovoSeven in the currently authorised indications.

2.3.2. Main studies

The data set to support the efficacy of the new indication consists of pivotal data provided from 1 open-label RCT (trial 4816), together with supportive observational data from 4 non interventional studies. The data from the non-interventional studies were based on patient-level data from a single hospital centre (study 4729), national-level data from 3 countries (study 4733) and data from 2 registries covering 3 countries describing off-label use of NovoSeven (studies 4731 and 4732).

Study 4816 (RCT)

As noted previously, Study 4816 (RCT) is the pivotal study to support the proposed indication.

Title: *Chronological place of the administration of recombinant activated factor VII in maternal salvage in severe postpartum haemorrhage: before or after invasive second-line therapies (embolisation, vascular ligation and haemostatic hysterectomy)*

(Lavigne-Lissalde G, Aya AG, Mercier FJ, Roger-Christoph S, Chauleur C, Morau E, et al. Recombinant human FVIIa for reducing the need for invasive second-line therapies in severe refractory postpartum haemorrhage: a multicentre, randomized, open controlled trial. Lavigne-Lissalde et al, J Thromb Haemost 2015). https://onlinelibrary.wiley.com/doi/10.1111/jth.12844

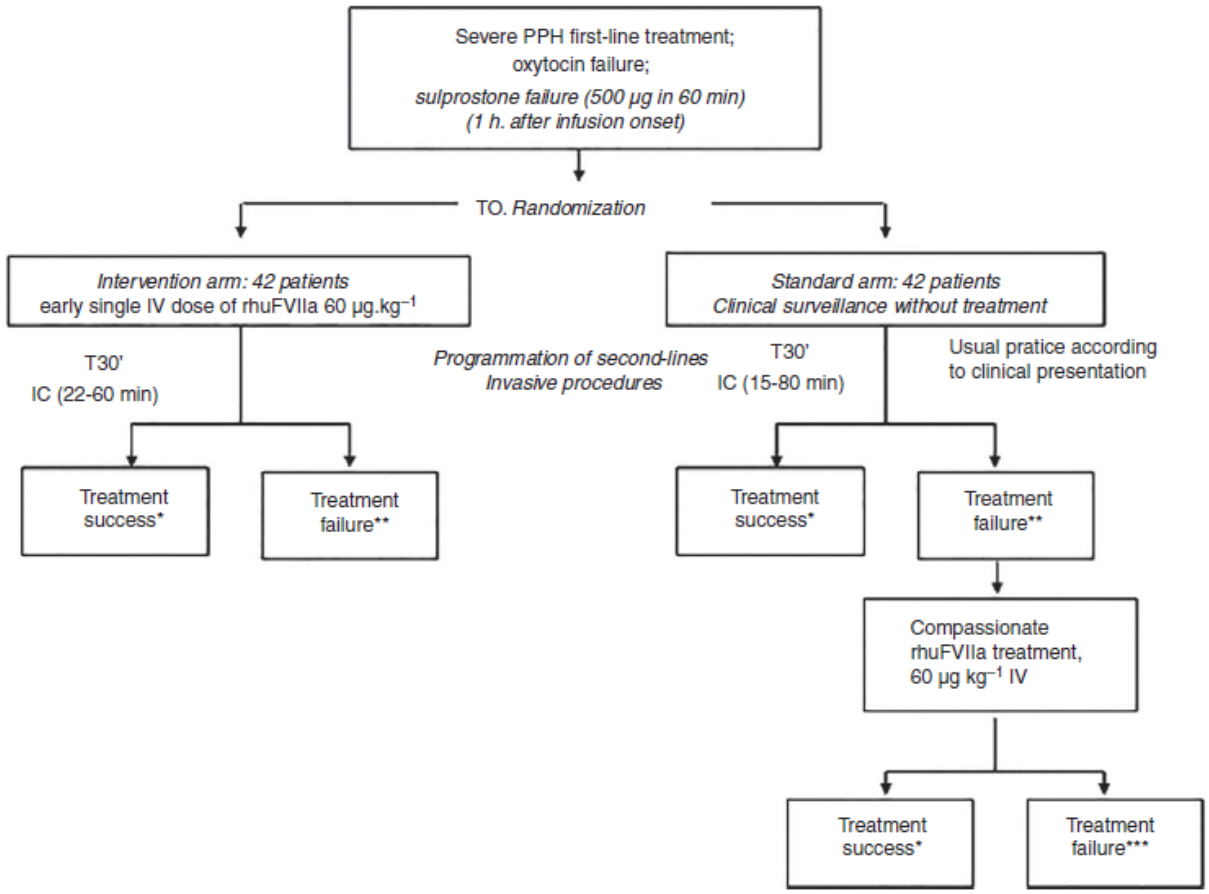
This trial was sponsored by Nîmes University Hospital. The trial was conducted in 2 countries: France: 7 University hospital sites screened and randomised patients, Switzerland: 1 site screened and randomised patients. The trial period was from Initiation date: 04 April 2007 to Trial completion date: 05 November 2010.

Methods

Study design

This was a multicentre, randomised, open-label, parallel-group trial in which women with severe PPH were randomised to treatment with NovoSeven or to no concurrent treatment (reference), following failure of sulprostone to control the bleeding. The RCT was open-label in design because, in the investigators' opinion, the emergency conditions of obstetrical haemorrhage onsets did not allow for a double-blind design. The trial was conducted in accordance with ICH GCP. Both groups received standard of care treatment in accordance with the treatment guidelines in place at the time of the trial, see Figure 4 below.

Figure 4 Trial design



*No need for specific second-line therapy embolization or ligation (primary outcome). **Need for specific second-line therapies (compression sutures and/or uterine artery embolization and/or vascular ligations and/or hysterectomy) depending on availability (primary outcome). ***Hysterectomy.

Study participants

A total of 84 women with severe PPH were planned to be randomised 1:1 to treatment with NovoSeven (in addition to standard of care) or to reference therapy (standard of care alone), see sample size calculations below. The care of patients at each site was according to the local care guidelines for severe PPH. The enrolment criterion was sulprostone failure 1 h after the infusion onset (or before the end of this period).

Severe primary PPH was defined as the loss of more than 1500 mL of blood within 24 h after birth. The contribution of any fluid used for washing was taken into account to prevent blood loss overestimation.

According to French practice guidelines, first-line therapies for PPH included: fluid resuscitation, bladder catheterisation, manual removal of retained placenta, genital tract examination, uterine exploration, oxytocin (20–30 IU every 10–30 min) and finally one sulprostone infusion (500 µg within 1 h).

Inclusion criteria/exclusion criteria

These are reflected in the table 4.

Table 4 Inclusion and exclusion criteria - trial 4816 RCT

Inclusion criteria	Exclusion criteria
• Severe haemorrhage at delivery defined by one of the following criteria: blood loss greater than 1500 mL measured in the graduated bag and/or hemodynamically unstable and/or need for packed cells transfusion • Inefficacy of sulprostone (Nalador®) • Age ≥18 years • Patient at more than 27 weeks of gestation (viability of the child) • No anthropometric limit • After a normal or pathological pregnancy	• Patient is a minor • Patient is an adult under guardianship • Personal history of venous or arterial thrombosis that could contraindicate treatment with NovoSeven®.

Treatments

After consent, the woman's platelet count was assessed and if the count was ≤50 × 109/L, an APC transfusion (containing platelets and plasma) was ordered, according to the immediate life-threatening emergency procedure.

One group received one early single intravenous dose of 60 µg/kg body weight rhuFVIIa (NovoSeven intervention arm) on top of standard care and the other group did not (standard care arm). This rhuFVIIa dose was, according to literature data, the lowest dose with clinical effect in the setting of severe PPH and was chosen to reduce, as far as possible, the thrombotic risk associated with this drug.

The NovoSeven group received a single dose of approximately 60 µg/kg via slow IV injection (2mL/min) immediately after randomisation whereas women in the reference group did not receive NovoSeven at the time of randomisation.

A compassionate use protocol was also established so that women in the reference group could receive NovoSeven after a decision had been made to perform a *haemostatic hysterectomy* (after assessment of the primary endpoint), if haemorrhage persisted and was not controlled by standard of care treatment.

The NovoSeven dose was determined according to the woman's 'maternal' bodyweight, calculated as her measured bodyweight at term (prior to delivery) minus 5 kg (or 7 kg in the case of twin pregnancies) to account for foetal-placental weight. To facilitate the emergency treatment with complete Novoseven packaging units (1.2, 2.4 and 4.8 mg vials), the theoretical rhuFVIIa dose was tabulated and adapted as described in Table 5. For example, a woman with calculated maternal weight of 60 kg would have a dose of 3.6 mg (administered as one 1.2-mg vial and one 2.4-mg vial); a woman with calculated maternal weight of 80 kg would have a dose of 4.8 mg (administered as one 4.8-mg vial). This table was not included in the protocol but was provided separately to the sites.

Table 5 NovoSeven planned dose according to maternal weight

Maternal weight (kg)	Planned dose (mg)	Vials to be administered (mg)
40-45	2.4	2.4
46-68	3.6	2.4 + 1.2
69-94	4.8	4.8
95-110	6.0	4.8 + 1.2
≥111	6.0	4.8 + 1.2

Maternal weight = patient's measured bodyweight prior to delivery minus 5 kg (or 7 kg in the case of twins)

Standard of care treatment:

According to French practice guidelines, first-line therapies for PPH included: fluid resuscitation, bladder catheterization, manual removal of retained placenta, genital tract examination, uterine exploration, oxytocin (20–30 IU every 10–30 min) and finally one sulprostone infusion (500 µg within 1h).

Definition of treatment success

Haemorrhage volume was to be measured at 30 minutes to 1 hour after the start of the injection of NovoSeven for patients in the NovoSeven group and at the end of conventional treatment (after embolisation or vascular ligation) for the reference group. Bleeding was considered to have stopped (i.e. treatment success) if the estimated blood flow decreased to less than 50 mL per 10 min within the 30 min following randomization.

Initiation invasive second line treatment

At any time and in both arms, invasive second-line treatments were considered if bleeding was uncontrolled (blood flow higher than 50 mL per 10 min) or intractable (defined as PPH > 2500 mL, or blood flow > 500 mL per 30 min, or haemorrhagic shock refractory to standard care).

Replacement therapy

- Packed red blood cells (PRBCs) were indicated if patient's haemoglobin concentration was lower than 8 g/dL.
- Platelet concentrates (PC) were administered when the platelet count was lower than 50 x 10^9/L.
- Fibrinogen concentrates were administered if the plasma fibrinogen concentration was lower than 1 g/L.
- Haemostatic drugs are not recommended and not routinely used as first-line intervention in PPH: therefore, they were not used in this RCT.
- The use of tranexamic acid (TXA) (0.5–1 g intravenously) was left to the attending physician's discretion.
- Vascular volume expansion was achieved using 500 mL of crystalloid and 500 mL of colloid expander for the first litre of blood loss, and thereafter an infusion, mostly of gelatine, was administered to compensate for the subsequent blood loss (vol/vol).
- Fresh frozen plasma (FFP) was infused by the attending anaesthetist, if clinically indicated.

TXA and fibrinogen data were collected for the time interval before randomisation and in hourly intervals for 7 hours after randomisation.

Thrombosis prophylaxis following PPH

Thromboprophylaxis initiated 6 h after the end of PPH (4000 IU enoxaparin, once a day).

Removal of patients from therapy and assessment

A woman could withdraw consent at will at any time.

At any time and in both groups, invasive second-line treatments were to be considered if bleeding was uncontrolled (blood flow higher than 50 mL per 10 min) or intractable (defined as PPH >2500 mL, or blood flow >500 mL per 30 min, or haemorrhagic shock refractory to standard care).

Duration of use

Single dose trial.

Follow-up:

The initial observation period was 5 days due to the limited NovoSeven biological half-life (4–6 h). To identify symptomatic venous thromboembolism events up to 6 weeks after PPH, data from the initial medical records were extracted and patients had to fill in a simple questionnaire concerning the first 6 weeks postpartum.

Objectives

Protocol primary objective (original protocol based primary objective)

To evaluate the interest in using NovoSeven in the treatment of severe PPH unresponsive to conventional treatment and to define, if applicable, the number of interventional embolisation procedures, vascular ligations, hysterectomies and transfusions prevented due to the early use of NovoSeven.

Protocol secondary objective

The various investigative University Hospitals for this project are reference centres for their region. Nimes University Hospital participates in a network aimed at improving the care of pregnant women in Gard Department. The secondary objective of this study is to propose within the network a protocol for the proper use of recombinant rFVIIa in severe refractory postpartum haemorrhages. This agreement on the proper use of rFVIIa in PPH could be useful in organising patient transfers from peripheral hospitals to the University Hospital, before arterial embolisation or the surgical procedure (vascular ligation) and, if applicable, in avoiding a haemostatic hysterectomy. In effect, it could be posited that the early administration of rFVIIa at the peripheral centres might allow both a reduction in the number of transfers by reducing the frequency of failures of conventional treatment and the transfer of these patients in a better hemodynamic condition.

Publication primary objective:

Treatment success was defined as the absence of need for specific second-line therapies. Interventional haemostatic procedures included uterine compression sutures (B-Lynch surgical technique or its various modifications), ligation of the uterine or iliac arteries, uterine artery embolisation and peripartum hysterectomy and the Bakri Balloon.

Outcomes/endpoints

Primary efficacy endpoint protocol:

1. absolute reduction in need for specific second-line therapies (rate of embolisation and/or ligation) in the rFVIIa (Novoseven) group versus the reference group.

2. relative reduction in the need for specific second-line therapies by number of subjects treated before reaching an embolisation or ligation.

Primary endpoint publication:

- Reduction in the need for specific second-line therapies (at least one ligation, suture, embolisation, intra-uterine balloon tamponade and/or hysterectomy).

Secondary outcomes (publication only)

- number (percentage) of patients in each arm who received PRBCs, FFP units or PC;
- all replacement treatments (infusion of colloids/crystalloids, transfusions of blood components such as PRBCs, FFP and PC, and additional procoagulant treatments such as TXA, fibrinogen concentrates and aprotinin) were recorded.
- Biological measures were collected before delivery and within the first 12 h after PPH.

Sample size

In the reference group, the expected rate of embolisation or surgical procedure, such as vascular ligature, is approximately 70% (Lédée et al, 2001, Mignon et al, 2004; Aledort et al, 2004; Tourné G et al, 2003). A 30% absolute decrease in the embolisation or vascular ligature rate is expected, that is, a 40% rate when rFVIIa is administered early after the conventional medical treatment. In order to show a statistically significant difference with a 5% bilateral risk and an 80% power, 42 patients were required in each group, that is, 84 patients for the study. The investigators chose to focus on an absolute reduction of only 30% based on their limited inclusion capacities.

Randomisation

A randomisation list stratified by site was prepared using the SAS software (Version 9.3, SAS Institute Inc, Cary, NJ, USA) by the Department of Medical Information at Nîmes University Hospital and accordingly, the eligible patients with severe PPH were randomised 1:1 to either of the 2 groups. As directed by the protocol, patients were randomised approximately 1 hour after sulprostone failure to control their bleeding. This was an open-label trial because in the investigators' opinion, the emergency conditions of PPH onset did not allow for a double-blind therapeutic trial.

Blinding (masking)

The RCT was open-label in design because, in the investigators' opinion, the emergency conditions of obstetrical haemorrhage onsets did not allow for a double-blind design.

Statistical methods

The following analysis sets were defined in accordance with ICH E9:

- Full analysis set (FAS) – included all randomised patients. In exceptional cases patients from the FAS may be excluded. In such cases the exclusion was to be justified and documented. The patients in FAS would contribute to the evaluation 'as randomised'.

- Per protocol (PP) analysis set – included all patients in the full analysis that did not have any major protocol violations including the violation of entry criteria.

The analysis for the primary endpoint, was done by calculating the relative risk (NovoSeven group versus reference group) with a 95% CI. The p-value was based on chi-square test for testing the equality of two proportions for NovoSeven and reference groups. If number of patients in either group was less than 5, this test was planned to be based on Fisher's exact test. All the tests were two-sided and assessed at the 5% significance level.

Relative risk = r1 / r0, 95% CI for relative risk was calculated by the method of Wald.

In addition, Risk difference (95% CI by the method of Wald), Relative reduction and Number of patients to be treated to prevent a studied endpoint event (NNT) were calculated.

Risk difference (RD) = r0 – r1

Relative reduction = 1 – Relative risk = (r0 - r1) / r0 = 1 – (r1/r0)

NNT = 1/(absolute Risk difference)

where r0 = proportion of reference group, r1 = proportion of NovoSeven group.

All analyses were performed based on the FAS. In addition, the primary endpoint and supportive endpoint analyses were repeated with the PP analysis set as post hoc analyses.

Quantitative variables will be expressed as mean and standard deviation if the distribution is Gaussian. Otherwise, they will be expressed as median and 25th and 75th percentiles. Qualitative variables will be expressed as number and percentage. The qualitative endpoints of the two groups will be compared with the help of a Chi2 test or a Fisher's exact test if the conditions for Chi2 are not met. The quantitative endpoints of the two groups will be compared by a Student's test or a Kruskall-Wallis test if the conditions for applying Student's test are not met. In the event of an imbalance between the two groups in one or more prognostic factors considered significant, an unconditional multivariate logistic regression analysis will be performed to explain the embolization or ligation rate (primary endpoint).

The 1st species risk will be set at 5% for all analyses. No interim analysis is planned for the study.

Analysis Primary (and secondary) endpoints publication:

Quantitative data are reported as medians with lower quartile (Q25%) and upper quartile (Q75%) values. Qualitative variables are reported as numbers and percentages. All analyses were performed based on the intention-to-treat (ITT) principle. The primary (and secondary outcomes) were compared between arms by estimating the relative risk (RR) using the Mantel-Haenszel method, with a 95% confidence interval (95% CI), providing a P-value from the associated Mantel-Haenszel chi-square test. The existence of treatment by centre interactions for the primary outcome was assessed using the Breslow-Day test, first applied to the eight centres and then only to the five centres that enrolled at least five patients. Among all the presented analyses, only the treatment by centre interaction and the effect of the delivery mode on the primary outcome were 'post hoc' analyses. All tests were two sided and assessed at the 5% significance level.

1. At least one ligation, suture, embolisation, intra-uterine balloon tamponade and/or hysterectomy

2. Peripartum Hysterectomy

3. At least one embolisation

4. At least one ligation

Subgroup analysis of the primary endpoint was further made by mode of delivery.

Protocol amendments

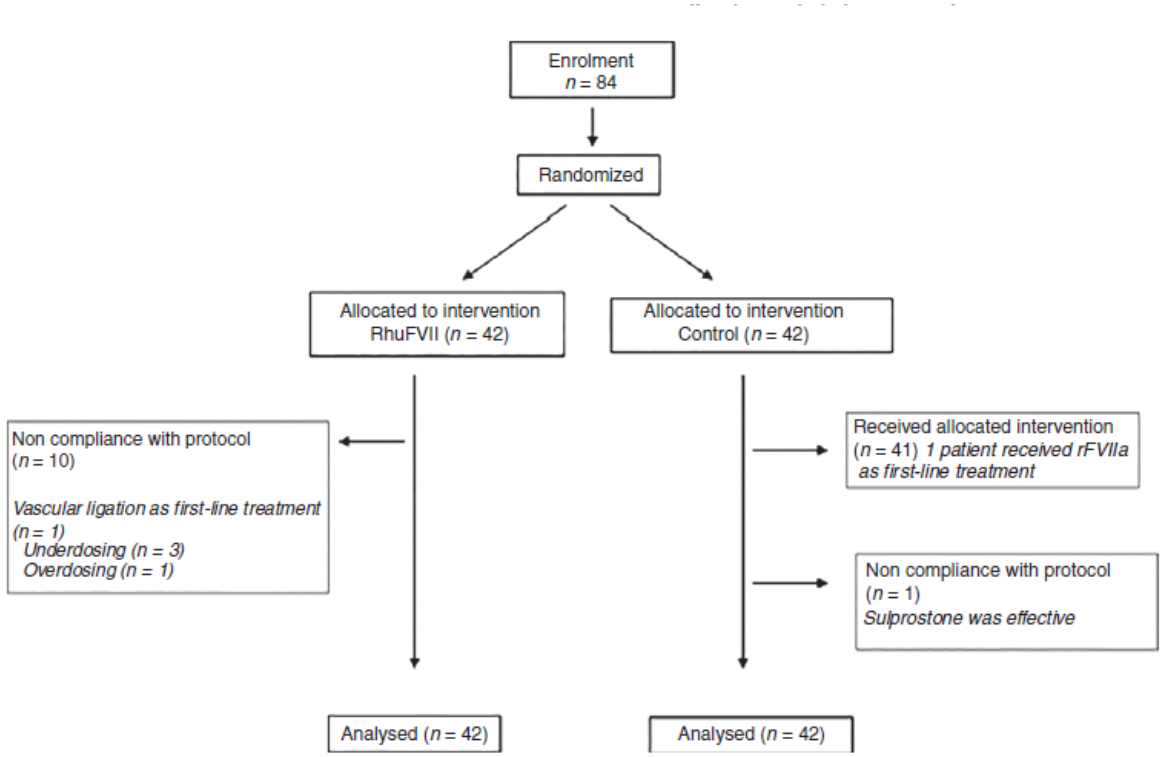
There were 2 amendments to the protocol,

- 23 Jun 2008 After FPFV Global Addition of a site (St Etienne) to increase the rate of patient recruitment.
- 06 Apr 2010 After FPFV Global One-year extension of the trial in order to reach the planned sample size of 84 patients.

Results

Participant flow

Figure 4 Flow chart of inclusions (extracted from the publication)



Recruitment

A total of 84 women with severe PPH were included in this trial; 42 patients were randomised to the NovoSeven group and 42 patients to the reference group. All women were considered to have completed the trial, that is, completed treatment for PPH.

Sixty patients were included 1 h after sulprostone infusion. Among the 24 remaining patients, the median randomization time (lower quartile–upper quartile) was 40 min (30–45 min) for the intervention arm and 30 min (30–30 min) for the standard care arm (P = 0.93).

Conduct of the study

Two important protocol deviations were identified (post hoc) from the available monitoring reports. They were as follows:

- One woman in the reference group did not meet the inclusion criteria (she had already responded to sulprostone).
- One woman in the NovoSeven group had ligation performed prior to NovoSeven injection.

In addition, one woman was randomised to the reference group, but received NovoSeven due to an error in reading the randomisation envelope.

Baseline data

All 42 women in the NovoSeven group were exposed to a single dose of NovoSeven. In addition, 8 women in the reference group received a single dose of NovoSeven after the treating physician had decided to proceed with hysterectomy, under the compassionate use protocol. One woman randomised to the reference group received NovoSeven in error. Therefore, a total of 51 women were exposed to NovoSeven.

Demographic and baseline characteristics

Demographic and baseline characteristics of women with severe PPH enrolled in the trial are presented in Table 6. The distribution of women across age classes was similar between treatment groups with half of the patients being in the age range of 31-40 years. Proportion of women above 35 years was numerically higher in the NovoSeven group compared to the reference group (40.5% versus 26.2%). The median maternal weight was also comparable between the two groups.

Approximately, 50% of women had a caesarean delivery with 54.8% (23/42 women) in the NovoSeven group and 47.6% (20/42 women) in the reference group. Seven women (16.7%) in each group had twin births.

A single cause of PPH was reported for majority of women, with more women in the NovoSeven group having multiple causes of PPH than in the reference group (31.0% versus 11.9%). Overall, uterine atony was recorded as the most common cause of PPH (89.3%) followed by AIP (16.7%).

Table 6 Demographic and baseline characteristics

	NovoSeven	Reference
Age classes (years), n (%)		
N	42	42
19-24	3 (7.1)	5 (11.9)
25-30	14 (33.3)	14 (33.3)
31-35	8 (19.0)	12 (28.6)
36-40	12 (28.6)	10 (23.8)
41-46	5 (11.9)	1 (2.4)
Maternal body weight,[a] kg		
N	42	40
Mean (SD)	70.3 (11.8)	71.1 (13.9)
Median (IQR)	68.0 (62.0-76.0)	70.0 (60.0-79.0)
Cause of PPH,[b] n (%)		
N	42	42
AIP	6 (14.3)	8 (19.0)
Placental retention	4 (9.5)	1 (2.4)
Uterine atony	39 (92.9)	36 (85.7)
Birth canal injury	3 (7.1)	1 (2.4)
Other	4 (9.5)	1 (2.4)

Single cause of PPH	29 (69.0)	37 (88.1)
Multiple cause of PPH	13 (31.0)	5 (11.9)
Delivery mode, n (%)		
N	42	42
Vaginal	19 (45.2)	22 (52.4)
Caesarean	23 (54.8)	20 (47.6)
Number of babies, n (%)		
N	42	42
Twin births	7 (16.7)	7 (16.7)

[a]Maternal body weight corresponds to weight without weight of baby. For all singleton, 5 kg were subtracted and 7 kg for twin pregnancy
[b]A patient may have more than one cause of PPH.
Abbreviations: AIP = abnormally invasive placenta; IQR = inter-quartile range; n = number of observations; N = number of women; PPH = postpartum haemorrhage; SD = standard deviation. n: Number of patients, %: Percentage of patients, SD: Standard deviation, IQR: Interquartile range (25th percentile - 75th percentile). PPH: Postpartum haemorrhage. Age is reported as class as available in data. Maternal weight (without weight of baby) (kg): For all singleton, 5kg were subtracted and 7kg for twin pregnancy.

Fibrinogen

The median fibrinogen levels at T0 were above the threshold of 2 g/L in both the NovoSeven (2.4 g/L) and reference group (3.2 g/L).

Details on tranexamic acid and fibrinogen use before and after randomisation

The time intervals before randomisation and during the first hour after randomisation are summarised in Table 7 below, since these data represent the concomitant use that potentially influences the efficacy of NovoSeven. For these two time intervals, data were available for approximately half the women which indicate either a specific dose or no dose.

Table 7 Tranexamic acid and fibrinogen use before and after randomisation in Trial 4816

Number of patients	NovoSeven® 42	Reference 42
Tranexamic acid (g)		
Before randomisation		
N obs	24	17
Number of women who received TXA (% of N obs)	10 (42%)	6 (35%)
Mean dose (SD)	2.3 (1.2)	1.7 (1.2)
Median (IQR)	2.0 (1.0–3.0)	1.0 (1.0–2.0)
Min, max	1, 4	1, 4
During the first hour after randomisation		
N obs	18	16
Number of women who received TXA (% of N obs)	8 (44%)	7 (44%)
Mean dose (SD)	1.0 (0.0)	1.4 (1.1)
Median (IQR)	1.0 (1.0–1.0)	1.0 (1.0–1.0)
Min, max	1, 1	1, 4
Fibrinogen (g)		
Before randomisation		
N obs	24	18
Number of women who received fibrinogen (% of N obs)	10 (42%)	6 (33%)
Mean dose (SD)	3.20 (2.46)	2.67 (1.83)
Median (IQR)	2.50 (1.50–3.00)	2.25 (1.50–3.00)
Min, max	1.5, 9	1, 6
During the first hour after randomisation		
N obs	19	18
Number of women who received fibrinogen (% of N obs)	7 (37%)	7 (39%)
Mean dose (SD)	2.86 (1.63)	3.64 (1.70)
Median (IQR)	3.00 (1.50–3.50)	3.00 (3.00–6.00)
Min, max	1.5, 6	1.5, 6

Abbreviations: IQR = interquartile range; Max = maximum; Min = minimum; N obs = number of women for whom TXA/fibrinogen data were collected; SD = standard deviation. Data source: Trial 4816 (M 5.3.5.1), Table 14.2.3

Exposure

All 42 women in the NovoSeven group were exposed to a single dose of NovoSeven. In addition, 8 women in the reference group received a single dose of NovoSeven after the treating physician had decided to proceed with hysterectomy, under the compassionate use protocol. One woman randomised to the reference group received NovoSeven in error. Therefore, a total of 51 women were exposed to NovoSeven.

Dosing

The median dose of NovoSeven was 57.6 µg/kg, with a range of 32 to 73 µg/kg, with most women receiving a dose between 55 and 65 µg/kg. The median dose of NovoSeven was similar between subgroups by concomitant use of tranexamic acid (TXA) and/or fibrinogen at T0, concomitant use of TXA and/or fibrinogen from T1H to T7H, fibrinogen level at T0 and PPH cause.

Planned doses by maternal weight are presented in Table 5 above. One woman received a dose higher than the planned dose (a woman with maternal weight of 66 kg received NovoSeven 4.8 mg, equating to 73 µg/kg). Ten women received doses lower than the planned dose for their maternal weight; actual dose for these women ranged between 32 and 60 µg/kg.

Numbers analysed

The number of patients analysed in is presented in table 8 below.

Table 8 Number of patients analysed - FAS

	NovoSeven (n%)	Reference (n%)	Total (n%)
Full analysis set	42	42	84

Outcomes and estimation

Efficacy results

An overview of primary efficacy endpoints is presented in table 9 below.

- **Protocol primary efficacy endpoint** of at least one embolisation and/or ligation:

  In the analysis of the primary endpoint, fewer women, 50% (21/42) in the NovoSeven group had at least one embolisation and/or ligation procedure compared to women in the standard care arm, 83% (35/42), with a statistically significant 40% relative reduction in risk compared to the reference group (21 vs 35 women; RR = 0.60 (95% CI, 0.43-0.84), p=0.0012).

  The mean number of patients who needed to be treated (NNT) with rhu-FVIIa (number needed to treat, NNT) to avoid one composite outcome was 3.

- **Publication primary efficacy endpoint** of at least one ligation, suture, embolisation, balloon and/or hysterectomy:

  In the analysis of the publication primary endpoint, fewer women, 52% (22/42) in the NovoSeven group had at least one embolisation, ligation, suture, balloon and/or hysterectomy procedure compared to women in the standard care arm, 93% (39/42), with a statistically significant 43.6%

relative reduction in risk compared to the reference group (22 vs 39 women; p<0.001), RR = 0.56; (95% CI, 0.42–0.76).

The mean number of patients who needed to be treated with rhu-FVIIa (number needed to treat, NNT) to avoid one composite outcome was 2.6.

Outcome per individual type of invasive procedure (publication)

Only the number of arterial embolisation procedures was significantly lower in the intervention arm than in the standard care arm. The percentage of peripartum hysterectomies was 7% (n = 3) in the intervention arm and 19% (n = 8) in the standard care arm (RR = 0.375 (0.107–1.32); P = 0.11).

Compassionate treatment with NovoSeven (publication information)

In the standard care arm, salvage ***peripartum hysterectomy*** was considered after vascular embolization or ligation failure. Therefore, eight of the 42 patients received late rhuFVIIa as a compassionate treatment in an attempt to avoid surgery. Peripartum hysterectomy was avoided in two cases.

Table 9 Invasive procedures – full analysis set

	NovoSeven	Reference arm	Absolute difference (Reference-NovoSeven) (95%CI)	Relative risk (NovoSeven/Reference) (95%CI)	Relative reduction %	NNT	p-value
N of patients	42	42					
Primary efficacy endpoint protocol							
At least one embolization and/or ligation, n (%)	21 (50.00)	35 (83.33)	33.33% (14.47;52.19)	0.60 (0.43;0.84)	40.00	3.0	0.0012
Primary efficacy endpoint publication (extracted from publication)							
At least one ligation, suture, embolization, balloon and/or hysterectomy	22 (52)	39 (93)	41% (18; 63)	0.56 (0.42;0.76)	44	2.6	<.0001
Outcome per individual type of invasive procedure (publication endpoints, extracted from publication)							
Arterial embolization, n (%)	12 (29)	24 (57)	28% (4;61)	0.50 (0.29;0.86)	50	3.5	0.0082
Arterial ligation, n (%)	9 (21)	12 (29)	7.14% (-11.31;25.60)	0.75 (0.35;1.59)	25	14	0.45
Peripartum hysterectomy, n (%)	3 (7)	8 (19)	12% (-28; 52)	0.38 (0.11;1.32)	62	8.4	0.11
Others (B-lynch sutures, Bakri Balloon and variants with haemostatic intention	4 (10)	6 (14)	4% (36; 44)	0.67 (0.20;2.19)	33	25	0.50

n: number of patients, %: Percentage of patients, CI: Confidence interval, NNT: Number of patients to be treated to prevent a studied endpoint event= 1/Absolute risk difference. Relative reduction= 1 – Relative risk.
p-value is based on chi-square test. Suture and balloon data are derived based on investigator comment from the CRF.
(a) Uterine compression suture

Outcome by delivery mode, i.e. vaginal delivery and caesarean section (publication endpoint)

The primary efficacy outcome measures were not affected by the delivery mode (absolute risk difference = 44% for vaginal delivery and 39% for Caesarean section). The significantly lower frequency of interventional haemostatic procedures in the intervention arm was confirmed also when these patients were classified based on the delivery mode (vaginal delivery, RR = 0.52, 95% CI, 0.32–0.81; Caesarean section, RR = 0.6, 95% CI, 0.41–0.86).

Relationship between rhuFVIIa dose and efficacy (publication endpoint)

The median rhuFVIIa dose infused into patients was 57.6 µg/kg (inter-quartile range, 52.9–60.8; range, 31.6–72.7 µg/kg). The infused rhuFVIIa dose was based on the conversion of the theoretical weight-adjusted dose into discrete total doses corresponding to the use of a number of complete product vials. Eight patients were categorized as '*under-treated'* and one as '*over-treated'*. The primary efficacy outcomes were not different between '*over-treated or appropriately treated*' women (n = 34) and '*under-treated*' women (n = 8) (P = 0.45, Fisher's exact test). The median value of the difference between theoretical rhuFVIIa dose and infused rhuFVIIa dose was −1.64 µg/kg for women who required some form of second-line intervention, and −3.2 µg/kg for successfully treated women who recovered without any second-line intervention (P = 0.55).

Time to initiation of a second-line treatment (publication endpoint)

The time to initiation of a second-line treatment was not different between groups: the median delay was 30 min (95% CI, 15–80 min) for the 39 patients in the standard care arm and also 30 min (95% CI, 22 min: 60 min; P = 0.93) for the 22 patients in the intervention arm who did not respond to rhuFVIIa.

Blood loss collection

In deviation from the trial protocol, blood loss collection failed to be measured. The use of a plastic collector bag to quantify postpartum blood loss was encouraged; the devices were provided to the different healthcare teams, but were only marginally used, thus rendering the systematic measurement of blood loss volumes impossible.

Requirement of blood products

To determine the proportion of patients in the two arms who required blood products, the transfusion needs were assessed before and after randomization. Before randomization, the absolute numbers of transfused PRBCs and FFP were (median value [Q25–Q75%] values): 0 [0–1] vs. 0 [0–2] in the standard care arm and 0 [0–0] vs. 0 [0–0] in the intervention group. The percentages of patients who required PRBCs, FFP and PC were 26% vs. 38% (P = 0.24), 14% vs. 14% and 4.8% vs. 2.4% in the standard care and in the intervention arm, respectively. After randomization, the absolute numbers of transfused PRBCs and FFPs were (median value [Q25–Q75%] values): 2 [0–4] vs. 2 [0–3] and 0 [0–4] vs. 0 [0–3] in the standard care and intervention arm, respectively.

The percentages of women requiring PRBCs, FFP and PC were 67% vs. 60%, 48% vs. 45% and 31% vs. 26%, respectively. No between-group difference was thus observed in the absolute numbers of administered blood products.

Secondary endpoints (only publication endpoints)

- *Replacement treatments (publication endpoint)*

Analysis of the replacement treatments (fibrinogen concentrates, TXA, apoprotinin)

At T0, 33% (6/18) of the evaluable women in the standard care arm and 42% (10/24) of those in the intervention arm had received fibrinogen concentrates; the percentages were identical for TXA. Aprotinin was administered to one patient only in each arm.

After T0, 67% (10/24) of the evaluable patients in the standard care arm and 48% (10/21) of those in the intervention arm received fibrinogen concentrates; 47% (7/15) of women in the standard care arm and 44% (8/18) in the intervention arm received TXA. Aprotinin was administered to 14% (2/14) of women in the standard care arm and to 6% (1/16) of patients in the intervention arm.

- *Haemoglobin concentration (publication endpoint)*

The fall in haemoglobin (Hb) concentration between T0 and T30 was significantly different between groups (P = 0.0377), with a median decrease of −0.2 g/dL (IQ = [−1, 1.8]) in the intervention arm and of −0.9 g/dL (IQ = [−2.3, 0.1]) in the standard care arm. The Hb concentration fall was thereafter categorized as higher than 2 g/dL vs. all the other values. The highest haemoglobin falls (> 2 g/dL) were detected in 15% (5/33) of patients in the intervention group and in 30% (8/27) in the standard care arm (P = 0.18).

Ancillary analyses

Not applicable.

Summary of main studies

The following table 10 summarises the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 10 Summary of Efficacy for trial 4816 (RCT)

Title: Chronological place of the administration of recombinant activated factor VII in maternal salvage in severe postpartum haemorrhage: before or after invasive second-line therapies (embolisation, vascular ligation and haemostatic hysterectomy)	
Study identifier	NCT00370877
Design	A therapeutic, prospective, controlled, multi-centre (Nimes, Nice, Cochin, Clamart, Montpellier and Lille and Geneva University Centres) multidisciplinary (obstetricians, anaesthetists and haematologists / haemostasis specialists), randomized trial conducted over a 4-year period. The primary objective was to evaluate the interest in using NovoSeven in the treatment of severe PPH unresponsive to conventional treatment and to define, if applicable, the number of interventional embolisation procedures, vascular ligations, hysterectomies and transfusions prevented due to the early use of NovoSeven.

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase: Duration of follow-up:		Single dose Randomization to study completion. There was no run-in phase, but time between the administration of sulprostone and enrolment into the trial was to be 1 hour. There was no extension phase Follow-up was 5 days based on NovoSeven half-life (4–6 h). To identify symptomatic VTE up to 6 weeks after PPH, data from initial medical records were extracted and patients had to fill in a questionnaire concerning the first 6 weeks postpartum.
Hypothesis	Exploratory: hypothesis of relatively early use of NovoSeven may, in some patients, avoid having recourse to invasive haemostasis procedures, save on transfusions or avoid transferring the patient to a referral centre in a hemodynamically unstable condition in order to improve the known mortality related to patient transfer.		
Treatments groups	NovoSeven + standard care		Standard care + NovoSeven (rhu-FVIIa) 60 µg/kg body weight, single dose N=42
	Standard care		Standard care N=42
Endpoints and definitions	Primary endpoint	**Protocol-defined:** reduction in the need for specific second-line therapies (at least one ligation or embolisation) NNT **Publication-defined:** reduction in the need for specific second-line therapies (at least one ligation, suture, embolisation, intra-uterine balloon tamponade and/or hysterectomy) NNT	Treatment success was defined as the absence of need for specific second-line therapies within 30 minutes after administration of NovoSeven
	Secondary endpoints	NA	
Database lock	05 November 2010		
<u>Results and Analysis</u>			
Analysis description	**Primary Analysis**		

Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	**NovoSeven + standard care**	**Standard care**
	Number of subject	**42 (100%)**	**42 (100%)**
	Primary endpoint		
	Protocol-defined: reduction in the need for specific second-line therapies (at least one ligation or embolisation), n (%)	21 (50.00)	35 (83.33)
	Publication-defined: reduction in the need for specific second-line therapies (at least one ligation, suture, embolisation, intra-uterine balloon tamponade and/or hysterectomy), n (%)	22 (52)	39 (93)

Protocol-defined/publication primary endpoint: Effect estimate per comparison	Primary endpoint	NovoSeven vs standard care	
		RR (95% CI)	0.60 [0.43;0.84] / 0.56 [0.42–0.76]
		p-value	0.0012 / P>0.001
		Number needed to treat (NNT)	2.6 / 3

Supportive studies

Non-interventional studies

Data from four non-interventional studies were collected from information of routine clinical practice to provide supportive data to the pivotal evidence, trial 4816 (RCT). Two non-interventional studies, study 4729 (Bern) and study 4733 (PPH consortium), included both women treated with NovoSeven and women not treated with NovoSeven; whilst the other two non-interventional studies (registries), study 4731(UniSeven) and study 4732 (ANZHR), only included women treated with NovoSeven. The results of these studies are summarised below.

- ***Study 4729 (Bern)***

Title*: Clinical outcomes of NovoSeven treatment in severe postpartum haemorrhage – a retrospective single-centre cohort study at the University Hospital of Bern.*

Study design and methodology

The current study was a single-centre, retrospective, non-interventional cohort study of women with severe PPH who were treated with NovoSeven or other standard of care during the period of January 2006 to April 2016 at Bern University Hospital, Switzerland. The present study included data of 165 women from 4 cohorts of women with severe PPH: historical cohort 1 (2006 to 2007), historical cohort 2 (2008 to 2010), study cohort (2010 to 2012) and new cohort (2013 to 2016). The treatment of sPPH in the 4 cohorts differed in study periods and PPH management protocols as shown Table 11, and described below:

- Historical cohort 1: women were treated according to an in-house guideline including use of uterotonics, fluid management, red blood cells (RBC), fresh frozen plasma (FFP), and/or fibrinogen and platelet transfusion according to current practice. If massive bleeding persisted, women were to receive NovoSeven at a dose of 60 µg/kg body weight and a second dose could be given if blood loss was still ongoing.
- Historical cohort 2: no specific treatment guidelines were followed.
- Study cohort: women were treated with a standardised management protocol which included early administration of uterotonics, fluids, and tranexamic acid (TXA). If bleeding persisted, an emergency package containing RBC, FFP, platelets, fibrinogen and NovoSeven (60 µg/kg body weight) was administered.
- New cohort: women were treated with a similar standardised management protocol to 'study cohort', except that the dose of NovoSeven was increased to 90 µg/kg body weight.

Table 11 Details of cohorts in study 4729 (Bern)

Cohort	Period	PPH management protocol[a]
Historical cohort 1	01-Jan-2006 to 31-Dec-2007	In-house guideline using low-dose (**60 µg/kg**) NovoSeven[3]
Historical cohort 2	01-Jan-2008 to 31-Mar-2010	No standard treatment protocol; at treating team's discretion[3]
Study cohort	01-Apr-2010 to 31-Dec-2012	As per standard PPH management protocol at the hospital, which included use of NovoSeven at **60 µg/kg**[3]
New cohort	01-Jan-2013 to 30-Apr-2016	As per standard PPH management protocol at the hospital, which included use of NovoSeven at **90 µg/kg**

[a] Details of PPH management protocol are in Appendix A of the protocol

Setting

The study was performed at the Department of Obstetrics and Gynaecology, University Hospital and University of Bern, Switzerland. The study is based on data already recorded in historical medical records. Data collection (extraction of data from historical medical records) was performed during the period 29 June 2020 to 13 January 2021.

Objectives

Primary objective

- To compare, in a propensity score (PS) matched population of women with severe PPH, the occurrence of any invasive procedure after first treatment with NovoSeven with the occurrence of any invasive procedure without treatment with NovoSeven. Invasive procedures were defined as uterine or iliac artery ligation, radiological arterial embolisation, uterine compression sutures or hysterectomy.

Estimand

The estimand addressed the relative effect of NovoSeven compared to PS matched controls on the occurrence of invasive procedures in women with severe PPH. The estimand was defined as follows:

A. The treatment conditions were NovoSeven versus PS matched controls.

B. The treatment effect was estimated for women with severe PPH defined by the inclusion criteria in the 4 cohorts exposed to NovoSeven and their matched controls.

C. The treatment effect was assessed by the occurrence of invasive procedures within 20 minutes to 24 hours following time0 (where time0 was equal to the period from onset of severe PPH to time of first administration of NovoSeven for the woman for whom she was a matched control).

D. Intercurrent events were handled by a hypothetical strategy or a treatment policy strategy (see below).

E. The treatment effect was quantified by the conditional odds ratio.

Handling of intercurrent events for the hypothetical estimand

Intercurrent event	Expected frequency of events	Data collection and analysis
Death	Rare	Death within the time window for the primary endpoint was counted as having an invasive procedure
Exposure to NovoSeven® after time0	Likely	In case a matched control was exposed to NovoSeven® after the matching or an exposed woman had additional doses, this event was treated according to a treatment policy strategy, i.e. these intercurrent events were ignored in the statistical analysis

Secondary objectives

- To compare frequency of thromboembolic events (TEs) in women with an event of severe PPH treated with NovoSeven versus women with an event of severe PPH not treated with NovoSeven.
- To compare the relative reduction in blood transfusions in women with an event of severe PPH treated with NovoSeven versus women with an event of severe PPH not treated with NovoSeven.
- To compare the relative reduction in blood loss in women with an event of severe PPH treated with NovoSeven versus women with an event of severe PPH not treated with NovoSeven.
- To compare the incidence of hysterectomy in women with an event of severe PPH treated with NovoSeven to the incidence of hysterectomy in women with an event of severe PPH not treated with NovoSeven.

Outcomes/endpoints

Among women who were at risk of further invasive procedures:

Primary endpoint

Endpoint title	Time frame	Unit
Occurrence of invasive procedures[a] (yes/no)	20 minutes to 24 hours following time0	Count of women

Secondary endpoints

Endpoint title	Time frame	Unit
Occurrence of thromboembolic events (yes/no)	From time0 until 5 days after time0	Count of women
Amount of blood products transfused	From delivery to 24 hours after time0	Units
Estimated blood loss	From delivery to 24 hours after time0	mL
Occurrence of hysterectomy (yes/no)	20 minutes to 24 hours following time0[a]	Count of women

Time0 was defined as time of first administration of NovoSeven. It occurred 'x' minutes after onset of severe PPH. For matched controls: time0 was derived from the matching process. It was equal to the period from onset of severe PPH to time of first administration of NovoSeven for the patient for whom she was a matched control.

Diagnosis, Inclusion/exclusion criteria

Inclusion criteria:

1. Severe PPH, defined as continuous bleeding of at least 1500 mL within 24 hours after delivery.
2. Inclusion in one of the 4 cohorts (historical cohort 1, historical cohort 2, study cohort and new cohort).

Exclusion criteria

None.

Sample size

There was no formal power calculation and the study included all women at the study site who were eligible according to the inclusion criteria.

Statistical analyses

Analysis sets

- Full analysis set (FAS): defined as all women who met the inclusion criteria for the study, i.e., all women with severe PPH (a subpopulation in the FAS is used for post-hoc analysis of a common project endpoint was analysed in the FAS, discussed in section analysis across studies).
- Propensity score (PS) analysis set: defined as all women in the FAS who were matched in the propensity scoring.
- Supplementary PS analysis set: defined as the PS analysis set excluding matched controls who were exposed to NovoSeven after time0.

The PS analysis was a pre-specified analyse as per SAP. For the PS analysis set it was possible that a woman could be selected as a control before the timepoint when she was exposed to NovoSeven. In such a case, the woman could be counted in both groups, once as a control and later as an exposed case, both with separate values for time0. In the FAS the two groups were mutually exclusive.

Propensity score matching

This non-interventional study 4729 (Bern) (and 4733 - PPH consortium) collected patient level information from hospital records both on women exposed to NovoSeven and women not exposed to NovoSeven. In an attempt to enhance the comparability between the two groups, subgroups were selected from women who were exposed and not exposed to NovoSeven via time dependent propensity score matching. The purpose of propensity score matching was to counteract the natural imbalance (confounding by indication) present between women exposed and not exposed to NovoSeven in the FAS from these real world data sources. The propensity score reflected the estimated probability of being exposed to NovoSeven at a given point in time during the course of severe PPH. The propensity score matching process selected two subgroups of women that had a comparable course of PPH up to exposure/matching time based on the recorded data. In this way exposed women and their controls were comparable because of similar development of severe PPH at the same (specific) time0 based on recorded data.

For NovoSeven exposed women, time0 was defined as time of first administration of NovoSeven, occurring x minutes after onset of severe PPH. For matched controls, time0 was equal to the period from onset of severe PPH to time of first administration of NovoSeven for the woman for whom she was a matched control. Both studies used the same approach for the propensity score matching process, adapted to the amount and type of data available within each study.

Characteristics that could be included as covariates are (not an exhausted list): gestational age, multiple pregnancy, cause of PPH, volume of blood loss at time of intervention, and haemostatic drugs used (other than NovoSeven) that had already been applied at the time of intervention. A matching algorithm for the propensity score will be used to match women with an event of sPPH exposed to NovoSeven with women with an event of sPPH that are not at that timepoint. Women will be censored when they have been hysterectomised, died, or stopped having PPH. Further details of the propensity score model will be defined in the SAP.

Matching will be done within patients with the same delivery mode with up to 1:4 matching with a calliper of 0.1. If this is not possible a calliper of 0.2 will be used instead. The criteria for switching to 0.2 will be described in the SAP.

A PS for every woman with severe PPH was estimated from time of start/diagnosis of severe PPH by a Cox proportional hazard regression model with NovoSeven as the dependent variable. A hazard was calculated for each woman at risk for each minute following onset of severe PPH. Covariates associated with initiation of NovoSeven administration were included in the model to calculate PS.

Primary endpoint analysis

The primary endpoint (invasive procedures) was compared between women who were exposed to NovoSeven and matched controls in the PS analysis set, using an exact conditional logistic regression to calculate the odds ratio, with a 95% confidence interval (CI), with conditional meaning that the pairing of patients based on the PS matching was taken into account. The test assessing the odds ratio was two-sided and assessed at the 5% significance level.

Secondary endpoint analysis

To address the secondary objectives, the comparisons were made using the matched women from the PS matching described above.

Results

Patient disposition

PS analysis set

For PS matching, a total of 18 women were included in the PS analysis set as matched exposed and 43 women were included in the PS analysis set as matched controls.

Flow of patients for the PS matching (and FAS) is shown table 12 below.

Table 12 Patient flow study 4729 (Bern)

	PS analysis set		FAS		
	NovoSeven®	Matched controls	NovoSeven®	No NovoSeven®	Total
Number of patients			52	113	165
Full analysis set with documented severe PPH, N			52	113	165
Number of patients with preplanned hysterectomy, N			0	3	3
Number of patients with hysterectomy before severe PPH, N			0	0	0
Number of patients not eligible for matching due to insufficient data, N			0	9	9
Number of patients eligible for matching, N			52	101	153
Number of patients with hysterectomy before NovoSeven®, N			5		
Number of patients with PPH stop before NovoSeven® administration, N			7		
Number of patients eligible for matching as exposed, N			40		
Number of patients that were included in matching process as exposed, N			41[a]		
Number of patients eligible for matching as controls, N			51	101	152
Number of patients in the PS analysis set, N	18	43[b]			
Number of weighted patients, N		18.0			

Abbreviations: FAS = full analysis set; PPH = postpartum haemorrhage; PS = propensity score; N = number of (weighted) patients.

a: After database lock for PS matching, 2 women that were originally included as eligible for matching as exposed were no longer eligible for matching and 1 woman became eligible for matching as exposed.

b: One matched control had hysterectomy in the conjoint period and was excluded from the primary analysis. Therefore 42 matched controls were included in the primary analysis.

Patient characteristics

For the PS analysis set, women were matched based on delivery type, therefore, the percentage of women with delivery by caesarean section and vaginal delivery was identical between NovoSeven and matched controls (caesarean section was 88.9% for both groups). The two groups of women were broadly similar with regard to other patient characteristics except there were some imbalances in the proportions of women with obesity (33.3% vs 19.0% for NovoSeven and matched controls, respectively), singleton birth (72.2% vs 91.2% for NovoSeven and matched controls, respectively), preeclampsia/eclampsia/HELLP (11.1% vs 4.2% for NovoSeven and matched controls, respectively) and pre-existing coagulation disorder (11.1% vs 0% for NovoSeven and matched controls, respectively).

Regarding primary cause of PPH, there were some imbalances in the PS analysis set in the proportions of women with uterine atony (72.2% vs 46.8% for NovoSeven and matched controls, respectively). Proportions of women with AIP were similar for NovoSeven and matched controls (22.2% vs 27.8%, respectively). The numbers of women with trauma or other causes of PPH were small in both groups. No woman in the PS analysis set had placental retention as primary cause of PPH.

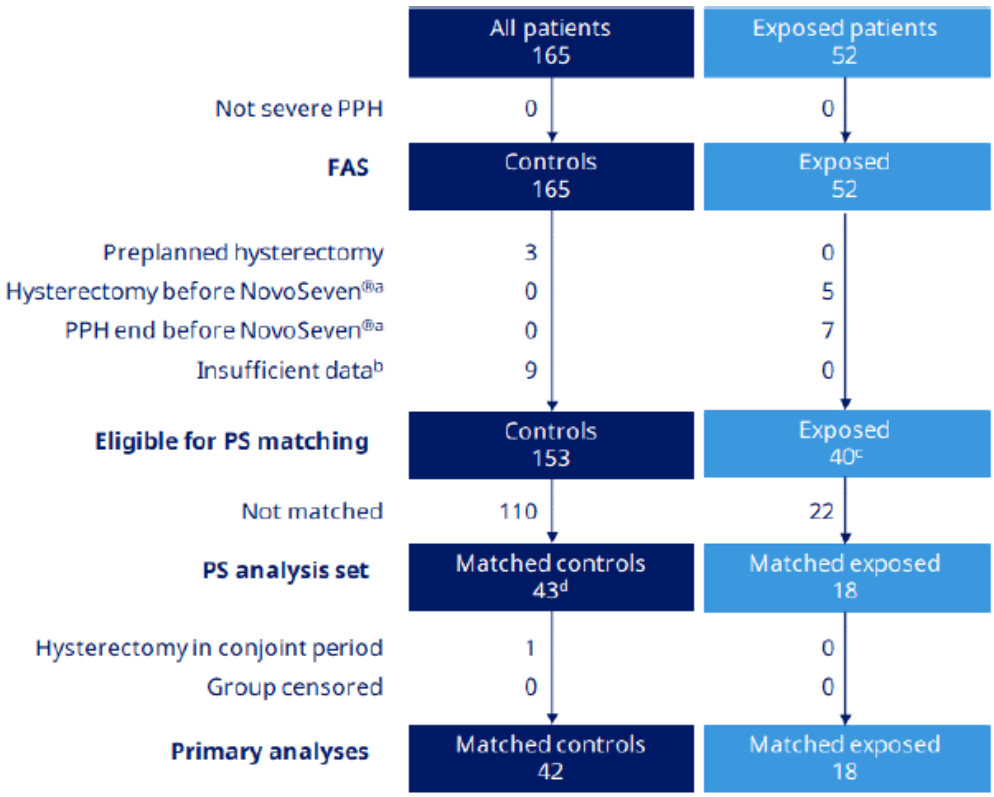
NovoSeven dose in study 4729

In the Propensity Score analysis set, 17 (94.4%) women who were treated with NovoSeven received one dose and 1 (5.6%) woman received two doses. Median first and total doses of NovoSeven were both 65 µg/kg (IQR 62 to 74 µg/kg).

For the 18 women exposed to NovoSeven in the PS analysis set, the first dose was <60 µg/kg for 2 (11.1%) women and 60-90 µg/kg for 16 (88.9%) women; no woman in the PS analysis set received a first dose >90 µg/kg.

Primary efficacy endpoint Invasive procedures – PS analysis

Figure 5 Flow of patients for propensity score matching and primary analyses



a Not eligible for matching as exposed women but eligible for matching as controls. b Some women had insufficient data on the time course of events to make a meaningful contribution to the PS matching. c PS matching was done before unmasked data were available; 2 patients were originally included as eligible that after PS database lock were not eligible for matching as exposed; 1patient became eligible for matching as exposed. d One patient was matched as control at the same time as PPH ended. One woman was matched as control after hysterectomy and was removed from the PS analysis set accordingly. Abbreviations: FAS = full analysis set; PPH = postpartum haemorrhage; PS = propensity score

Patient set included in the PS analysis is presented in table 13.

Table 13 Invasive procedures – summary – PS analysis set

Weighted data	NovoSeven®	Matched controls
Number of patients, N	18	43
Number of weighted patients, N		18.0
Any invasive procedure after time0, N (%)	3 (16.7)	5.6 (31.0)
Hysterectomy	2 (11.1)	3.1 (17.1)
Radiological arterial embolisation	1 (5.6)	1.0 (5.6)
Uterine compression sutures	1 (5.6)	2.8 (15.3)
Uterine or iliac artery ligation	0	0.8 (4.2)

Results primary endpoint PS analysis

- In the PS analysis set, the occurrence of any invasive procedure in the period from 20 minutes to 24 hours following time0 was 16.7% (3/18) for NovoSeven exposed women compared to 31.5% (5.6/17.8) for matched controls, among women who were at risk of further invasive procedures (see Section 1.5 for definition of population). The odds ratio of any invasive procedure was 0.33, numerically favouring NovoSeven, though this difference was not statistically significant (p=0.2691).
- The odds ratio of hysterectomy from 20 minutes to 24 hours after time0 was 0.52 (95% CI: 0.05 to 3.03; p=0.6815) in women with severe PPH treated with NovoSeven compared to matched controls.

Table 14 Invasive procedures in the period from 20 minutes to 24 hours after time0 – statistical analysis – PS analysis set

	NovoSeven®			Matched controls					
Weighted data	N	n	Estimate	N	n	Estimate	Odds ratio	[95% CI]	P-value
Any invasive procedure (primary endpoint)	18	3	16.7	17.8	5.6	31.5	0.33	[0.03; 1.75]	0.2691
Hysterectomy (secondary endpoint)	18	2	11.1	17.8	3.1	17.4	0.52	[0.05; 3.03]	0.6815

Supplementary analyses also supported the findings of the primary analysis. In the analysis in which women selected as matched controls who were later exposed to NovoSeven were excluded (7 family clusters excluded), the adjusted odds ratio was 0.22a (95% CI: 0.00 to 1.30; p=0.1667).

Control of bleeding

In the PS analysis set, the mean rates of transfusion (units per hour) for RBC and FFP were lower after time0 than before or at time0 for both NovoSeven exposed women and matched controls. The reductions in rates (rate ratios, i.e., after time0/before or at time0) were numerically greater for NovoSeven exposed women compared to matched controls for RBC (NovoSeven exposed: 0.19; matched controls: 0.33) and FFP (NovoSeven exposed: 0.21; matched controls: 0.35) transfusions, with a relative rate ratio after time0 of 0.58 (95% CI: 0.29, 1.17; p=0.1253) and 0.61 (95% CI: 0.28, 1.32; p=0.2044), respectively.

In the PS analysis set, the duration of bleeding (from onset of severe PPH to stop of severe PPH) was numerically shorter for NovoSeven exposed women (median: 167.5 minutes; IQR: 101.0, 235.0 minutes) than matched controls (median: 250.0 minutes; IQR: 138.0, 673.5 minutes). However, the duration of bleeding in the FAS was numerically longer for the NovoSeven group than the no NovoSeven group.

For the small number of women in the PS analysis set, the study did not show a reduction in the occurrence of any invasive procedure in the NovoSeven exposed women compared to matched controls (odds ratio: 0.33; 95% CI: 0.03, 1.75), though there was a numerical treatment effect in favour of NovoSeven.

- ***Study 4733 (PPH consortium)***

Title: *Clinical use and outcome of NovoSeven treatment in severe postpartum haemorrhage – experiences from an observational multi-country (UK, DK, FR, NL) retrospective cohort study*

Study based on established cohort data from Denmark (DK), The Netherlands (NL), and the United Kingdom (UK). In each country, data were collected either nationally or from multiple regions on a population basis. Data analysis is performed at the Department of Clinical Epidemiology of the Leiden University Medical Centre, The Netherlands.

Study design

The current study, NN7711-4733, was a retrospective non-interventional cohort study of women with severe PPH who were treated with NovoSeven or other standard of care. The analyses were done utilising retrospective data that were collected for other purposes from three previously established cohorts in DK, NL and UK. Data analyses were performed at the Department of Clinical Epidemiology of the Leiden University Medical Centre.

Setting

The data include three previously established cohorts from three countries (DK, NL and UK). The study is based on secondary use of data.

- DK - data were identified and collected from the Danish Medical Birth Registry (DMBR) and the Danish Transfusion Database (DTD) over the period 2001-2009.
- NL – data were identified and collected from TeMpOH-1, a national retrospective cohort study conducted between January 2011 and January 2013, which included 75% of all hospitals in the Netherlands
- UK– data were identified and collected from the United Kingdom Obstetric Surveillance System, a national surveillance database, during the period between July 2012 to June 2013.

Follow-up

Duration of follow-up was up to 6 months from delivery for the DK cohort, from delivery up to discharge or death for the UK cohorts and from delivery to end of bleeding for the NL cohort.

Primary objective

- The primary objective was identical to the primary objective of Study 4729 (Bern)

Estimand

The estimand was identical to Study 4729 (Bern)

Secondary objectives

- Secondary objectives were identical to Study 4729 (Bern).

Outcomes/endpoints

Primary efficacy endpoint

Identical to study 4729 (Bern).

Secondary endpoints

Identical to study 4729 (Bern).

Inclusion/exclusion criteria

Inclusion in one of the four cohorts (DK, FR1, NL, UK). Women from each cohort were identified as PPH patients using specific identification criteria:

Denmark – women who had a birth identified in the DMBR and had transfused 10 or more units of RBC within 24 hours identified from DTD were included in study

The Netherlands - women who experienced an obstetric haemorrhage and had received at least one of the following were included: received ≥4 units of red blood cells (RBC), multicomponent blood transfusion (RBC and fresh frozen plasma and/or platelet concentrates), plasma in addition to RBCs as a result of obstetric haemorrhage

United Kingdom - women who fulfilled the following criteria were included: received ≥8 units of RBC transfused within 24 hours, 20 or more weeks of gestation.

Exclusion criteria: None.

Sample size

The identification of women with severe PPH in each of the datasets was based on being an obstetric case and requirement for transfusion of blood or blood products. There was no formal power calculation and the study included all women from the datasets who were eligible according to the inclusion criteria.

Statistical methods

Analysis sets

- Full analysis set (FAS): defined as all women who met the inclusion criteria for the study, i.e., all women with severe PPH (a subpopulation in the FAS is used for post-hoc analysis of a common project endpoint was analysed in the FAS, discussed in section analysis across studies).
- Data from DK and NL include time varying information and data from these two countries were included in the time varying propensity score (PS) matched analyses.

Propensity score matching

The PS analysis was a pre-specified analyse as per SAP and identical to study 4729 (Bern)

Primary endpoint analysis

Identical to study 4729 (Bern)

Secondary endpoint analysis

To address the secondary objectives, the comparisons were made using the matched women from the propensity score matching described above (data from DK and NL). A significance level (alpha) of 0.05 was used.

Control of bleeding:

- The total number of blood products (RBC and FFP, separately) units was analysed using a negative binomial regression with treatment, period (pre/post time0) and the interaction between treatment and period as factors. Subject and matched groups (defined as an exposed woman and her matched controls) were included as a random effect, and (log) duration of each period was included as an offset. The interaction term gave a statistical test for difference in the relative change in blood product use pre and post time 0 between the two groups. Ratio of the relative reduction was presented with 95% CI and two-sided p-value. A similar analysis was performed with only post time0 count as outcome and the pre-count divided by the (log) duration of the pre-period as covariates.

- Several women did not have repeated blood loss measurements before and after time0, therefore, the secondary endpoint "Estimated volume of blood loss" could not be analysed.

Hysterectomy:

- The comparison of the incidences was analysed using same approach as for the primary endpoint. After matching, women with a hysterectomy in the conjoint period (defined as the period from 20 minutes before and 20 minutes after time0) were excluded.

Results

Patient disposition

PS analysis set

PS matching was done for women in the DK and NL cohorts. PS matching could not be done for the UK cohort due to lack of time varying data.

The FAS for the DK and NL cohorts combined included 1499 women and 1482 of these women were eligible for PS matching, of which 53 were exposed to NovoSeven. A total of 17 women were not eligible for PS matching due to hysterectomy before onset of severe PPH (12 women) or pre-planned hysterectomy (5 women). In addition, 21 exposed women had hysterectomy before NovoSeven administration; these women were not eligible for matching in the exposed group of women but were eligible for matching as controls.

For the DK and NL cohorts combined, a total of 40 exposed women (75.5% of the 53 exposed women eligible for PS matching) were included in the PS analysis set as matched exposed and 115 women were included as matched controls (1 to 4 controls per exposed woman) based on the final PS model. Thirteen NovoSeven exposed women could not be matched in the final PS model.

Nine of the matched controls were later exposed to NovoSeven after matching at time0 but only 5 of these women were included in the matched exposed group (i.e., included in both the matched control and matched exposed groups with different time0 for each group).

Patient characteristics PS

In the PS analysis set, the two groups were comparable in terms of age, previous caesarean section, previous PPH, parity, and multiple birth. The most common cause of PPH was uterine atony with its proportions being similar between the two groups (NovoSeven exposed: 57.5%; matched controls: 60.2%). Some difference was observed in the proportions of women with AIP as the primary cause for PPH (6/40 women (15.0%) and 3.5/40 women (8.8%) for NovoSeven and matched controls, respectively). Patient characteristics for the PS analysis (DK + NL) sets are presented below in Table 15.

Table 15 Patient characteristics – DK and NL combined – PS analysis set (and FAS)

	PS analysis set		Full analysis set	
	NovoSeven®	Matched controls	NovoSeven®	No NovoSeven®
Number of patients, N	40	115	77	1422
Number of weighted patients, N		40.0		
Maternal age (years)				
Median (IQR)	31.5 (27–35.5)	32 (29–36)	32 (29–36)	32 (28–35)
Min, max	22, 43	20, 42	22, 44	16, 49
Obesity, n (%)	1 (2.5)	4.83 (12.1)	5 (6.5)	131 (9.2)
Previous caesarean section, n (%)	6 (15.0)	5.33 (13.3)	21 (27.3)	227 (16.0)
Previous PPH, n (%)	2 (5.0)	3.33 (8.3)	4 (5.2)	186 (13.1)
Delivery type, n (%)				
Vaginal	24 (60.0)	24 (60.0)	38 (49.4)	1010 (71.0)
Caesarean section	16 (40.0)	16 (40.0)	39 (50.6)	412 (29.0)
Multiple birth, n (%)	2 (5.0)	1.83 (4.6)	4 (5.2)	83 (5.8)
Parity (count), median (IQR)	1.90 (1–2)	1.98 (1–2)	2.04 (1–2)	2.15 (1–3)
Primary cause of PPH, n (%)				
Uterine atony	23 (57.5)	24.08 (60.2)	36 (46.8)	817 (57.5)
Placental retention	3 (7.5)	4.42 (11.0)	6 (7.8)	238 (16.7)
AIP	6 (15.0)	3.50 (8.8)	17 (22.1)	170 (12.0)
Trauma	3 (7.5)	4.58 (11.5)	10 (13.0)	139 (9.8)
Placental abruption	2 (5.0)	2.67 (6.7)	4 (5.2)	25 (1.8)
Other	3 (7.5)	0.75 (1.9)	4 (5.2)	33 (2.3)

Abbreviations: N = number of (weighted) patients in analysis set; n = number of (weighted) patients in category; % = percentage of (weighted) patients; AIP = abnormally invasive placenta; DK = Denmark; IQR = interquartile range (25th percentile - 75th percentile); NL = Netherlands; PPH = postpartum haemorrhage; PS = propensity score matched

NovoSeven dose

No information was available on number of doses of NovoSeven administered in DK. Where number of doses was available in the NL data, most patients (28 of 36 patients; 77.8%) received a single dose. Median dose for DK and NL cohorts combined was 5 mg (IQR 2.4–7.2 mg) in the PS analysis set. Median time from onset of severe PPH to first dose of NovoSeven for DK and NL cohorts combined was 144 minutes in the PS analysis set.

Primary efficacy endpoint PS analysis

- Among women who were at risk of further invasive procedures, 57.9% (22/38) of NovoSeven exposed women had an invasive procedure in the period from 20 minutes to 24 hours following time0 compared to 35.1% (13.3/38) of matched controls, with an odds ratio of 2.46 (95% CI: 1.06, 5.99; p=0.0355) favouring matched controls. The odds ratio was 2.23 (95% CI: 0.84, 6.05) for hysterectomy. The results of the PS analysis on the primary efficacy endpoint and other endpoints are presented in Table 16.

Table 16 Invasive procedures after conjoint period – DK and NL combined – PS analysis Set

	NovoSeven® n (%)	Matched controls n (%)	Odds ratio [95% CI]	p-value
Number of patients, N	38	108		
Number of weighted patients, N		38.0		
Primary endpoint				
Any invasive procedure	22 (57.9)	13.3 (35.1)	2.46 [1.06, 5.99]	0.0355
Secondary endpoint				
Hysterectomy	13 (34.2)	7.75 (20.4)	2.23 [0.84, 6.05]	0.1160
Other invasive procedures				
Ligation	0 (0)	0.75 (2.0)	NA	NA
Embolisation	9 (23.7)	4.5 (11.8)	NA	NA
Uterine compression sutures	1 (2.6)	1.8 (4.8)	NA	NA
Other invasive procedure	9 (23.7)	5.6 (14.7)	NA	NA

Abbreviations: N = Number of (weighted) patients in analysis set; n = number of (weighted) patients with event; % = percentage of (weighted) patients with event; CI = confidence interval; DK = Denmark; NA = not applicable; NL = The Netherlands; PS = propensity score matched

- In the subgroup of women who had not received any invasive procedure before concurrent period, 54.8% (17/31) of NovoSeven exposed women had an invasive procedure in the period from 20 minutes to 24 hours following time0 compared to 40.7% (12.3/30.1) of matched controls, with an odds ratio of 1.66 (95% CI: 0.63; 4.62; p=0.3681).
- The sensitivity analysis that excluded matched controls that were exposed to NovoSeven after matching broadly supported the findings of the primary statistical analysis (OR 2.62 [1.11, 6.54])

Control of bleeding

DK plus NL cohort (PS analysis set): For RBC and FFP, the mean rates of transfusion (units per hour) were lower after time0 than before time0 for both NovoSeven exposed women and matched controls. The rate ratios (after time0/before time0) were similar between NovoSeven exposed women and the matched controls both for RBC and FFP transfusions, with relative rate ratio after time0 of 1.09 (95% CI: 0.70, 1.69; p=0.694) and 0.76 (95% CI: 0.45, 1.28; p=0.297), respectively.

- ***Study 4731 (UniSeven)***

Title: *Clinical use and outcome of NovoSeven treatment in severe postpartum haemorrhage – a retrospective cohort study of Czech women from the UniSeven registry*

Study design

The current study NN7711-4731, was a retrospective cohort study describing the clinical use of NovoSeven and clinical outcomes in Czech women with an event of sPPH treated with NovoSeven. The study analysed the data from the UniSeven registry that were evaluated retrospectively.

Data source

UniSeven is a retrospective observational data registry that was established in 2004 to collect data on NovoSeven administration in non-haemophiliac people from the Czech Republic, Slovakia, Slovenia and Hungary. The registry recorded data on off-label use of NovoSeven between July 2003 to April 2014. The

data in the UniSeven registry were owned by the Institute of Biostatistics and Analysis at the Masaryk University in the Czech Republic. The registry was multinational; however, the current study (NN7711-4731) included data on women only from the Czech Republic as this subset of data had undergone data quality control.

Setting

The UniSeven registry recorded data on various off-label use of NovoSeven, however, the current study analysed the variables which are relevant to PPH. Data collection was performed between 27 July 2020 and 31 July 2020.

Study period

The UniSeven registry recorded off-label use of NovoSeven between July 2003 to April 2014.

Objectives

Primary objective:

- The primary objective was to describe the proportion of women with an event of sPPH that avoided invasive procedures (uterine or iliac artery ligation, radiological arterial embolisation, uterine compression sutures, and hysterectomy) following treatment with NovoSeven.

Secondary objectives:

- To describe the frequency of TEs in women with an event of sPPH treated with NovoSeven
- To describe the proportion of women with an event of sPPH treated with NovoSeven that achieve control of bleeding (as assessed by the health care professional [HCP] as decreased or ceased bleeding) after the last NovoSeven dose.

Outcomes/endpoints

Primary endpoint

- Occurrence of invasive procedures (yes/no) in the study population following NovoSeven administration (within a timeframe of 20 mins to 24 hours following NovoSeven administration). Invasive procedures were defined as: uterine or iliac artery ligation, radiological arterial embolisation, uterine compression sutures, or hysterectomy. The population for primary analysis included women who did not have any invasive procedure before or concurrent with NovoSeven administration.

  A 20 minutes lag-time was chosen due to the following reasons:

- Peak coagulation ability is attained approximately 10 minutes after NovoSeven administration. A 20 minute lag time was chosen to allow leeway for circulation of the drug and time for observers to appropriately assess any decrease in blood loss.
- The 20 minutes lag-time is chosen to disregard any case where a conjoint decision has been taken to administer NovoSeven and perform an invasive procedure consecutively.
- Cases where decision to perform invasive procedure is taken simultaneous with administration of NovoSeven, NovoSeven would not have had sufficient time to be effective and the procedure is performed with in the lag time, these are avoided to be considered as lack of efficacy of NovoSeven.

Secondary endpoints

- Occurrence of thromboembolic events, yes/no From first administration of NovoSeven to end of hospitalisation
- Control of bleeding, yes/no Within 24h after NovoSeven administration.

Inclusion/exclusion criteria

Inclusion criteria:

- Czech women Treated with NovoSeven due to sPPH, defined as ≥1,500 mL blood loss within the period of 24h after delivery, registered in UniSeven, identified as PPH patients from UniSeven registry using the following identification criteria: postpartum/postpartal haemorrhage, delivery/caesarean section, or birth (relating to giving birth), amniotic embolism, eclampsia, or a known cause of PPH in the comments (in English or Czech), ICD10 codes belonging to the group O60-O75 ("Complications of labour and delivery") or O80-O84 ("Delivery").

Exclusion criteria: none.

Product and mode of administration

Patients were treated with commercially available NovoSeven according to local routine clinical practice at the discretion of the treating physician.

Statistical methods

Data were summarised for the Full Analysis Set (FAS), which included all women who met the inclusion criteria for the study. No other analysis sets were used.

Main statistical methods

This was a retrospective, single-cohort, observational study and hence no formal testing of statistical hypotheses was performed. Evaluation of data was based upon descriptive statistics, i.e. summary tables and figures. Continuous variables were summarised using standard statistical measures, i.e. number of observations, mean, standard deviation, median (IQR), minimum and maximum. Categorical data were summarised by frequency tables.

Primary endpoint analysis

- The primary endpoint was analysed by summarising the number and proportion of women who received NovoSeven and underwent or not underwent any invasive procedure within a time-frame of 20 mins to 24 hours following the first NovoSeven administration. This was calculated for the population at risk for invasive procedure, which is defined as the women who were at the risk of invasive procedure after the first NovoSeven administration. Women who had a hysterectomy before or conjoint with first NovoSeven administration were considered to be no longer at risk of invasive procedure and thus excluded from the population at risk.
- Additionally, the number and proportion of women, who received at least one invasive procedure at the time of NovoSeven administration and again received any invasive procedure within a time-frame of 20 mins to 24 hours following NovoSeven administration, were summarised.
- An overall summary of women with or without any invasive procedure prior to first NovoSeven administration but receiving any invasive procedure after the first NovoSeven administration was also provided.

Secondary endpoint analyses

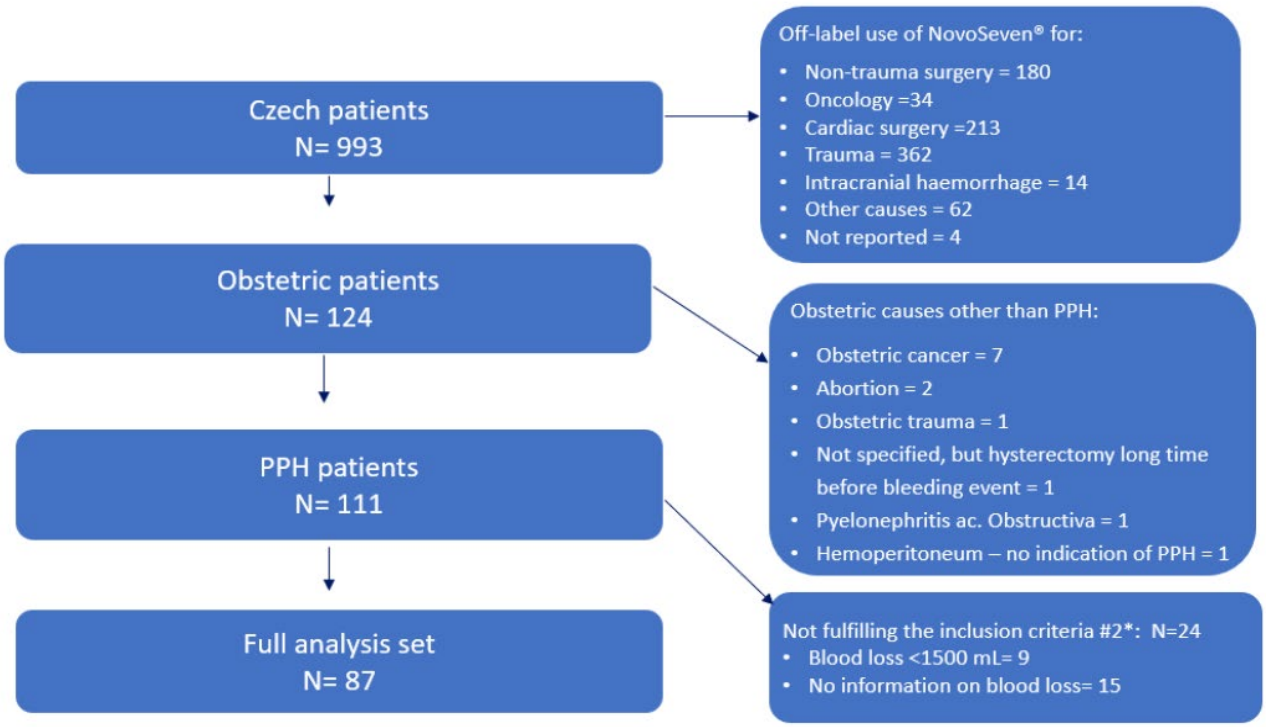
The proportion of the study population with severe PPH that achieved control of bleeding within 24 hours after administration of NovoSeven was calculated. Control of bleeding was defined as achieved/not achieved as assessed by the health care professional.

Results

Patient disposition

A total of the 993 Czech patients were registered with UniSeven registry during the period from July 2003 to April 2014. Of these, 111 women treated with NovoSeven were identified as PPH patients. Of these 111 women, 24 women did not fulfil the inclusion criteria #2 and were excluded from the FAS: 9 due to blood loss <1500 mL (0-1440 mL) and 15 due to no information on blood loss (Data on file). Thus, FAS included a total of 87 women with sPPH who had ≥1,500 mL blood loss within the period of 24 hours prior to first dose of NovoSeven administration, see figure 6.

Figure 6 Patient disposition in the UniSeven registry



*inclusion criterion #2: treated with Novoseven due to severe PPH, defined as >1500 ml blood loss within the period of 24 hours prior to the first dose of NovoSeven administration

Patient demographic and characteristics

The mean (SD) age at delivery was 31.7 (5.1) years; the majority of women were aged between 25 to 44 years (56.3% in 25-34 age category and 32.2% in 35-44 age category). The mean maternal body weight was 73.5 kg. Overall, 46.0% (40/87) of women had caesarean section as mode of delivery, 8.0% (7/87) had vaginal delivery and for 46.0% (40/87) the information was missing. Overall, 44.8% (39/87) of women had singleton births, 3.4% (3/87) had twin babies, 3.4% (3/87) had multiple babies (gave birth to more than one child, but information on number of children was not available) and the information was missing for 48.3% (42/87) of women.

Overall, 64.4% (56/87) of the women had a single cause of PPH; 19.5% (17/87) of the women had multiple causes of PPH and the cause of PPH was missing for 16.1% (14/87) of the women. The most common cause of PPH were "other' (36.8% [32/87]) and uterine atony (27.6% [24/87]) followed by abnormally invasive placenta (AIP) (18.4% [16/87]).

The mean (SD) estimated blood loss before NovoSeven administration was 3687.9 (1927.3) mL (range: 1500 to 12000 mL).

NovoSeven dose

Number of doses:

- Majority of women (72.4% [63/87]) received only one dose;
- 23.0% (20/87) women received exactly two doses
- 4.6% (4/87) women received exactly three doses.

Dose per kg:

- The median first dose in the FAS was 105 µg/kg (range: 50-200 µg/kg).
- The median second (100 µg/kg; range: 28-140 µg/kg) and third doses (100 µg/kg, range: 85-110 µg/kg) in the FAS were similar.
- For approximately two-thirds (65/87) of women the first dose of NovoSeven was >90 µg/kg, for 17 women the first dose was 60-90 µg/kg, and for 5 women it was <60 µg/kg.

Numbers analysed

Of the 87 women included in the FAS, a total of 44 women were excluded from the primary endpoint analysis due to a hysterectomy performed before or conjoint with NovoSeven administration. Thus, the population at risk of further invasive procedures included 43 women. Of the 43 women, 7 women had an invasive procedure (other than hysterectomy) and 36 women did not have any invasive procedure prior to or conjoint with first NovoSeven administration; these 36 women were included in the primary analysis.

Primary efficacy endpoint

- Of the 36 women who did not have any invasive procedures before or conjoint with NovoSeven administration included in the primary analysis, 10 (27.8%, 95% CI: 14.2; 45.2) had an invasive procedure 20 minutes to 24 hours after first NovoSeven administration. This suggests that after NovoSeven treatment invasive procedures were avoided in 72.2% (26/36) of women who did not have any invasive procedure prior to or conjoint with first NovoSeven administration.
- Of the 43 women who were at risk of further invasive procedures after first NovoSeven administration, 33 (76.7%) did not have an invasive procedure after the first NovoSeven administration (irrespective of whether they had an invasive procedure [other than hysterectomy] prior to first NovoSeven administration) and 10 women (23.3%, CI: 11.8; 38.6) had an invasive procedure after the first NovoSeven administration.

Of the 10 women who had invasive procedures following NovoSeven administration, 9 underwent hysterectomy and 1 underwent radiological arterial embolisation.

Secondary endpoints

Control of bleeding

- Of the 87 women included in the FAS, 85 (97.7%) women achieved control of bleeding and 2 (2.3%) women did not achieve control of bleeding within 24 hours of NovoSeven administration.
- The mean estimated blood loss decreased after NovoSeven administration (blood loss after NovoSeven administration, mean [SD]: 868.14 [974.73] mL and blood loss before NovoSeven administration, mean [SD]: 3688 [1927] mL). Women who required more than one dose of NovoSeven lost more blood (1239 mL and 1936 mL in women receiving 2 doses and 3 doses of NovoSeven, respectively) than women who required only one dose (670 mL). The mean estimated blood loss was the highest in women who received more than 2 doses of NovoSeven.

Summary

A total of 111 women with PPH registered in the UniSeven registry, of these, 87 women with severe PPH met the inclusion criteria of the study. Analysis of the use of NovoSeven as a haemostatic agent in the 87 women with severe PPH demonstrated:

- The median first dose of NovoSeven was 105µg/kg, the median second and third doses were 100 µg/kg each. The median total dose of NovoSeven was 120 µg/kg. The majority of women (72.4% [63/87]) received only one dose of NovoSeven; 23.0% (20/87) women received two doses and 4.6% (4/87) women received three doses of NovoSeven.
- 36 women did not have any invasive procedure prior to or during NovoSeven administration. Of these, 27.8%, (10/36) had and 72.2% (26/36) did not have any invasive procedures after NovoSeven administration.
- 97.7% (85/87) women achieved control of bleeding within 24 hours following NovoSeven administration.

- ***Study 4732 (ANZHR)***

Title: *Clinical use and outcome of NovoSeven treatment in severe postpartum haemorrhage – a retrospective cohort study of women from the Australian and New Zealand Haemostasis Registry*

Study design

The current study NN7711-432, was a retrospective cohort study describing the clinical use of NovoSeven and clinical outcomes in women with an event of sPPH treated with NovoSeven using data collected from the ANZHR. The study population was treated according to local routine clinical practice at the discretion of the treating physician. The study protocol and analysis plan were co-developed by Monash University and Novo Nordisk.

Setting

The ANZHR recorded data on various off-label uses of NovoSeven, however, the current study analysed the variables which are considered relevant for PPH.

For this study NN7711-4732, the Australian and New Zealand Haemostasis Registry (ANZHR) team at Monash University was responsible for patient registration, data collection and data analyses and the study clinician made causality assessments of the adverse events.

Data source

The ANZHR is a comprehensive registry documenting off-label use of NovoSeven in patients who do not have congenital haemophilia at participating hospitals throughout Australia and New Zealand. The ANZHR was established by the Department of Epidemiology and Preventive Medicine, Monash University (Australia) and funded through an educational grant from Novo Nordisk Pharmaceuticals Pty Ltd., Baulkham Hills, NSW, Australia. The registry began receiving data in May 2005 and included retrospective data from the period 2000–2009, with the first use of NovoSeven in obstetric haemorrhage reported in 2002.

Ninety-six hospitals participated across Australia and New Zealand. These included all major metropolitan hospitals in the two countries and were estimated to account for more than 95% of off-label use of NovoSeven during the period.24 Patients receiving NovoSeven to prevent or treat critical bleeding episodes outside the approved indications were eligible for inclusion in the registry. Of the 96 participating hospitals, 75 hospitals from Australia and New Zealand contributed data, the remaining 21 hospitals did not use NovoSeven for off-label conditions. Patients were identified by local investigators at each hospital using blood bank and/or pharmacy records. It was mandated by the registry that participating hospitals register each case of off-label use of NovoSeven at their institution.

Data collected as part of the registry were managed according to guidelines stipulated by the Australian Therapeutic Goods Administration and conformed to Commonwealth and State privacy principles.

Study period:

The Australian and New Zealand Haemostasis Registry (ANZHR) recorded off-label use of NovoSeven between 2000 and 2009. Publication by Phillips LE, 2009.

Primary objective:

- The primary objective was to describe the proportion of women with an event of sPPH that avoided invasive procedures following treatment with NovoSeven. Invasive procedures are defined as: uterine or iliac artery ligation, radiological arterial embolisation, uterine compression sutures (e.g. B-lynch sutures), and hysterectomy. Avoided does not infer causality, but rather should be understood as "did not have".

Secondary objectives:

- To describe the frequency of thromboembolic events (TEs) in women with an event of sPPH treated with NovoSeven
- To describe the proportion of women with an event of sPPH treated with NovoSeven that achieve control of bleeding (as assessed by the health care professional as decreased or ceased bleeding) after the last NovoSeven dose.

Outcomes/endpoints

Primary endpoint

- Occurrence of invasive procedures (yes/no) between 20 min-24 hours following NovoSeven administration. Invasive procedures included uterine or iliac artery ligation, radiological arterial embolisation, uterine compression sutures (e.g. B-lynch sutures) or hysterectomy.

  A 20 minutes lag-time was chosen for the same reasons as presented for study 4731 (UniSeven):

  - Peak coagulation ability is attained approximately 10 minutes after NovoSeven administration.

- A 20 minute lag time was chosen to allow leeway for circulation of the drug and time for observers to appropriately assess any decrease in blood loss.28
- The lag-time was chosen to disregard any case where a decision had been taken to administer NovoSeven and perform an invasive procedure concurrently.
- Cases where the decision to perform invasive procedure is taken simultaneously with administration of NovoSeven, where NovoSeven would not have had sufficient time to be effective if the procedure is performed within the lag time, are not considered as lack of efficacy of NovoSeven.

Secondary endpoints

- Occurrence of thromboembolic events, from first administration of NovoSeven until 7 days after last administration of NovoSeven
- Control of bleeding, yes/no After last dose of NovoSeven as reported in the data collection sheet

Criteria for inclusion/exclusion

The study population included women from Australia and New Zealand with an event of sPPH, treated with NovoSeven due to a critical bleed and were registered in the ANZHR.

Inclusion criteria

- Treated with NovoSeven due to severe PPH defined as an obstetric case with a registration of a delivery in ANZHR

Exclusion criteria

- Delivery at <24 weeks of gestational age

Product and mode of administration

Patients were treated with commercially available NovoSeven according to local routine clinical practice at the discretion of the treating physician.

Statistical methods

Analysis sets

Data were summarised for the Full Analysis Set (FAS), which included all women who met the inclusion criteria for the study.

Main statistical methods

This was a retrospective, single-cohort, observational study and hence no formal testing of statistical hypotheses was performed. Evaluation of data was based upon descriptive statistics, i.e. summary tables and figures. Continuous variables were summarised using standard statistical measures, i.e. number of observations, mean, standard deviation, median (IQR), minimum and maximum. Categorical data were summarised by frequency tables.

Exploratory univariate analyses were performed to evaluate the influence of different factors on the control of bleeding after the first and last dose of NovoSeven.

Primary endpoint analysis

The primary endpoint was analysed by summarising the number and proportion of women who received NovoSeven and did undergo any invasive procedure within a timeframe of 20 mins to 24 hours following

the first administration. This was calculated for the population at risk of invasive procedure after the first NovoSeven administration. Women who had a hysterectomy before or concurrent with first NovoSeven administration were considered to be no longer at risk of invasive procedure and thus excluded from the population at risk. Women, where the timing of an invasive procedure compared to first NovoSeven administration was unknown, were also excluded.

For the main analysis all women who had any invasive procedure prior to the first NovoSeven administration were excluded. The results of this analysis are also presented by number of NovoSeven doses received.

The analysis of the primary endpoint was repeated for the subgroup of women that had an "other invasive procedure" (not hysterectomy) prior to their first NovoSeven administration.

Secondary endpoint analyses

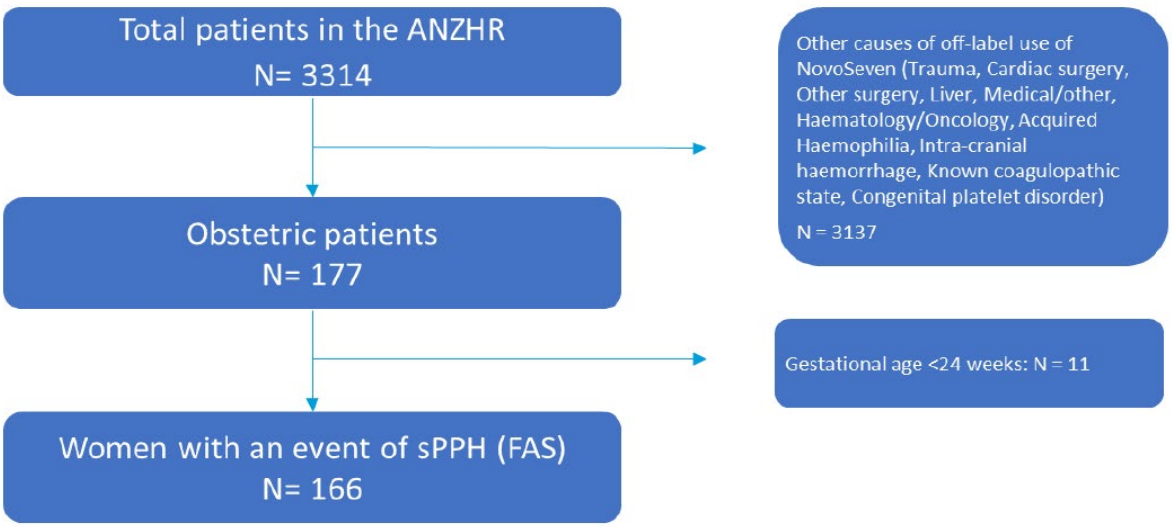
The proportion of the study population with severe PPH that achieve control (yes/no) of bleeding after the last dose of NovoSeven were reported. Control of bleeding was defined as an assessment by the health care professional of decreased or ceased bleeding. Whether control of bleeding was achieved (yes/no) in women with an event of severe PPH was summarised by subgroups based on doses of NovoSeven (receiving one dose of NovoSeven, two doses of NovoSeven and more than two doses of NovoSeven).

Results

Patient disposition

Patient disposition in the ANZHR is illustrated in Figure 7. A total of 3314 patients were registered in the ANZHR. Of these, 177 women treated with NovoSeven were identified as obstetric patients with a delivery recorded in ANZHR. Of the 177 women, 11 were excluded because the gestational age that was recorded was <24 weeks. The remaining 166 women were included in the FAS for this study.

Figure 7 Patient disposition in the ANZHR



Demographics and patient characteristics

The mean age at delivery was 32.3 years, with the majority (59.6%, 99/166) of women aged between 31 and 40 years. The mean maternal body weight was 68.8 kg and the mean gestation period was 36.6 weeks. In total, 70.5% of deliveries were by caesarean section: 52.4% by emergency caesarean section and 18.1% by elective caesarean. Singleton births were recorded in 158 of the women (95.2%) while 8 women (4.8%) gave birth to twins. The most common causes of PPH (more than one cause could be

indicated) were "other' (52.4%) and uterine atony (23.5%) followed by AIP (16.9%). The cause of PPH was missing for 24 women (14.5%).

NovoSeven dose

Number of doses:

The majority of women (76.5%, 127/166) received only one dose; 16.3% (27/166) of women received two doses and 7.2% (12/166) of women received three or more doses.

- The median time from onset of bleeding to first dose of NovoSeven was 291 minutes IQR: 160- 525 minutes.
- The median time between the first and the second dose of NovoSeven was 105 minutes IQR: 46-300 minutes and the median time between the second and third dose was 175 minutes (IQR: 60-310 minutes).

Dose per kg:

- The median first dose in the FAS was 96 µg/kg (interquartile range (IQR): 74 - 109 µg/kg). The median second (83 µg/kg, IQR: 62 - 97 µg/kg) and third doses (80 µg/kg, IQR: 44 - 96 µg/kg) were lower than the median first dose.
- For 60% (81/135) of women the first dose of NovoSeven was >90 µg/kg, for 34 women the first dose was 60-90 µg/kg, and for 20 women it was <60 µg/kg.

Numbers analysed

Of the 166 women included in the FAS, a total of 92 women were excluded from the primary endpoint analysis due to a hysterectomy performed before or concurrent with NovoSeven administration (n=54) or a missing timing of an invasive procedure (n=38). Thus, the population at risk of further invasive procedures included 74 women. Of the 74 women, 14 women had an invasive procedure (other than hysterectomy) and 60 women did not have any invasive procedure before first NovoSeven administration; these 60 women were included in the primary efficacy analysis.

Efficacy results

Primary endpoint

- Of the 74 women who were at risk of further invasive procedures after first NovoSeven administration, 52 (70%) did not require an invasive procedure after the first NovoSeven administration (irrespective of whether they had an invasive procedure [other than hysterectomy] prior to first NovoSeven administration) and 22 women (30%, 95% CI: 20%; 41%) required an invasive procedure 20 minutes to 24 hours after the first NovoSeven administration.
- Subgroup analysis:

  Of the 60 women included in the primary analysis who had not any invasive procedures before NovoSeven administration, 21/60 (35%, 95% CI: 23%; 48%) had an invasive procedure 20 minutes to 24 hours after first NovoSeven administration. No invasive procedures were required for 65% (39/60) of the women who had not had any invasive procedure before first NovoSeven administration.

Additional analysis in women with confirmed severe PPH

The primary endpoint analyses were repeated in the subgroup of women with confirmed severe PPH. The results were consistent with the results from the FAS.

Additional analysis by number of doses

Of the 60 women included in the primary endpoint analysis, 44 women received one dose, 12 women received 2 doses and 4 women received more than 2 doses.

- Of the 44 women who received one dose of NovoSeven, 12 (27%) had an invasive procedure within a timeframe of 20 mins to 24 hours following the NovoSeven administration. Therefore 32 (73%) women did not have an invasive procedure within a timeframe of 20 mins to 24 hours following the NovoSeven administration.
- Of the 12 women who received 2 doses of NovoSeven, 6 (50%) had an invasive procedure within a timeframe of 20 mins to 24 hours following first NovoSeven administration. Therefore 6 (50%) women did not have an invasive procedure within a timeframe of 20 mins to 24 hours following the first NovoSeven administration.
- Of the 4 women who received more than 2 doses of NovoSeven, 3 (75%) had an invasive procedure within a timeframe of 20 mins to 24 hours following the NovoSeven administration. Therefore 1 (25%) woman did not have an invasive procedure within a timeframe of 20 mins to 24 hours following the first NovoSeven administration.

Secondary endpoints

Control of bleeding

Control of bleeding was assessed by the treating physician following the last NovoSeven dose in 142 women while no information was available for 24 women. These 24 women with no information have been excluded from the analysis of bleeding control but are included in the various subgroup analyses as "missing".

- Bleeding was controlled after the last NovoSeven administration in 73.9% of women (105/142). NovoSeven dose.
- The proportion of women with confirmed severe PPH who achieved bleeding control was 73% (94/128).
- The proportion of women with confirmed severe PPH who achieved bleeding control was 76% (75/99) in those women who only received a single dose of NovoSeven and 65% (15/23) in those women who received 2 doses of NovoSeven.

Summary

A total of 166 women with sPPH met the inclusion criteria of the study. Analysis of the use of NovoSeven as a haemostatic agent in the 166 women with sPPH demonstrated:

- The median first dose of NovoSeven was 96 µg/kg. The median second was 83 µg/kg and the median third dos was 80 µg/kg. The median total dose was 103 µg/kg. The majority of women (127/166; 76.5%) received only one dose; 16.3% (27/166) women received two doses and 7.2% (12/166) women received three or more doses.
- 60 women had not had any invasive procedure before first NovoSeven administration. Of these, 39 (65%) did not have any invasive procedures after NovoSeven administration.
- 74 women had not had a hysterectomy before or concurrent with the first NovoSeven administration. Of these 52 (70%) did not have any invasive procedures after NovoSeven administration.
- 73.9% (105/142) women achieved control of bleeding following the last NovoSeven administration.

Of the 60 patients who had not any invasive procedures before NovoSeven administration, 21/60 (35%, 95% CI: 23%; 48%) had an invasive procedure 20 minutes to 24 hours after first NovoSeven administration. This outcome suggests that after NovoSeven treatment invasive procedures were avoided for 65% (39/60) of the women who had not had any invasive procedure before first NovoSeven administration.

Analysis performed across trials (pooled analyses and meta-analysis)

Post-hoc analysis of a common primary efficacy endpoint (project endpoint) in RCT and non-epidemiological studies

Project endpoint

To support the regulatory submission, a common '**project endpoint'** was defined by the MAH, in accordance with regulatory guidance from NL and FR and external experts across relevant medical specialties, to evaluate efficacy of NovoSeven both in RCT and non-interventional studies.

- The predefined **RCT protocol endpoint** was defined as:

  the absolute and relative reduction in the need for specific second-line therapies (*rate of embolisation and/or ligation)*.

- The primary endpoint in the **RCT publication** was defined as:

  reduction in the need of specific second line therapies (*uterine compression sutures, uterine artery embolization, vascular ligation or peripartum hysterectomy*).

- The MAH defined '**project endpoint'** as:

  "*occurrence of any invasive procedure after first treatment with NovoSeven", where invasive procedure was defined as uterine or iliac artery ligation, radiological arterial embolisation, uterine compression sutures, and/or hysterectomy*"

Data sources

For trial 4816 (RCT), study 4729 (Bern) and study 4731 (UniSeven), Novo Nordisk had access to anonymised/pseudonymised patient-level data and performed descriptive and statistical analyses of the data as relevant. For study 4733 (PPH consortium) and study 4732 (ANZHR), descriptive and statistical analyses were performed by academic institutions (Department of Clinical Epidemiology, Leiden University Medical Centre and Department of Epidemiology and Preventive Medicine, Monash University, respectively) based on patient-level data. These academic institutions then provided population-level data to Novo Nordisk for reporting purposes.

These analyses of the project endpoint were conducted of all exposed women in the FAS who were at risk of further invasive procedures after NovoSeven administration (i.e., the population of women at risk).

Additionally, analyses of the project endpoint were conducted for the subpopulation of women who did not receive any invasive procedure before first NovoSeven administration. These analyses were either prespecified in the SAP (UniSeven, NZ) or were conducted post hoc (RCT, Bern, PPH consortium) for consistency across the data sources.

Trial 4816 (RCT)

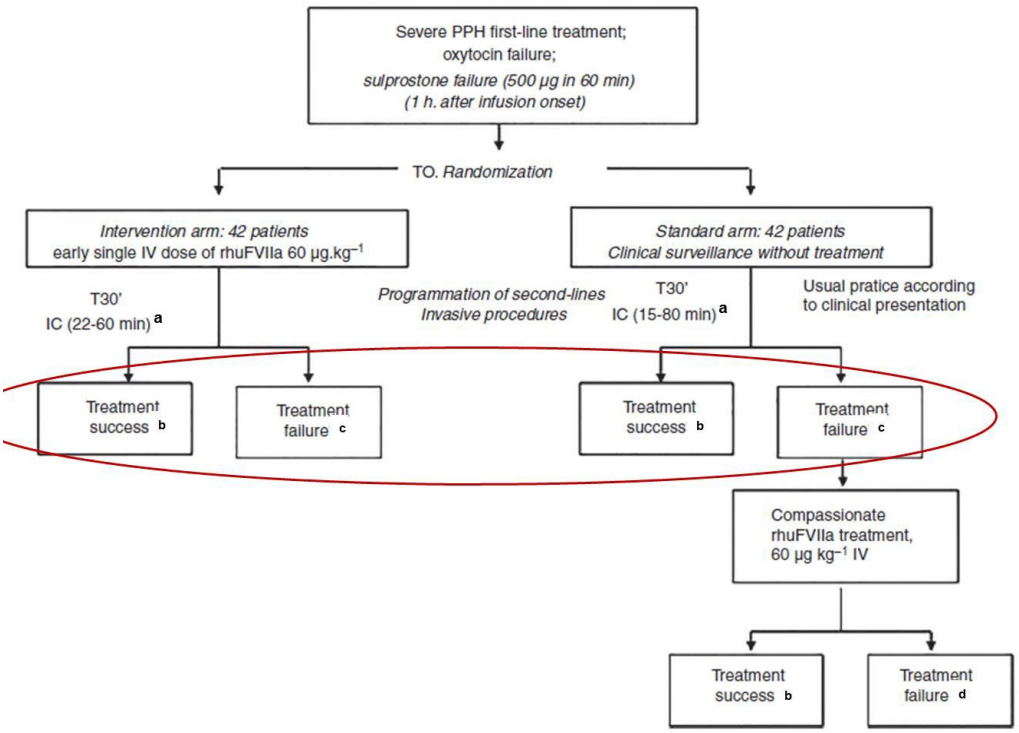
In trial 4816 (RCT), efficacy of NovoSeven was evaluated post hoc through the **'project endpoint'** to be consistent with other data sources, and not by the protocol defined primary endpoint of *rate of embolisation and/or ligation,* but both endpoints were based on the primary objective of the trial.

For the RCT, the post hoc analysis included:

- 'project endpoint' (at least one uterine or iliac arterial ligation, radiological arterial embolisation, uterine compression suture, and/or hysterectomy)
- the new secondary endpoint of occurrence of hysterectomy.

As directed by the RCT protocol, patients were randomised approximately 1 hour after sulprostone failure to control their bleeding. The intention of the RCT was to administer NovoSeven ***before any invasive procedure*** in those randomised to NovoSeven. The 'project endpoint' was assessed at the encircled time point in Figure 8 below.

Figure 8 Trial design



Note: The figure is based on the publication by Lavigne-Lissalde et al. The 'project endpoint' was assessed at the encircled time point. Second-line treatment includes uterine or iliac artery ligation, radiological arterial embolisation, uterine compression sutures, and/or hysterectomy. Abbreviations: IC = confidence interval; IV = intravenous
[a]Time to initiation of a second-line treatment was same for both groups. Median delay was 30 minutes (95% CI: 15 minutes to 80 minutes) in the reference group and 30 minutes (95% CI:22 minutes to 60 minutes) in the NovoSeven group.
[b]No need for specific second-line therapies; [c]Need for specific second-line therapies; [d]Hysterectomy

Statistical analysis of 'project endpoint' in RCT

The '**project endpoint'** was analysed post hoc at any time point after randomisation until stop of PPH. Analysis for occurrence of hysterectomy was also added. As directed by the RCT protocol, patients were randomised approximately 1 hour after sulprostone failure to control their bleeding. The intention of the RCT was to administer NovoSeven before any invasive procedure in those randomised to NovoSeven.

The occurrence of invasive procedures and hysterectomy was compared between the NovoSeven and reference groups by the relative risk, the risk difference, and the relative reduction, and presented with 95% CI. For the relative risk, the p-value was calculated from the chi-square test. All tests and

confidence intervals were two-sided, assessed at 5% significance level and were performed in the FAS. To facilitate alignment with the analyses in the other data sources, the odds ratio was estimated with a logistic regression analysis also providing a p-value and a 95% CI.

CTR follows all the data decision made by the original trial team outside Novo Nordisk (Nîmes University Hospital). However, one woman in the NovoSeven group underwent a ligation (invasive procedure) prior to NovoSeven administration and she had no further invasive procedures after NovoSeven administration. This case was counted by the investigators as having an invasive procedure following NovoSeven dose. This issue was subsequently addressed post hoc by the study group at Novo Nordisk by not counting the woman with prior ligation to have an invasive procedure post NovoSeven administration and was subsequently removed from the numbers of the 'project endpoint'. Furthermore, she was not included in the subpopulation of 'women without any invasive procedure prior to randomisation'.

Summary of various qualitative and quantitative characteristics for both groups (NovoSeven and reference) were presented using descriptive statistics. Descriptive statistics of categorical data were summarised by frequency tables (number and proportion) while continuous data were summarised by mean (SD), median (IQR), minimum and maximum value. Additional statistical and post hoc analyses were also carried out and additional endpoints defined.

Four non-interventional studies

- For the four non-interventional studies, the **'project endpoint'** was evaluated within a timeframe of 20 minutes to 24 hours following first administration of NovoSeven. The pattern of NovoSeven administration in the non-interventional studies was different to the RCT with women receiving NovoSeven at any time in the course of PPH.

Populations included:

studies 4729 (Bern) and 4733 (PPH consortium)

- In both studies 4729 (Bern) and 4733 (PPH consortium), the 'project endpoint' was evaluated for NovoSeven exposed women who were at risk of further invasive procedures after NovoSeven administration (population at risk). The subpopulation of the FAS was defined post hoc as:
    - For studies 4729 (Bern) and 4733 (PPH consortium-DK and NL cohort): The population of patients at risk was defined as women in the FAS who received NovoSeven without pre-planned hysterectomy, or hysterectomy performed before onset of severe PPH, or insufficient data to be part of the PS matching, or hysterectomy before or concurrent with NovoSeven administration, or with PPH stop before receiving NovoSeven.
    - For study 4733 (PPH consortium-UK cohort): The population of patients at risk was defined as women in the FAS without hysterectomy before or concurrent with first administration of NovoSeven.

This subpopulation represents those women in the FAS that, after receiving NovoSeven, were still relevant for evaluating the 'project endpoint' of occurrence of invasive procedure after the concurrent period. This population was added post hoc, as it was not anticipated that a number of patients would have an order of events that made the evaluation of the primary endpoint not at all meaningful or with limited meaning after NovoSeven administration. Women who received NovoSeven after PPH stop due to restart of a bleed or other reasons were also excluded as they might have a different risk profile. This post hoc analysis was added to have a subgroup aligned with the data from studies 4731 (UniSeven) and 4732 (ANZHR).

Studies 4731 (UniSeven) and 4732 (ANZHR)

- Pre-specified analyses: The primary endpoint for both studies 4731 (UniSeven) and 4732 (ANZHR) was occurrence of invasive procedures (i.e. uterine or iliac artery ligation, radiological arterial embolisation, uterine compression sutures, and/or hysterectomy) within a timeframe of 20 minutes to 24 hours following NovoSeven administration.

  It is to be noted that the studies did not pre-specify an estimand but it was defined post hoc to be consistent with the predefined estimands for studies 4729 (Bern) and 4733 (PPH consortium), with relevant modification due to study design. The estimand was defined by the following five inter-related attributes as outlined in the ICH E9 (R1):

  - Treatment conditions: NovoSeven treatment.
  - Population of interest: The 'population at risk' without any invasive procedure before treatment with NovoSeven (see below how 'before' was defined for each study).
  - Endpoint of interest: Occurrence of invasive procedures (uterine or iliac artery ligation, radiological arterial embolisation, uterine compression sutures, and/or hysterectomy) within a timeframe of 20 minutes to 24 hours following NovoSeven administration.
  - Approach to handle intercurrent events: Intercurrent events of death and exposure to additional doses of NovoSeven were handled by a hypothetical strategy and a treatment policy strategy respectively.
  - Population level summary: The observed proportion of women with invasive procedures.

  This estimand was also used for the post hoc analysis in studies 4729 (Bern) and 4733 (PPH consortium) for the population at risk.

Statistical analysis of 'project endpoint' in non-interventional studies

The post hoc analysis for study 4729 (Bern) and study 4733 (PPH consortium) was added to have a subgroup aligned with the data from studies 4731 (UniSeven) and 4732 (ANZHR).

Across the non-interventional studies, women meeting the inclusion criteria during the study period were included as part of the FAS to analyse the clinical outcomes in women treated with NovoSeven for severe PPH.

The clinical outcomes of invasive procedures ('project endpoint') were evaluated within a timeframe of 20 minutes to 24 hours following first administration of NovoSeven. A lag-time of 20 minutes following NovoSeven administration was implemented based on inputs from external experts across relevant medical specialties. The rationale for this decision is described below:

- It would take 10 minutes for NovoSeven to reach peak coagulation ability.
- The 20-minute lag-time was chosen to disregard any case where the decision for both invasive procedure and NovoSeven was taken concurrently, with the execution being short time interval apart.
- For cases where the decision to perform an invasive procedure was taken simultaneously with administration of NovoSeven, NovoSeven would not have had sufficient time to be effective.

To reflect the decision relating to this 20 minute lag, a concurrent period was defined across the non-interventional studies. It corresponds to the period between 20 minutes before and 20 minutes after NovoSeven administration (for studies 4731 (UniSeven) and 4732 (ANZHR)) or time0 (for studies 4729 (Bern) and 4733 (PPH consortium); see below for definition of time0). It corresponds to the period between 20 minutes before and 20 minutes after NovoSeven administration (for studies 4731 (UniSeven) and 4732 (ANZHR)) or time0 (for studies 4729 (Bern) and 4733 (PPH consortium).

General considerations regarding the clinical data sources

The variety of data sources included in this application enable an evaluation of NovoSeven usage across a broad population of women with severe PPH, including pivotal data from an RCT and data from real world clinical practice. However, there are differences across the RCT and observational data, including the eligibility criteria, dose of NovoSeven, number of doses, and timing of NovoSeven administration in the treatment cascade, that should be considered when comparing and interpreting the results.

- ***Definition of trial/study populations***

In trial 4816 (RCT), study 4729 (Bern) and study 4731 (UniSeven), severe PPH was defined as blood loss of at least 1500 mL within 24 hours after delivery or within the period of 24 hours prior to first dose of NovoSeven administration.

- ***Dose size, number of doses and timing of NovoSeven***

In trial 4816 (RCT), a single dose of NovoSeven 60 µg/kg was administered early in the treatment cascade (after failure of sulprostone). The intention by trial design was that NovoSeven should be administered before any invasive procedure. A clinical trial in the setting of severe PPH with a baseline later than "failure of uterotonics" would be difficult to conduct.

In the non-interventional studies, the dose of NovoSeven, number of doses, and timing of administration relative to an invasive procedure (before, with, or after invasive procedure) were at the discretion of the treating physician, local clinical practice, or regional/hospital guidelines in place at the time the patient was treated. In some cases, women were treated late in the treatment cascade as a uterus- or life-saving measure. Factors concerning timing of NovoSeven administration relative to invasive procedures, dose and number of doses have been evaluated to the extent possible in this application.

- ***Data collection***

The course of severe PPH is an acute and highly dynamic situation which can be difficult to capture, both in prospective clinical trials and retrospective observational studies. The data recorded in the non-interventional studies reflected routine clinical practice rather than mandatory assessments at pre-specified time points. Details in the medical records may not exactly match the complete set of information of interest for evaluation of study endpoints. Data in the non-interventional studies were also masked or anonymised, as per data transfer agreements, to prevent identification of individual patients. Consequently, in some cases, only partial information is available for some events.

- ***Severity or progression of PPH at time of NovoSeven administration***

Current treatment guidelines in severe PPH that recommend the use of NovoSeven often do so as a last resort just before or after hysterectomy, which may bias the group of NovoSeven treated women toward more severe or more progressed cases. Thus, in the real world, women treated with NovoSeven may have a worse or more progressed event of severe PPH than women not treated with NovoSeven, which phenomenon is referred to as *'confounding by indication'*. This is reflected in the meta-analysis conducted as part of the literature review by the fact that on average 41.5% of women treated with NovoSeven had a hysterectomy performed before NovoSeven was administered, while only 27.7% of the women with severe PPH who were not treated with NovoSeven had a hysterectomy performed at any point.

To reduce the effects of confounders in the observational data, propensity score matching was used in studies 4729 (Bern) and 4733 (PPH consortium), see separate summaries of these studies in section supportive studies.

- **Historical context**

Data from the sources presented were collected over a period from 1996 onwards, with much of the data being collected more than 5 years ago. Treatment for PPH, including the use of fibrinogen and tranexamic acid (TXA), has developed over recent years. The standard of care for PPH is continually being updated.

Results

Patient disposition RCT and non-interventional studies

Overall, in the FAS across these clinical data sources (4816, 4729, 4733, 4731 and 4732), a total of 437 women were included in the NovoSeven group and 1726 women were included in the no NovoSeven group. In the RCT, 9 women in the reference group also received NovoSeven (8 women on a compassionate use basis and 1 woman in error). An overview of the numbers of women with severe PPH in the FAS in the RCT and 4 non-interventional studies is presented in Table 17.

Demographic and baseline characteristics RCT and non-interventional studies

The eligibility criteria applied in trial 4816 (RCT) facilitated an evaluation of the **early use** of NovoSeven (after failure of sulprostone) in women with severe PPH. The eligibility criteria applied in the 4 non-interventional studies were broad and reflected populations of women with severe PPH in clinical practise.

An overview of demographic and baseline characteristics for women with severe PPH across the different clinical data sources is presented in Table 17. Not all characteristics are available for each study due to the different anonymisation/pseudonymisation requirements and data collection specifications for the individual studies.

- Causes of PPH across data sources varied with 11.9−31.0% of women having multiple causes. Overall, the most common primary causes of PPH were uterine atony and AIP, but a substantial proportion of women in study 4731 (UniSeven) and 4732 (ANZHR) had a missing cause of PPH.
- In the RCT, there was an approximately even distribution on mode of delivery (caesarean or vaginal); while across the non-interventional studies (except for the NL cohort of study 4733 (PPH consortium)) more women tended to have caesarean delivery (range 46.0−76.9%) than vaginal delivery.
- Timing of NovoSeven administration: Women in the non-interventional studies were in a more severe or more progressed condition at the time of NovoSeven administration than women in the RCT. In the RCT, women with severe PPH could be included in the trial if sulprostone had failed to control their bleeding after 60 minutes, or a shorter period if the anaesthetist's subjective assessment was that the PPH was not controlled following use of sulprostone. In the non-interventional studies, the median (IQR) time from onset of severe PPH to first dose of NovoSeven ranged from 127.5 (71.0−290.5) minutes in study 4729 (Bern) to 291.0 (160.0−525.0) minutes in study 4732 (ANZHR).

Table 17 Overview of demographic and baseline characteristics – RCT and non-interventional studies – full analysis set

	Trial 4816 (RCT)[a]		Study 4729 (Bern)		Study 4733 (PPH consortium)						Study 4731 (UniSeven)	Study 4732 (ANZHR)
					DK		NL		UK			
	NovoSeven	Reference	NovoSeven	No NovoSeven	NovoSeven	No NovoSeven	NovoSeven	No NovoSeven	NovoSeven	No NovoSeven	NovoSeven	NovoSeven
FAS, N	42	42	52	113	40	199	37	1223	13	149	87	166
Age at delivery (years)												
N	–	–	–	–	40	199	37	1223	13	149	84	166
Mean (SD)	–	–	–	–	33.5 (5.5)	32.5 (4.8)	31.2 (4.8)	31.6 (5.0)	32.4 (5.7)	32.5 (5.9)	31.7 (5.1)	32.3 (6.1)
Median (IQR)	–	–	–	–	33.0 (29.0–38.0)	33.0 (30.0–36.0)	31.0 (28.0–34.0)	32.0 (28.0–35.0)	34.0 (28.0–36.0)	33.0 (29.0–36.0)	31.5 (28.0–36.0)	33.0 (29.0–37.0)
Maternal body weight (kg)[a]												
N	42	40	52	108	–	–	–	–	–	–	87	135
Mean (SD)	70.3 (11.8)	71.1 (13.9)	73.8 (17.0)	75.1 (12.5)							73.5 (10.8)	68.8 (19.2)
Median (IQR)	68.0 (62.0–76.0)	70.0 (60.0–79.0)	70.0 (61.0–83.0)	72.5 (67.0–82.0)	–	–	–	–	–	–	72.0 (66.0–80.0)	65.0 (55.0–75.0)
Delivery type, n (%)												
N	42	42	52	113	40	199	37	1223	13	149	87	166
Caesarean section	23 (54.8)	20 (47.6)	40 (76.9)	57 (50.4)	25 (62.5)	133 (66.8)	14 (37.8)	279 (22.8)	7 (53.9)	101 (67.8)	40 (46.0)	117 (70.5)
Multiple birth, n (%)												
N	42	42	52	113	40	199	37	1223	13	149	87	166
Yes[e]	7 (16.7)	7 (16.7)	8 (15.4)	15 (13.3)	1 (2.5)	12 (6.0)	3 (8.1)	71 (5.8)	3 (23.1)	4 (2.7)	6 (6.9)	8 (4.8)

	Trial 4816 (RCT)[a]		Study 4729 (Bern)		Study 4733 (PPH consortium)						Study 4731 (UniSeven)	Study 4732 (ANZHR)
					DK		NL		UK			
	NovoSeven	Reference	NovoSeven	No NovoSeven	NovoSeven	No NovoSeven	NovoSeven	No NovoSeven	NovoSeven	No NovoSeven	NovoSeven	NovoSeven
Multiple cause of PPH, n (%)												
N	42	42	52	113	–	–	–	–	–	–	87	166
Yes	13 (31.0)	5 (11.9)	15 (28.8)	26 (23.0)							17 (19.5)	-
Primary cause of PPH[b], n (%)												
N	42	42	52	113	40	199	37	1223	13	149	87	166
AIP[c]	6 (14.3)	8 (19.0)	9 (17.3)	17 (15.0)	11 (27.5)	51 (25.6)	6 (16.2)	119 (9.7)	1 (7.7)	28 (25.5)	16 (18.4)	28 (16.9)
Placental abruption	NA	NA	5 (9.6)	8 (7.1)	4 (10.0)	13 (6.5)	0	12 (1.0)	1 (7.7)	14 (9.4)	9 (10.3)	15 (9.0)
Placental retention	4 (9.5)	1 (2.4)	1 (1.9)	31 (27.4)	4 (10.0)	21 (10.6)	2 (5.4)	217 (17.7)	–	–	1 (1.1)	NA
Trauma[d]	7 (16.6)	2 (4.8)	1 (1.9)	9 (8.0)	7 (17.5)	50 (25.1)	3 (8.1)	89 (7.3)	1 (7.7)	26 (17.5)	6 (6.9)	5 (3.0)
Uterine atony	39 (92.9)	36 (85.7)	34 (65.4)	48 (42.5)	11 (27.5)	37 (18.6)	25 (67.6)	780 (63.8)	8 (61.5)	56 (37.6)	24 (27.6)	39 (23.5)
Other	NA	NA	2 (3.8)	0	3 (7.5)	27 (13.6)	1 (2.7)	6 (0.5)	2 (15.4)	14 (9.4)	32 (36.8)	87 (52.4)
Missing	0	0	0	0	0	0	0	0	0	1 (0.7)	14 (16.1)	24 (14.5)
Prior RBC (count)[f]												
N	16	11	48	NA	40	NA	37	NA	–	NA	87	165
Mean (SD)	2.7 (1.3)	3.1 (2.3)	6.9 (4.1)		13.7 (9.2)		9.0 (7.2)				9.1 (6.3)	11.6 (8.4)
Median (IQR)	2.0 (2.0–3.0)	2.0 (1.0–4.0)	6.0 (4.0–10.0)		11.0 (8.0–18.5)		7.0 (4.0–13.0)				8.0 (5.0–12.0)	11.0 (6.0–16.0)
Prior FFP (count)[f]												
N	6	6	45	NA	40	NA	36	NA	–	NA	87	164
Mean (SD)	3.3 (2.2)	4.0 (1.1)	6.0 (3.2)		7.0 (5.3)		6.2 (5.8)				8.8 (6.2)	7.1 (6.1)
Median (IQR)	2.5	4.0	5.0		5.5		4.5				8.0	6.0

	Trial 4816 (RCT)[a]		Study 4729 (Bern)		Study 4733 (PPH consortium)						Study 4731 (UniSeven)	Study 4732 (ANZHR)
					DK		NL		UK			
	NovoSeven (2.0–6.0)	Reference (3.0–4.0)	NovoSeven (4.0–8.0)	No NovoSeven	NovoSeven (4.0–8.5)	No NovoSeven	NovoSeven (2.0–8.0)	No NovoSeven	NovoSeven	No NovoSeven	NovoSeven (5.0–10.0)	NovoSeven (4.0–9.5)
Prior platelets (count)[f]												
N	1	2	24	NA	40	NA	30	NA	–	NA	87	163
Mean (SD)	3.0 (NA)	8.5 (3.5)	1.5 (0.9)		2.5 (2.5)		1.9 (2.3)				2.7 (18.2)	2.6 (4.4)
Median (IQR)	3.0 (3.0–3.0)	8.5 (6.0–11.0)	1.0 (1.0–2.0)		2.0 (1.0–3.0)		1.0 (1.0–2.0)				0.0 (0.0–1.0)	1.0 (1.0–3.0)
Invasive procedure(s) prior to NovoSeven, n (%)[g]												
N	42	42	52	NA	40	NA	37	NA	13	NA	87	166
Any invasive procedure	1 (2.4)	0	32 (61.5)		23 (57.5)		15 (40.5)		3 (23.1)		21 (24.1)	63 (38.0)
Hysterectomy	0	0	3 (5.8)		15 (37.5)		6 (16.2)		1 (7.7)		16 (18.4)	45 (27.1)
Time from onset of severe PPH to first NovoSeven administration (minutes)												
N	42	42	52	NA	40	NA	37	NA	–	NA	87	149
Mean (SD)[h]	≤60	NA	228.2 (266.6)		294.5 (472.8)		444.6 (480.1)				409.9 (555.5)	517.3 (700.9)
Median (IQR)[h]	≤60		127.5 (71.0–290.5)		132.5 (60.0–312.5)		289.0 (134.0–535.0)				210.0 (120.0–480.0)	291.0 (160.0–525.0)

[a] End-of-pregnancy weight (adjusted for the weight of baby). [b]A woman may have more than one cause of PPH; cumulative sum of all reasons may be greater than N.

Results

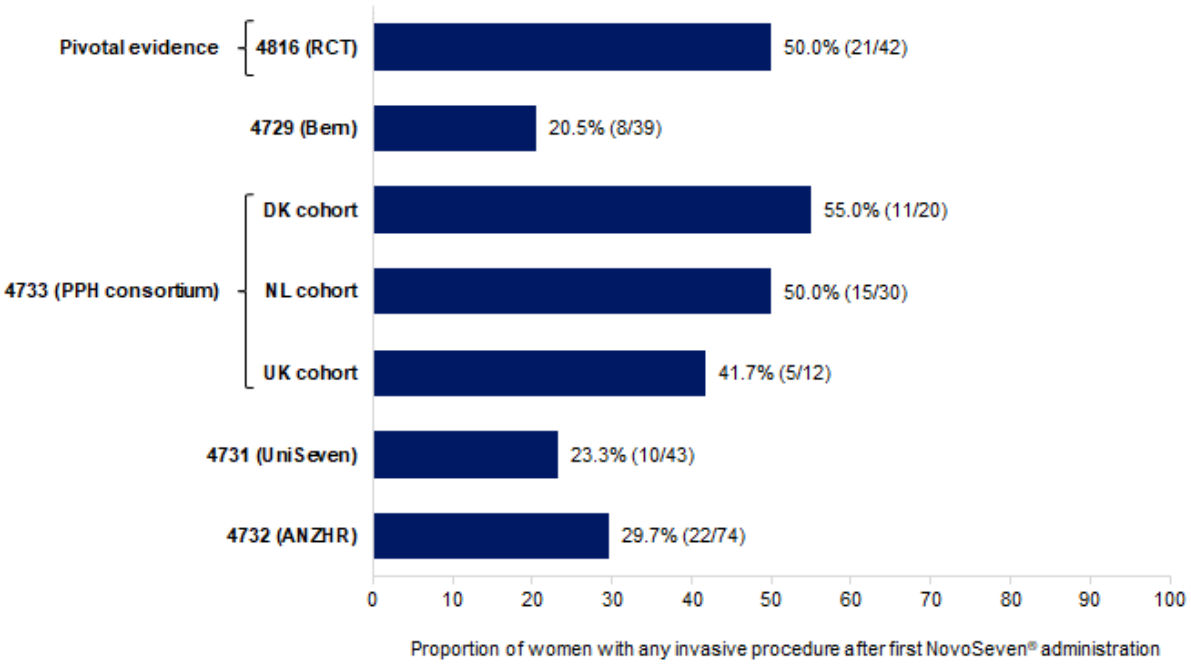
Invasive procedures (project endpoint)

Population of women with or without any previous invasive procedure, except hysterectomy, prior to NovoSeven administration:

In trial 4816 (RCT), the proportion of women at risk with any invasive procedure, 50% of women underwent an invasive procedure after NovoSeven treatment. In the non-interventional studies, a similar or lower proportion of women at risk had an invasive procedure after receiving NovoSeven.

An overview across the RCT and 4 non-interventional studies of the occurrence of any invasive procedure (project endpoint) after NovoSeven administration for women in the FAS at risk of invasive procedure is presented in Figure 9:

Figure 9 Proportion of women at risk of any invasive procedure after first NovoSeven administration across data sources



Notes: Invasive procedures are defined as uterine or iliac arterial ligation, radiological arterial embolisation, uterine compression suture, and/or hysterectomy (project endpoint).
Abbreviations: ANZHR = Australian and New Zealand Haemostasis Registry; DK = Denmark; NL = Netherlands; PPH = postpartum haemorrhage; RCT = randomised controlled trial; UK = the United Kingdom.

Population of women without any invasive procedure prior to NovoSeven administration:

In trial 4816 (RCT), in the population of women without any prior invasive procedure, the number of women with an invasive procedure after NovoSeven administration was 51%.

In non-interventional studies, these proportions varied between 64% and 25%.

In table 18, the outcome of the proportion of women requiring an invasive procedure after NovoSeven administration analysed in both populations is presented:

Table 18 Occurrence of invasive procedures: Women treated with NovoSeven across data sources – population at risk

	Proportion of women with any invasive procedure after first NovoSeven administration, n/N (%)	
	Women at risk of further invasive procedures[a]	***Women <u>without</u> any prior invasive procedure***[b]
Pivotal evidence		
Trial 4816 (RCT)[c]	21/42 (50.0)	21/41 (51.2)
Non-interventional studies		
Study 4729 (Bern)	8/39 (20.5)	2/12 (16.7)
Study 4733 (PPH consortium) – *DK cohort*	11/20 (55.0)	9/14 (64.3)
Study 4733 (PPH consortium) – *NL cohort*	15/30 (50.0)	11/22 (50.0)
Study 4733 (PPH consortium) – *UK cohort*	5/12 (41.7)	5/10 (50.0)
Study 4731 (UniSeven)	10/43 (23.3)	10/40 (25.0)[d]
Study 4732 (ANZHR)	22/74 (29.7)	21/60 (35.0)

Notes: Invasive procedures are defined as uterine or iliac arterial ligation, radiological arterial embolisation, uterine compression suture, and/or hysterectomy ('project endpoint').
Data on occurrence of any invasive procedure was captured after randomisation for trial 4816 (RCT), for the period between 20 minutes to 24 hours after time0 (i.e., after concurrent period) in studies 4729 (Bern) and 4733 (PPH consortium) or after first NovoSeven administration in 4731 (UniSeven) and 4732 (ANZHR).
a Across the non-interventional studies, data are presented for women who were at risk of further invasive procedures.
b Project endpoint' was evaluated for a subpopulation of women from the population at risk who did not receive any invasive procedure before first NovoSeven administration across all the non-interventional studies except for study 4733 (PPH consortium-DK and NL cohort), where it was defined as women who did not receive any invasive procedure before the concurrent period.
c For trial 4816 (RCT), the updated numbers for the 'project endpoint' are presented by addressing for the woman in the NovoSeven group who underwent ligation prior to NovoSeven administration but was counted to have an invasive procedure following NovoSeven dose (see Section 1.4.7.3 for details).
d Project endpoint' was evaluated post hoc for this subpopulation of woman without any invasive procedure before first NovoSeven administration.
Abbreviations: ANZHR = Australian and New Zealand Haemostasis Registry; DK = Denmark; n = number of observations; N = number of women; NL = the Netherlands; PPH = postpartum haemorrhage; UK = the United Kingdom.

Results of individual studies

Pivotal data from trial 4816 (RCT)

Invasive procedures (project endpoint)

Trial 4816 (RCT) provides pivotal evidence for the efficacy of NovoSeven in the treatment of severe PPH. There was a 44.7% relative reduction in risk of invasive procedure after randomisation for the NovoSeven group compared to the reference group (21/42 vs 38/42 women; p<0.0001) (Table 19).

Similar results were observed for the subpopulation of women ***without any invasive procedure*** before randomisation, with a relative reduction in risk of 43.4% for the NovoSeven group compared to the reference group (21/41 vs 38/42 women; p<0.0001, see Table 18.

Table 19 Occurrence of any invasive procedure after randomisation – trial 4816 (RCT) – full analysis set

	NovoSeven	Reference	Risk difference (Reference - NovoSeven) (95% CI)	Relative risk (NovoSeven / Reference) (95% CI)	Relative reduction (%)	p-value
Women with or without other invasive procedure before randomisation						
At least one invasive procedure after randomisation, n/N (%)	21/42 (50.0)	38/42 (90.5)	40.48 (22.94; 58.01)	0.55 (0.40; 0.76)	44.7	<0.0001
Women without invasive procedure before randomisation						
At least one invasive procedure after randomisation, n/N (%)	21/41 (51.2)	38/42 (90.5)	39.26 (21.57; 56.95)	0.57 (0.41; 0.78)	43.4	<0.0001

Note: Invasive procedures are defined as uterine or iliac arterial ligation, radiological arterial embolisation, uterine compression suture and/or hysterectomy (project endpoint).
The subpopulation of women without any invasive procedure before randomisation was defined post hoc as described above. This subpopulation excluded 1 woman in the NovoSeven group who had a ligation before NovoSeven administration.
Abbreviations: CI = confidence interval; n = number of observations; N = number of women; RCT = randomised controlled trial.

Hysterectomy

The number of women with hysterectomy was numerically lower in the NovoSeven group (3/42 women; 7.1%) compared to the reference group (8/42 women; 19.1%) with a relative reduction of 62.5% (p=0.1944).

Non-interventional studies

- The proportions of women at risk having an invasive procedure following first NovoSeven dose from study 4733 (PPH consortium) were similar to the proportions noted in the RCT, ranging between 41.7% to 55.0% across the 3 cohorts (DK 55%, NL 50%, and UK 41.7%).
- Proportions of women at risk having an invasive procedure following first NovoSeven dose were lower in the other 3 non interventional studies to the proportions noted in the RCT, varying between 20.5% to 29.7% (Bern 20.5%, UniSeven 23.3%, ANZHR 29.7%).
- A similar pattern was also observed for the subpopulation of women **without** any invasive procedure prior to NovoSeven administration (Table 18), except for this subpopulation in the DK cohort from study 4733 (PPH consortium), in which women 64% of women underwent an invasive procedure following first dose of NovoSeven.

Summary of separate study results of non-interventional studies:

Studies 4729 (Bern) and 4733 (PPH consortium)

- **Study 4729 (Bern)**

In study 4729 (Bern), 39/52 women treated with NovoSeven in the FAS were at risk of further invasive procedures after NovoSeven administration. Of these, 20.5% (8/39) had an invasive procedure after the concurrent period (post hoc summary).

For those women in the FAS without any invasive procedure prior to or concurrent with first NovoSeven administration, 16.7% (2/12) had an invasive procedure between 20 minutes to 24 hours after first NovoSeven administration.

- **Study 4733 (PPH consortium)**

In study 4733 (PPH consortium), 62/90 women treated with NovoSeven in the FAS across all 3 countries were at risk of further invasive procedures after NovoSeven administration. Of these, 50.0% (31/62) women had an invasive procedure after the concurrent period (post hoc summary).

For those women in the FAS without any invasive procedure prior to or concurrent with first NovoSeven administration, 64% (9/14 DK), 50% (11/22 NL), and 50% (5/10 UK) had an invasive procedure between 20 minutes to 24 hours after first NovoSeven administration.

Studies 4731 (UniSeven) and 4732 (ANZHR)

- **Study 4731 (UniSeven)**

In study 4731 (UniSeven), for those women in the FAS at risk of further invasive procedure, 23.3% (10/43) had an invasive procedure between 20 minutes to 24 hours after first NovoSeven administration.

For those women in the FAS without any invasive procedure prior to or concurrent with first NovoSeven administration, 27.8% (10/36) had an invasive procedure between 20 minutes to 24 hours after first NovoSeven administration.

- **4732 (ANZHR)**

In study 4732 (ANZHR), for those women in the FAS at risk of further invasive procedure, 29.7% (22/74) had an invasive procedure between 20 minutes to 24 hours after first NovoSeven administration (Figure 9).

For those women in the FAS without any invasive procedure prior to first NovoSeven administration, 35.0% (21/60) had an invasive procedure between 20 minutes to 24 hours after first NovoSeven administration.

Analysis of clinical information relevant to dosing recommendations

The MAH has presented a separate analysis of dose and dose frequency used and an overview of the dose recommendations for NovoSeven in the treatment of severe PPH used in all studies.

RCT single dose study

In the pivotal evidence, trial 4816 (RCT), a single target dose of 60 µg/kg NovoSeven was chosen. This rhuFVIIa dose was, according to literature data, the lowest dose with clinical effect in the setting of severe PPH and was chosen to reduce, as far as possible, the thrombotic risk associated with this drug. However, there was some variation around the target dose due to full vials being administered. The median NovoSeven dose administered in the RCT trial was 58 µg/kg, with 25 women receiving <60 µg/kg dose, 17 women receiving 60-90 µg/kg dose and none receiving >90 µg/kg (Table 20).

Non-interventional studies

In contrast, based on the FAS from the non-interventional studies, it was observed that physicians often administered higher NovoSeven doses, as indicated from median first dose of 63 µg/kg to 105 µg/kg. Furthermore, in some cases more than one dose was administered. Proportion of women who received ≥2 doses of NovoSeven was between 11.5% and 27.6% across the non-interventional studies. The majority

of the women in study 4729 (Bern) received a NovoSeven dose of 60-90 µg/kg (71.2%); whilst the other 2 non interventional studies, 4731 (UniSeven) and 4732 (ANZHR), had most patients in the >90 µg/kg dose interval (Table 20).

The non-interventional studies showed administration of higher doses of NovoSeven and some women were administered more than one dose. These dose intervals were selected based on the dosing recommendations found in various guidelines (see table 1). For studies 4729 (Bern), 4731 (UniSeven), and 4732 (ANZHR), data on clinical outcome of invasive procedures ('project endpoint') are provided here for the population at risk in the FAS (Table 20). Data from study 4733 (PPH consortium) are not presented as information on dose per kg body weight was not available; however, the median total dose of NovoSeven was 5 mg (corresponding to 71 µg/kg in a woman weighing 70 kg.

First dose

The proportion of women receiving a first dose of NovoSeven of <60 µg/kg, 60−90 µg/kg and >90 µg/kg varied across data sources. The 60−90 µg/kg dose range was administered to between 19.5% and 71.2% of women by trial/study.

Second and third dose (median)

In the non-interventional studies, median second and third doses in the FAS for those women who received more than one dose ranged from 73 µg/kg to 100 µg/kg across studies, and were therefore broadly similar to first dose in these studies (63 µg/kg to 105 µg/kg).

In the literature review, most women received a single dose of NovoSeven. Doses usually ranged between 50 and 100 µg/kg.

Table 20 Overview of NovoSeven dosing and exposure – FAS

		Pivotal evidence	Non-interventional studies		
		Trial 4816 (RCT)[a]	Study 4729 (Bern)	Study 4731 (UniSeven)	Study 4732 (ANZHR)
		FAS	FAS	FAS	FAS
Total no. of women receiving NovoSeven, N		42	52	87	166
Number of NovoSeven doses received, n (%)	1 dose	42 (100.0)	46 (88.5)	63 (72.4)	127 (76.5)
	2 doses	0	6 (11.5)	20 (23.0)	27 (16.3)
	3 doses	0	0	4 (4.6)	9 (5.4)
	> 3 doses	0	0	0	3 (1.8)
Dose size, n (%)	<60 µg/kg	25 (59.5)	14 (26.9)	5 (5.7)	20 (12.0)
	60-90 µg/kg	17 (40.5)	37 (71.2)	17 (19.5)	34 (20.5)
	>90 µg/kg	0	1 (1.9)	65 (74.7)	81 (48.8)
	Missing	0	0	0	31 (18.7)
Total dose, µg/kg	N	42	52	87	133
	Mean (SD)	57.1 (7.5)	71.0 (24.1)	138.1 (58.8)	111.0 (47.3)
	Median (IQR)	57.6 (52.9−60.8)	64.0 (60.8−73.7)	120.0 (100.0−175.0)	102.9 (88.6–120.0)
First dose, µg/kg	N	42	52	87	135

	Mean (SD)	57.1 (7.5)	62.7 (16.7)	107.0 (26.3)	90.4 (30.0)
	Median (IQR)	57.6 (52.9–60.8)	63.4 (56.4–72.7)	105.0 (90.0–120.0)	96.0 (73.9–109.1)
Second dose, µg/kg	N	NA	6	24	29
	Mean (SD)	NA	72.1 (14.4)	96.4 (30.1)	81.6 (30.4)
	Median (IQR)	NA	73.2 (65.8–84.7)	100.0 (90.0–120.0)	82.8 (62.2–97.3)
Third dose, µg/kg	N	NA	0	4	9
	Mean (SD)	NA	0	98.8 (13.2)	70.2 (25.3)
	Median (IQR)	NA	0	100.0 (87.5–110.0)	80.0 (44.4–96.0)

aThe NovoSeven dose was adapted to allow complete use of vials (1.2, 2.4 and 4.8 mg vials) and was based on the woman's maternal weight at term accounted with foetal-placental weight deducted.
Abbreviations: ANZHR = Australian and New Zealand Haemostasis Registry; IQR = interquartile range; n = number of observations; N = number of women; NA = not applicable; PPH = postpartum haemorrhage; RCT = randomised clinical trial; SD = standard deviation Cross-reference: Modified from Appendix 6.1, Table 1-3; Trial 4816 (M 5.3.5.1), Table 14.2.5; Study 4729 (M 5.3.5.2), Tables 10-5 and 14.2.90; Study 4731 (M 5.3.5.2), Tables 10-2 and 14.2.8; Study 4732 (M 5.3.5.2), Tables 10-4 and 14.2.73

In trial 4816 (RCT), on administration of target NovoSeven single dose of 60 µg/kg (median dose: 58 µg/kg), there was significant reduction in risk of invasive procedures ('project endpoint') after randomisation in the NovoSeven group compared to the reference group (relative reduction = 44.7%; p<0.0001).

For the non-interventional studies, data on invasive procedures ('project endpoint') for different dose intervals of the first NovoSeven dose, i.e., <60 µg/kg, 60 90 µg/kg, and >90 µg/kg are presented in Table 21. The groups cannot be directly compared due to lack of randomisation to different dose groups. It was observed that for women who received a first dose of 60-90 µg/kg, 0% to 33.3% received an invasive procedure after the first administration of NovoSeven, which was numerically lower than for the group of women that received a first dose of <60 µg/kg.

This is in line with the median first dose of NovoSeven administered across data sources (58 µg/kg to 105 µg/kg) and it would also be aligned with clinical practice of using entire vials; for example, for a 70 kg patient (approximate median weight of women across presented data sources), one 5 mg vial would correspond to 71 µg/kg.

Table 21 Project endpoint of occurrence of invasive procedure by dose of NovoSeven – non-interventional studies – population at risk

	Project endpoint, n/N (%)			
	<60 µg/kg	**60-90 µg/kg**	**>90 µg/kg**	**Total**
Non-interventional studies				
4729 (Bern)	3/7 (42.9)	4/31 (12.9)	1/1 (100.0)	8/39 (20.5)
4731 (UniSeven)	2/3 (66.7)	0/7 (0)	8/33 (24.2)	10/43 (23.3)
4732 (ANZHR)[a]	5/10 (50.0)	6/18 (33.3)	8/34 (23.5)	19/62 (30.6)

Note: Invasive procedures are defined as uterine or iliac arterial ligation, radiological arterial embolisation, uterine compression suture, and/or hysterectomy ('project endpoint'). Across the non-interventional studies, data are presented for the population at risk.
Study 4733 (PPH consortium) is not included in this table because dose was provided in mg as information on dose per kg body weight was not available.
a In study 4732 (ANZHR), dosing details were missing for 12 women at risk of further invasive procedure. Three of these 12 women had an invasive procedure within 20 minutes to 24 hours after first NovoSeven administration.
Abbreviations: ANZHR = Australian and New Zealand Haemostasis Registry; n = number of observations; N = Number of women.

Rationale for posology of NovoSeven in severe PPH

The recommended posology for NovoSeven for the currently approved indications (except for factor VII deficiency) is an initial dose of 90 µg/kg with further injections administered approximately every 2−3 hours, depending on indication, to secure haemostasis.

The proposed posology for NovoSeven in severe PPH is *an initial dose of 60–90 µg/kg body weight administered by intravenous bolus injection. Peak coagulant activity can be expected at 10 minutes. A second dose can be administered based on clinical response of the individual patient. It is recommended that in case of insufficient haemostatic response, a second dose can be administered after 30 minutes.*

Efficacy by first dose

In trial 4816 (RCT), where a single planned dose of approximately 60 µg/kg NovoSeven was administered, there was a significant reduction in risk of invasive procedures (project endpoint; post hoc analysis of the population at risk) in the NovoSeven group compared to the reference group (relative reduction = 44.7%; p<0.0001; Table 19).

For three non-interventional studies (Bern, UniSeven, ANZHR), data on the project endpoint are presented by dose interval for the population at risk in Table 21, see above. Between 0% and 33.3% of women in the 60−90 µg/kg dose interval received an invasive procedure.

TEs by dose

In the RCT and non-interventional studies, TEs were reported in 7 women treated with NovoSeven across the dose range. The doses of NovoSeven were 32, 55, 104 and 125 µg/kg for 4 women, 3.6 and 5 mg for 2 women (where bodyweight was unknown; assuming a bodyweight of 70 kg, these doses equate to 51 and 71 µg/kg) and not available for 1 woman. Six of the 7 women with TEs received a single dose of NovoSeven; number of doses was not available for 1 woman (dose was recorded as 3.6 mg).

There was no evidence of a pattern of association between dose size and TEs.

Dose range 60−90 µg/kg recommendation

The proposed dose range for NovoSeven in severe PPH is 60−90 µg/kg. This dose range is based on the doses used in the RCT and non-interventional studies and on treatment guidelines on use of NovoSeven in PPH, which generally recommend 60 µg/kg, 90 µg/kg, or 60−90 µg/kg (see PPH guidelines Table 2). Across the data sources in this submission, there was no evidence of a pattern of association between dose size and TEs in women with severe PPH. The proposed dose range is also aligned with the current off-label use of NovoSeven where physicians usually prescribe doses higher than that used in RCT trial 4816 (60 µg/kg). The proposed dose range of 60−90 µg/kg provides flexibility for physicians to adjust the dose according to individual patient need and is consistent with the clinical practice of using entire vials which leads to some variation in the µg/kg dose.

Timing of NovoSeven relative to other interventions

Evidence from already approved indications in various clinical settings indicates that NovoSeven should be given as early as possible after the start of a bleeding episode (SmPC NovoSeven). The same principle applies in severe PPH, where women with massive ongoing haemorrhage and associated complications (such as dilutional coagulopathy) benefit from early intervention. For women with severe PPH, the key goal of treatment is to stop bleeding as soon as possible to limit the risk to life and reduce the need for hysterectomy, which can be life-changing.

Trial 4816 (RCT) demonstrated that administration of NovoSeven early in the treatment cascade (after failure of uterotonics and before any invasive procedure) was effective in reducing the risk of invasive procedures and in reducing duration of bleeding.

In the non-interventional studies, NovoSeven was used at the treating physician's discretion and was used at different timepoints in the treatment cascade (before, during or after invasive procedure). NovoSeven was generally used later in the course of PPH in the non-interventional studies than in the RCT. In the non-interventional studies, median time from start of severe PPH to NovoSeven administration was between 127.5 and 291.0 minutes (Table 17), whereas in the RCT, NovoSeven was administered within 60 minutes after start of PPH.

Together, the RCT and non-interventional studies showed that there were no safety concerns with either early or later use of NovoSeven.

Although the non-interventional studies (with their inherent limitations) did not show a reduction in the occurrence of invasive procedures when NovoSeven was used later in the course of PPH, the MAH believes that, given the lack of safety concerns, timing of NovoSeven should not be limited to early in the treatment cascade and should be at the discretion of the treating physician.

Rationale for repeat dosing

The course of severe PPH varies considerably from patient to patient and, while a single dose of NovoSeven may be sufficient for most patients, it may be necessary to repeat the dose to gain control of bleeding for some patients. Most of the PPH treatment guidelines that offer advice on the use of NovoSeven recommend 1 to 2 doses, with one set of guidelines (Bern 2018) recommending up to 3 doses.

In the non-interventional studies, most women received a single dose of NovoSeven. Repeat dosing of NovoSeven was observed in the non-interventional studies for between 11.5% and 27.6% of women across the studies. A small proportion of women in study 4731 (4/87 women; 4.6%) and study 4732 (12/166 women; 7.2%) received 3 or more doses (Table 20).

Based on this information, it is proposed that a second dose of NovoSeven can be administered if control of bleeding is not achieved with the first dose.

Timing of repeat dosing

The proposed label will recommend that a second dose can be given after 30 minutes if bleeding has not been controlled by the first dose. This increases the effect of NovoSeven in the short term. The proposed 30-minute interval allows time for clinical assessment of the haemostatic effect of the first dose. Dose interval should be based on clinical response and adapted to the individual patient.

2.3.3. Discussion on clinical efficacy

The main efficacy data for this type II application to extend the indication with treatment of severe PPH consisted of pivotal data are provided from 1 French open-label RCT (trial 4816) sponsored by Nîmes University Hospital and conducted in 2 countries (France: 7 University hospital sites, Switzerland: 1 site) the trial is published in 2015 https://onlinelibrary.wiley.com/doi/10.1111/jth.12844

The pivotal data is supported with observational evidence from 4 non-interventional studies based from a single hospital centre in Bern (study 4729), national-level data from 3 countries (PPH consortium study 4733) and data from 2 registries covering 3 countries describing off-label use of NovoSeven, including treatment of PPH (studies 4731 and 4732).

Support for the recommended dose regimen in this new indication was collected from the RCT trial and supportive data from non-interventional studies.

For trial 4816 (RCT), study 4729 (Bern) and study 4731 (UniSeven), the MAH had access to anonymised/pseudonymised patient-level data and performed descriptive and statistical analyses of the

data as relevant. For study 4733 (PPH consortium) and study 4732 (ANZHR), descriptive and statistical analyses were performed by academic institutions (Department of Clinical Epidemiology, Leiden University Medical Center and Department of Epidemiology and Preventive Medicine, Monash University, respectively) based on patient-level data. These academic institutions then provided population-level data to the MAH for reporting purposes. Based on these patient-level data, an analysis was made of a common primary endpoint, i.e. project endpoint.

Design and conduct of clinical studies

Pivotal evidence

Pivotal RCT 4816

Of note, in the publication of this RCT, an extended primary objective and primary endpoint were selected, i.e. the number of specific second-line therapies is increased with at least one ligation, suture, embolisation, intra-uterine balloon tamponade and/or hysterectomy. Although, the CSR is the leading document, in this case, the CHMP considered that the data of the publication provide additional supportive information, and therefore the results as described in the publication are taken into account. It should be noted that while the protocol primary endpoint was predefined, the publication primary endpoint was defined post hoc, and therefore should be viewed as exploratory.

Study design

This was a multicentre, randomised, open-label, parallel-group trial with a randomisation ratio of 1:1. A total of 84 women with severe PPH receiving standard of care were randomised to treatment with NovoSeven or to no concurrent treatment (reference), following failure of sulprostone to control the bleeding. The rationale of the investigators that the emergency conditions of obstetrical haemorrhage onsets did not allow for a double-blind design are agreed. Both groups received standard of care treatment in accordance with the treatment guidelines in place at the time of the trial, which is considered acceptable.

Of note, NovoSeven was administrated in addition to standard of care not as a replacement for any part of the conventional standard of care for severe PPH.

The 60 µg/kg NovoSeven selected dose in the RCT in the treatment of severe PPH was not based on a formal dose response study, but was, according to literature data, the lowest dose with clinical effect in the setting of severe PPH and was chosen to reduce, as far as possible, the thrombotic risk associated with this drug. This is considered acceptable for this setting.

Standard of care was given according to French practice guidelines of which first-line therapies for PPH included: fluid resuscitation, bladder catheterization, manual removal of retained placenta, genital tract examination, uterine exploration, oxytocin (20–30 IU every 10–30 min) and finally one sulprostone infusion (500 µg within 1 h).

The following replacement therapies were allowed in the study:

- Packed red blood cells (PRBCs) were indicated if patient's Hb concentration was <8 g/dL.
- Platelet concentrates (PC) were administered when the platelet count was lower than 50 x 10^9/L.
- Fibrinogen concentrates were administered if the plasma fibrinogen concentration was <1 g/L.
- Use of tranexamic acid (TXA) (0.5–1 g intravenously) was left to the attending physician's discretion.
- Vascular volume expansion was achieved using 500 mL of crystalloid and 500 mL of colloid expander for the first litre of blood loss, and thereafter an infusion, mostly of gelatine, was administered to compensate for the subsequent blood loss (vol/vol).
- Fresh frozen plasma (FFP) was infused by the attending anaesthetist, if clinically indicated.

Based on the description of first line therapies, replacement therapies and second line invasive therapies applied, the management of severe PPH in this study in general is in agreement with current guidelines on PPH.

Study participants

The enrolment criterion was sulprostone failure 1 h after the infusion onset (or before the end of this period). Key inclusion criteria were women who delivered their babies after the end of the 27th week of amenorrhoea with severe primary PPH defined as more than 1500 mL blood loss within 24 h after birth; key exclusion criterion was a history of thromboembolic events. The follow-up period after delivery was 5 days.

Efficacy endpoints (protocol and publication endpoint)

The primary efficacy endpoint of the RCT study protocol and the primary endpoint applied in the publication varied in the selection of invasive procedures. Both selected the absolute and relative reduction in need of specific second-line invasive therapies, but the protocol endpoint was more restrictive with including only a reduction in the rate of embolisation and/or ligation, while in the publication a reduction in the need all relevant invasive procedures were taken into account ((at least one ligation, suture, embolisation, intra-uterine balloon tamponade and/or hysterectomy). The publication endpoint is considered supportive for the protocol-defined endpoint and has added value from a clinical point of view.

The RCT protocol did not select secondary endpoints, while in the publication secondary endpoints included the number (percentage) of patients in each arm who received PRBCs, FFP units or PC; all replacement treatments (infusion of colloids/crystalloids, transfusions of blood components, and additional procoagulant treatments such as TXA, fibrinogen concentrates and aprotinin), and biological measures were collected before delivery and within the first 12 h after PPH. While not pre-specified, these are considered of additional value as these reflect the background conditions of the patients treated in both arms. The secondary endpoints were:

- Time point of evaluation of treatment success: Bleeding was considered to have stopped (i.e., treatment success) if the estimated blood flow decreased to less than 50 mL per 10 min within the 30 min following randomization.
- Initiation invasive second line treatment was started at any time and in both arms, invasive second-line treatments were considered if bleeding was uncontrolled (blood flow higher than 50 mL per 10 min) or intractable (defined as PPH > 2500 mL, or blood flow > 500 mL per 30 min, or haemorrhagic shock refractory to standard care).

Assumptions for the sample size calculation were based on public literature indicating that in the reference group the expected rate of embolization or surgical procedure, such as vascular ligature, is approximately 70% (Lédée et al, 2001, Mignon et al, 2004; Aledort et al, 2004; Tourné G et al, 2003). The investigators focused on a 30% absolute decrease in the embolization or vascular ligature rate based on their limited inclusion capacities, i.e. a 40% rate when rFVIIa is administered early after the conventional medical treatment. In order to show a statistically significant difference with a 5% bilateral risk and an 80% power, 42 patients were required in each group. The assumed treatment effect of 30% is considered acceptable, as well as the sample size calculation.

The statistical methods contained only a general description in the protocol and no statistical analysis plan. There is no multiplicity adjustment and therefore no type I error control for secondary analyses.

As acknowledged by the MAH, there was no separate statistical analysis plan (SAP) prepared by the trial sponsor (Nîmes Univeristy Hospital). In the absence of any further statistical documentation, the protocol is the only source of analysis specification. As a consequence, any analysis that was not described in the original protocol should be considered post-hoc and viewed as exploratory. This would for example apply to the publication primary endpoint, or the project endpoint.

Nevertheless, study design is relatively simple and analysis straightforward. The analysis sets and the statistical analysis of the endpoints of the study protocol, using Chi-square statistics, and publication, using Mantel-Haenszel, are considered standard and acceptable.

Of note, pivotal study 4816 was conducted during the period of 2007-2010, main results were published in 2015, and the data cut-off date for this application was on 14 April 2021.

Efficacy data and additional analyses

Patient flow

As planned, a total of 84 women with severe PPH were included in this trial; 42 patients were randomised to the NovoSeven group and 42 patients to the reference group. All women were considered to have completed the trial, that is, completed treatment for PPH.

Sixty patients were included 1 h after sulprostone infusion. Among the 24 remaining patients, the median randomization time (lower quartile–upper quartile) was 40 min (30–45 min) for the intervention arm and 30 min (30–30 min) for the standard care arm (P = 0.93). These results indicate that it is manageable to provide this treatment within a certain time frame despite the serious circumstances of this possibly life threatening condition. Two important protocol deviations were identified from the available monitoring reports. One woman in the reference group did not meet the inclusion criteria (she had already responded to sulprostone), and one woman in the NovoSeven group had ligation performed prior to NovoSeven injection, which was not noted by the investigators. In addition, one woman was randomised to the reference group, but received NovoSeven due to an error in reading the randomisation envelope. In the post-hoc analysis of the MAH, the patient with a ligation prior to NovoSeven administration has been taken into account.

Demographics and disease characteristics

Generally, the recruited patients reflect a hospital population of women with severe PPH regarding demographics, and patient characteristics, and causes of severe PPH, with the majority due to atony, are well distributed across the two treatment groups. There is a comparable distribution of patients who had vaginal delivery and caesarean section, with no relevant differences between groups in delivery mode.

There were only minor imbalances between the randomised groups for some baseline characteristics (age, multiple causes of PPH, fibrinogen level, RBC transfusions).

Primary efficacy analyses

In the protocol primary efficacy analysis of at least one embolization and/or ligation, fewer patients (50%, n=21/42) in the NovoSeven group had at least one embolisation and/or ligation procedure, compared to patients in the standard care group (83%, n=35/42), RR = 0.60 (0.43;0.84), corresponding with a statistically significant 40% relative reduction in risk compared to the reference group; p=0.0012). The mean number of patients who needed to be treated with NovoSeven (number needed to treat, NNT) to avoid one ligation or embolization was 3.

In the publication primary efficacy analysis of the post-hoc, composite endpoint of ligation, suture, embolization, balloon and/or hysterectomy, fewer patients (52%, n=22/42)) in the NovoSeven group

required an invasive procedure compared to patients in the standard care group (93%, n= 39/42, RR = 0.56; 95% CI, 0.42–0.76), corresponding with a 44% relative reduction in risk compared to the reference group; nominal p<0.001). The mean number of patients who needed to be treated with NovoSeven (number needed to treat, NNT) to avoid one composite endpoint was 2.6. In both analysis, this effect was independent from the delivery mode (vaginal delivery or caesarian section).

Based on the results of both analyses, a significant and clinically relevant beneficial effect has been shown that with early infusion of one single rhuFVIIa dose after sulprostone failure the need for specific second-line interventions can be reduced from 93% (in the standard of care arm) to 52% (absolute difference of 41%). This was further supported by the low number of NNT to avoid at least one second-line therapy of 2.6 and 3. Further, this positive effect was independent from the delivery mode (caesarian section or vaginal delivery).

In the reference group, the rate of embolization or surgical procedure in Study 4816 was 83% and 93% according to protocol and project primary endpoint respectively, which were higher than that initially expected: 70% derived from literature (Lédée et al, 2001, Mignon et al, 2004; Aledort et al, 2004; Tourné G et al, 2003) (cf sample size calculation).

Supportive evidence from non-interventional studies

Data from four non-interventional studies were collected from information of routine clinical practice to provide supportive data to the pivotal evidence, trial 4816 (RCT). In these non-interventional studies, use of NovoSeven was more varied than its early use, after failure of sulprostone, in study 4816 (RCT), with physicians choosing to administer NovoSeven at different timepoints in the treatment cascade of PPH, both in women who already had an invasive procedure and those without any previous invasive procedure. Two non-interventional studies, study 4729 (Bern) and study 4733 (PPH consortium), included both women treated with NovoSeven and women not treated with NovoSeven; whilst the other two non-interventional studies (registries), i.e. study 4731(UniSeven) and study 4732 (ANZHR), only included women treated with NovoSeven. The efficacy results of these studies are discussed below.

Due to substantial differences in terms of inclusion criteria, dose, timing of NovoSeven administration, severity of PPH, standard of care associated, data collection methods, etc., all these non-interventional studies are considered exploratory in nature when comparing and interpreting the results.

Study 4729 (Bern) the study design was a single-centre, non-interventional retrospective cohort study of women with severe PPH who were treated with NovoSeven or other standard of care at the department of obstetrics and gynaecology of the University Hospital of Bern, Switzerland during the period of January 2006 to April 2016. Data for the current study included women with severe PPH from 4 cohorts (2 historical cohorts, 1 prospective study cohort and a new cohort), through review of medical patient chart and electronical medical records. Inclusion criterion was severe PPH defined as continuous bleeding of at least 1500 mL within 24 hours after delivery, while exclusion criteria were none. Duration of follow-up: from time of diagnosis of severe PPH (including baseline data) until end of hospitalisation. The recommended dose in the 2 historical cohorts was 60 µg/kg or at discretion of the physician, while the more recent cohorts followed hospital guidance, 60 µg/kg and 90 µg/kg.

The primary objective was to compare, in a propensity score matched population of women with severe PPH, the occurrence of any invasive procedure after first treatment with NovoSeven with the occurrence of any invasive procedure without treatment with NovoSeven evaluated within a timeframe of 20 minutes to 24 hours following first administration of NovoSeven. Invasive procedures are defined as: uterine or iliac artery ligation, radiological arterial embolisation, uterine compression sutures, or hysterectomy. The primary efficacy endpoint was defined as the "*occurrence of any invasive procedure in the period from 20 minutes to 24 hours following time0* (was defined as time of first administration of NovoSeven) *among women who were at risk of further invasive procedures*". For matched controls: time0 was derived from

the matching process and was equal to the period from onset of severe PPH to time of first administration of NovoSeven for the patient for whom she was a matched control).

Statistical methods NovoSeven exposed women were compared to their matched controls by the method of propensity score (PS) matching. The purpose of propensity score matching was to counteract the natural imbalance (confounding by indication) present between women exposed and not exposed to NovoSeven in the FAS from these real world data sources. A PS score was estimated for each woman by a Cox proportional hazard regression model with NovoSeven as the dependent variable. In general, using PS matching is an acceptable approach in the analysis of 2 observational datasets. Women were matched within delivery mode, and variables included in the final model were cumulative RBC, cumulative blood loss, cumulative number of invasive procedures including balloon, cumulative FFP and cumulative crystalloids and colloids. The matching on delivery mode, and selection of variables are considered adequate. However, the proposed estimand and study populationis not completely endorsed. Matched control patients can receive NovoSeven after their matching date and although this would lead to a bias towards the null and can be considered conservative, it is unclear whether it gives a realistic view on the effect of NovoSeven. Furthermore, matched control patients could be re-used as case patients as well, if they indeed received NovoSeven at a later timepoint.

Results: A total of 165 women were included in the Bern University hospital database of which 52 women received NovoSeven and 113 women did not receive NovoSeven. Of these, 18 NovoSeven exposed women were compared to 43 matched controls by the method of PS matching. Participants in PS set in both the groups were broadly similar with regard to different patient characteristics, though some differences were noted with regard to proportions of women with singleton and women with uterine atony as primary cause of PPH. The median first dose was 63 µg/kg, the median second dose was 73 µg/kg.

Outcome primary analysis: In the PS analysis set, among women who were at risk of further invasive procedures, 16.7% (3/18) of NovoSeven exposed women had an invasive procedure in the period from 20 minutes to 24 hours following time0 compared to 31.5% (5.6/17.8) of matched controls, with an odds ratio of 0.33 (95% CI: 0.03, 1.75) numerically favouring NovoSeven, but this difference was not statistically significant (p=0.2691). Further, the applied method for collection of matched control patients was prone to bias and matched controls could be re-used as case patients. Thus the data in the analysis is not always independent. This hampers the interpretation of results and the study can therefore only be regarded as supportive at most.

Study 4733 (PPH consortium) the study design was a retrospective non-interventional cohort study of women with severe PPH who were treated with NovoSeven or other standard of care. The study utilised retrospective data that were collected for other purposes from three previously established cohorts in DK, NL and UK. From these cohorts women with severe PPH were selected. Inclusion criteria for severe PPH were ≥10 or more units of RBC within 24 hours after birth (DK), ≥4 units of RBC, multicomponent blood transfusion (RBC and fresh frozen plasma and/or platelet concentrates), plasma in addition to RBCs (NL), women who had a birth received ≥8 units of RBC transfused within 24 hours (UK). Exclusion criteria were none. The NovoSeven dose used in these patients with severe PPH was at the discretion of the physician and as per the local clinical practice. Duration of follow-up was up to 6 months from delivery for the DK cohort, from delivery up to discharge or death for the UK cohorts and from delivery to end of bleeding for the NL cohort. Data analyses were performed at the Department of Clinical Epidemiology of the Leiden University Medical Center. This study protocol and analysis plan were developed by Novo Nordisk. The primary efficacy endpoint selected and applied statistical analysis based on PS matching were similar to study 4729 (Bern), see above. These were collected from the DK and NL cohorts, PS matching could not be done for the UK cohort due to lack of time varying data. Similar to study 4729 (Bern), matched controls were allowed to receive NovoSeven after the matching date, and these same patients could be re-used as case patients in the analysis. Thus the data in the analysis is not always independent. This hampers the interpretation of results.

Results Based on final PS model, 40 NovoSeven exposed women were matched to 115 controls (matched controls) and were included in the PS analysis set for the DK plus NL cohort. Participants in PS set in both the groups were broadly similar with regard to different patient characteristics. Dose: Median NovoSeven first dose was slightly higher in NL (6 mg) than in DK (5 mg).

Outcome primary analysis: Among women who were at risk of further invasive procedures, 57.9% (22/38) of NovoSeven exposed women had an invasive procedure in the period from 20 minutes to 24 hours following time0 compared to 35.1% (13.3/38) of matched controls, with an odds ratio of 2.46 (95% CI: 1.06, 5.99; p=0.0355) favouring matched controls. The results of this PS analysis did not favour NovoSeven, further, the applied method for collection of matched control patients was prone to bias and matched controls could be re-used as case patients. Thus the data in the analysis is not always independent. This hampers the interpretation of results.

Study 4731 (UniSeven) Study design: retrospective cohort study describing the off-label use of NovoSeven and clinical outcomes in Czech women with severe PPH. The study utilised data from the UniSeven registry, which captured off-label use of NovoSeven non-haemophiliac patients for multiple conditions during the period July 2003 to April 2014. Inclusion criterion: Czech women treated with NovoSeven due to severe PPH, defined as ≥1,500 mL blood loss within the period of 24h after delivery, registered in UniSeven; exclusion criteria were none. The NovoSeven dose was at the discretion of the treating physician. The post-hoc defined, alternative primary efficacy endpoint was similar to those used in both comparative cohort studies 4729 (Bern) and 4733 (PPH consortium). Statistical methods: Evaluation of data was based upon descriptive statistics.

Results A total of the 993 Czech patients were registered with UniSeven registry during July 2003 to April 2014. Of these, 87 fulfilled the inclusion criteria of having ≥1,500 mL blood loss within 24 hours prior to first dose of NovoSeven administration and were included in the FAS. Of these women, 44 women were excluded from the primary endpoint analysis due to a hysterectomy performed before or concurrent with NovoSeven administration. Thus, the population at risk of further invasive procedures included 43 women. The population for primary analysis included women who did not have any invasive procedure before or concurrent with NovoSeven administration comprised of 36 women. Dose: not specified for the population selected for the primary efficacy analysis. Outcome of the post-hoc defined, alternative, primary analysis: Of the 36 women selected, 27.8% (10/36) had and 72.2% (26/36) did not have an invasive procedure within 20 minutes to 24 hours after first NovoSeven administration. However, results are not interpretable in the absence of an adequate control and no information on dose in relation to efficacy is available, except that it fell within the range of 50-200 µg/kg as recorded for the FAS.

Study 4732 (ANZHR) Study design: retrospective cohort study describing the clinical use of NovoSeven and clinical outcomes in women with an event of sPPH treated with NovoSeven utilising data collected from the Australian and New Zealand Haemostasis Registry *(*ANZHR). The ANZHR recorded data on various off-label uses of NovoSeven in non-haemophilic patients at participating hospitals throughout Australia and New Zealand, including its use in obstetric haemorrhage during the period 2000-2009. Inclusion criterion: treated with NovoSeven due to severe PPH defined as an obstetric case with a registration of a delivery in ANZHR, exclusion criteria included a delivery at <24 weeks of gestational age. The NovoSeven dose was according to local routine clinical practice at the discretion of the treating physician. The study protocol and analysis plan were co-developed by Monash University and Novo Nordisk. The primary efficacy endpoint was similar to the original primary endpoint selected in the study 4731 (UniSeven), see above. Statistical methods: Evaluation of data was based upon descriptive statistics.

Results: Of the 166 women included in the FAS, 92 women were excluded from the primary endpoint analysis due to a hysterectomy performed before or concurrent with NovoSeven administration (n=54) or a missing timing of an invasive procedure (n=38). Thus, the population at risk of further invasive

procedures included 74 women, for whom 60 women did not have any invasive procedure before first NovoSeven administration and were included in the primary analysis. Dose: not specified for the population selected for the primary efficacy analysis. Outcome primary analysis: Of the 60 women selected, 65.0% (39/60) did not have an invasive procedure within 20 minutes to 24 hours after first NovoSeven administration. However, results are not interpretable in the absence of an adequate control and no information on dose in relation to efficacy is available, except that fell within the (interquartile) range (IQR): 74 - 109 µg/kg.

Based on the efficacy data provided by the 4 non-interventional studies that utilised retrospective data from different cohorts in Europe and Australia/New Zealand the following is concluded:

- The results of the PS analyses failed suggest an effect in favour of NovoSeven with regard to reduction in invasive procedures, but the applied method for collection of matched control patients was prone to bias and further matched control patients could be re-used as case patients. This hampers the interpretation of results. Therefore, these studies can therefore only be regarded as supportive at most.
- For the retrospective cohort studies, the results of the analyses utilising data collected from registries in the Czech Republic (NovoSeven) and Australian and New Zealand Haemostasis Registry *(*ANZHR) are not interpretable in the absence of an adequate control. Also, no adequate information on the dose is available.

Supportive evidence from analyses performed across trials

Post-hoc analysis of a common primary efficacy endpoint (project endpoint) in RCT and non-epidemiological studies

Project endpoint

To support the regulatory submission for this new indication, the MAH defined a common '**project endpoint'**, in accordance with SA from NL and FR and external experts, to evaluate efficacy of NovoSeven across the RCT and non-interventional studies. The 'project endpoint' was defined as follows: *"occurrence of any invasive procedure after first treatment with NovoSeven", where invasive procedure was defined as uterine or iliac artery ligation, radiological arterial embolisation, uterine compression sutures, and/or hysterectomy"*. To be evaluated within a timeframe of 20 minutes to 24 hours following first administration of NovoSeven.

The project endpoint differs from the protocol primary efficacy endpoint and the publication endpoint of the RCT, as in these analyses, only women without previous invasive procedures were included, i.e. following failure of sulprostone to control the bleeding. The project endpoint includes also women who could have had a previous invasive procedure prior to NovoSeven administration. However, subgroup analyses were also presented for those women with no invasive procedure prior to the NovoSeven administration, i.e. the primary endpoint applied in the publication of the RCT. This approach to define a common endpoint across all available data to further support the RCT with data from the 4 non-interventional studies that contain additional information on the current off-label use of NovoSeven in severe PPH is accepted. However, as is also indicated by the MAH, such approach has its limitations as there are distinct differences across the RCT and observational data, including the eligibility criteria, dose of NovoSeven applied, number of doses, and timing of NovoSeven administration in the treatment cascade. The project point analyses were either prespecified in the SAP (UniSeven, ANZHR) or were conducted post hoc (RCT, study 4729 Bern, study PPH consortium). Data sources For trial 4816 (RCT), study 4729 (Bern) and study 4731 (UniSeven), the MAH had access to anonymised/pseudonymised patient-level data and performed descriptive and statistical analyses. For study 4733 (PPH consortium) and study 4732 (ANZHR), analyses were performed by academic institutions (Department of Clinical Epidemiology, Leiden University Medical Center and Department of Epidemiology and Preventive

Medicine, Monash University, respectively) based on patient-level data. These academic institutions then provided population-level data to Novo Nordisk for reporting purposes. Patient disposition The analyses of the project endpoint were conducted on all exposed women with severe PPH in the FAS who were at risk of further invasive procedures after NovoSeven administration. Additionally, analyses of the project endpoint were conducted for the subpopulation of women without any invasive procedure before first NovoSeven administration (endpoint of the publication of the RCT).

Statistical methods: For the ***RCT***, the 'project endpoint' was analysed post hoc at any time point after randomisation until stop of PPH. Analysis for occurrence of hysterectomy was also added. The occurrence of invasive procedures and hysterectomy was compared between the NovoSeven and reference group by relative risk, risk difference, and relative reduction, with 95% CI. For the ***non-interventional studies***, the project endpoint based on the FAS was analysed as per SAP in the two registries, and as a post hoc analysis for study 4729 (Bern) and study 4733 (PPH consortium) to have a subgroup aligned with the data from studies 4731 (UniSeven) and 4732 (ANZHR). Across the non-interventional studies, the clinical outcomes of invasive procedures ('project endpoint') were evaluated within a timeframe of 20 minutes to 24 hours following first administration of NovoSeven. A lag-time of 20 minutes following NovoSeven administration was implemented based on inputs from external experts. The rationale for this decision is that it would take 10 minutes for NovoSeven to reach peak coagulation ability, to disregard any case where the decision for both invasive procedure and NovoSeven was taken concurrently, with the execution being short time interval apart and for cases where the decision to perform an invasive procedure was taken simultaneously with administration of NovoSeven, NovoSeven would not have had sufficient time to be effective. Further, to reflect the decision relating to this 20 minute lag, a concurrent period was defined across the non-interventional studies, corresponding to the period between 20 minutes before and 20 minutes after NovoSeven administration (for studies 4731 (UniSeven) and 4732 (ANZHR)) or time0 (= time of 1st NovoSeven administration for studies 4729 (Bern) and 4733 (PPH consortium). Based on the presented argumentation, the selected time frame can be considered acceptable.

Results: Overall, in the FAS across these clinical data sources (4816, 4729, 4733, 4731 and 4732), a total of 437 women were included in the NovoSeven group and 1726 women were included in the no NovoSeven group. In the RCT, 9 women in the reference group also received NovoSeven (8 women on a compassionate use basis and 1 woman in error).

- In study 4733 (PPH consortium), the proportions of women in the population at risk of further invasive procedure in whom an invasive procedure between 20 minutes to 24 hour after first NovoSeven dose could not be prevented were similar to the proportions noted in the RCT, ranging between 41.7% to 55.0% across the 3 cohorts (DK 55%, NL 50%, and UK 41.7%).
- In the three other non-interventional studies, the proportions in the population of women at risk of further invasive procedures in whom an invasive procedure between 20 minutes to 24 hour after first NovoSeven dose could not be prevented were lower to the proportions noted in the RCT, varying between 20.5% to 29.7% (Bern 20.5%, UniSeven 23.3%, ANZHR 29.7%).

A similar pattern was also observed for the subpopulation of women without any invasive procedure prior to NovoSeven administration, except for this subpopulation in the DK cohort (64%) from study 4733 (PPH consortium):

- In study 4733 (PPH consortium) the proportions in the subpopulation of women without any invasive procedure prior to NovoSeven in whom an invasive procedure between 20 minutes to 24 hour after first NovoSeven dose could not be prevented were 50% in the NL, and 50% in the UK 50% and comparable to the percentage in the RCT, while in the DK cohort (64%) the percentage was higher.

- In the three other cohorts the proportions in the subpopulation of women without any invasive procedure prior to NovoSeven in whom an invasive procedure between 20 minutes to 24 hour after first NovoSeven dose could not be prevented were lower than observed in the RCT, 16.7% (Bern 16.7%, UniSeven 27.8% (UniSeven) and ANZHR 35.0%.

Based on above, it can be concluded that, as expected, the outcome of analysis of the pivotal data of the RCT based on the project point is comparable with the results of the per-protocol (and publication) primary efficacy analysis in the RCT. In the non-interventional studies, the analyses based on the project endpoint were generally supportive of the results observed in the RCT. However, the general comments made with regard to the presented efficacy data from the non-interventional studies also apply to the additional analysis of a common project endpoint based on the FAS populations, i.e. these are considered of limited value to further support efficacy of NovoSeven in severe PPH.

Dose selection and dose interval

The posology for NovoSeven for currently approved indications (except for factor VII deficiency) is an initial dose of 90 µg/kg with further injections administered approximately every 2−3 hours, depending on indication, to secure haemostasis.

The proposed posology for the treatment of severe post-partum bleeding *is 60 – 90 µg kg body weight administered by intravenous bolus injection. Peak coagulant activity can be expected at 10 minutes. A second dose can be administered based on clinical response of the individual patient. It is recommended that in case of insufficient haemostatic response, a second dose can be administered after 30 minutes..*

The proposed dose range is based on the doses used in the RCT and non-interventional studies and on current treatment guidelines on use of NovoSeven in PPH, which generally recommend 60 µg/kg, 90 µg/kg, or 60−90 µg/kg. Across the data sources in this submission, there was no suggestion of a dose-related pattern of risk of TEs in women with severe PPH, which is agreed, though the low number of cases and large variation in dose do not allow definite conclusions (see safety section). In the pivotal evidence, trial 4816 (RCT), a single target dose of 60 µg/kg NovoSeven was chosen. This rhuFVIIa dose was, according to literature data, the lowest dose with clinical effect in the setting of severe PPH and was chosen to reduce, as far as possible, the thrombotic risk associated with this drug. There was some variation around the target dose due to full vials being administered. The median NovoSeven dose administered in the RCT trial was 58 µg/kg, with 25 women receiving <60 µg/kg dose, 17 women receiving 60-90 µg/kg dose. In the RCT, the use of this dose range demonstrated a statistical and clinically relevant reduction in the need of second line interventions. Therefore, the proposed dose range of 60−90 µg/kg is acceptable. In addition, it provides flexibility for physicians to adjust the dose according to individual patient need and is consistent with the clinical practice of using entire vials which leads to some variation in the µg/kg dose.

Use of NovoSeven in relation to other interventions: The RCT demonstrated that administration of NovoSeven within 60 minutes after start of PPH after failure of uterotonics and before any invasive procedure, was effective in reducing the risk of invasive procedures. In the non-interventional studies, NovoSeven was generally used later in the course of PPH, i.e. before, during or after invasive procedure, with median time from start of severe PPH to NovoSeven administration between 127.5 and 291.0 minutes. During the evaluation, it was agreed to revise the proposed indication to be in line with the population as studied in the RCT: "NovoSeven is indicated for the treatment of severe postpartum haemorrhage when uterotonics are insufficient to achieve haemostasis".

Repeat dosing Most of the PPH treatment guidelines that offer advice on the use of NovoSeven recommend 1 to 2 doses, with one set of guidelines (Bern 2018) recommending up to 3 doses. The RCT was a single dose study. In the non-interventional studies, most women received a single dose of NovoSeven, while repeat dosing of NovoSeven varied between 11.5%-27.6% of women, and in study

4731 4.6% and study 4732 7.2% received 3 or more doses. Based on this information, it is proposed that a second dose of NovoSeven can be administered if control of bleeding is not achieved with the first dose.

Timing of repeat dosing The proposed label recommends that a second dose can be given after 30 minutes if bleeding has not been controlled by the first dose. This increases the effect of NovoSeven in the short term. The proposed 30-minute interval allows time for clinical assessment of the haemostatic effect of the first dose. The evidence of non-interventional studies suggest that dose interval varies widely. Data from studies 4731 (UniSeven) and 4732 (ANZHR) suggest that a longer dosing interval is more common than a short dosing interval. In study 4729 (Bern), median interval between first and second dose was shorter, at 40 minutes. PPH treatment guidelines that offer advice on repeat dosing of NovoSeven indicate a second dose could be administered 15−30 minutes after the first dose (table 2). The rationale for a second dose in case of insufficient response can be accepted. The selected 30 minute dose-interval is considered adequately supported by the available pharmacodynamic data of NovoSeven indicating time to maximum coagulant effect at 10 minutes after dosing, PPH guidelines recommending a second dose 15-30 minutes after the first dose of NovoSeven[3,4] as well as the RCT where clinical response (evaluation of treatment effect) was evaluated within 30 minutes of NovoSeven administration.

Considering the different dose recommendations proposed for this indication, i.e. a different dose interval of 30 minutes in case of insufficient response, this information is reflected in section 4.2 and section 5.1 of the SmPC.
Finally, a recommendation is also made in section 4.2 of the SmPC that it is recommended that in case of insufficient haemostatic response, a second dose can be administered after 30 minutes.

2.3.4. Conclusions on the clinical efficacy

Based on the pivotal evidence of the RCT in patients with severe PPH, a significant and clinically relevant 40% reduction in need of invasive procedures (ligation or embolisation) was noted on top of standard therapy. This is supported by the results for the publication endpoint with a 43% reduction in need of invasive procedures extended (at least one ligation, suture, embolisation, intra-uterine balloon tamponade and/or hysterectomy). The applied standard of care management is generally in line with the recommendations present in most recent guidelines (RCOG 2017).The support for efficacy of Novoseven in severe PPH from the 4 non-interventional studies of different sources across Europe and from Australia/New Zealand, is very limited.

Efficacy of haemostatic products such as NovoSeven will be limited when fibrinogen levels or platelet count are low. Maintenance of adequate fibrinogen concentration and platelet count is recommended in order to optimise the benefit of NovoSeven treatment (see SmPC section 4.2).

In conclusion, it can be considered sufficiently substantiated that NovoSeven when used early in the treatment cascade of PPH could relevantly reduce the risk of an invasive procedure in a target population as studied in the RCT. The revised indication reflects the target population as studied in the RCT, i.e. after failure of uterotonics and before start of invasive treatment. The selected dose-interval of 30 minutes for a second dose in case of insufficient control of bleeding is sufficiently substantiated.

[3] Affronti G, Agostini V, Brizzi A, Bucci L, De Blasio E, Frigo MG, et al. The daily-practiced post-partum hemorrhage management: an Italian multidisciplinary attended protocol. Clin Ter. 2017;168(5):e307-e16.
[4] Abdul-Kadir R, McLintock C, Ducloy AS, El-Refaey H, England A, Federici AB, et al. Evaluation and management of postpartum hemorrhage: consensus from an international expert panel. Transfusion. 2014;54(7):1756-68.

2.4. Clinical safety

Introduction

The safety profile of NovoSeven reported in the current indications:

NovoSeven is indicated for the treatment of bleeding episodes and for the prevention of bleeding in those undergoing surgery or invasive procedures in the following patient groups:

- in patients with congenital haemophilia with inhibitors to coagulation factors VIII or IX > 5 Bethesda Units (BU)
- in patients with congenital haemophilia who are expected to have a high anamnestic response to factor VIII or factor IX administration
- in patients with acquired haemophilia
- in patients with congenital FVII deficiency
- in patients with Glanzmann's thrombasthenia with past or present refractoriness to platelet transfusions, or where platelets are not readily available.

Known safety profile in above mentioned indications (extracted from the SmPC of NovoSeven)

Clinical trials conducted in 484 patients (including 4297 treatment episodes) with haemophilia A and B, acquired haemophilia, factor VII deficiency or Glanzmann's thrombasthenia have shown that adverse drug reactions are common (≥1/100 to < 1/10). The most frequent adverse drug reactions are pyrexia and rash (uncommon: ≥1/1,000 to < 1/100), and the most serious adverse drug reactions are thromboembolic events (venous and arterial thrombo-embolic events). In post-marketing experience, there have been no reports of inhibitory antibodies against NovoSeven or FVII in patients with haemophilia A or B. Development of inhibitory antibodies to NovoSeven has been reported in a post-marketing observational registry of patients with congenital FVII deficiency.

Safety data in support of the new indication of treatment of severe PPH

Safety data are presented from the RCT and non-interventional studies, literature review and Novo Nordisk safety database (Argus). Some women in the RCT and non-interventional studies overlapped with the patient population included in the published studies. With overlap taken into account, at least 834 women were exposed to NovoSeven across the RCT, studies and literature review.

In support of the assessment of the safety profile of NovoSeven in the requested new indication, i.e. NovoSeven is indicated for the treatment of severe postpartum haemorrhage, the main focus of the MAH is on thromboembolic events (TEs). In the context of the NovoSeven safety profile, TE is an identified risk. TEs were captured in the RCT and non-interventional studies, together with other maternal outcomes. Other AEs were reported in some studies, but the data were not captured consistently across data sources.

Risk of thromboembolic events in pregnancy and post-partum period

Pregnancy and the post-partum period is associated with an increased risk of venous thrombo-embolic events. Pregnancy is associated with a shift of the coagulation and fibrinolytic systems towards hypercoagulability, which leads to an increase in the risk of thromboembolic complications during pregnancy and the puerperal period. Additionally, many of the clinical conditions associated with PPH are known contributing factors for thromboembolic risk (e.g. delivery, severe haemorrhage, transfusions, DIC, surgery/invasive procedures and coagulopathy). In the peri- and postpartum period, factors such as caesarean section, body mass index >30 kg/m^2, pre-eclampsia/eclampsia, systemic infection, surgery

and immobilisation in the perioperative period also increase the risk of venous TEs. When compared to non-pregnant women, the incidence of venous TEs was significantly higher during the first postpartum week, declining rapidly thereafter. Women with obstetric complications are at highest risk of postpartum venous TEs, and this risk remains elevated throughout the first 12 weeks after delivery.

The incidence of TEs in women with PPH in general has been reported to range from <1−7.8% and in women with PPH treated with NovoSeven to range from 2.5−4.8% (Bouma et al, 2008; Francini, 2010; Abdul Sultan, Blood 2014.

Rationale MAH for focussing on TEs

Due to its mechanism of action, promoting the coagulation cascade, there is theoretically an even higher risk of TEs when NovoSeven is administered to women who are already in a hypercoagulable state. Therefore, the assessment of the safety of NovoSeven in women with severe PPH focussed on TEs, and whether there was an increased risk of TEs following NovoSeven administration.

Given the variation in clinical outcomes used and reported in PPH trials, Meher *et al.* defined a core clinical outcome set for PPH trials, based on a Delphi consensus study (Meher S, *et al.* Core outcome sets for prevention and treatment of postpartum haemorrhage: an international Delphi consensus study, BJOG. 2019). One of the core outcomes related to safety in the consensus study was adverse effects defined as "*number of women (and babies if relevant) with intervention-specific side effects and serious adverse effects as considered by triallists as appropriate*". Based on guidance from the Delphi consensus study and the safety events captured in clinical data sources, this safety summary focuses on TEs to assess safety of NovoSeven in women with severe PPH.

Data sources

The MAH presented the following clinical, patient-level data sources:

1. Pivotal data for the application are provided from an open-label RCT (trial 4816).
2. The pivotal data are supported with observational data derived from 4 non-interventional studies based on single hospital level data from a single centre (study 4729), national or population level data from 3 countries (study 4733) and 2 registries covering 3 countries describing off-label use of NovoSeven (study 4731 and study 4732).
3. Supportive data are also provided from the Novo Nordisk safety database (Argus) and from a literature review (of published clinical studies and case-reports) that report safety data of women with severe PPH treated with NovoSeven.

Trial 4816 (RCT)

Nîmes University Hospital, France was the sponsor of the randomised clinical trial and was responsible for the design, protocol, conduct, and original analysis of trial 4816. Novo Nordisk reproduced the analysis as per the protocol and further performed exploratory analysis on data from this study. The clinical trial recorded AEs occurring from T0 (time of inclusion in the protocol, pre-dose NovoSeven) up to 5 days after T0, as a part of safety assessments. SAEs were reported on the SAE page in the CRF. Death and all unexpected symptoms that occurred during the trial or within a maximum period of 5 days postpartum (which were life threatening, required extended hospitalisation, or involved injuries or after-effects) were considered as a serious adverse event. The occurrence of thrombosis with onset after NovoSeven administration was considered an SAE. Appearance of thrombosis was systematically screened based on clinical signs and symptoms after delivery, and supplemented, if there was any clinical doubt, with an Echo Doppler. This complication was treated with the appropriate intensive care measures.

Study (Bern)

This non-interventional study was based on original database collected at University Hospital of Bern, Switzerland, of women with severe PPH treated with NovoSeven or other standard of care. This study included data on 4 cohorts, of which part of the data covering the first 3 cohorts (historical cohort 1 and 2, and prospective study cohort) has already been published, with the supplemental data of a 'new cohort' retrospectively collected for the current study from electronic medical records. Additionally, information on timing of different interventions for the women in the first 3 cohorts was collected for this study. The MAH provided a data collection sheet for capture of study specific data. The data included in the study covered the period from hospitalisation for delivery (including baseline data) until the end of hospitalisation. The current study was based on data collected retrospectively from medical records of women with severe PPH. Only data captured in the medical records concerning TEs, cardiac arrest, allergic reactions, haemorrhagic shock, and maternal death occurring until end of follow-up period i.e., end of hospitalisation or death, were reported as AEs in the report.

Study 4733 (PPH consortium)

This study was based on data collected from 3 previously established cohorts from 3 countries (DK, NL and UK), which included women with severe PPH treated with NovoSeven or other standard of care. This study was based on secondary use of data and therefore individual case safety reporting was not performed. Maternal deaths were captured in all cohorts. Cardiac arrest and TEs were captured in the DK and UK cohorts but not in the NL cohort. However, in the NL cohort, TEs that occurred as complications of embolisation procedure were recorded. Therefore, data on TEs were incomplete in NL and hence not suitable for statistical analysis. Follow up time was up to 6 months after delivery (DK), up to end of bleeding (NL) and up to death or discharge (UK).

Study 4731 (UniSeven)

This study was based on a subset of data on Czech women with severe PPH from UniSeven registry, which is a multinational registry that recorded data on off label use of NovoSeven. The study was based on secondary use of data and therefore individual case safety reporting was not performed. However, TEs and maternal deaths occurring from first NovoSeven administration to end of hospitalisation were captured in the registry. Events of DIC and superficial thrombophlebitis were reported separately; however, they were not designated as a TE as per the protocol.

Study 4732 (ANZHR)

This study was based on a subset of data on obstetric cases of women with severe PPH in the ANZHR, which is a comprehensive registry documenting off-label use of NovoSeven at participating hospitals throughout Australia and New Zealand. The study was based on secondary use of data from registry and therefore individual case safety reporting was not performed. However, all TEs occurring up to 28 days from first NovoSeven administration were reported. Events of DIC were reported separately; however, they were not designated as a TE as per the protocol.

Literature review report MAH

ProQuest and Insight Meme databases were used to search and identify published clinical studies as well as case-reports in women with severe PPH treated with NovoSeven or other therapies. The literature search was performed for a period between 01 January 1996 (the start date was based on the marketing authorisation of NovoSeven in EU) to 01 July 2020 with no limits on geography, language, publication types or study type. The search excluded guidelines, search websites specialising in guidelines, reviews, publication on abortions, publications on approved indications of NovoSeven and non-clinical studies. Based on this search strategy and process, retrieved publications were manually assessed for duplicates and relevancy. Publications with PPH population with ≥5 women with an event of PPH and information on

TE and mortality were shortlisted for the review. Case-reports were defined as publications having <5 women with PPH. The detailed search strings for the literature search were provided in Appendix 1 of the literature review. The search retrieved 18 publications which reported data from clinical studies on women with sPPH treated with NovoSeven and the number of women included in each study ranged from 5-108. For women with PPH not treated with NovoSeven, in total 47 publications reported data from clinical studies and the number of women included in each study ranged from 7-20762. In women not treated with NovoSeven, 29 publications reported data from women with severe PPH, 5 publications from women with mixed PPH severity, 1 publication from women with non-severe PPH and in 12 publications, PPH severity was not reported. The studies originated from 6 regions with most of the reports originating from Europe. There were 6 publications which reported clinical study data both from women with PPH treated with NovoSeven and from women not treated with NovoSeven. In addition, 3 publications23-25 reported clinical study data both from women treated with NovoSeven and from women not treated with NovoSeven but the number of women treated with NovoSeven was <5 and, therefore, data from the women treated with NovoSeven were described among the case reports and data from the women not treated with NovoSeven were included in the meta-analyses. A meta-analysis was performed and the raw and adjusted proportion (95% (prediction intervals (PI)) of TEs, VTEs, ATEs (and maternal mortalities, see further below) was estimated for women with severe PPH treated with NovoSeven and those not treated with NovoSeven. Prediction intervals (PIs) are presented due to the substantial heterogeneity of the data. For estimating the proportions, a generalized linear mixed model was used based on the binomial distribution, with study as random effect.

Novo Nordisk safety database (Argus) report

Cases reported to the Argus database, where NovoSeven was used off-label to treat women with severe PPH, cumulatively from approval of NovoSeven in 1996 in EU until 30 June 2020 were retrieved, evaluated, and reviewed, retrospectively. It should be noted that AEs recorded in the Argus database represent an unknown fraction of the true number of AEs due to under-reporting in the post-marketing setting. Cases were reported for indications outside the 4 approved indications for NovoSeven. Cases reporting abortions and gynaecologic or obstetric cases unrelated to PPH were excluded from the dataset. Cases with all AEs in women with PPH receiving NovoSeven during the reporting period were reviewed with focus on TEs and cases with a fatal outcome that were manually screened.

Table 22 Overview of data sources supporting safety of NovoSeven in severe PPH

Trial or Study ID / Countries / Location	Trial or Study design / Study period / Final data cut-off date	Number of women with severe PPH		NovoSeven dose regimen	Safety assessments
		NovoSeven	No NovoSeven[a]		
Randomised controlled trial					
Trial 4816 (RCT) / FR, CH / Module 5.3.5.1	Prospective, multicentre, randomised, open label, parallel-group, comparative trial to assess efficacy and safety of NovoSeven in women with severe PPH after sulprostone (uterotonic) failure / 04-Apr-2007 to 05-Nov-2010 / 14-Apr-2021	42 (FAS)[b]	42 (FAS)	Single intravenous dose of 60 µg/kg NovoSeven	All relevant AEs, SAEs and maternal deaths occurring up to 5 days after 'randomisation were assessed. A compassionate use protocol was also established whereby women in the reference group could receive NovoSeven once it had been decided to perform a haemostatic hysterectomy, if haemorrhage persisted and was not controlled by standard of care treatment
Non-interventional studies					
Study 4729 (Bern) / CH / Module 5.3.5.2	Retrospective, single-centre, non-interventional, cohort study to evaluate clinical outcomes of NovoSeven in women with severe PPH / 01-Jan-2006 to 30-Apr-2016 / 13-Jan-2021	52 (FAS)	113 (FAS)	At the discretion of the physician and as per the local clinical practice	TEs occurring in all women with severe PPH until end of follow-up period were assessed. Maternal deaths that occurred in the follow-up periods, were assessed. Cardiac arrest, haemorrhagic shock and allergic reactions, were collected until end of follow-up period i.e., end of hospitalisation or death, whichever came first.
Study 4733 (PPHc) / DK, NL, UK[c] / Module 5.3.5.2	Retrospective, multi-country, non-interventional, cohort study to evaluate clinical outcomes of NovoSeven in women with severe PPH / DK: 2001 to 2009 NL: Jan-2011 to Jan-2013 UK: Jul-2012 to Jun-2013/ 8-Jan-2021	40 (DK FAS) 37 (NL FAS) 13 (UK FAS)	199 (DK FAS) 1223 (NL FAS) 149 (UK FAS)	At the discretion of the physician and as per the local clinical practice	Data on cardiac arrest and TEs were collected in the DK and UK cohorts; no data on cardiac events or TEs were collected for the NL cohort, except TEs that occurred as a complication of embolisation. Follow-up period was up to 6 months after delivery (DK), up to end of bleeding (NL) or up to death or hospital discharge, whichever came first (UK). Maternal deaths (that occurred in the follow-up periods), were assessed.
Study 4731 (UniSeven) / CZ / Module 5.3.5.2	Retrospective, non-interventional, cohort using data from UniSeven registry to describe clinical outcomes in women with severe PPH treated with NovoSeven / Jul-2003 to Apr-2014 / 31-Jul-2020	87 (FAS)[d]	NA	At the discretion of the physician and as per the local clinical practice	TEs and maternal deaths occurring from first administration of NovoSeven to end of hospitalisation were assessed.

Study 4732 (ANZHR) / AU, NZ / Module 5.3.5.2	Retrospective, non-interventional, cohort study using data from the ANZHR to describe clinical outcomes in women with severe PPH treated with NovoSeven / 2000 to 2009 / 20-Apr-2021	166 (FAS)	NA	At the discretion of the physician and as per the local clinical practice	TEs and maternal deaths occurring up to 28 days from first administration of NovoSeven were assessed.
Other data sources					
Literature review report / Module 5.3.5.4	Literature review of safety and other clinical outcomes in women with severe PPH who were treated with NovoSeven or other therapies based on published clinical studies and case-reports / 01-Jan-1996 to 01-Jul-2020	672 (meta-analysis) 100 (case-reports)	2181 (meta-analysis)	Dose and number of doses varied across published studies and case-reports	TEs reported in NovoSeven exposed and non-exposed patients and maternal deaths were assessed.
Novo Nordisk safety database (Argus) report/ Module 5.3.5.4	Review of all cases of women with severe PPH reported cumulatively in the NovoSeven Argus database until 30-Jun-2020 with a focus on TEs and cases with a fatal outcome. Subgroups of women treated with NovoSeven with or without TEs were analysed. / 1995 to 30-Jun-2020	123 (39 with TEs; 84 without TEs)	NA	At the discretion of the treating physician and as per the local clinical practice	All AEs with a focus on TEs. Maternal deaths.

Note: Trial 4816 (RCT) was sponsored and conducted by Nîmes University Hospital. Novo Nordisk performed reanalysis of patient-level data for trial 4816 and analysis of patient level data for studies 4729 (Bern) and 4731 (UniSeven). Department of Clinical Epidemiology, Leiden University Medical Centre performed analysis of patient-level data for study 4733 (PPHc). Department of Epidemiology and Preventive Medicine, Monash University performed analysis of patient-level data for study 4732 (ANZHR).
a For the FAS, "No NovoSeven" refers to women in reference group (trial 4816) or those who did not receive NovoSeven (studies 4729 and 4733).
b Total NovoSeven exposed women were 51:women randomised to NovoSeven (N=42) plus those that received NovoSeven in error or on compassionate basis.
c It was planned to also include data from France. However, these could not be collected primarily due to burden on hospital staff due to the COVID-19 pandemic at the time.
d A total of 111 women with PPH were exposed to NovoSeven but this includes 24 women for whom severe PPH was not confirmed (blood loss <1500 mL or no blood loss information) Abbreviations: AE = adverse event; ANZHR = Australian and New Zealand Haemostasis Registry; AU = Australia; CH = Switzerland; CZ = Czech Republic; DK = Denmark; FAS = full analysis set; FR = France; NA=not applicable; NL = the Netherlands; NZ = New Zealand; PPH = postpartum haemorrhage; PPHc = PPH consortium; TE = thromboembolic event; UK = United Kingdom.

Patient exposure

Studies 4816 (RCT), 4729, 4733, 4731 and 4732

A total of 446 women with severe PPH combined across the RCT (study 4816) and the four non interventional studies (4729, 4733, 4731 and 4732) were exposed to NovoSeven (Table 22).

Literature review

In the literature review, 672 women with severe PPH were reported as having been exposed to NovoSeven. Some patients in the RCT and non-interventional studies overlapped with the patient population included in the published studies. With overlap taken into account, at least 834 women were exposed to NovoSeven and are reported in the trial, studies and literature review.

Dosing

Details of exposure in terms of total median NovoSeven dose, number of NovoSeven doses, median first, second and third dose, time from onset of severe PPH to NovoSeven and time between NovoSeven doses for all the clinical data-sources (4816 (RCT), 4729, 4733, 4731 and 4732) are summarised in the Table 17.

Trial 4816 (RCT)

This was a single dose study.

Non-interventional studies (4729, 4733, 4731 and 4732)

Across the non-interventional studies, majority of women required only a single dose of NovoSeven; information on number of doses administered was not available for DK and UK cohorts in the study 4733 (PPH consortium). The proportion of women receiving only one dose of NovoSeven ranged from 36.4%−88.5% across the non-interventional studies; proportion of women receiving a second dose ranged from 7.8%−23.0%; and proportion of women receiving a third dose ranged from 1.3%−5.4%. Women requiring more than 3 doses of NovoSeven was observed rarely; the proportion of women requiring >3 doses of NovoSeven in study 4732 and study 4733 were 1.8% and 1.3%, respectively.

Total exposure first dose:

Across the RCT and non-interventional studies, the median first dose of NovoSeven in the FAS ranged from 58 µg/kg in trial 4816 (RCT) to 105 µg/kg in study 4731 (UniSeven). In study 4729 (Bern), most women received a first dose of 60-90 µg/kg, whereas in studies 4731 (UniSeven) and 4732 (ANZHR), most women received a first dose >90 µg/kg. The proportion of women receiving a first dose of NovoSeven of <60 µg/kg, 60−90 µg/kg and >90 µg/kg varied across data sources. The 60−90 µg/kg dose range was administered to between 19.5% and 71.2% of women by trial/study.

Total exposure second and third dose (median)

In the non-interventional studies, median second and third doses in the FAS for those women who received more than 1 dose ranged from 73 µg/kg to 100 µg/kg across studies, and were therefore broadly similar to first dose in these studies (63 µg/kg to 105 µg/kg).

Table 23 Overview of NovoSeven dosing and exposure across all data sources – full analysis set

		Trial 4816 (RCT)[a]	Study 4729 (Bern)	Study 4733 (PPH consortium)		Study 4731 (UniSeven)	Study 4732 (ANZHR)
				DK+NL[c]	UK		
Total number of women receiving NovoSeven, N		**42[b]**	**52**	**77**	**13**	**87**	**166**
Number of NovoSeven doses received, N (%)	**1 dose**	42 (100)	46 (88.5)	28 (36.4)	–	63 (72.4)	127 (76.5)
	2 doses	0	6 (11.5)	6 (7.8)	–	20 (23.0)	27 (16.3)
	3 doses	0	0 (0)	1 (1.3)	–	4 (4.6)	9 (5.4)
	> 3 doses	0	0 (0)	1 (1.3)	–	0 (0)	3 (1.8)
	Missing	0	0	41 (53.2)	-	0	0
Dose units		**µg/kg**	**µg/kg**	**mg**	**mg**	**µg/kg**	**µg/kg**
Total dose	**N**	42	52	73	13	87	133
	Mean (SD)	57.1 (7.5)	71.0 (24.1)	5.9 (4.0)	5.3 (2.7)	138.1 (58.75)	111.0 (47.3)
	Median (IQR)	57.60 (52.9–60.8)	64.0 (60.8 - 73.7)	5.0 (2.4, 7.2)	6.0 (4.0–7.0)	120.0 (100.0–175.0)	102.9 (88.6–120.0)
	Min ; Max	31.6 ; 72.7	33.9 ; 169.5	1.0 , 21.0	1.0 ; 10.0	51.4 ; 354.0	10.0 ; 291.9
1st dose	**N**	57.1 (7.5)	52	–	–	87	135
	Mean (SD)	57.60 (52.9–60.8)	62.7 (16.7)	–	–	107.0 (26.34)	90.4 (30)
	Median (IQR)	31.6 ; 72.7	63.4 (56.4 - 72.7)	–	–	105.0 (90.0–120.0)	96.0 (73.9–109.1)
	Min ; Max	57.1 (7.5)	12.0 ; 121.2	–	–	50.0 ; 200.0	10.0 ; 174.6
2nd dose	**N**	NA	6	-	-	24	29
	Mean (SD)	NA	72.1 (14.4)	–	–	96.4 (30.10)	81.6 (30.4)
	Median (IQR)	NA	73.2 (65.8 - 84.7)	–	–	100.0 (90.0–120.0)	82.8 (62.2–97.3)
	Min ; Max	NA	48.0 ; 87.7	–	–	28.0 ; 140.0	40.0 ; 160.0
3rd dose	**N**	NA	NA	–	–	4	9
	Mean (SD)	NA	NA	-	-	98.8 (13.15)	70.2 (25.3)
	Median (IQR)	NA	NA	–	–	100.0 (87.5–110.0)	80.0 (44.4–96.0)

	Min ; Max	NA	NA	–	–	85.0 ; 110.0	35.8 ; 97.3
Time from severe PPH onset to NovoSeven administration (minutes)							
1st dose	**N**	42	52	77	–	87	149
	Mean (SD)	Within 60 minutes[d]	228.2 (266.6)	366.6 (479.1)	–	409.9 (555.5)	517.3 (700.9)
	Median (IQR)	Within 60 minutes[d]	127.5 (71.0 - 290.5)	165 (72, 405)	–	210.0 (120.0–480.0)	291.0 (160.0–525.0)
2nd dose	**N**	NA	–	–	–	23	35
	Mean (SD)	NA	–	–	-	825.0 (840.4)	960.1 (1589.1)
	Median (IQR)	NA	–	–	–	510.0 (270.0–960.0)	480.0 (240.0–1026.0)
3rd dose	**N**	NA	NA	–	–	4	9
	Mean (SD)	NA	NA	-	–	1085.0 (660.8)	1046.7 (1166.0)
	Median (IQR)	NA	NA	–	–	1065.0 (595.0–1575.0)	710.0 (555.0–895.0)
Time between doses (minutes)							
1st and 2nd dose	**N**	NA	6	–	–	23	38
	Mean (SD)	NA	216.3 (431.7)	–	–	278.5 (302.4)	411.1 (1385.92)
	Median (IQR)	NA	40.0 (18.0 - 100.0)	–	–	160.0 (120.0–420.0)	105.0 (46.0–300.0)
2nd and 3rd dose	**N**	NA	NA	–	–	4	11
	Mean (SD)	NA	NA	-	-	321.3 (327.6)	219.6 (203.4)
	Median (IQR)	NA	NA	–	–	225.0 (87.5–555.0)	175.0 (60.0–310.0)

[a]NovoSeven dose adapted to allow complete use of vials (1.2, 2.4 and 4.8 mg vials) and based on the woman's maternal weight at term with foetal-placental weight deducted

[b]Total NovoSeven exposed women were 51:women randomised to NovoSeven (N=42) plus those that received NovoSeven in error or on compassionate basis.

[c]Data for number of NovoSeven dose in the DK cohort were not available

[d]The time allowed for the dosing interval of 60 minutes was pre-specified in the protocol

Literature review reported dose

The systematic literature review identified 18 published studies and 68 case-reports with 672 and 100 women with severe PPH, respectively, who received treatment with NovoSeven. Of the 672 women, number of doses administered was reported only for 494 women (14 studies). Most women (80.0%) received only 1 dose of NovoSeven, 16% of women received 2 doses, and 3% of women received 3 doses. More than 2 doses were rarely given. The dose of NovoSeven and number of doses varied between the studies. The administered NovoSeven doses usually ranged between 50 and 100 µg/kg but as low doses such as 9 µg/kg and as high as 139 µg/kg were also administered. In many studies, only the mean or median or total dose in mg were reported without any information about the maternal body weight and therefore the actual range of given doses may even be larger than 9 to 139 µg/kg.

In case-reports, the dose of NovoSeven ranged from 15−120 µg/kg; most cases reported use of only one dose of NovoSeven.

Novo Nordisk safety database (Argus) reported dose

The Argus database had 123 post-marketing cases of women with severe PPH treated with NovoSeven. In the NovoSeven treated group with TEs (N=39); the median total dose was 130 µg/kg for cases reporting dose in µg/kg (n=7) and was 6 mg for cases reporting dose in mg (n=23). Of the 21 women with information about the number of doses in this group, 11 women (28.2%) received 1 dose, 7 women (17.9%) received two doses and 3 women (2.6%) received ≥3 doses; dosing data were missing for 46.2% of women. In the NovoSeven treated group that did not report any TEs (N=84); the median total dose was 90 µg/kg for cases reporting dose in µg/kg (n=17) and was 6 mg or cases reporting dose in mg (n=38). In this group too, the majority of women received only one dose (Novo Nordisk safety database (Argus) report.

Grouping and pooling of trials and data

The data sources included enable an evaluation of safety of NovoSeven across a broad population of women with severe PPH. As the data sources varied in nature, some differences across the data sources, such as definition of severe PPH, data collection methods, severity of PPH at the time of NovoSeven administration, dose size and timing of NovoSeven in the treatment cascade were observed. Moreover, Novo Nordisk did not have access to patient-level data from all the clinical data sources. Therefore, it was not possible to universally pool data across the data sources. Exposure, disposition, demographic data, overview of TEs and deaths are presented individually and side-by-side to provide an overview across clinical data sources.

Meta-analyses were performed for occurrence of any TEs, VTEs, ATEs in all NovoSeven exposed patients across the clinical data sources.

The data from the literature review and Argus report are described separately and are not pooled with other clinical data sources as some of the women were overlapping between these two and between them and the other clinical data sources. Some of the published studies included in literature review had women who were also included in the trial 4816 (RCT) and the non-interventional studies (studies 4729, 4731 and 4732). Similarly, some cases from the Argus report partially overlapped with the RCT and non-interventional studies, but the full extent of overlap is unknown.

The safety evaluation of the MAH is based on the following data:

- Extent of exposure
- Study population: disposition, demography and baseline characteristics
- Safety assessments
- Type and frequency of TEs: overall, and by VTEs and ATEs
    - Maternal mortality along with the cause
    - Any other AEs (cardiac arrest, allergic reactions and haemorrhagic shock) and SAEs (SAEs were planned to be captured only in trial 4816)
- Laboratory assessment: baseline laboratory parameters (antithrombin, fibrinogen, platelets, D-dimer levels) and pH
- Vital signs: baseline body temperature

Patient disposition

All data sources included women that had received NovoSeven treatment in event of severe PPH. All data sources except studies 4731 and 4732 included data for non-exposed women.

An overview of disposition of women with severe PPH by analysis sets in the RCT and non-interventional studies is presented in Table 24. Overall, in the FAS across the clinical data-sources (trial 4816, study 4729, 4733, 4731, 4732), a total of 446 women were exposed to NovoSeven (including 8 women in the RCT exposed under the compassionate use protocol and 1 woman exposed in error) and 1726 women were not exposed to NovoSeven. Due to geographical location and study period, it is unlikely that there is any overlap between the RCT and non-interventional studies or between any of the non-interventional studies. For comparative analyses (in trial 4816, study 4729 and study 4733), a total of 100 women were included in the NovoSeven group and 200 women were included in the Control group.

Table 24 Overview of patient disposition

Trial or Study ID		Analysis set	Number of women	
			NovoSeven	No NovoSeven [a]
Trial 4816 (RCT)		**FAS**	42[b]	42
Study 4729 (Bern)		**FAS**	52	113
Study 4733 (PPH consortium)	**DK**	**FAS**	40	199
	NL	**FAS**	37	1223
	UK	**FAS**	13	149
Study 4731 (Uniseven)		**FAS**	87[c]	NA
Study 4732 (ANZHR)		**FAS**	166	NA
Literature review		**Meta-analysis**	672	2181

[a] No NovoSeven" refers women in the reference group (in trial 4816) or those who did not receive NovoSeven (studies 4729, 4731, 4732, 4733 in the FAS).
[b] The total number of NovoSeven exposed women in this study was 51.
[c] A total of 111 women with PPH were exposed to NovoSeven but this includes 24 women for whom severe PPH was not confirmed (blood loss <1500 mL or no blood loss information)

There was a partial overlap of cases (11 cases) from the Argus report with other published data sources, all of which were also included in the literature review. Out of the 11 cases (13 TEs), 2 cases (2 TEs) overlapped with 2 women reported in study 4732. The overlapping cases were included in the Argus report not to miss any safety information, but the exact extent of overlap is unknown.

Similarly, a partial overlap of at least 284 women was also observed between clinical data sources (trial 4816, and studies 4729, 4731 and 4732) and the population included in literature review. With overlap taken into account, a total of at least 834 women were exposed to NovoSeven and are reported in the trial, studies, and literature review.

Patient characteristics

Patient characteristics of full analysis set are presented in table 17, see above.

Summary safety data set and dose applied

A total of 446 women with severe PPH were exposed to NovoSeven across the trial/studies (4816, 4729, 4733, 4731 and 4732). A total of 672 women were also exposed and reported in the literature review and 103 in the safety database Argus. With overlap taken into account, at least 834 women were exposed to NovoSeven and are reported in the trial, studies, and literature review. The exact total of unique women exposed cannot be calculated because, although there was no overlap between the trials/studies, there is insufficient information to trace the full extent of the overlap of the literature and database with the trial/studies.

The median total dose of NovoSeven ranged between 57.6 −120.0 µg/kg across the trial/studies (4816, 4729, 4733, 4731 and 4732). All women in trial 4816 received only one dose of NovoSeven, as per the protocol. Across the non-interventional studies (4729, 4733, 4731 and 4732), the proportion of women requiring only 1 dose of NovoSeven ranged from 36.4%−88.5%, a second dose from 7.8%−23.0%, and third dose from 1.3%-5.4%

Adverse events

Thromboembolic events

An overview of TEs across all data sources is presented in the table 25 below:

Table 25 Proportion of women with all ATEs, VTEs and All TEs across data sources

Data source	Analysis set	ATE		VTE		All TE	
		NovoSeven	No NovoSeven[a]	NovoSeven	No NovoSeven[a]	NovoSeven	No NovoSeven[a]
Trial 4816 (RCT), n/N (%)	FAS	0/51 (0)[b]	0/33 (0)	2/51 (3.9)	0/33 (0)	2/51 (3.9)	0/33 (0)
Study 4729 (Bern), n/N (%)	FAS	0/52 (0)	0/113 (0)	0/52 (0)	1/113 (0.9)	0/52 (0)	1/113 (0.9)
Study 4733 (PPH consortium), n/N (%)	FAS (UK)	0/13 (0)	0/149 (0)	0/13 (0)	4/149 (2.9)	0/13 (0)	4/149 (2.9)
	FAS (DK)[c]	0/40 (0)	1/190 (0.5)[d]	1/40 (2.5)	2/190 (1.1)[d]	1/40 (2.5)	3/190 (1.6)[d]

Data source	Analysis set	ATE		VTE		All TE	
		NovoSeven	No NovoSeven[a]	NovoSeven	No NovoSeven[a]	NovoSeven	No NovoSeven[a]
	FAS (NL)[e]	0/23 (0)	1/144 (0.7)	1/23 (4.3)	2/144(1.4)	1/23 (4.3)	3/144 (2.1)
Study 4731 (UniSeven), n/N (%)	FAS[f]	0/87 (0)	NA	0/87 (0)	NA	0/87 (0)	NA
Study 4732 (ANZHR), n/N (%)	FAS[g]	1/166 (0.6)[h]	NA	2/166 (1.2)	NA	3/166 (1.8)	NA
		Meta-analysis[i]					
Raw proportion, n/N (%)	Meta-analysis	1/409 (0.2)	1/485 (0.2)	5/409 (1.2)	7/485 (1.4)	6/409 (1.5)	8/485 (1.6)
Adjusted proportion % (95% PI)	Meta-analysis	0.2 (0, 1.7)	0.2 (0, 1.4)	1.2 (0.5, 2.9)	1.4 (0.7, 3.0)	1.5 (0.7, 3.2)	1.6 (0.8, 3.3)
		Literature review report					
Raw proportion, n/N (%)	Meta-analysis	1/669 (0.1)	6/1558 (0.4)	12/669 (1.8)	17/2181 (0.8)	13/669 (1.9)	22/1558 (1.4)
Adjusted proportion, % (95% PI)	Meta-analysis	0.1 (0.02, 1.1)	0.005 (0, 44.5)	1.6 (0.6, 4.8)	0.5 (0.03, 8.1)	1.6 (0.4, 6.6)	0.8 (0.05, 12.2)

Note: Data sources include Trial 4816, Studies 4729, 4733, 4731, 4732 and published studies from the literature review. Data from the literature review overlaps with data described in other clinical data sources
a"No NovoSeven" women who did not receive NovoSeven (studies 4729 and 4733).
b9 women from the reference group were exposed to NovoSeven and thus the total of women exposed to NovoSeven was N=51
cFor DK cohort, 1 ATE was reported in NovoSeven treated women; however, it occurred prior to (15 mins) NovoSeven administration and hence considered not relevant. The ATE is not included in the above table or for calculation of proportions.
dTE data were missing for 9 of the 199 women who did not receive NovoSeven in the DK cohort.
eFor NL (FAS), no data on TEs were available except reported as complication of embolisation procedure; type of TEs are based on the clinical expert assessment of the available data (data on file)
fA total of 111 women with PPH were exposed to NovoSeven but this includes 24 women for whom severe PPH was not confirmed (blood loss <1500 mL or no blood loss information)

Pivotal Study 4816 (RCT)

In the RCT, 2 of 42 women in the NovoSeven group developed a total of 2 VTEs:

- The woman had severe PPH following delivery of twins by CS. Information on blood transfusions or haemostatic treatments was not available. Two days after NovoSeven injection, a CT scan revealed an ovarian vein thrombosis, which resolved on enoxaparin treatment. Due to the time course of the TE, it was assessed as unlikely related to NovoSeven by the investigators and sponsor physician.
- The woman had severe PPH following CS delivery performed due to placental abruption and intrauterine foetal death. Severe PPH developed due to uterine atony. Blood transfusion and NovoSeven did not control bleeding. A DVT and associated PE was diagnosed by echo doppler, 5 days after NovoSeven treatment that resolved on enoxaparin and warfarin treatment. In the opinion of the

investigators, low dose of NovoSeven (32 µg/kg) was unlikely to be related to TEs; additionally, placental abruption, intrauterine foetal death, CS and transfusion may have contributed to events.

No woman developed a VTE in the reference group. No women developed an ATE in either of the groups.

In the reference group, 8 women received NovoSeven on compassionate use basis after the primary endpoint was evaluated and just before hysterectomy; also, 1 woman from the reference group received NovoSeven in error at time of randomisation) developed a TE. Therefore, a total of 51 women (42 randomised treatment and 9 exposed later) were exposed to NovoSeven in this trial.

The proportion of women with TEs and VTEs accounting for the total women exposed to NovoSeven in the RCT was 2/51 (3.9%) versus 0% in the women non-exposed to NovoSeven.

Non-interventional studies

Study 4729 (Bern)

In this study, none of the 52 women in the FAS who received NovoSeven developed a TE. One of 113 women (0.9%) in the FAS, who did not receive NovoSeven, developed a TE (VTE) (Table 25). The VTE was a PE that occurred on day 13 after delivery. The woman had received TXA and underwent a hysterectomy.

Study 4733 (PPH consortium)

DK cohort

In this cohort, 2 out of 40 women in the FAS who received NovoSeven developed a total of 2 TEs. Of these, one TE (an ATE) developed in a woman 15 minutes prior to NovoSeven administration and hence was not related to NovoSeven. The second TE (a PE) occurred in 1 of the 40 women (2.5%) and had onset and/or diagnosis 35 days after receiving NovoSeven. Three of 190 women (1.6%) in the FAS who did not receive NovoSeven, developed 4 TEs; one woman had an ATE and 2 women had a total of 3 VTEs.

NL cohort

In this cohort, data on TEs were only collected for the subset of women who had '*complication after embolisation'*, ie. an invasive procedure. Hence, NL cohort data was not combined with the other data sources.
Of 23 women who received NovoSeven and underwent embolisation, 1 woman (4.3%) developed a TE (time of diagnosis of severe PPH not known). Of the 144 women in the FAS, who did not receive NovoSeven but had an embolisation, 3 women (2.1%) developed a total of 3 TEs (one each), time of diagnosis was not known. It was not known whether the TEs reported post embolisation were arterial or venous except for 1 NovoSeven treated woman had a VTE.

UK cohort

In this cohort, none of 13 (0.0%) women in the FAS who received NovoSeven developed a TE. Four of 149 women (2.7%) who did not receive NovoSeven developed TEs (all VTEs).

Study 4731 (Uniseven)

In this study, no records of women developed TE after receiving NovoSeven.

Study 4732 (ANZHR)

In this study, 5 of 166 women in the FAS developed TEs (one each). Of these, one was a cerebrovascular accident, and another was a PE; both TEs developed ***prior*** to NovoSeven administration and hence were

not related to NovoSeven. The remaining 3 TEs occurred in 3 women after NovoSeven treatment (Table 25). One of 166 women (0.6%) developed an ATE (acute MI); the time of onset and/or diagnosis of TE was within 36 minutes of NovoSeven administration. The women eventually died due to uncontrolled haemorrhage. Two out of 166 women (1.2%) developed VTEs (DVT and PE); both had onset and/or diagnosis within 7 days of NovoSeven administration.

Meta-analysis of pooled data from RCT and non-interventional studies

In the meta-analysis, the proportion (95% PI) of women with a TE from meta-analysis pooled data for RCT and non-interventional studies was calculated.

The overall adjusted proportion (95% PI) of women with a TE from meta-analysis using pooled data from the FAS for RCT and non-interventional studies was 0.015 (0.007, 0.032) in NovoSeven treated women and 0.016 (0.008, 0.033) in women not treated with NovoSeven, indicating no increase in TE risk following NovoSeven administration. (Please note: In the NL cohort of study 4733, a TE was only recorded if it was a complication of an embolisation, therefore, TE data from the NL cohort are excluded from the meta-analysis), see figure 10.

Figure 10 Proportion of women with severe PPH with a thromboembolic event NovoSeven treated and not treated with NovoSeven full analysis set

TEs, NovoSeven treated

	N	Events	Proportions
French RCT	51	2	0.039[0.011;0.132]
Bern	52	0	0[0;0.069]
PPH cons DK	40	1	0.025[0.001;0.129]
PPH cons UK	13	0	0[0;0.228]
ANZHR	166	3	0.018[0.006;0.052]
UniSeven	87	0	0[0;0.042]
Adjusted proportion			**0.015[0.007;0.032]**
Raw proportion			**0.015**

TEs, not NovoSeven treated

	N	Events	Proportions
French RCT	33	0	0[0;0.104]
Bern	113	1	0.009[0;0.048]
PPH cons DK	190	3	0.016[0.005;0.045]
PPH cons UK	149	4	0.027[0.010;0.067]
Adjusted proportion			**0.016[0.008;0.033]**
Raw proportion			**0.016**

Note: The arrow in the forest plot for PPH cons UK shows confidence interval range is outside of X axis

Literature review report

In the literature review, a total of 14 TEs were reported in 13/669 women with severe PPH who received NovoSeven and a total of 22 TEs were reported in 1558 women with severe PPH who did not receive NovoSeven. As expected, the majority of the TEs were VTEs. The predominance of women reporting VTEs versus ATEs was more pronounced in women with sPPH treated with NovoSeven than in women with severe and mixed PPH severity not treated with NovoSeven. Furthermore, the proportion of women with ATEs was less in the severe group of women treated with NovoSeven (7.7%) than the severe group not treated with NovoSeven (27.3%).

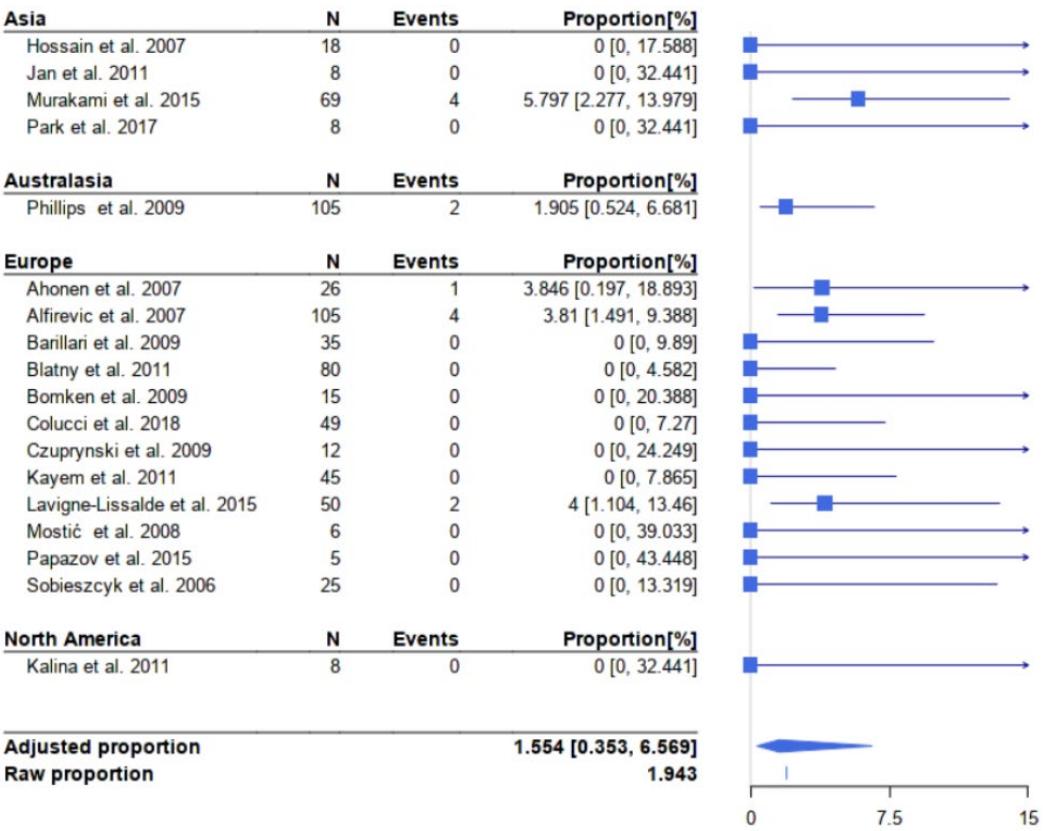
	Treated with NovoSeven®	Not treated with NovoSeven®			
Severity of PPH	**Severe**	**Severe**	**Mixed**	**Non-severe**	**Not reported**
Number of women with TEs	13	22	69	1	16
Number of women with ATE (%)	1 (7.7)	6 (27.3)	20 (29.0)	0	2 (12.5)
Number of women with VTE (%)	12 (92.3)	16 (72.7)	49 (71.0)	1 (100)	14 (87.5)

In all regions, the adjusted proportions of women with sPPH reporting ATEs and VTEs were 0.15% and 1.6%, respectively, in women with sPPH treated with NovoSeven. In women with sPPH not treated with NovoSeven, the adjusted proportions of women reporting ATEs and VTEs were 0.005% and 0.5%, respectively.

Additional details of adjusted proportion for all TEs, VTEs and ATEs of each individual publication included in meta-analysis is included in Figure 11.

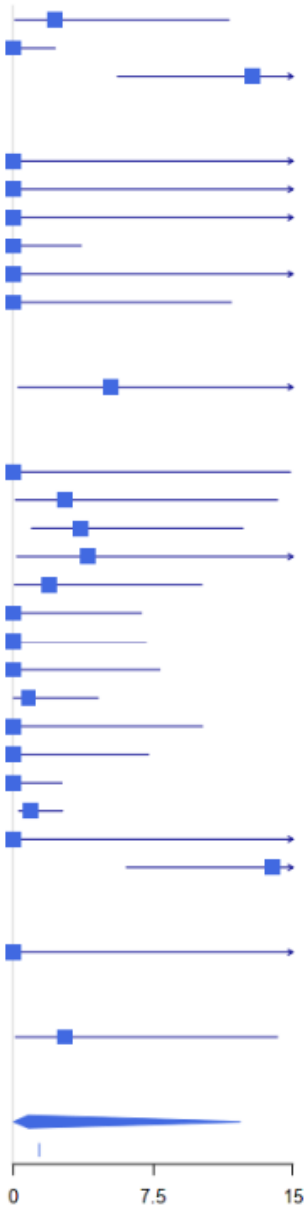
Figure 11 Proportions of women with severe PPH with a TE (overall) in all regions

Women treated with NovoSeven



Women not treated with NovoSeven

Africa	N	Events	Proportion[%]
Khouadja et al. 2016	45	1	2.222 [0.114, 11.567]
Mouna et al. 2018	166	0	0 [0, 2.262]
Touhami et al. 2016	39	5	12.821 [5.603, 26.706]
Asia	**N**	**Events**	**Proportion[%]**
Bloom et al. 2004	9	0	0 [0, 29.915]
Horng et al. 2011	9	0	0 [0, 29.915]
Hossain et al. 2007	16	0	0 [0, 19.361]
Makino et al. 2015	101	0	0 [0, 3.664]
Park et al. 2017	7	0	0 [0, 35.433]
Yong et al. 2006	29	0	0 [0, 11.697]
Australasia	**N**	**Events**	**Proportion[%]**
Wong et al. 2011	19	1	5.263 [0.27, 24.639]
Europe	**N**	**Events**	**Proportion[%]**
Ahonen et al. 2007	22	0	0 [0, 14.865]
Boulleret et al. 2004	36	1	2.778 [0.142, 14.17]
Collins et al. 2017	55	2	3.636 [1.003, 12.323]
Colucci et al. 2018	25	1	4 [0.205, 19.544]
Ferrazzani et al. 2014	52	1	1.923 [0.099, 10.121]
Fusari et al. 2012	52	0	0 [0, 6.879]
Grönvall et al. 2013	50	0	0 [0, 7.135]
Grönvall et al. 2014	45	0	0 [0, 7.865]
Guash et al. 2009	120	1	0.833 [0.043, 4.57]
Lavigne-Lissalde et al. 2015	34	0	0 [0, 10.151]
Martin et al. 2015	49	0	0 [0, 7.27]
Pasquier et al. 2013	142	0	0 [0, 2.634]
Ramler et al. 2017	327	3	0.917 [0.312, 2.662]
Ruprai et al. 2011	18	0	0 [0, 17.588]
Stensaeth et al. 2017	36	5	13.889 [6.082, 28.66]
North America	**N**	**Events**	**Proportion[%]**
Kalina et al. 2011	19	0	0 [0, 16.818]
South America	**N**	**Events**	**Proportion[%]**
Korin et al. 2000	36	1	2.778 [0.142, 14.17]
Adjusted proportion			**0.833 [0.051, 12.17]**
Raw proportion			**1.412**



A majority of the TEs were VTEs in both the groups. One of 13 women who received NovoSeven group had an ATE (asymptomatic MI) and the remaining 12 of 13 women had VTEs (7 DVT and 7 PE). Six of 22 women in the No NovoSeven group had ATEs (1 MI and 5 TEs in iliac or femoral artery) and the remaining 16 of 22 women had VTEs (10 DVT and 7 PE).

In case-reports from literature review, 6 TEs were reported in 4 women who received NovoSeven; all were VTEs. Onset and/or diagnosis of TEs after NovoSeven administration ranged from 3 hours to 4 weeks (time was not known in one case).

VTEs are more commonly reported than ATEs in women with sPPH, however, ATEs still occur in some women, as PPH increases the risk of both venous and arterial TEs. The predominance of VTEs versus ATEs was also confirmed in the present meta-analysis. It can be seen that there were modest differences in the occurrences of TEs (both for overall events, ATEs and VTEs) between the 2 populations with adjusted proportions of TEs generally being higher in the women treated with NovoSeven compared with women not treated with NovoSeven. However, both the prediction intervals (PIs) of the adjusted TE proportions of the women treated with NovoSeven in the studies and those not treated with NovoSeven overlapped

and the adjusted proportion of the women treated with NovoSeven laid within the PIs of those not treated with NovoSeven. Therefore, it cannot be concluded that there is a difference between the occurrence of TE in these populations.

Novo Nordisk safety database (Argus) report

A search performed in the Novo Nordisk safety database yielded 123 postmarketing cases of women with sPPH treated with NovoSeven (hereafter referred to as sPPH cases). The first case was reported in January 2003 and the latest in April 2020. The countries reporting the highest number of cases were France (21%), Lebanon (16%) and the United States (11%). Thirty-two of the 123 sPPH cases (26%) were reported as off-label use without an associated AE (i.e., off-label use with no harm). Off-label use without an associated AE is not considered a safety information. However, if such information is reported to Novo Nordisk or identified in the literature, it will still be recorded in the safety database.

Thirty-nine women with severe PPH experienced at least one TE (total 46 TEs) after being treated with NovoSeven. Of these, 21 women had a VTE, 13 women had ATEs and 5 women had multiple TEs (5 ATEs and 7 VTEs). Additional details of TEs are provided in the report.

Onset/diagnosis of TE: the timing of the first TE was reported in 27 of the 39 cases. Eleven TEs had an onset and/or were diagnosed within 48 hours after treatment with NovoSeven, whereas the rest of the TEs had an onset and/or were diagnosed within 4-28 days after treatment with NovoSeven. According to the label, the half-life of NovoSeven is 3.9 to 6.0 hours in healthy subjects. Therefore, it is considered unlikely that TEs appearing more than 48 hours after treatment are caused by NovoSeven. However, some of the TEs could have occurred days before they were diagnosed.

Dosing regimen: The dosing of NovoSeven varied between the cases. Of the 21 women, where information about the number of doses was available, 11 women (52.4%) received 1 dose, 7 women (33.3%) received two doses and 3 women (14.3%) received ≥3 doses. For cases reporting dose in milligram (n = 23), the median total dose was 6 mg. For cases reporting dose in µg/kg (n = 7), the median total dose was 130 µg/kg. The risk of TEs was confounded by several patient related risk factors, concomitant conditions, use of invasive procedures and development of complications.

Risk factors: The risk of TEs was confounded by several patient related risk factors, concomitant conditions, use of invasive procedures and development of complications. The most common risk factors identified in the case narratives were major abdominal surgery (e.g., caesarean section, hysterectomy and laparotomy), massive transfusions and DIC. Most of the women (≥70%) underwent invasive procedures (i.e., uterine or iliac artery ligation, radiological arterial embolisation, uterine compression sutures or hysterectomy) and/or received massive blood transfusions. NovoSeven was often given late in the management of sPPH (i.e. during/after hysterectomy) at a time when the women were at an even further increased risk of developing TEs.

A causality assessment of the TE was provided by the reporter in most cases; 4 TEs were assessed as 'probably related to NovoSeven', 23 TEs were assessed as 'possibly related to NovoSeven' and 10 TEs were assessed as 'unlikely related to NovoSeven'.

Causality assessment of TE by MAH

Of the 7 TEs reported after NovoSeven administration in the RCT and non-interventional studies, 5 TEs (4 VTEs and 1 ATE) were assessed as unlikely to be related and the remaining 2 TEs (both VTEs) were assessed as possibly related to NovoSeven, per reporter's assessment. Per Novo Nordisk assessment, 1 of 7 TEs (a VTE) was assessed as possibly related and the remaining 6 TEs (1 ATE and 5 VTEs) were assessed as unlikely to be related to NovoSeven, see table 26 below.

Table 26 Causality assessment of TEs

Data sources	TE type		Reporter's causality	Novo Nordisk causality	
Clinical data sources[a]	N	7		7	
	ATE (n)	1	Unlikely	1	Unlikely
	VTE (n)	4	Unlikely	5	Unlikely
		2	Possible	1	Possible
Literature review report	N	6		6	
	VTE (n)	2	Unlikely	5	Unlikely
		3	Not reported	1	Possible
		1	Potentially related (verbatim)		
Argus report[b]	N	46		NA	
	All TEs	10	Unlikely		
		23	Possible		
		4	Probable		
		9	Not reported		

[a]Clinical data sources included trial 4816 and studies 4729, 4733, 4731, 4732

[b]No causality assessments were made by Novo Nordisk due to the implied possible causality for spontaneous cases (established by the report of the event as an adverse drug reaction).

Abbreviations: ATE = arterial thromboembolic events; NA = Not available; TE = Thromboembolic events; VTE = venous thromboembolic events

Serious adverse event/deaths/other significant events

Overview of maternal mortality

Causes of death in women with severe PPH include bleeding, organ failure, sepsis, pulmonary embolism, DIC and other reasons. Key contributory factors to severe maternal outcomes (including death) in women with severe PPH may include demographics (maternal age, education), clinical variables (parity, gestational age, maternal anaemia, caesarean section delivery), late presentation, referral from another facility, and poor infrastructure. Interventions used in the treatment cascade, such as hysterectomy and massive transfusion can result in complications of disseminated intravascular coagulation (DIC), multiple organ dysfunction syndrome (MODS) / MOF and shock that may result in a fatal outcome. Massive transfusion alone is an independent predictor of multiorgan failure (MOF), systemic inflammatory response syndrome (SIRS) and increased mortality as it can precipitate a triad of acidosis, hypothermia, and coagulopathy.

An overview of maternal mortality in women with sPPH across data sources is presented in table 27 below.

Table 27 Proportion of maternal mortality across data sources[a]

Data source	Analysis set	NovoSeven	No NovoSeven[c]
Trial 4816 (RCT), n/N (%)	**FAS**	0/51 (0)[b]	0/33 (0)
Study 4729 (Bern), n/N (%)	**FAS**	0/52 (0)	0/113 (0)
	FAS (NL)	2/37 (5.4)	5/1223 (0.4)
Study 4733 (PPH consortium), n/N (%)	**FAS (DK)**	0/40 (0)	2/199 (1.0)
	FAS (UK)	0/13 (0)	2/149 (1.3)
Study 4731 (UniSeven), n/N (%)	**FAS[d]**	0/87 (0)	NA
Study 4732 (ANZHR), n/N (%)	**FAS**	13/166 (7.8)	NA
Literature review report			
Raw proportion, n/N (%)	**Meta-analysis**	27/664 (4.1)	15/1285 (1.2)
Adjusted proportion, % (95%PI)	**Meta-analysis**	1.8 (0.1, 26.9)	0.2 (0.0, 25.0)

Note: Some data from the literature review overlap with data described in other clinical data sources.

[a]Data sources include trial 4816, studies 4729, 4733, 4731, 4732 and published studies from literature review.
[b]9 women from the reference group were exposed to NovoSeven which means that the total number of women exposed to NovoSeven was 51.
[c]No NovoSeven group includes women not treated with NovoSeven in the FAS (trial 4816, study 4729 and 4733).
[d]A total of 111 women with PPH were exposed to NovoSeven but this includes 24 women for whom severe PPH was not confirmed (blood loss <1500 mL or no blood loss information), hereof one women died.

- **Studies (RCT and non-interventional studies)**

Trial 4816 (RCT)

No maternal deaths were reported in any of the groups.

Study 4729 (Bern)

No maternal deaths were reported in any of the groups.

Study 4733 (PPH consortium)

in DK cohort, no death was reported among women who were treated with NovoSeven while 2 deaths were reported among women who were not treated with NovoSeven.

In NL cohort, two deaths were reported among women who were treated with NovoSeven, while 5 deaths were reported among women who were not treated with NovoSeven. Cause of the death was not reported for the 2 women who died after treatment with NovoSeven in the NL cohort. As per the study clinician, a causal relationship between NovoSeven and the fatal outcome was 'possible'; as per the company assessment, both the deaths were considered 'unlikely related' to NovoSeven.

For UK cohort, no deaths were reported among women who were treated with NovoSeven, while 2 deaths were reported in women who were not treated with NovoSeven.

Study 4731 (UniSeven)

One woman died after NovoSeven treatment. This woman did not have confirmed severe PPH as her blood loss before NovoSeven was not reported. Therefore, she was not included in the FAS. The data from this study were published earlier (Blatný J. et al, 2011), and the publication reported 2 maternal deaths; however, during further analysis it was confirmed that only one woman in this study died as described above. This woman died due to shock after NovoSeven treatment. The causal relationship with

NovoSeven of the fatal outcome was not reported in the study. As per company assessment, the death was 'unlikely related' to NovoSeven

Study 4732 (ANZHR)

A total of 13 maternal deaths were reported in the NovoSeven treated women with severe PPH. In this study 4732, a registry, there was remarkably higher maternal mortality (13/166 (7.8%)) as compared to the maternal mortality reported in other data-sources. The reason for the higher mortality rate in study 4732 (ANZHR) is not known, but patient risk factors, geographical location (e.g., remoteness from speciality care), social and/or cultural factors may be involved. A summary of maternal mortality events is presented in Table 28.

Table 28 Summary of maternal mortality events by subgroups in 4732 (ANZHR)

Total	N
Mode of delivery	
Vaginal	5
Caesarean section	8
Median first dose of NovoSeven	
<60 ug/kg	0
60-90 ug/kg	4
>90 ug/kg	4
Not known	5
Massive transfusion	
Yes	12
No	1
Cause of PPH[a]	
Uterine atony	1
Placental abruption	1
Other[b]	10
Not known	1
Gestational age	
Preterm (≤37 weeks)	7
Full term (38 to 42 weeks)	4
Not known	2
DIC	
Yes	3
No	10
Transferred to reporting hospital	
Yes	6
No	2
Missing	5

[a]Other as causes of PPH included, 3 women with pre-eclampsia; 2 women with intrauterine foetal death; 1 woman each with severe SLE, APLS and arthritis; HELLP syndrome; ruptured splenic artery aneurysm; ruptured subcapsular hematoma; and one woman with other cause not known.
[b]Some women can have more than one (multiple) cause of PPH

Subgroup analyses of the deaths by concomitant medication, fibrinogen level, timing of first dose with respect to start of bleeding and timing of first dose with respect to first invasive procedure showed that the deaths were spread between the subgroups with no obvious pattern or the numbers in one of the subgroups was too low to allow comparison. A clinician affiliated with Monash University assessed all 13 deaths as 'unlikely related' to NovoSeven. Also as per company assessment, all the 13 death were '*unlikely related'* to NovoSeven.

- **Literature review**

In literature review, a total of 27 maternal deaths were reported among women with severe PPH treated with NovoSeven. A total of 15 maternal deaths were reported among women with severe PPH not treated with NovoSeven (No NovoSeven group). The adjusted proportion (PI) of maternal mortality was 1.8% (0.1, 26.9) in women who received NovoSeven and 0.2% (0.0, 25.0) in the 'No NovoSeven group'. Four women who received NovoSeven died during severe PPH as described in 4 case reports in the literature review.

Of 27 deaths reported in NovoSeven treated women the most reported causes of deaths were 'organ failure or sepsis' (26%), 'missing cause of death' (26%) or 'obstetric haemorrhage or hypovolemic shock' (22%) in women with severe PPH treated with NovoSeven. One death in women with severe PPH treated with NovoSeven was due to a TE and this was a 'multisystem failure after emergency pulmonary embolectomy', a procedure which was performed before NovoSeven was administered. This woman was also included in the publication based on ANZHR.25 The causal relation to NovoSeven to 4 maternal deaths in NovoSeven treated women from case-reports were not reported by the authors. After company assessment, 3 of the 4 maternal deaths were assessed to be 'unlikely related' to NovoSeven. One death from a case-report could not be assessed as information was insufficient.

- **Argus safety report**

In ARGUS report, a total of 28 maternal deaths were reported in women with severe PPH. According to the MAH, the high number of fatal cases is most likely due to bias introduced by the nature of post-marketing reporting; the more serious an event, the more likely it is to be reported, the long reporting duration (since 1995 to 2020) and global reporting. The most common risk factors for fatal outcomes, as identified in the case narratives, were major abdominal surgery (e.g., caesarean section, hysterectomy, and laparotomy), DIC, cardiac arrest, haemorrhagic shock, coagulopathy and multiple organ failure. The cause of maternal death was missing in approximately 50% of the fatal cases, however, the most commonly reported causes of deaths were multiple organ failure (4 cases) and DIC (3 cases). In 3 of the 28 fatal cases, the women had one or multiple TEs. The time of death after NovoSeven administration was reported in very few cases.

Summary of maternal deaths across data presented

Across the trial/studies, 16 maternal deaths were reported in women treated with NovoSeven, 13 of which were in study 4732 (ANZHR). The one death reported in study 4731 (UniSeven) was included in the exposed population but was not confirmed as a case of severe PPH. A total of 27 maternal deaths of women treated with NovoSeven were reported in the literature review. One death in the literature review was assessed to be due to a TE ('multisystem failure after emergency pulmonary embolectomy'). All but one death were assessed to be 'unlikely related' to NovoSeven as per company assessment, with the one death unable to be assessed. In cases reported in the Argus database, causality assessment was provided

by the reporter in most of the Argus cases; 4 TEs were assessed as 'probably related', 23 TEs were assessed as 'possibly related' and 10 TEs were assessed as 'unlikely related' to NovoSeven.

Other serious adverse events

- **Studies (RCT and non-interventional studies)**

No protocols planned to capture SAEs other than trial 4816 (RCT). However, in study 4729, apart from TEs, additional cardiac arrest, allergic reactions and haemorrhagic shock were captured.

Trial 4816 (RCT)

No SAEs were reported in the NovoSeven treated women.

Study 4729 (Bern)

In this study, apart from TEs, additional AEs of cardiac arrest, allergic reactions and haemorrhagic shock were captured. Cardiac arrest is an expected AE as an outcome of uncontrolled severe PPH and is not related to NovoSeven treatment. It was reported in 1 of 52 (1.9%) women who were treated with NovoSeven and 1 of 113 (0.9%) women who were not treated with NovoSeven. Two of 52 (3.8%) women who were treated with NovoSeven experienced allergic reactions, while none of the 113 women who were not treated with NovoSeven experienced any allergic reactions. Six of 52 (11.5%) women who were treated with NovoSeven and 4 of 113 (3.5%) women who were not treated with NovoSeven had an event of haemorrhagic shock recorded. One woman in the NovoSeven group had a prolonged hospital stay due to acute renal failure. The woman was hospitalised prior to delivery due to pre-eclampsia. Caesarean section was performed pre-term after start of PPH.

Study 4733 (PPH consortium)

Cardiac arrest was reported for 2/40 (5.0%) women who were treated with NovoSeven and 6/199 (3.1%) women who were not treated with NovoSeven in the DK cohort.

Cardiac events were not collected for the NL cohort.

In the UK cohort, no cardiac events (defined as cardiac arrest, cardiac infection or cardioversion and inotropic support) were reported for women treated with NovoSeven (0/40, 0%) whereas 8/149 (5.4%) women not treated with NovoSeven experienced a cardiac event.

In the NL cohort, of the 37 women treated with NovoSeven in the FAS, 31 (83.8%) women experienced haemorrhagic shock; 1 did not experienced haemorrhagic shock and data was missing for 5 (13.5%) women prior to time0.

- **Other adverse events in Novo Nordisk safety database (Argus) report**

In the Argus report, apart from TEs, the other most frequently reported AEs in women with severe PPH receiving NovoSeven were drug ineffective/drug ineffective in unapproved indication (14 AEs), multiple organ dysfunction syndrome (8 AEs) and DIC (6 AEs). The majority of the AEs were only reported only once.

Laboratory findings

Haematology and coagulation monitoring are routinely performed during severe PPH considering the risk of associated morbidity and mortality with uncontrolled bleeding. In the clinical data sources presented in this application, the available results of haematological laboratory parameters are presented, i.e.

fibrinogen levels, platelet count and pH that are relevant to safety have been captured and are described in this section.

Role of fibrinogen levels, platelet count and pH in severe postpartum haemorrhage

- Efficacy of haemostatic products such as NovoSeven will be limited when fibrinogen levels or platelet count are low (RCOG 2017). Additionally, acidosis (i.e., pH <7.2) may exacerbate dilutional coagulopathy and impair the haemostasis.
- Fibrinogen levels >2 g/L are required for clot formation and stabilisation. Fibrinogen level ≤2 g/L and decreased platelet count has been shown to be associated with an increased risk of severe PPH.
- Acidosis can impair coagulation by delaying clot formation and reducing clot strength, thereby worsening the risk of serious haemorrhage. Furthermore, massive transfusion often exacerbates acidosis as stored blood has a reduced pH and can lead to dilution coagulopathy. A study showed that a reduction in pH from 7.4 to 7.0 nearly abolished FVIIa activity and severely reduced activity of FXa/FVa complex.

Current guidelines recommend maintaining fibrinogen concentration ≥2 g/L and platelet count ≥50 × 109/L with correction of acidosis, during ongoing PPH (RCOG 2017, Muñoz M et al, 2019).

An overview is presented of these relevant laboratory outcomes per study (except PPH consortium) is presented in Table 29 below:

Table 29 Overview of baseline laboratory parameters – by category

	Trial 4816 (RCT)[a]		Study 4729 (Bern)[b]	Study 4731 (UniSeven)[c]	Study4732 (ANZHR)[c]
	NovoSeven	**Reference**	**NovoSeven**	**NovoSeven**	**NovoSeven**
Fibrinogen (n, %)					
N	42 (100.0)	42 (100.0)	22 (100.0)	87 (100.0)	166 (100.0)
<2 g/L	8 (19.0)	5 (11.9)	12 (54.5	57 (65.5)	91 (54.8)
≥2 g/L	27 (64.3)	33 (78.6)	10 (45.5))	27 (31.0)	42 (25.3)
Missing	7 (16.7)	4 (9.5)	0 (0)	3 (3.4)	33 (20.0)
Platelets (n, %)					
Baseline					
N	42 (100.0)	42 (100.0)	25 (100.0)	87 (100.0)	166 (100.0)
$<50 \times 10^9$/L	1 (2.4)	0 (0)	6 (24.0)	14 (16.1)	21 (12.7)
$\geq 50 \times 10^9$/L	38 (90.5)	41 (97.6)	19 (76.0)	73 (83.9)	131 (78.9)
Missing	3 (7.1)	1 (2.4)	0 (0)	0 (0)	14 (8.4)
pH (n, %)					
Baseline					
N	NA	NA	18 (100.0)	87 (100.0)	166 (100.0)
<7.2	NA	NA	1 (5.6)	4 (4.6)	30 (18.1)
≥7.2	NA	NA	17 (94.4)	74 (85.1)	84 (50.6)
Missing	NA	NA	NA	9 (10.3)	52 (31.3)

Note: In trial 4816 (RCT), the baseline and T0 values are not clearly differentiated for samples from one site (Geneva).

aFor trial 4816, baseline refers to T0 samples collected immediately after randomisation and pre-dose NovoSeven; for study 4729, baseline refers to closest values to time0 within a time frame of 60 minutes before time0; and for studies 4731 and 4732, baseline refers to closest values prior to first NovoSeven dose

In the trial 4816 (RCT), median fibrinogen levels (2.4 g/L and 3.2 g/L) were above the threshold of 2 g/L and the median platelet counts (136.0 × 109/L and 145.0 × 109/L) were similar, at T0 in the NovoSeven and reference groups, respectively. The median fibrinogen level and platelet count in the 2 groups suggested that the women had comparable clinical severity at baseline. The majority of women had a fibrinogen level ≥2 g/L in the NovoSeven group (64.3%) and the reference group (78.6%), at T0. Similarly, the majority of women had platelet count ≥50 × 109/L in the NovoSeven group (90.5%) and the reference group (97.6%), at T0. These optimum levels observed were likely due to early use of NovoSeven in this study (within 1 hour of sulprostone failure), before the condition of women worsened due to bleeding.

In study 4729 (Bern), the majority of women had baseline fibrinogen level less than the threshold of 2 g/L (54.5%) and platelet count higher than the minimum threshold of 50 × 109/L (76.0%).

In study 4731 and study 4732 were 1.54 g/L and 1.50 g/L, respectively, the majority of women in both studies had baseline fibrinogen level less than the threshold of 2 g/L and platelet count higher than the minimum threshold of 50 × 109/L. In both studies, the majority of women had baseline measurement pH ≥7.2 (85.1% and 50.6%). Overall, the baseline fibrinogen levels in the single-cohort non-interventional studies were lower, suggesting that the women in these real-world studies were clinically more severe at baseline as compared to the women in trial 4816 (RCT).

Safety in special populations

Not applicable.

Safety related to drug-drug interactions and other interactions

Not applicable.

Discontinuation due to adverse events

Not applicable.

Post marketing experience

See Argus report above.

2.4.1. Discussion on clinical safety

As NovoSeven is on the EU market since 1996, previous safety experience collected in the approved indications is available. As part of this application, the safety data set to support safety of NovoSeven use in women with severe PPH included:

- Pivotal data from the open-label RCT (trial 4816).
- Supportive data from 4 non-interventional studies based on single hospital level data from a single centre (study 4729, Bern, Switzerland), national or population level data from UK, DK, and NL (study 4733 PPH consortium) and 2 registries describing off-label use of NovoSeven (study 4731 in CZ and study 4732 in New Zealand and Australia).

- Supportive data from the Novo Nordisk safety database (Argus) and from a literature review (of published clinical studies and case-reports) that report safety data of women with severe PPH treated with NovoSeven.

Although limited, the key safety data are considered to be derived from the RCT, which are further supported with the data from the non-interventional studies. With the additionally provided literature review (including a meta-analysis) on incidence of thrombosis, and the safety database of the MAH, it is considered that most of the available data on the safety of NovoSeven in the treatment of PPH have been captured.

Rationale MAH for focussing on thrombo-embolic events (TEs)

Due to its mechanism of action, promoting the coagulation cascade, a relevant safety concern with the use of NovoSeven in severe PPH is the likelihood of developing TEs due to potential overstimulation of the coagulation system. In pregnancy and during the postpartum period, women are already in a hypercoagulable state and the incidence of TEs is higher in all patients during the first 6 weeks after delivery, and also factors such as caesarean section, PPH or a body mass index of >30 kg/m2 may further increase the risk. The incidence of venous TEs has been reported to range from <1−7.8% in women with PPH and from 2.5−4.8% in women with PPH treated with NovoSeven. Therefore, the assessment of the safety of NovoSeven in women with severe PPH focussed on TEs, and whether there was an increased risk of TEs following NovoSeven administration. The argumentation to specifically focus on the risk of TE in the population of women with severe PPH is supported, taking into account that this population is already at increased risk of VTE. The general safety pattern of NovoSeven, which is on the market since 1996, is considered sufficiently known. The VTE and (ATE) risk is currently reflected as a warning in section 4.4 of the SmPC.

In addition, also Maternal mortality along with the cause and any other AEs (cardiac arrest, allergic reactions and haemorrhagic shock) and SAEs (SAEs were planned to be captured only in trial 4816) were evaluated.

Patient exposure A total of 446 women with severe PPH combined across the RCT (study 4816) and the four non-interventional studies (4729, 4733, 4731 and 4732) were exposed to NovoSeven. In the literature review, 672 women with severe PPH were reported as having been exposed to NovoSeven. Some patients in the RCT and non-interventional studies overlapped with the patient population included in the published studies. With overlap taken into account, at least 834 women were exposed to NovoSeven and are reported in the trial, non-interventional studies, and literature review. This exposure exceeds the requirements of ICH-E1 and is considered sufficient for adequate assessment of the safety profile of NovoSeven in this new indication. As to dosing, the RCT was a single dose study of 60 µg/kg, although some variation occurred, varying between 60-90 µg/kg, due to the use of whole vials.

Across the non-interventional studies, majority of women required only a single dose of NovoSeven; the proportion of women receiving a second dose ranged from 7.8%−23.0%; and proportion of women receiving a third dose ranged from 1.3%−5.4%. Based on the FAS from the non-interventional studies, the median first dose of 63 µg/kg to 105 µg/kg. The majority of the women in study 4729 (Bern) received a NovoSeven dose of 60-90 µg/kg (71.2%); whilst the other 2 non interventional studies, 4731 (UniSeven) and 4732 (ANZHR), had most patients received >90 µg/kg. median second and third doses in the FAS for those women who received more than one dose ranged from 73 µg/kg to 100 µg/kg across studies. In the literature review, most women received a single dose of NovoSeven, in which doses were between 50 and 100 µg/kg.

AEs of special interest: thromboembolic events

In the ***pivotal trial 4816 (RCT)***, 2/42 women in the NovoSeven group developed a VTE; a VTE in the ovarian vein 2 days after NovoSeven treatment, and a deep vein thrombosis (DVT) + pulmonary

embolism (PE) 5 days after NovoSeven treatment, while no VTE occurred in the reference group. No women developed an ATE in either of the groups. No TEs occurred in the 8 women from the reference group received NovoSeven on compassionate use basis after the primary endpoint was evaluated and just before hysterectomy, and 1 woman from the reference group received NovoSeven in error at time of randomisation. Based on a total of 51 women (42 randomised to Novoseven treatment and 9 exposed later in the reference group (in an attempt to avoid salvage peripartum hysterectomy), the proportion of women with TEs and VTEs accounting for the total women exposed in this trial was 2/51 (3.9%). Causality assessment: Both VTEs were considered unlikely related to the exposure to NovoSeven by the hospital investigators and sponsor physician: the first case was considered unlikely related due to the time course of the VTE, i.e. two days after administration of NovoSeven, the second case was considered unlikely related due to the low dose (32 µg/kg) and additional circumstances of placental abruption, intrauterine foetal death, caesarean section and transfusion may have contributed to events. As a contribution of NovoSeven to the occurrence of these VTEs cannot be ruled out, SmPC section 4.8 reflects that in an open-label randomised clinical trial, venous thromboembolic events were reported in 2 of 51 patients treated with a single dose of NovoSeven (median dose 58 µg/kg) and none of 33 patients not treated with NovoSeven; no arterial thromboembolic events were reported in either group.

Non-interventional studies: in these (studies 4729, 4731, 4732 and 4733), 5 TEs were reported in 395 women after administration of NovoSeven in the FAS (including 1 TE in the NL cohort of study 4733, not included in the meta-analysis). Of these 5 TEs, 1 event was a fatal ATE of acute myocardial infarction in study 4732 (ANZHR). The remaining 4 events were VTEs: 2 VTEs in study 4733 (PPH consortium) (PE; not reported), and 2 VTEs in study 4732 (ANZHR) (DVT; PE). Causality assessment: Of the 5 TEs reported after NovoSeven administration in the non-interventional studies, 3 TEs (2 VTEs and 1 ATE) were assessed as unlikely to be related and the remaining 2 TEs (both VTEs) were assessed as possibly related to NovoSeven, per reporter's assessment. Per Novo Nordisk assessment, 1 of 5 TEs (a VTE) was assessed as possibly related and the remaining 4 TEs (1 ATE and 3 VTEs) were assessed as unlikely to be related to NovoSeven. It can be debated whether or not the relationship to NovoSeven is possibly related or unlikely related, as most women with TEs had confounding factors that may have contributed to development of thrombosis, including HELLP syndrome/pre-eclampsia, emergency caesarean section, intra-uterine foetal death, twin birth or large volume of transfusions. Further, some women were had decreased mobility due to hospitalisation. Also, the temporal relationship between NovoSeven administration and the TE is not always clear in the women with TEs after NovoSeven treatment. Nevertheless, despite confounding factors, a contribution of NovoSeven to occurrence of TEs cannot be ruled out. SmPC section 4.4 reflects that in severe postpartum haemorrhage and pregnancy, the clinical conditions (delivery, severe haemorrhage, transfusion, DIC, surgery/invasive procedures and coagulopathy) are known contributing factors to the thromboembolic risk; and in particular venous thromboembolic risk associated with the administration of NovoSeven. Section 4.8 of the SmPC reflect that in 4 non-interventional studies, venous thromboembolic events were reported in 3 of 358 (0.8%) patients treated with NovoSeven (median dose range 63-105 µg/kg) and arterial thromboembolic events were reported in 1 (0.3%) patient treated with NovoSeven.

In the **meta-analysis**, performed on pooled data from the FAS of the RCT and non-interventional studies estimated an overall adjusted proportion (95% PI) of women with a TE of 0.015 (0.007, 0.032) in NovoSeven treated women and 0.016 (0.008, 0.033) in women not treated with NovoSeven, indicating no increase in TE risk following NovoSeven administration. (note: In the NL cohort of study 4733, a TE was only recorded if it was a complication of an embolisation, therefore, TE data from the NL cohort are excluded from the meta-analysis.)

In the **literature review**, a total of 14 TEs were reported in 13/669 women with severe PPH who received NovoSeven. Twenty-two TEs (in 22 women) were reported in 22/1558 women with severe PPH who did not receive NovoSeven. The overall adjusted proportion for all TEs, VTEs and ATEs after a meta-

analysis of all published studies is 1.6% (0.4%, 6.6%). In women with severe PPH not treated with NovoSeven, the adjusted proportion of women reporting TEs was 0.8% (0.05%, 12.7%)95% PI with adjusted proportions of ATEs and VTEs of 0.005% and 0.5%, respectively. As there was a large overlap between the PIs of the adjusted proportion of TEs (also for ATEs and VTEs) for the populations of women treated with NovoSeven and not treated with NovoSeven, it cannot be concluded that there is a difference between the occurrence of TE in these populations.

In the **Novo Nordisk safety database (Argus)**, 39 women experienced at least one TE among the 123 post-marketing cases of women with severe PPH treated with NovoSeven since 1996. Of these, 21 women had a VTE, 13 women had an ATE and 5 women had multiple TEs (5 ATEs and 7 VTEs). The timing of the first (or only) TE was reported in 27 of the 39 cases. Eleven (11) TEs had an onset and/or were diagnosed within 48 hours after treatment with NovoSeven, whereas the rest of the TEs had an onset and/or were diagnosed within 4 to 28 days after treatment with NovoSeven. The risk of TEs was confounded by several patient related risk factors, concomitant conditions, use of invasive procedures and development of complications. Further, NovoSeven was often given late in the management of severe PPH (i.e., during/after hysterectomy) at a time when the women were at an even further increased risk of developing TEs. A causality assessment of the TE was provided by the reporter in most cases; 4 TEs were assessed as 'probably related to NovoSeven', 23 TEs were assessed as '*possibly related to NovoSeven*' and 10 TEs were assessed as '*unlikely related to NovoSeven*'.

Maternal mortality

Worldwide, postpartum haemorrhage accounts for 8% of maternal deaths in developed regions of the world and 20% of maternal deaths in developing regions (WHO syst. Analys., Lancet 2014). Causes of death in women with PPH include bleeding, organ failure, sepsis, pulmonary embolism, DIC and other reasons.

Trial 4816 (RCT) No maternal deaths were reported in any of the groups.

In the non-interventional studies, a total of 16 maternal deaths were reported for women who received NovoSeven. The maternal death rate ranged from 0% to 7.8% in the NovoSeven group and from 0% to 1.3% in the no NovoSeven group. It cannot be concluded that there is a difference between the occurrence of maternal deaths in these 2 groups of women since a randomised control was only included in trial 4816 (RCT), where no deaths occurred. It might be hypothesised, that the rates in the non-interventional studies results might be affected by 'confounding by indication', i.e. women who are treated with NovoSeven often have a more severe condition than women who are not treated with NovoSeven and might therefore be at risk of higher mortality. However, considering the variety of background complications, it is not possible to draw definite conclusions. The reporter assessment of causal relationship to NovoSeven was 'unlikely' for 13 of the 16 deaths in NovoSeven-treated women, 'possible' for 2 deaths and not available for the remaining death. The Novo Nordisk assessment of causal relationship to NovoSeven was 'unlikely' for all 16 maternal deaths.

The maternal death rate was higher in study 4732 (ANZHR) (7.8% [13/166]) than in the RCT and the other 3 non interventional studies. The reason for the higher mortality rate in study 4732 (ANZHR) is not known, but patient risk factors, geographical location (e.g., remoteness from speciality care), social and/or cultural factors may be involved. All 13 deaths in study 4732 (ANZHR) were assessed as unlikely related to NovoSeven by a physician affiliated with Monash University.

The most commonly reported causes of death were 'multiple organ failure' (2 women), 'cerebral ischaemia' (2 women) and cardiac arrest (4 women in total: 'cardiac arrest', 'cardiac arrest due to uncontrolled bleeding', 'cardiac arrest secondary to pulmonary embolism'. Other causes of death (1 woman each) were 'shock', 'sepsis', 'secondary to uncontrolled haemorrhage' and 'uncontrolled blood

loss'. Cause of death was not available for 4 women. Conditions that could have contributed to a fatal outcome were reported in most cases.

Literature review In literature review, 27 maternal deaths were reported among women with severe PPH treated with NovoSeven, and 15 maternal deaths were reported among women with severe PPH not treated with NovoSeven (No NovoSeven group). The adjusted proportion (PI) of maternal mortality was 1.8% (0.1, 26.9) in women who received NovoSeven and 0.2% (0.0, 25.0) in the 'No NovoSeven group'. Of 27 deaths reported in NovoSeven treated women, the most reported causes of deaths were 'organ failure or sepsis' (26%), 'missing cause of death' (26%) or 'obstetric haemorrhage or hypovolemic shock' (22%), and one death was due to a TE (a 'multisystem failure after emergency pulmonary embolectomy') performed before NovoSeven administration.

Argus safety report In ARGUS report, 28 maternal deaths were reported in women with severe PPH. The high number of fatal cases is most likely due to bias introduced by the nature of post-marketing reporting i.e. the more serious an event, the more likely it is to be reported, the long reporting duration (since 1995 to 2020) and global reporting. The most common risk factors for fatal outcomes, as identified in the case narratives, were major abdominal surgery (e.g., caesarean section, hysterectomy, and laparotomy), DIC, cardiac arrest, haemorrhagic shock, coagulopathy and multiple organ failure. The cause of maternal death was missing in approximately 50% of the fatal cases, however, the most commonly reported causes of deaths were multiple organ failure (4 cases) and DIC (3 cases). In 3 of the 28 fatal cases, the women had one or multiple TEs. The time of death after NovoSeven administration was reported in very few cases.

Other serious adverse events No protocols planned to capture SAEs other than trial 4816 (RCT). Trial 4816 (RCT): No SAEs were reported in the NovoSeven treated women.

In Study 4729 (Bern) additional AEs of cardiac arrest, allergic reactions (known adverse event of NovoSeven) and haemorrhagic shock were captured. Cardiac arrest is an expected AE as an outcome of uncontrolled severe PPH and is not related to NovoSeven treatment. Cardiac arrest was reported in 1/52 (1.9%) in the NovoSeven group vs. 1/113 (0.9%) in the non-treated group. Haemorrhagic shock was noted in 6/52 (11.5%) in the NovoSeven group vs. 4/113 (3.5%) non-treated group. Although these reports suggest numerical higher number of SAEs in the NovoSeven group vs the non-treated group of women with severe PPH, data are too limited to draw any conclusions. In Study 4733 (PPH consortium) additionally cardiac AEs were captured, which was reported for 2/40 (5.0%) women treated with NovoSeven and 6/199 (3.1%) women who were not treated with NovoSeven (DK cohort). In the UK cohort, no cardiac events (defined as cardiac arrest, cardiac infection or cardioversion and inotropic support) were reported for women treated with NovoSeven (0/40, 0%) whereas 8/149 (5.4%) women not treated with NovoSeven experienced a cardiac event. In the NL cohort, 31/37 (83.8%) women treated with NovoSeven experienced haemorrhagic shock, which was defined as "*at least one measurement of systolic blood pressure ≤90 mmHg and/or a heart rate ≥120 beats per minute from start of haemorrhage until time of diagnosis of persistent PPH*" according to the WHO guideline on evaluating the quality of care for severe pregnancy complications.[5] However, the percentage of women with haemorrhagic shock at any time (period from delivery to 24 hours after childbirth) was comparable between the 2 groups in the full analysis set (FAS) (NovoSeven: 32/37 (86.5%) versus No NovoSeven: 1052/1223 (86.0%), indicating no increased rates of haemorrhagic shock in the NovoSeven exposed group. The high proportion of women with haemorrhagic shock might be related with the more progressed course of severe PPH observed in this NL population as indicated by their inclusion criteria, i.e., women with obstetric haemorrhage who had either received ≥4 units of red blood cells (RBC), multicomponent blood transfusion (RBC, fresh frozen plasma and/or platelet concentrates) or plasma in addition to RBCs.

[5] WHO. Evaluating the quality of care for severe pregnancy complications. 2011.

2.4.2. Conclusions on clinical safety

As NovoSeven is on the EU market since 1996, previous safety experience collected in the approved indications is available. Due to its mechanism of action, i.e. promoting the coagulation cascade, the most relevant safety concern with the use of NovoSeven in severe PPH is the likelihood of developing TEs due to potential overstimulation of the coagulation system. In this respect, due to pregnancy and during the postpartum period, this patient group is already in a hypercoagulable state. The increased risk of TE, which is largely concerning an increased risk of venous thromboembolic events (VTEs) is also established in this new treatment population. Although the higher baseline risk of VTE in this specific patient group will have contributed, this increased risk of VTE is considered the most important safety issue. It can be debated whether or not the relationship to NovoSeven is possibly related or unlikely related, as most women with TEs had confounding factors that may have contributed to development of thrombosis. Therefore, the increased risk is difficult to quantify. Nevertheless, despite confounding factors, a contribution of NovoSeven to occurrence of TEs cannot be excluded. This has been adequately reflected in section 4.4 of the SmPC.

2.4.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.5. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 8 is acceptable.

The CHMP endorsed the Risk Management Plan version 8 with the following content:

Safety concerns

Table SVIII.1: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance plan

Routine pharmacovigilance is considered to be sufficient.

There are no ongoing or planned additional pharmacovigilance studies/activities (imposed, mandatory or required [Category 1–3]).

Risk minimisation measures

Not applicable, because there are no risks or missing information in the list of safety concerns.

2.6. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.6.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

NovoSeven is an activated recombinant coagulation factor VII which is structurally similar to human plasma factor VIIa authorised in the EU in 1996 and in the US in 1999. The approved indications include the treatment of bleeding episodes and for the prevention of bleeding in those undergoing surgery or invasive procedures in patients with congenital or acquired haemophilia, haemophilia with inhibitors to coagulation factors VIII or IX, in patients with congenital FVII deficiency, and in patients with Glanzmann's thrombasthenia. The recommended initial dose, administered by intravenous bolus injection, is 90 µg/kg body weight.

In this application, the indication of NovoSeven is proposed to be extended with the treatment of severe postpartum haemorrhage (PPH). The recommended dose range is 60 – 90 µg per kg body weight. Dose and dose interval are proposed to be based on clinical response and adapted to the individual patient. In case of insufficient haemostatic response, a second dose is proposed to be administered after 30 minutes.

Current off-label use of NovoSeven in severe postpartum haemorrhage

NovoSeven is not currently approved for use in severe PPH. Nevertheless, there is a growing body of evidence from off-label use, including patient registries and literature reports, describing the use of NovoSeven for the treatment of women with severe PPH. Reviews of published clinical studies and case reports suggest a beneficial role for NovoSeven in the management of severe PPH (Francini 2007, 2010, Lavigne 2015 (included in this dossier)). Off-label use of NovoSeven as a haemostatic agent in the treatment of PPH is recommended in several local guidelines on PPH.

3.1.1. Disease or condition

NovoSeven is indicated for the treatment of severe postpartum haemorrhage when uterotonics are insufficient to achieve haemostasis.

3.1.2. Available therapies and unmet medical need

Treatment of PPH

The treatment options for PPH relate to the underlying cause of haemorrhage. A combination of pharmacological, blood products, mechanical and surgical interventions are used presently; additionally, clinicians can consider the use of haemostatic agents. Several medicinal products are approved for treatment of PPH due to uterine atony, of which oxytocin is considered first choice. Additional medicinal products include methergine, prostaglandin E2 agonists (dinoprost, sulprostone). Misoprostol is used off-label, but has less efficacy than oxytocin. Additionally, also intravenous tranexamic acid is used off-label, since the WOMAN trial (Shakur et al, Lancet), at the time of uterotonic treatment, has been included in many PPH management protocols.

If bleeding persists after failure of uterotonics, clinicians can use a combination of haemostatic agents (fibrinogen), transfusion of blood products (RBC, FFP, platelets, cryoprecipitate), fluid replacement and minimally invasive mechanical interventions (removal of retained placenta, intrauterine balloon tamponade, etc) (RCOG 2016). Non-invasive mechanical methods such as uterine compression and aortic compression may be applied concomitantly as needed.

It is noted that, although guidelines in standard of care will have been updated over time, in general, first line and second line treatments generally have not relevantly changed since the last decade, though existing techniques of invasive procedures will have been further refined.

It's agreed that there is an unmet need for approved non-invasive treatments to improve the standard of care in severe PPH and to avoid a hysterecrtomy or for life-saving situations.

Additionally, Novoseven, which consists of the coagulation factor VIIa, is used off-label as an haemostatic agent. Various international and national guidelines have been developed for the management of PPH, based on collective experience and results from registry studies, in which in several the use of Novoseven is also included as an option.

3.1.3. Main clinical studies

The main evidence of efficacy submitted is a single randomized, parallel-group, open-label multicentre clinical outcome trial evaluating the efficacy and safety of NovoSeven, when added to background standard of care in subjects with severe post-partum haemorrhage (PPH) defined as having > 1500 ml blood loss within 24 hours after delivery who were randomised following failure of sulprostone to control the bleeding one hour after onset of infusion. Further, the patient should have a gestation of > 27 weeks and aged 18 years or older. Patients with a personal risk of thrombosis (VTE or ATE) were excluded.

The study included 2 treatment groups (NovoSeven versus standard therapy, 1:1 randomization). The Novoseven group received a single dose of approximately 60 µg/kg via slow IV injection (2mL/min) immediately after randomisation. The protocol primary endpoint was the absolute and relative reduction in need for specific second-line therapies (rate of embolisation and/or ligation) in the rFVIIa (Novoseven) group versus the reference group. The primary endpoint applied in the subsequent publication consisted of the "Reduction in the need for specific second-line therapies (at least one ligation, suture, embolisation, intra-uterine balloon tamponade and/or hysterectomy)".

The results of 4 non-interventional studies provided additional efficacy (and safety) data. These were based on single hospital level data from a single centre (study 4729, Bern, Switzerland), national or population level data from UK, DK, and NL (study 4733 PPH consortium) and 2 registries describing off-label use of NovoSeven in non-haemophilic patients (study 4731 in CZ and study 4732 in New Zealand and Australia).

Further, data from the Novo Nordisk safety database (Argus) and from a literature review (of published clinical studies and case-reports) that report safety data of women with severe PPH treated with NovoSeven have been provided.

3.2. Favourable effects

Primary endpoint RCT protocol. In the pivotal study RCT, treatment with Novoseven following failure of sulprostone to control the bleeding resulted in a significant relative risk reduction of 40% in the need for specific second-line therapies (at least one ligation or embolisation) (RR 0.60 [0.43;0.84]); 0.0012. The absolute risk reduction was 33.3% (14.47; 52.19). The NNT to avoid at least one second-line therapy was 2.6. This positive effect was independent from the delivery mode (vaginal delivery or caesarean section).

Primary endpoint RCT publication. For the adapted primary endpoint in the subsequent publication of this RCT, treatment with NovoSeven resulted in a relative risk reduction of 44% in the need for specific second-line therapies (*at least one ligation, suture, embolisation, intra-uterine balloon tamponade and/or hysterectomy*) (RR 0.56 [0.42;0.76]). The absolute risk reduction was 41% (18; 63). The NNT to avoid at least one second-line therapy was 3. This positive effect was independent from the delivery mode.

Secondary endpoints RCT publication. The protocol of the RCT did not include secondary endpoints. In the publication of the RCT, the components of the primary endpoint were tested (although not defined a secondary endpoints), without multiplicity correction, and therefore these analyses are considered exploratory. The analyses showed that the significant beneficial effect is mainly driven by a reduction in arterial embolisation, the procedure which was applied most frequently. In deviation from the RCT trial protocol, blood loss was not measured. Determination of the transfusion needs were assessed before and after randomization showed no between-group difference in absolute numbers of administered blood products (RBCs, FFP (fresh frozen plasma), and PCs (platelet cells)). Analysis of replacement treatments (fibrinogen concentrates, tranexamic acid (TXA), aprotinin), showed no clear between group difference in the use of these products. A significant greater fall in Hb concentration between T0 and T30 was noted, with a median decrease of −0.2 g/dL in the intervention arm and of −0.9 g/dL in the standard care arm.

Laboratory data In the RCT, baseline fibrinogen concentration was ≥2 g/L and baseline platelet count were ≥50 × 109/L) in the majority of women, according to PPH guidelines (RCOG 2017). Efficacy of haemostatic products such as NovoSeven will be limited when fibrinogen levels or platelet count are low.

Supportive data. Data from 4 non-interventional studies of different sources across Europe and from Australia/New Zealand have been provided.

3.3. Uncertainties and limitations about favourable effects

Novoseven was used in addition to standard of care. At T0, the median fibrinogen levels were above the threshold of 2 g/L in both the NovoSeven (2.4 g/L) and reference group (3.2 g/L). After T0, the use of tranexamic acid and fibrinogen was permitted in the SoC in the pivotal trial. The MAH presented an overview of the use of tranexamic acid (TXA) and fibrinogen as additional treatment in the pivotal trial during the first hour after Novoseven treatment. However, the information on TXA and fibrinogen is incomplete as there is a substantial amount of missing data on fibrinogen and TXA. Therefore, the exact concomitant use of TXa and fibrinogen remains uncertain. Nevertheless, this information is considered of importance for prescribers and information that data collection on fibrinogen and TXA was incomplete is included in section 5.1 the SmPC.

The additional data, consisting of 4 non-interventional studies of different sources across Europe and from Australia/New Zealand, have provided limited evidence for efficacy. Also, the non-interventional studies

did not provide information on dose in relation to efficacy. Hence, these studies can only be considered as supportive and the main evidence of efficacy comes from the RCT study 4816.

3.4. Unfavourable effects

Thromboembolic events

Due to its mechanism of action, promoting the coagulation cascade, the most relevant safety concern with the use of NovoSeven in severe PPH is the likelihood of developing TEs, including VTEs. In the pivotal trial 4816 (RCT), the incidence of VTE was increased (4.8% (2/42)) in comparison to non-treated patients (0% (0/42)). No TEs occurred in the 8 women in the reference group who received NovoSeven for compassionate use, and 1 woman in reference group received NovoSeven in error at time of randomisation. Based on this total of 51 women (42 randomised treatment and 9 exposed later), the proportion of women with TEs and VTEs accounting for the total women exposed in this trial was 2/51 (3.9%).

Section 4.4 of the SmPC provides the following recommendation: In severe postpartum haemorrhage and pregnancy, the clinical conditions (delivery, severe haemorrhage, transfusion, DIC, surgery/invasive procedures and coagulopathy) are known contributing factors to the thromboembolic risk; and in particular venous thromboembolic risk associated with the administration of NovoSeven.

3.5. Uncertainties and limitations about unfavourable effects

It can be debated whether or not the relationship to NovoSeven is possibly related or unlikely related, as most women with TEs had confounding factors that may have contributed to development of thrombosis. Nevertheless, despite confounding factors, a contribution of NovoSeven to occurrence of TEs cannot be ruled out and this will be followed-up post-approval via PSURs.

3.6. Effects Table

Table 30 Effects Table for NovoSeven in patients with severe PPH in study 4816 (RCT)

Effect	Short description	Unit	Standard care + NovoSeven	Standard care	Uncertainties / Strength of evidence	References
Favourable Effects						
Primary endpoint protocol	Reduction in need for specific second-line therapies (at least one ligation or embolisation)	N (%)	21/42 (50%)	35/42 (83%)	**SoE**: RR 0.60 [0.43;0.84]; p=0.0012 NNT= 3	Study 4816 (RCT)
Unfavourable Effects						
VTE		N (%)	2/51 (3.9%)*	0%		Study 4816 (RCT)

Abbreviations: VTE: venous thromboembolic event;
*: 8 women in standard care group received NovoSeven on compassionate use basis after the primary endpoint was evaluated and just before hysterectomy; also, 1 woman from the reference group received NovoSeven in error at time of randomisation) developed a TE. Therefore, a total of 51 women (42 randomised treatment and 9 exposed later)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

There remains a significant unmet need to optimise standard of care of severe PPH and reduce the need for hysterectomy and other invasive procedures. Several local guidelines describe off-label use of NovoSeven for management of severe PPH rather late in the treatment cascade, to avoid a hysterectomy or for life saving situations.

The current application to extend the indication of NovoSeven r(FVIIa) with the treatment of severe PPH when uterotonics are insufficient to achieve haemostasis is primarily based on the results of a single pivotal well-conducted randomised controlled study, in which 8 French and Swiss hospitals participated, sponsored by the University of Nimes, France. The investigated primary endpoint is considered a robust objective outcome and highly relevant to patients in an emergency situation of severe post-partum haemorrhage (PPH). In the intervention arm, Novoseven treatment with 60 µg/kg was initiated when, according to applied French practice guidelines, first-line therapies for PPH failed.

The results demonstrated a significant and clinically relevant reduction of 40% in need of invasive procedures (ligation or embolisation) when Novoseven was used on top of standard therapy. This was supported by the results of the publication endpoint with a reduction of 44% in invasive procedures extended (at least one ligation, suture, embolisation, intra-uterine balloon tamponade and/or hysterectomy).

As to the relevancy of the efficacy and safety data collected in the pivotal RCT performed more than 10 years ago, it is noted that based on the description of first line therapies, replacement therapies and second line invasive therapies applied, the management of severe PPH in this study in general is in agreement with current guidelines on management of PPH. Therefore, these results are still able to inform the benefit/risk of NovoSeven assessed in this study when taking into account the updated current standard of care for severe PPH.

As to the dose range of 60-90 µg/kg proposed in the posology, it is noted that there was some variation around the target dose in the RCT (60 µg/kg) due to full vials being administered. The median NovoSeven dose administered in the RCT trial was 58 µg/kg, with 25 women receiving <60 µg/kg dose, 17 women receiving 60-90 µg/kg dose. Therefore, the proposed dose range of 60−90 µg/kg is acceptable. In addition, it provides flexibility for physicians to adjust the dose according to individual patient need and is consistent with the clinical practice of using entire vials which leads to some variation in the µg/kg dose.

The indication was revised during the evaluation of this application to reflect the population treated in the RCT, i.e. the treatment of severe PPH when uterotonics are insufficient to achieve haemostasis.

Further, the recommendation of a second dose in case of insufficient haemostatic response is considered acceptable, and the recommended dose interval of 30 minutes is considered adequately justified.

As NovoSeven is on the EU market since 1996, previous safety experience collected in the approved indications is available. Safety data in this dossier are primarily based on the data of the RCT, but supported with data from the 4 non-interventional studies. Further, data from the Novo Nordisk safety database (Argus) and from a literature review (of published clinical studies and case-reports) that report safety data of women with severe PPH treated with NovoSeven. Due to its mechanism of action, promoting the coagulation cascade, the most relevant safety concern with the use of NovoSeven in severe PPH is the likelihood of developing TEs, including VTEs.

3.7.2. Balance of benefits and risks

Benefit of NovoSeven is established in terms of a significant reduction in the need for specific second line therapies compared to patients on standard treatment when administered early after failure of conventional medical treatment in patients with severe PPH. The exact contribution of NovoSeven in the development of VTE in severe PPH cannot be established as both the treated patient has increased baseline risk due to her pregnancy/delivery status, and the condition of PPH itself and other complications such as caesarean section may further increase the risk of VTE. Nevertheless, VTE can be considered a manageable risk in most cases, and considering that this is an emergency situation to be treated within a hospital setting, the risk of delay in diagnosis and treatment is expected to be low. Therefore, the benefit/risk balance is considered positive for the treatment of severe postpartum haemorrhage when uterotonics are insufficient to achieve haemostasis.

3.7.3. Additional considerations on the benefit-risk balance

Although not investigated in the RCT, the clinical relevance of a second dose is acknowledged. The selected 30 minute dose-interval is considered adequately supported by the available pharmacodynamic data of NovoSeven indicating time to maximum coagulant effect at 10 minutes after dosing, PPH guidelines recommending a second dose 15-30 minutes after the first dose of NovoSeven[6,7] as well as the RCT where clinical response (evaluation of treatment effect) was evaluated within 30 minutes of NovoSeven administration.

3.8. Conclusions

The overall B/R of Novoseven is positive for the treatment of severe PPH when uterotonics are insufficient to achieve haemostasis.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of severe postpartum haemorrhage when uterotonics are insufficient to achieve haemostasis. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet is also updated in accordance. Version 8.0 of the RMP has also been submitted.

[6] Affronti G, Agostini V, Brizzi A, Bucci L, De Blasio E, Frigo MG, et al. The daily-practiced post-partum hemorrhage management: an Italian multidisciplinary attended protocol. Clin Ter. 2017;168(5):e307-e16.
[7] Abdul-Kadir R, McLintock C, Ducloy AS, El-Refaey H, England A, Federici AB, et al. Evaluation and management of postpartum hemorrhage: consensus from an international expert panel. Transfusion. 2014;54(7):1756-68.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'NovoSeven II-116'