28 February 2019
EMA/347546/2019
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Ondexxya

International non-proprietary name: andexanet alfa

Procedure No. EMEA/H/C/004108/0000

Note

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

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Administrative information

Name of the medicinal product:	Ondexxya
Applicant:	Portola Netherlands B.V. Prins Bernhardplein 200 1097 JB Amsterdam Netherlands
Active substance:	Andexanet alfa
International Non-proprietary Name/Common Name:	Andexanet alfa
Pharmaco-therapeutic group (ATC Code):	All other therapeutic products, antidotes (V03AB38)
Therapeutic indication(s):	For adult patients treated with a direct factor Xa (FXa) inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.
Pharmaceutical form(s):	Powder for solution for infusion
Strength(s):	200 mg
Route(s) of administration:	Intravenous use
Packaging:	Vial (glass)
Package size(s):	4 vials

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List of abbreviations

ACT	activated clotting time
ADA	anti-drug antibody
AE	adverse event
AET	analytical evaluation threshold
andexanet alfa	Recombinant factor Xa inhibitor antidote, PRT064445
aPCC	activated prothrombin complex concentrate
aPTT	Activated Partial Thromboplastin Time
ATIII	antithrombin III
ATC	Anatomical Therapeutic Chemical (Classification System)
AUC	Area under the curve
BID	administration twice daily (lat. bis in dies)
CHO	Chinese hamster ovary
CI	continuous infusion
CI	confidence interval
CIP	Cleaning in place
Cmax	maximum concentration
Cmin or Ctrough	minimum (trough) plasma concentration
CNS	Central Nervous System
CQA	Critical quality attribute
CPP	Critical process parameters
DEAE	Diethyl amino ethyl
D-dimer	fibrin degradation fragment
DoE	Design of Experiment
DP	Drug product
DS	Drug substance
DVT	deep vein thrombosis
ECG	Electrocardiography
EOP	End of production
ETP	endogenous thrombin potential
F1+2	prothrombin fragment 1+2
FX	Coagulation factor X
fXa	activated coagulation Factor Xa
GC	Gas chromatography
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HC	Heavy chain
HCP	Host cell protein
HPLC	High performance liquid chromatography
ICH	International Conference of Harmonization
ICH	intra-cranial haemorrhage
IEF	Isoelectric Focusing
IEX	Ion Exchange Chromatography
ITIH5	Inter-alpha-Trypsin Inhibitor Heavy Chain H5
IPC	In-process control
IS	International Standard
IU	International units
IV	intravenous
Kd	dissociation constant
Ki	inhibitory constant
LC	Light chain
LMWH	low molecular weight heparin
LoQ	Limit of quantitation
MAA	Marketing authorisation application
MCB	master cell bank
MedDRA	Medical Dictionary for Regulatory Activities
MFD	maximum feasible dose
MI	myocardial infarction
NaCl	Sodium chloride
nM	nanomolar
NOAEL	No Observed Adverse Effect Level

NOR	Normal operating range
OOS	Out-of-specification
PD	Pharmacodynamic
PCC	prothrombin complex concentrate
PK	Pharmacokinetic
PO	orally, oral
PPQ	Process Performance Qualification
PT	prothrombin time
PQA	Product quality attribute
q12h	every 12 hours
QD	once daily
rfVIIa	recombinant activated factor VII
RCB	research cell bank
RP	Reversed Phase
SAE	serious adverse event
SD	Standard deviation
SDS-PAGE	Sodium dodecyl sulfate polyacrylamide gel electrophoresis
SEC	Size Exclusion Chromatography
SEM	standard error of the mean
SOC	System Organ Class
SOP	Standard Operating Procedure
SWFI	Sterile Water for Injections
t1/2	half life
TAT	thrombin-antithrombin III complex
TEAE	treatment-emergent adverse event
TFPI	Tissue Factor Pathway Inhibitor
TK	Toxicokinetic
TOC	Total organic carbon
UF/DF	Ultrafiltration/diafiltration
VTE	venous thromboembolism
VF	Virus filtration
WCB	Working cell bank

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Portola Pharma UK Limited submitted on 1 August 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Ondexxya, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication: "For adult patients treated with a direct or indirect factor Xa (FXa) inhibitor when reversal of anticoagulation is needed in situations such as;

- in life-threatening or uncontrolled bleeding
- for emergency surgery/urgent procedures".

The legal basis for this application refers to: Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that andexanet alfa was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0199/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0199/2016 was not yet completed as some measures were deferred.

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 applicant 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.

Applicant's requests for consideration

Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14-a of the above mentioned Regulation (EC) No 726/2004.

New active Substance status

The applicant requested the active substance andexanet alfa contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific Advice

The applicant received Scientific Advice on 25 April 2014 (EMEA/H/SA/2735/1/2014/III) and 23 October 2014 (EMEA/H/SA/2735/1/FU/1/2014/II) for the development programme supporting the indication granted by the CHMP. The Scientific Advice pertained to the following quality, non-clinical, and clinical aspects:

- Integration of commercial-scale material into the programme.
- In vitro and in vivo pharmacology data to establish the mechanism of action and proceed to clinical studies. Toxicology studies to support safety, including thromboembolic risk. Need for reproductive toxicity studies and carcinogenicity studies.
- The initial advice discussed, in light of challenges to provide comprehensive data from a randomized controlled clinical trial in the target population, proposed registration studies in healthy volunteers dosed with fXa inhibitors demonstrating reversal of anticoagulation based on a reduction of anti-fXa activity, supported by studies in special populations (elderly and chronic kidney disease). Justification for marketing authorisation under Exceptional Circumstances or Conditional Approval. Dosage strategy. Proposed indication. Design and the timing of a post-marketing authorisation open-label safety study in fXa inhibitor anticoagulated patients experiencing major bleeding or requiring urgent/emergent surgery. Monitoring for infusion reactions, thrombotic events, and formation of antibodies to test article and native fX/fXa.
- The follow-up advice discussed design and timing of a prospective, phase 3b open-label safety and efficacy study of andexanet alfa in patients receiving a fXa inhibitor who are experiencing an acute major bleeding episode. Acceptance of achievement of haemostatic efficacy of stopping an ongoing major bleed at 24 hours from the start of the andexanet bolus as primary endpoint and criteria for success. Inclusion/exclusion criteria. Dosing regimens. Proposed clinical package to support a marketing authorisation, including acceptance to include data from the first 10-20 patients from the phase 3b study.
- In the follow-up advice 23 October 2014, CHMP agreed with the choice of primary and secondary endpoint.

  Primary endpoint:

  o achievement of haemostatic efficacy of stopping an ongoing major bleed at 24 hours from the start of the andexanet bolus,

  Secondary endpoint:

  o The percent change from baseline in anti-fXa activity to the nadir from the evaluation period
- Nevertheless, the applicant changed the primary objective and as a consequence the secondary efficacy endpoint of “change in anti-fXa activity” was studied as an additional primary endpoint in order to establish the correlation between anti-fXa levels as a surrogate marker following andexanet treatment and effective haemostasis.
- No specific CHMP guideline on antidotes to the anticoagulants is available. However, the Guideline on clinical investigation of medicinal products for prevention of stroke and systemic embolic events in patients with non-valvular atrial fibrillation (EMA/CHMP/341363/2014) includes a chapter on the need for reversal and laboratory monitoring.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Concepcion Prieto Yerro

The application was received by the EMA on	1 August 2016
The procedure started on	18 August 2016
The Rapporteur's first Assessment Report was circulated to all CHMP members on	9 November 2016
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	7 November 2016
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	18 November 2016
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	15 December 2016
The applicant submitted the responses to the CHMP consolidated List of Questions on	8 September 2017
The following GMP and GCP inspections were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GCP inspection at 3 sites: an investigator site, CRO site and sponsor site, all located in the USA, was performed between 16/01/2017 and 10/02/2017. The outcome of the inspection carried out was issued on	10 May 2017
– A GMP inspection at one manufacturing site responsible for the active substance and the finished product in the Unites States of America between 27 February 2017 and 03 March 2017. The outcome of the inspection carried out was issued on	12 April 2017
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	17 October 2017
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	26 October 2017
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	9 November 2017
The applicant submitted the responses to the CHMP List of Outstanding Issues on	22 January 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	08 February 2018 and 15 February 2018
The outstanding issues were addressed by the applicant during an oral	20 February 2018

explanation before the CHMP during the meeting on	
The CHMP agreed on a 2nd list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	22 February 2018
The applicant submitted the responses to the 2nd CHMP consolidated List of outstanding issues on	13 November 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	29 November 2018 and 06 December 2018
The CHMP agreed on a 3rd list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	14 December 2018
The applicant submitted the responses to the 3rd CHMP consolidated List of outstanding issues on	29 January 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	14 February 2019 and 21 February 2019
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ondexxya on	28 February 2019

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The initially applied target indication for andexanet was for adult patients treated with a direct or indirect activated factor X (FXa) inhibitor when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding or for emergency surgery/urgent procedures.

Anticoagulation therapy for prevention of thrombotic and thromboembolic complications in several underlying diseases (e.g. atrial fibrillation) or for covering major surgical procedures is a commonly used approach mainly in the elderly population worldwide.

Standard" anticoagulant products e.g. coumarin derivatives (Vitamin-K-antagonists, VKAs) are well-known and widely used in standard medical care. Small therapeutic window and risk of threatening bleeding has to be considered when caring for respective patients. For emergency-reversal of the therapeutic effect, Vitamin K and Coagulation factors are available.

Novel oral anticoagulants (NOACs, or Direct oral FXa inhibitors [DOACs] have been developed in similar indications. Main advantage is that in general no monitoring of the effect is necessary. However, NOACs also account for unintended bleeding situations with comparable incidences and similar disabling or life-threatening risks as VKAs. Apixaban, rivaroxaban and edoxaban are approved in the European Union (EU). These approved direct FXa inhibitors are indicated for prevention of stroke in patients with atrial fibrillation (AF) (all of them), prevention of venous thromboembolism (VTE) in hip and knee replacement surgery (all except edoxaban), treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), including the prevention of recurrence of VTE (all of them), and for prevention of atherothrombotic events after acute coronary syndrome (ACS) (rivaroxaban only).

Indirect FXa inhibitors such as fondaparinux and enoxaparin have been widely used for years. Indications for fondaparinux include prevention of VTE in adults undergoing major orthopaedic surgery of the lower limbs or abdominal surgery at high risk of thromboembolic complications; prevention of VTE in adults at high risk who are immobilised with acute illness; treatment of adults with acute symptomatic spontaneous superficial-vein thrombosis of the lower limbs without concomitant DVT. Indications for enoxaparin include treatment of DVT and PE; treatment of unstable angina and non-Q-wave myocardial infarction (MI), as well as treatment of acute ST segment Elevation Myocardial Infarction (STEMI); prophylaxis of VTE in medical patients bedridden due to acute illness and associated with orthopaedic or general surgery.

Following the evaluation of this application the CHMP agreed to grant a conditional Marketing Authorisation for the following indication: for adult patients treated with a direct factor Xa (FXa) inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.

2.1.2. Epidemiology and risk factors

2.1.2.1. Epidemiology of severe/life-threatening bleeding

Direct factor Xa inhibitors: In clinical trials of patients with atrial fibrillation (AF) receiving FXa inhibitors, major bleeding occurred at an annualised rate of 2.1 to 3.5%. However, the target population for andexanet alfa includes patients with severe/life-threatening bleeding, which comprises about only a half of all major bleedings, occurring at an approximately 1.2% to 1.5% yearly rate with the DOACs and 1.8%/year with warfarin in patients with AF [Connolly et al. N Engl J Med. 2009; 361:

1139-51]. Most of these bleedings comprise intracranial hemorrhages (ICH) and severe extracranial hemorrhages in similar proportion. Of all severe extracranial hemorrhages, approximately 90% correspond to gastrointestinal hemorrhages (GIH) [Niessner A, et al. Eur Heart J. 2015; DOI: 10.1093/eurheartj/ehv676]. Based on data available from the idarucizumab study [Pollack et al. N Engl J Med. 2015; 373: 511-20], approximately 90% of severe bleedings with DOACs will occur in the AF indication and 10% in other indications (i.e.: mainly VTE), while the localisation of the severe bleeding will be intracranial in 40% of cases, gastrointestinal in another 40% of cases, 10% will occur in trauma patients and 10% in other localisations (i.e.: retroperitoneal, pericardial, etc).

Indirect factor Xa inhibitors: Given that LMWHs and fondaparinux are not used in AF, severe bleedings with these compounds will mainly occur during thromboprophylaxis in surgical patients, as well as with the use of high doses in the context of treatment of VTE and acute coronary syndromes (ACS). The localisation of the severe bleeding will depend on the indication, with most cases being excessive wound bleedings in surgical patients and intracranial and/or gastrointestinal in patients with VTE or ACS.

2.1.2.2. Epidemiology of emergency surgery/urgent procedures in patients anticoagulated with a factor Xa inhibitor.

Annually, 10% of patients taking antithrombotic agents undergo elective or urgent surgery/procedure that requires temporary discontinuation of therapy [Baron et al. N Engl J Med. 2013; 368: 2113-24]. Approximately 1% of anticoagulated patients require interruption of anticoagulation due to urgent surgery/procedure (i.e.: 1 in every 10 surgeries/procedures are urgent), according to a recent subanalysis of the RE-LY study [Douketis et al. Thromb Res. 2016;139:77-81]. In anticoagulated patients who undergo an urgent surgery/procedure, rates of major bleeding are between 17% and 23%, but thromboembolism rates are also quite significant, ranging between 7% to 16%, while mortality rates are between 2%-6%. Rates of these outcomes are multi-fold higher in patients having an urgent rather than an elective surgery/procedure [Douketis et al. Thromb Res. 2016;139:77-81].

2.1.2.3. Risk factors for bleeding

The main risk factors for bleeding are the association of anticoagulation with surgery, advanced age, comorbidities (e.g.: renal or hepatic impairment, organic injuries at risk of bleeding) and the use of concomitant antiplatelet medications.

Patients receiving FXa inhibitors are at increased risk of bleeding if emergency surgery is required [Lopes et al. Eur Heart J. 2013; 34(Suppl.1): 98-99]. Patient characteristics constitute another important determinant of the bleeding risk [Levi. Critical Care. 2016; 20: 249]. Older patients have a 2-fold increased risk of bleeding, and the relative risk of intracranial hemorrhage (ICH) (in particular at higher intensities of anticoagulation) is about 2.5 in patients aged >85 years compared with patients 70–74 years old [Fang et al. Ann Intern Med. 2004; 141: 745–52]. Comorbidity may also significantly increase the risk of bleeding. The presence of concomitant mild renal insufficiency, hepatic dysfunction, or diabetes may increase the risk of bleeding by about 2.5 [Levi et al, Blood. 2008; 111: 4471–6]. Patients with previous stroke or transient ischemic attack are also at increased risk of ICH [Hankey GJ, et al. Stroke. 2014; 45: 1304-12] [Hylek et al. J Am Coll Cardiol. 2014; 63: 2141-7]. Another very important determinant of the risk of bleeding is the combined use of anticoagulation with antiplatelet medications like aspirin and clopidogrel, which may result in an 11-fold higher risk of hospitalization for gastrointestinal bleeding as compared with the general population [Mellemkjaer et al. Br J Clin Pharmacol. 2002; 53: 173–81].

2.1.3. Biologic features, aetiology and pathogenesis

Hemorrhage induced by anticoagulants is closely linked to their systemic mechanism of action [i.e.: direct inhibition of anticoagulant factor Xa in case of the DOACs and indirect inhibition of factor Xa by binding to AT in case of indirect FXa inhibitors, like LMWHs and fondaparinux].

Intracranial hemorrhages (ICH): compared with no anticoagulation, VKA increases by approximately 3 to 4-fold the risk of ICH, while DOACs may increase the risk by approximately 1.5-2-fold. In the four major trials comparing DOACs with warfarin for stroke prevention in AF, the hazard ratio for ICH was of 0.48 overall [Ruff et al. Lancet. 2014; 383: 955-62]. Therefore, patients receiving DOACs have a halved risk of ICH compared to those receiving warfarin, although the yearly rates of ICH reported with the DOACs in AF are not negligible (0.2-0.5%/yr). It has been hypothesized that, by selectively targeting thrombin and not interfering with the formation of TF-VIIa complexes, DOACs preserve hemostatic mechanisms in the brain, while warfarin does not. The lower rate of ICH reported for these drugs compared with warfarin can also be explained by the peculiar interaction of DOACs with the transport mechanism of P-glycoprotein (P-gp) [Hankey et al. Curr Cardiol Rep. 2014; 16: 480]. Since DOACs are actively removed from the nervous system by this protein, it has been speculated that the non-increase of ICH with these drugs is also connected with this P-gp interaction.

Gastrointestinal hemorrhages (GIH): Orally-administered antithrombotic drugs may potentiate the tendency of the GI tract to bleed via at least four mechanisms [Desai et al. Thromb Haemost. 2013; 110: 205–212]: 1) systemic anticoagulant effect; 2) topical anticoagulant effect; 3) topical direct caustic action; 4) topical biological action of the drug unrelated to coagulation (e.g. inhibition of mucosal healing). These mechanisms may occur in combination: for example, aspirin may promote gastroduodenal ulcer bleeding via topical injury and systemic anti-platelet effects. It is uncertain why dabigatran 150 mg twice daily (BID), rivaroxaban 20 mg once daily (OD) and edoxaban 60 mg OD are associated with a higher rate of major gastrointestinal bleeding than warfarin in AF, but simultaneously lower rates of intracranial haemorrhage and have similar or lower rates of all-site major bleeding. One hypothesis relates to the incomplete absorption of the DOACs across the GI mucosa and thus the potential for topical drug activity. Warfarin is over 95% absorbed, and non-absorbed warfarin within the gut lumen has no anticoagulant activity. Thus, the increase in major GI bleeding observed in patients taking warfarin likely reflects the systemic anticoagulant action of the drug, and not a topical effect on the gastrointestinal mucosa. In contrast, the absorption of the DOACs is variable. The prodrug dabigatran etexilate has only 6% oral bioavailability; the remainder traverses the GI tract and is excreted in the faeces. During this passage, at least two-thirds of the prodrug is converted to active dabigatran by gut esterases. The bioavailability of rivaroxaban (60-80%), apixaban (50%) and edoxaban (62%) is higher than that of dabigatran; however, even with these agents a significant amount of active drug is recovered in the faeces. Therefore, with all four DOACs, active anticoagulant is present within the lumen of the GI tract after oral ingestion, and in theory could (in combination with systemic drug) potentiate bleeding from vulnerable lesions. Furthermore, this could explain the relative increase of lower GI bleeding observed in patients receiving dabigatran compared to those receiving warfarin.

Wound bleedings (surgical patients): the pathogenesis of surgical bleedings is the vessel disruption caused by the surgical procedure, coupled with the inhibition of coagulation by the direct or indirect FXa inhibitors.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Intracranial hemorrhages: Intracranial hemorrhage (ICH) is an inclusive term referring to several different conditions, including hemorrhagic stroke, subdural hematoma, and epidural hematoma, and is characterized by the extravascular accumulation of blood within the skull. Approximately 20% of all

strokes are due to ICH. Of these, most consist of intracerebral hemorrhage and subarachnoid hemorrhage [Van Gijn et al. Lancet. 2007; 369: 306-18]. Moreover, it is also important to remember two other, less common, pathological entities: subdural and epidural hematoma, which are both frequently associated with head trauma, especially in the elderly. These bleeding events are a growing cause of death and disability worldwide due to the increasing number of elderly people, and the increasing use of oral anticoagulation and antiplatelet agents. In particular, ICH is the most serious complication of oral anticoagulation, with mortality rates in excess of 50%, and three times higher than that of ischemic stroke [Kleindorfer et al. Stroke. 2006; 37: 2473-8].

Extracranial hemorrhages: severe gastrointestinal bleeding represents the main type of extracranial haemorrhages with oral anticoagulation. The use of adjusted dose-warfarin for stroke prevention in non-valvular AF increases the risk of major GI bleeding approximately three-fold. Based on the DOAC pivotal trials in AF, it appears that the rate of major GI bleeding in patients treated with apixaban is not far different from that seen in patients treated with adjusted dose-warfarin, whereas the major GI bleeding rate in patients treated with rivaroxaban 20 mg OD, edoxaban 60 mg OD or dabigatran 150 mg twice daily could is approximately 1.5 times higher. Fortunately, the majority of major GI bleeding events in patients receiving NOACs are not life-threatening. The short half-life of the DOACs in the absence of renal or hepatic failure is an important advantage to the clinician confronted with major GIH [Desai et al. Thromb Haemost. 2013; 110: 205–12].

Wound bleedings (surgical patients): the risk of surgical bleedings is highly heterogeneous depending on the type of surgery (hip fracture, hip replacement, knee replacement, major abdominal surgery for cancer, etc.), timing between surgery and start of anticoagulation, as well as on the major bleeding definition used [Gomez-Outes, et al. BMJ. 2012; 344: e3675]. Compared with enoxaparin in major orthopaedic surgery, rivaroxaban and fondaparinux tend to increase the risk of major bleeding compared with enoxaparin, while apixaban tends to decrease the risk of major bleeding.

2.1.5. Management

The management of bleeding complications (from simple observation/monitoring in case of mild-moderate bleeding to the more aggressive measures in case of uncontrollable bleeding, including the administration of potentially prothrombotic clotting factor products and/or surgery) depends on ongoing assessment of the severity of bleeding. Patients with serious/major bleeding should be managed in an intensive care setting with appropriate hemodynamic support.

Non-pharmacological general measures: In many cases, simple non-pharmacological measures and stabilization of the patient whist the antithrombotic is eliminated are sufficient to treat or prevent bleeding [Makris M. Br J Haematol. 2012;160:35-46]. The following general measures should be considered: a) Stop the antithrombotic drug; b) Document the timing and amount of the last drug dose and presence of pre-existing renal or hepatic impairment; c) Estimate the half-life and length of functional defect induced by the drug; d) Assess the source of bleeding; e) Request full blood count, prothrombin time, activated partial thromboplastin time, thrombin time, fibrinogen concentration, creatinine concentration; f) If available, request a specific laboratory test to measure the antithrombotic effect of the drug; g) Correct haemodynamic compromise with intravenous fluids and red cell transfusion; h) Apply mechanical pressure, if possible; i) Use endoscopic, radiological or surgical measures.

Management of bleeding associated to direct FXa inhibitors:

Management of bleeding is especially concerning with the direct factor Xa inhibitors because antidotes or specific reversal agents are currently lacking. Additionally, routine coagulation tests cannot be used

to determine the degree of anticoagulation, making it more challenging to determine when the anticoagulant effect has resolved.

Should a bleeding complication arise in a patient receiving a direct FXa inhibitor, the next anticoagulant administration should be delayed or treatment should be discontinued as appropriate. The use of activated charcoal to reduce absorption in case of overdose may be considered. Management should be individualised according to the severity and location of the haemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g. for severe epistaxis), surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.

If bleeding cannot be controlled by the above measures, administration of a specific procoagulant reversal agent should be considered, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa). However, there is currently very limited clinical experience with the use of these products in individuals receiving direct FXa inhibitors. Re-dosing of recombinant factor VIIa shall be considered and titrated depending on improvement of bleeding. Depending on local availability, a consultation with a coagulation expert should be considered in case of major bleedings [Kirchhof et al. Eur Heart J. 2016; pii: ehw210].

Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of the direct FXa inhibitors. There is limited experience with tranexamic acid and no experience with aminocaproic acid and aprotinin in individuals receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with the use of the systemic haemostatic desmopressin in individuals receiving direct FXa inhibitors. Due to the high plasma protein binding, rivaroxaban, apixaban or edoxaban, are not expected to be dialysable.

Management of bleeding associated to Indirect FXa inhibitors:

Fondaparinux: There is no known antidote to fondaparinux. Overdose associated with bleeding complications should lead to treatment discontinuation and search for the primary cause. Initiation of appropriate therapy such as surgical haemostasis, blood replacements, fresh plasma transfusion, plasmapheresis should be considered. At the doses used for treatment, fondaparinux does not affect routine coagulation tests such as activated partial thromboplastin time (aPTT), activated clotting time (ACT) or prothrombin time (PT)/International Normalised Ratio (INR) tests in plasma nor bleeding time or fibrinolytic activity. However, rare spontaneous reports of aPTT prolongation have been received. At higher doses, moderate changes in aPTT can occur. At the 10 mg dose used in interaction studies, fondaparinux did not significantly influence the anticoagulation activity (INR) of warfarin. Therefore, routine coagulation tests cannot be used to determine the degree of anticoagulation, making it more challenging to determine when the anticoagulant effect has resolved.

LMWHs: for enoxaparin, the more widely prescribed LMWH, the anticoagulant effects can be largely neutralised by the slow intravenous injection of protamine, but even with high doses of protamine, the anti-Xa activity of enoxaparin sodium is never completely neutralised (maximum about 60%) [Clexane SmPC. Available from: http://www.medicines.org.uk/emc/medicine/10054]. The initial dose of protamine depends on the dose of enoxaparin given and also consideration of the maximum recommended protamine dose (50 mg). Data on protamine dosing in humans for enoxaparin overdose is extremely limited. The available data suggest that in the first 8 hours after enoxaparin administration 1mg protamine should neutralise the effects of 1 mg of enoxaparin. Where the dose of enoxaparin has exceeded 50 mg, an initial dose of 50 mg protamine would be appropriate, based on the maximum recommended single protamine dose. Decisions regarding the necessity and dose of subsequent protamine injections should be based on clinical response rather than measurement of

anti-Xa or anti-IIa results. The physician should also consider that the amount of enoxaparin in the body drops to 50% after 8 hours and 33% or less after 12 hours. The dose of protamine should be adjusted depending on the length of time since enoxaparin was administered.

About the product

Andexanet alfa (andexanet) (molecular weight ~41 kDa) is a recombinant, engineered modified version of human fXa, obtained in Chinese Hamster Ovary (CHO) cells. Andexanet is being developed for the urgent reversal of anticoagulation in patients administered either direct or indirect factor Xa (fXa) inhibitors who experience a major bleeding episode or require urgent surgery.

Andexanex alfa has modifications in 3 regions compared to wild type FXa:

- A fragment of 34 residues in the Gla-domain containing the 11 γ-carboxyglutamic acid residues was deleted by ligating the native fX signal peptide and the native fX light chain amino terminal residues (ANSFL) from the remaining light chain (lack of anticoagulant activity).
- The active site serine at position 419 of the heavy chain was changed to an alanine to remove the fXa catalytic activity (lack of procoagulant activity).
- The C-terminus of the light chain of fX is linked to the N-terminus of the fXa heavy chain using an amino acid linker to connect the two polypeptides by deleting the activation peptide in the heavy chain of native fX, to facilitate processing of the andexanet precursor into a two-chain molecule in transfected CHO cells.

As a result, andexanet is expected to retain high binding affinity for both direct and indirect (AT-dependent) inhibitors, but lacks catalytic (procoagulant) activity of native fXa due to the replacement of the active site serine with an alanine, thereby ensuring andexanet is unable to cleave and activate prothrombin, and also lacks the Gla domain, preventing incorporation of andexanet into the prothrombinase complex, thus eliminating anticoagulant activity.

Andexanet is supplied as a sterile, lyophilized powder (200mg), formulated at a concentration of 10 mg/mL after reconstitution and packaged in clear Type I glass vials with rubber closures and flip-off caps.

Type of Application and aspects on development

This is a European Union (EU) Marketing Authorisation Application (MAA) for Ondexxya (andexanet alfa) 200 mg Powder for Solution for Infusion. The CHMP did not agree to the applicant's request for an accelerated assessment. This was based on the fact that this application was considered complex with several FXa inhibitors and indirect fXa inhibitor involved, several dosing regimens and indications and some concerns about the maturity of the data therefore not considered appropriate for the purpose of accelerated assessment.

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the Regulation, based on the following criteria:

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide comprehensive data.
- Unmet medical needs will be addressed,
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

The applicant provided the following justification to support his claim for a conditional MA

There is no approved reversal agent/antidote for the direct fXa inhibitors (rivaroxaban, apixaban and edoxaban). For LMWHs, like enoxaparin, protamine sulfate is an approved antidote with a known risk of allergic reaction. For direct FXa antagonists, no specific antagonist is available in contrast to PCCs and Vitamin K to reverse coumarin derivatives. Use of procoagulant reversal agents such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC), or recombinant factor VIIa (rfVIIa) may be considered, but have not been evaluated in clinical trials. There is urgent unmet medical need for a more targeted therapy specifically directed at the fXa inhibition with a better benefit/risk profile than coagulation factor infusions. The ongoing development of andexanet alfa aims to fulfil these immediate, unmet medical needs. Andexanet has been specifically designed to neutralise the anticoagulant effect of direct and indirect fXa inhibitors. Similar to native fXa, andexanet binds to small molecule fXa inhibitors with high affinity and a 1:1 stoichiometry, and acts as a decoy molecule that is able to sequester the inhibitor, thereby rapidly reducing the free plasma concentration and neutralising the anticoagulant effect of the fXa inhibitor. Andexanet also binds and sequesters ATIII complexed with LMWH or fondaparinux, similarly to endogenous fXa. Andexanet has been characterised in non-clinical in vitro and in vivo studies. Non-clinical data, both in vitro and in vivo, have demonstrated that andexanet reverses fXa inhibitor-induced anticoagulation by sequestering, and effectively neutralising, the anticoagulant. This mechanism of action is in contrast to overloading the coagulation system through the administration of upstream procoagulant factors (e.g., fresh frozen plasma, prothrombin complex concentrate [PCC], and recombinant activated factor VII [rfVIIa]). Anti-fXa-activity was considered the most relevant PD-marker as it is a direct measure of the inhibition of fXa enzymatic activity by this class of anticoagulants.

Anti-fXa activity was chosen as a co-primary endpoint of confirmarory Study 14-505 that is conducted in bleeding patients. Upon completion, this study will demonstrate, a correlation between the effects of andexanet on anti-fXa activity and haemostatic outcomes.

Therefore, anti-fXa activity was chosen as co-primary andpoint of the ongoing confirmatory study (14-505). In addition, anti-fXa activity directly correlates with fXa inhibitor concentrations and increased bleeding risk for all the fXa inhibitors. A multinational, open-label, single-arm, Phase 3b/4 (Study 14-505) study in patients presenting with acute major bleeding and receiving apixaban, rivaroxaban, edoxaban, or enoxaparin is currently ongoing. This study aims at demonstrating a correlation between the effects of andexanet on anti-fXa activity and haemostatic outcomes.

The CHMP agreed that there is a high unmet medical need in this field. Given that the CHMP considered benefit-risk balance is positive, immediate availability of an antidote for FXa-inhibitors was considered to be of significant impact for the target population and outweighed the risks due to need for further data to further assure safety and efficacy of this product. The company committed to provide missing additional data as specific obligations according to agreed deadlines. The details for specific obligations for a conditional marketing authorisation are listed in section 4.

2.2. Quality aspects

2.2.1. Introduction

Ondexxya has been developed for the urgent reversal of anticoagulation in patients administered either direct or indirect factor Xa (FXa) inhibitors who experience a major bleeding episode or require urgent surgery. The active substance andexanet alfa (molecular weight ~40 kDa) is a recombinant modified version of human factor Xa (FXa) that lacks the coagulation activity of native FXa but retains the functional activity capable of binding both direct and ATIII-dependent indirect FXa inhibitors with high

affinity. Andexanet alfa is produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells.

Ondexxya is presented as a powder for solution for infusion. Each single-use vial contains 200 mg andexanet alfa to be reconstituted with 20 mL of sterile water for injections (WFI). Andexanet alfa is formulated with tris base, tris hydrochloride, L-arginine hydrochloride, sucrose, mannitol, and polysorbate 80.

2.2.2. Active Substance

General information

Andexanet alfa is a modified human factor Xa (FXa) protein with 359 amino acid residues lacking enzymatic activity of native FXa but retaining the binding site for both direct and ATIII-dependent indirect FXa inhibitors. It is a two chain molecule comprising a light chain (LC) of approximately 12 kDa and a heavy chain (HC) of approximately 28 kDa, connected by a single inter-chain disulphide bond between Cys98 of the light chain and Cys108 of the heavy chain, as shown in Figure 1.

It is devoid of the γ-carboxyglutamic acid (Gla)-containing domain to eliminate membrane binding necessary for incorporation into the prothrombinase complex. It lacks proteolytic activity due to a change of active site serine residue to alanine in the Heavy Chain (HC).

Andexanet alfa is directly expressed in CHO cells as a functional antidote. Conversion to the activated form is accomplished by replacement of the activation peptide with a cleavable linker peptide connecting the light and heavy chain of andexanet.

The following post-translational modification (PTM) sites are present in andexanet alfa: β-hydroxylation of an aspartate residue (Asp29) in the LC, O-linked glycosylation of a threonine (Thr354) in the HC and O-linked glycosylation in the LC. These PTMs were reported for human FX as well.

Cleavages observed in andexanet alfa include cleavage after Ala345 in the heavy chain to produce the beta form (HC-β), cleavage at Trp7 in the light chain (LC-N7) and cleavage to remove the C-terminal lysine of the heavy chain.

The structures of FX and andexanet alfa are shown in Figure 1.

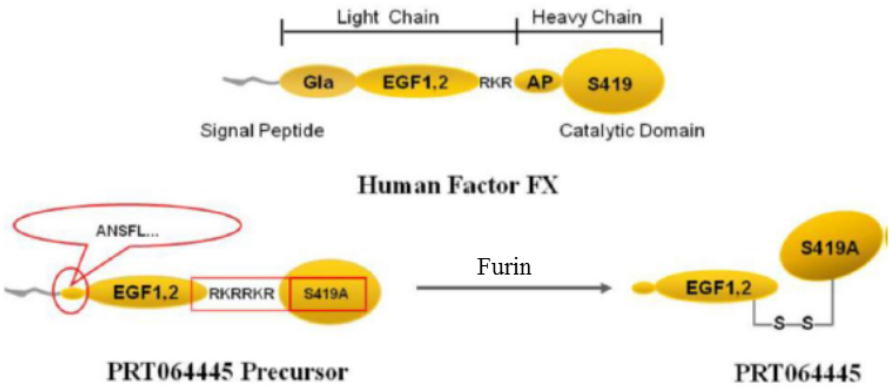


Figure 1 Structures of human FX and andexanet alfa

Manufacture, characterisation and process controls

Manufacture

Active substance (AS) Generation 2 (GEN 2) manufacturing process for recombinant andexanet alfa secreted by CHO cells is divided into upstream and downstream manufacturing.

The major considerations for developing the Generation 2 Process for AS relative to the Generation 1 used in clinical development were to:

- Increase cell density and overall protein yield while maintaining the same protein production per cell from the cell line through the use of new cell culture media.
- Increase the bioreactor working volume.
- Implement an affinity column purification step to improve AS purification process control and robustness, improve process-related impurity clearance and increase overall yield.
- Maintain comparability with Generation 2 andexanet alfa AS.

A single andexanet alfa AS batch is produced from a single cell production culture. The manufacturing process for andexanet alfa active substance is performed as a continuous set of linked unit operations. There is no pooling of harvests or intermediates.

Control of materials

No materials of animal origin are used in the manufacture of andexanet alfa AS, except for the andexanet alfa Working Cell Bank (WCB) and Master Cell Bank (MCB).

Raw materials used in the manufacture of andexanet alfa are specified with respect to their source and quality grade, and are assessed for criticality to the process, following internal policies. The supply chain department is responsible for the execution and recording of the applicable sampling, and Quality Assurance is responsible for the review and approval of the qualifications and lists of qualified materials.

Cell banking system

Andexanet alfa production cell line is a CHO clone that was stably transfected with an expression vector containing andexanet alfa cDNA, resulting in a clone (14G1-6A8 cell line). The cells were maintained in puromycin. At the end of the selection process, pools of transfected cells with good growth performance in the presence of the selective agent were obtained.

All cell banks were manufactured under GMP.

The results from characterisation study reports of the MCB confirmed the identity and genetic stability. Except for intracytoplasmic A-type particles absence of adventitious agents is demonstrated as well.The WCB was found to be free from any adventitious agent contamination and found suitable as starting material for the manufacture of andexanet alfa bulk active substance. A respective Certificate of Analysis (CoA) has been provided. This WCB will be used for commercial manufacturing. A protocol for the establishment of new WCBs from the MCB has been implemented. In line with ICH Q6D this protocol defines testing and acceptance criteria for establishing a new Working Cell Bank (WCB) for GMP manufacture of andexanet alfa. All WCB study protocols are presented and it is indicated, which WCB is currently used in the manufacture of the commercial product. MCB and WCB stability are monitored. The proposed plan for testing is based on relevant ICH guidance and on historical data.

The results from EOP cell bank testing indicated equivalency to the MCB with respect to safety, identity and genetic stability.

In summary, the section control of materials provides assurance that the cell banks as well as all other materials used in the manufacture of the active substance are qualified for the intended use. The genetic stability of the MCB and the WCBs used has been demonstrated beyond the maximum cell age; also the limit of *in vitro cell* age for the cell culture process has been defined, in line with ICH Q5D.

Absence of adventitious agents in the WCBs has been demonstrated, except for intracytoplasmic A-type particles and C-type retrovirus-like particles, which is not uncommon and considered non-critical.

Control of critical steps and intermediates

The Process Control Strategy (PCS) to control the manufacturing steps is a systematic science and risk-based approach where process parameters (inputs) are controlled within pre-determined criteria to ensure successful performance attributes (outputs) and final product quality. This PCS was defined based on data from process development, process characterisation = process limits evaluation (PLE), process performance qualification (PPQ), and manufacturing-scale experience. By this, critical quality attributes (CQA), critical process parameters (CPPs) have been defined. In-process limits for impurities have been defined based on qualified test methods and acceptable limits have been set.

Process Validation

The validation approach is in line with process validation guidance and followed a Process Validation Master Plan (PVMP) to qualify the Andexanet alfa “Generation 2” active substance manufacturing process from WCB vial thaw to filling of active substance into the storage bottles. During process development critical process parameters and critical quality attributes have been established. The optimum ranges for process operations were confirmed during process verification on several PPQ batches and consistency runs. Based on the successful completion of several consecutive batches, process reproducibility and robustness is demonstrated for the upstream and downstream process. Ongoing process verification is in place to provide ongoing assurance that routine production of the Generation 2 andexanet alfa manufacturing process remains in a state of control.

The following aspects have been addressed in separate validation studies and most of them can be considered adequately validated: i) reprocessing operations on an ongoing basis, iii) hold times for product solution, buffers and media, iv) mixing procedures for product solutions, buffers and media, v) filter compatibility and functionality, vi) extractable and leachables from product contact materials, vii) resin and membrane life time, viii) clearance of process- and product related impurities and ix) shipping conditions of active substance from AS to the finished product (FP) manufacturing site.

Manufacturing process development

A number of changes and improvements were made throughout the clinical development. These changes are identified as Generation 1 and Generation 2. These changes include the following:

- Increase cell density and overall protein yield while maintaining the same protein production per cell from the cell line through the use of new cell culture media and no significant impact on product quality was expected from the increased Viable Cell Density (VCD).
- Increase the bioreactor working volume.
- Implement an affinity column purification step to improve AS purification process control and robustness, improve process-related impurity clearance and increase overall yield.

Comparability exercise for active substance

AS manufactured using Process 2 and Process 3: All FP batches used for clinical trials, except those for phase 3b/4 clinical trial and planned trials in 2016, were manufactured from AS of Process 2, not from AS of the intended commercial Process 3.

In line with ICH Q5E a comparability study was conducted to investigate the potential impact of process changes on product quality. To demonstrate andexanet alfa AS comparability between AS Process 2 (clinical) and AS Process 3 (commercial), three lots from AS Process 2 and two GMP lots from AS Process 3 were evaluated by: i) Release testing, ii) Supplemental characterization testing, and iii) Side-by-side stability testing.

Based on the results, AS from the Process 2 and Process 3 were considered comparable.

AS manufactured using Generation 2 process: The development of the large scale commercial AS process (Generation 2 process) and changes to Process 3 AS process are outlined in sufficient detail to follow the development of the “Generation 2” (GEN 2) active substance process. The rationale for the substantial changes to the existing manufacturing process is clearly described and is comprehensible. The comparability evaluation of the AS lots from the Generation 2 process *versus* Process 3 was based on assessments from release testing, supplemental characterisation testing and side-by-side stability testing.

Testing of Generation 2 Process AS lots met release specifications of Process 3 AS for most but not all attributes. As a consequence, the Applicant adapted the AS release specifications to address the observed differences between GEN 1 and GEN 2 AS. The GEN 2 AS release specifications were further tightened with more data available for GEN 2 AS.

Supplemental characterisation of primary sequence and posttranslational modifications showed a consistent good agreement between AS from both processes. Confirmation was made that the pI range of variants present in all lots of GEN 2 AS is comparable. Disulphide mapping confirms comparable disulphide connectivity, and CD spectra confirmed comparable secondary structure.

The real-time stability data from GEN 2 Process AS comply with the shelf-life specifications and are comparable to those from Generation 1 AS. The higher levels of aggregates observed by SEC with the GEN 2 Process AS stored under the stressed conditions are most likely due to the higher protein concentration of GEN 2 Process AS.

Based on the comparability exercise including batch release data and supplemental characterisation testing, Andexanet alfa AS/FP manufactured by GEN 2 is considered comparable to AS/FP manufactured by GEN 1.

Characterisation

Elucidation of structure and other characteristics

Andexanet alfa has 359 amino acid (AA) residues and an approximate molecular weight of 40 kDa. It is a two chain molecule comprising a Light Chain (LC) of approximately 12 kDa and a HC of approximately 28 kDa, connected by a single inter-chain disulfide bond.

Functional activity assays on the affinity of andexanet alfa towards the target direct FXa inhibitors (apixaban, betrixaban, edoxaban, rivaroxaban) and towards tissue factor pathway inhibitor (TFPI) demonstrate a consistent activity of andexanet alfa GEN 2 AS lots towards all Direct Inhibitors and the Indirect inhibitor, as well as TFPI.

These binding studies indicate that potency assays using betrixaban are representative for all direct FXa inhibitors, for which reversal of anticoagulation is claimed. More data of interaction of andexanet

alfa with TFPI show a similar TFPI affinity of andexanet alfa and native plasma FXa. Equivalent functional properties of truncated andexanet alfa species and parent andexanet alfa generated during processing (product-related substances) have been demonstrated.

The *in vitro* thermodynamic, kinetic, and clinically relevant bioassays demonstrate for four lots of GEN 2 Process AS and the PRS from GEN 1 comparable thermodynamic properties, binding affinities (Kd's), and equivalent thrombin generation reversal for all four direct inhibitors and TFPI.

Impurities

An overview on potential product-and process-related impurities in GEN 2 AS has been provided. It is demonstrated in characterisation studies and in the PPQ of the GEN 2 process that the majority of impurities are routinely reduced to low levels. Criticality of impurities is determined by a ranking approach following ICH Q9 to assess the possible impact of each impurity on safety, PK/PD, immunogenicity and efficacy. In line with ICH Q 6B release limits at AS level were specified reflecting detection method sensitivity, process capability and toxicological risk.

In summary, GEN 2 andexanet alfa AS has been characterised with respect to its primary, secondary and higher order structure. The set of methods to identify structural and functional characteristics and to define the impurity profile of GEN 2 AS, compared to the GEN 1 AS, appears adequate and in line with ICH 5E.

With respect to physico-chemical properties, the GEN 2 AS and the GEN 1 AS are not comparable. These differences seem to have no significant impact on the functional activity of andexanet alfa GEN 2 AS, which shows a comparable affinity to betrixaban and other FXa inhibitors as GEN 1 AS. Hence, with respect to its *in vitro* functional activity, GEN 2 AS and GEN 1 AS can be considered comparable.

Specification

The list of test parameters for the active substance specification, have been established in line with ICH Q6B and contain tests for appearance, osmolality, potency and purity.

The GEN 2 AS is controlled by an adequate set of analytical methods that are based on a risk analysis intended to identify critical quality attributes to be tightly controlled at AS release. The analytical procedures applied in the routine release testing and/or stability testing are mainly the same analytical methods as applied in the AS testing of GEN 1 AS. The selected analytical methods have been validated in line with ICH Q2(R1) and ICH Q6B, using a matrix approach to cross-validate the methods to support GEN 2 Process AS, 200 mg strength finished product (FP), produced from the GEN 2 Process AS, and in-process testing where relevant.

Acceptance criteria for GEN 2 AS are based on experience gained during development, manufacturing history, process capability, method capability, safety aspects and pharmacopoeial requirements. Setting acceptance ranges based on limited set of GEN 2 process data is considered in line with ICH Q6B.

Functional assays

Direct potency of andexanet alfa is determined by its ability to bind to direct FXa inhibitor betrixaban and reverse the inhibition of human FXa by betrixaban in an assay mixture composed of andexanet alfa, human FXa, and betrixaban. The restored human FXa activity is measured with an FXa-specific chromogenic substrate, which releases a chromophore upon cleavage by FXa.

Potency of the test sample is determined by comparing the test sample response to the response obtained for the andexanet alfa reference standard and is reported as *% Functional activity,* and also as Specific Activity in Units/mg.

Batch analyses

Batch analysis data for GEN 2 Process active substance (AS) lots used in nonclinical, clinical and stability studies during drug development are presented. The specifications and test methods listed are those in effect at the time the lot was produced. All results meet the specifications in effect at the time.

Reference standards or materials: The andexanet alfa primary reference standard RM-K-0030 (GEN 1 BDS, July 2017) for potency has been calibrated in the Direct inhibitor assay using betrixaban as FXa inhibitor and a commercial bovine FXa preparation calibrated against the International Standard for bovine FXa (NIBSC 75/595). In the Indirect inhibitor assay, the LMW heparin WHO International Standard (NIBSC code 11/176) has been used, beside the IS for bovine FXa. Key to establishing the PRS was defining both the Direct and Indirect Potency units, traceable to the international reference preparations distributed by the NIBSC.

The test methods that are selected to analyse the reference material appear adequate to identify changes in quality attributes that may affect its functional activity. The release and shelf life specifications of reference material are identical to the commercial AS lots.

Stability

Stability studies were performed under long-term storage conditions, accelerated storage conditions, and stress conditions. The selected conditions and test parameters are in line with ICH Q 5C. Under long-term storage conditions, no significant changes have been observed on any batch at the intended storage condition. Generation 2 Process andexanet alfa AS demonstrated sensitivity only to stress light conditions and under extreme forced degradation conditions. Based on the data presented the claimed shelf life for the active substance is acceptable.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Description and composition of the finished product

Andexanet alfa final finished product is a lyophilised concentrate of recombinant modified human factor Xa (FXa) protein. Excipients included Tris base/Tris hydrochloride as buffer, L-arginine HCl, sucrose and Polysorbate 80 as stabilisers as well as mannitol as bulking agent. It is supplied as single dose size of 200 mg to be reconstituted with sterile Water for Injections (sWFI) to give a final concentration of 10 mg/mL before intravenous administration.

The final product is a sterile, white to off-white lyophilized cake or powder supplied in a Ph. Eur. Type I glass vial to be reconstituted with 20 mL of sWFI.

Pharmaceutical development

A 200 mg strength FP which is the only strength intended for marketing in the EU using GEN 2 Process (200 mg/20 mL) has been developed.

The appropriateness of the product vial has been demonstrated through compliance of six reconstituted finished product batches with the acceptance criteria during batch release requiring proper reconstitution.

Formulation development

In pre-formulation studies, a panel of adequate methods had been used to detect protein unfolding transitions at increasing temperatures and different pH. Based on the results, a library of common excipients has been screened for the ability to ensure solubility and stability of andexanet alfa.

Development of 20 mg/mL andexanet alfa liquid formulations was initiated to reduce the number of vials needed to deliver the desired dose. Stability was monitored by protein concentration, RP-HPLC, IEX-HPLC and SEC-HPLC.

AS from GEN 2 Process (20 mg/mL andexanet alfa) is filled into the final containers with a target fill volume of 10.35 mL and lyophilised to give the 200 mg strength FP to be reconstituted with 20 mL of sWFI prior to administration. Consequently, reconstituted FP contains 10 mg/mL andexanet alfa in Tris, L-arginine hydrochloride, sucrose, mannitol, and polysorbate 80.
The formulation composition was developed considering the number of vials needed for patient dosing, solubility, osmolality, protein stability, and manufacturability.

Formulation characterisation: Robustness of AS (GEN 2 Process) and lyophilised FP formulation was evaluated by varying the components within the formulation in a fractional factorial experimental design

Lyophilisation cycle development

Knowledge of the physical properties of the formulation gained during development served as basis for developing the lyophilisation process including lyophilisation cycle parameters (e.g. freezing temperature, shelf temperature, annealing temperature, time duration). An annealing step, where the product temperature is cycled was included in the lyophilisation process to obtain more complete crystallization.

Control strategy

In accordance with ICH guideline Q8(2) critical process parameters that should be monitored or controlled to ensure the product is of the desired quality, have been identified for the finished product production process during developmental studies. The risk analysis, evaluating process parameters on the potential to affect andexanet alfa FP quality attribute or process performance, has been included in the application dossier.

According to ICH guideline Q8(2) “Pharmaceutical development”, an overall control strategy established for 200 mg strength andexanet alfa finished product manufacturing process including e.g. controls on material attributes, in-process controls, release testing, container closure and stability specifications has been inserted in section 3.2.P.5.6 “Justification of Specifications” of the application dossier.

Comparability of andexanet alfa FP

To demonstrate comparability between the commercial process and previous versions of the processes, the Applicant submitted data on validation (active substance and finished product), stability (active substance and finished product) and comparability (active substance and finished product). These validation data were considered adequate to confirm comparability in a head-to-head comparison. The

comparability of the commercial manufacturing process with previous versions of the process was considered to be demonstrated.

Compatibility

The 200 mg strength andexanet alfa finished product is provided as a lyophilised product in a 20 mL glass vial for reconstitution with 20 mL of sterile water for injections. Multiple reconstituted vials of FP are transferred to an infusion bag for administration.

Compatibility study of the reconstituted 200 mg strength FP with various commonly used intravenous administration components revealed no loss of andexanet alfa protein through adsorption and the protein was stable at room temperature in ambient light for 16 hours. Reconstituted finished product was shown to be stable at room temperature for up to 20 hours in its primary container/closure.

Andexanet alfa is considered an emergency care dose preparation. Chemical and physical in-use stability has been demonstrated for up to 16 hours at 2 to 8°C in primary container/closure and for up to 8 hours at room temperature in the IV bag. However, from a microbiological point of view, once reconstituted, the product should be used immediately.

Manufacture of the product and process controls

Manufacturing process

The manufacturing process of andexanet alfa finished product involves thawing, pooling of one or more GEN 2 Process active substance batches into single-use bags, mixing, sterile filtration, aseptic filling into the final containers, and partial stoppering of vials followed by lyophilisation. Subsequently, the FP vials are fully stoppered in the lyophiliser and capped upon removal from the lyophiliser. Each vial is coded with the batch number on the aluminium crimp.

The vials are 100% visually inspected, packaged, and stored at 2 to 8°C before transport to the labelling and packaging facility.

The manufacturing process has been described in sufficient detail. No reprocessing is foreseen for the manufacturing of andexanet alfa FP. Consequently, there are no validated reprocessing steps included in the application dossier.

Process controls

During manufacture of the 200 mg strength andexanet alfa FP the pooling/mixing step (pH, protein concentration, osmolality, bioburden), filtration (pre-use and end of run WFI integrity testing) and filling (fill volume) are controlled by in-process controls. Fill volume limits are converted to weight limits for filling. Weight checks are automated and performed on 100% of the vials on-line during filling operations. The target fill volume is 10.35 mL. Vials outside of the fill weight range are rejected.
In-process controls performed during manufacturing process of andexanet alfa finished product are also indicated as controls of critical steps and intermediates. Criticality of the process parameters has been determined through characterisation studies using a risk-assessment based approach.

Process validation

Process performance qualification (PPQ) using four consecutive PPQ batches according to PPQ protocol 414-21-04-003-P1, was performed to demonstrate reproducibility of the manufacturing process. Two filters in series are required to achieve microbial retention. A third Opticap-XL4® filter is used to ensure at least two of three filters connected in series are integral for sterility assurance. Filter validation studies were performed to confirm the compatibility and functionality of the sterile filter in the

presence of GEN 2 Process andexanet alfa AS at the operating conditions specified in the 200 mg strength FP process. The studies included microbial retention, product bubble point ratio determination, filter compatibility as well as filter extractables studies demonstrating negligible risk to patients from potential leachables.
The aseptic manufacturing process has been qualified using media fills.
Process time limits have been challenged and are considered validated.Overall, developmental studies and PPQ results provided documented evidence that the routine commercial 200 mg andexanet alfa finished product manufacturing process, when operating within defined parameters, consistently produces product meeting established specifications and quality attributes. The approach to process validation including process design, prospective process qualification and ongoing process verification (on-going activities) is considered appropriate to maintain the process in a state of control during routine commercial production.

Excipients

Excipients selected for andexanet alfa FP comprise Tris base/Tris hydrochloride as buffer, L-arginine HCl, sucrose and Polysorbate 80 as stabilisers as well as mannitol as bulking agent. Nitrogen serves as headspace gas. All excipients are of Ph. Eur. quality except for Tris HCl which is made from USP grade Trometamine following cGMP. Quality of the excipients is controlled as raw materials at the active substance manufacturing stage according to compendial requirements.

None of the excipients in andexanet alfa finished product are of human or animal origin. There are no novel excipients used in the finished product formulation. All excipients used are well-known agents.

Product specification

The FP release and shelf-life specifications are defined based on the manufacturing capabilities, assay performance, qualification through nonclinical and clinical testing experience, pharmacopoeial standards, and stability studies.

Shelf life specifications defined for stability testing are identical to the batch release specifications.

Analytical Methods

An appropriate set of analytical procedures has been established and validated to control the 200 mg strength andexanet alfa finished product at batch release. A matrix approach with AS and FP was applied to the method validation studies.

The quantitative, product-specific analytical procedures were validated in accordance with ICH Q2(R1) and ICH Q6B. The analytical methods used for the physicochemical characterization of the FP complying with the appropriate compendial chapters of Ph. Eur. were verified for their intended use.

Batch Analysis

Batch data from six andexanet alfa 200 mg strength finished product batches used in nonclinical, clinical, validation or stability studies manufactured at the proposed commercial scale have been provided. Results comply with the specifications and demonstrate batch to batch consistency.

Justification of specifications

Control Strategy

Andexanet alfa FP quality attributes with the potential of impacting product efficacy, PK-PD, immunogenicity, or safety have been identified. Risk scoring of the quality attributes was performed.

Quality attributes osmolality, cake integrity, and reconstitution time were identified as obligatory CQAs with the potential to impact safety and efficacy, independent of their criticality score. Non-critical quality attributes are included in the integrated control strategy to demonstrate the ability of the process to produce FP of consistent quality. The experience and data accumulated during the development of andexanet alfa FP formed the basis for the setting of the specifications associated with the integrated control strategy.

In addition to the statistical approach, manufacturing experience, method capability, and formulation development studies were considered. Pharmacopoeia specifications were applied to the respective compendial assays where appropriate.

Reference standards or materials

The GEN 2 Process active substance Working Reference Standard (WRS) is utilized for direct potency assays of 200 mg strength finished product batch release. Data and information relating to the GEN 2 Process active substance WRS has been provided.

Container closure

Andexanet alfa FP 200 mg strength is filled and lyophilised in 20 mL clear Ph. Eur. Type 1 glass vials with a 20 mm finish. A grey 20 mm FluroTec® and B2-coated chlorobutyl rubber stopper is used to stopper the vial. A 20 mm aluminium flip-off seal serves as the final seal for vial and stopper.

Technical specification schematics as well as representative certificates of compliance have been provided for the glass vial, stopper and flip-off seal used for primary packaging of andexanet alfa finished product.

Specifications established for glass vial, stopper and flip-off seal component established by the respective manufacturers have been presented. Leachable/extractable studies have been performed.

Container closure system conforms to current Ph. Eur. requirements and is considered suitable for the intended use with respect to compatibility and container closure integrity.

Stability of the product

A shelf life of 24 months for 200 mg strength andexanet alfa finished product, when stored at 2 to 8°C is claimed. Stability studies have been initiated according to ICH guideline Q1A(R2) investigating six 200 mg production scale batches manufactured from Generation 2 AS batches. The studies cover:

i) long-term stability studies at 2 to 8°C for up to 36 months

ii) stability studies under accelerated conditions (25°C/60% RH for up to 6 months)

iii) stability studies under stress conditions (40°C/75% RH) for up to 3 months.

All results are within the specification.

Commitment to continue the on-going ICH registration stability study has been provided. Overall, available real-time stability data (obtained from long-term, accelerated and stressed storage) is considered sufficient to confirm the shelf life of 2 years claimed for the 200 mg strength andexanet alfa FP, when stored at 2-8°C.

Reconstituted finished product (primary container): In-use stability data for one batch has been provided and demonstrates that the reconstituted FP can be stored at 2 to 8°C for up to 16 hours prior to dosing.

Reconstituted finished product (Infusion bag): Andexanet alfa is considered an emergency care dose preparation. Storage condition limits of up to 16 hours at 2 to 8°C in primary container/closure and up to 8 hours at room temperature in the IV bag are recommended for the reconstituted FP.

During development, compatibility study of the reconstituted 200 mg strength FP with various commonly used intravenous administration components revealed that the protein was stable at room temperature in ambient light for 16 hours. The reconstituted FP was also held in the primary container closure as control at room temperature exposed to ambient light for the duration of the study of approximately 20 hours and found to be stable.

Adventitious agents

TSE compliance

Compliance with the TSE Guideline, current version has been sufficiently demonstrated. The active substance of andexanet alfa Generation 2 process is produced in a serum-free culture medium. No other animal derived material is added during fermentation of andexanet alfa. Therefore, the MCB which has been established are free from TSE-risk substances.

Virus safety

The fermentation of andexanet alfa GEN 2 process is carried out in a serum-free medium which minimizes a possible contamination for adventitious viruses. The cells used for production of andexanet alfa have been extensively screened for viruses. These tests failed to demonstrate the presence of any viral contaminant in the master cell bank (Lot G0101), except intracellular A-type retroviral particles which are well known to be present in CHO cell lines. However, this is acceptable since there is sufficient capacity within the manufacturing procedure of andexanet alfa for reduction of this type of viral particles.

Therefore, there are no concerns for the use in the production process of andexanet alfa. The purification process of andexanet alfa includes several steps for inactivation/removal of enveloped viruses. The effectiveness of these steps has been sufficiently demonstrated.

In summary, the virus safety of andexanet alfa GEN 2 process has been sufficiently demonstrated.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Active substance

The manufacturing process of andexanet alfa and the process development have been described in sufficient detail to understand the commercial process and its history. During clinical development a smaller scale manufacturing was used (Generation 1), with the commercial scale (Generation 2) introduced during late stage clinical development.

Based on the comparability exercise including batch release data and supplemental characterisation testing, Andexanet alfa AS/FP manufactured by GEN 1 is considered comparable to AS/FP manufactured by GEN 2.

The *in vitro* functional activity and the stability of the andexanet alfa AS from GEN 1 and GEN 2 process are comparable. The active substance and finished product commercial manufacturing processes have been validated following process validation guidance documents and the GEN 2 AS, as well as FP produced with GEN 2 AS consistently meet acceptance criteria.

Andexanet alfa AS has been characterised with respect to its primary, secondary and higher order structure, as well as its impurity profile.

As a consequence of structural and purity differences, the current AS release specifications were adjusted, where necessary. This appears justified and most of the revised acceptance ranges/limits can be accepted. A few parameters with relatively wide acceptance ranges should be re-evaluated once sufficient data for GEN 2 AS batches are available.

Characterisation of the functional activity (affinity) of andexanet alfa towards the direct FXa inhibitors apixaban, betrixaban, edoxaban, rivaroxaban and towards TFPI has been completed. It is demonstrated that the potency assays using betrixaban as assay component are representative for all direct FXa inhibitors, for which reversal of anticoagulation is claimed, based on *in vitro* binding studies on a representative number of andexanet alfa batches. In plasma FXa interacts and is inhibited by TFPI. The interaction of andexanet alfa with TFPI has been characterised, as this interaction contributes to the function of andexanet alfa in clinical use. Additionally, the applicant showed equivalent functional properties of truncated andexanet alfa species generated during processing (product-related substances) compared to andexanet alfa.

Analytical methods used at batch release have been adequately validated in line with ICH Q2(R1). The acceptance limits/ranges for the AS release parameters are adequately set in line with ICH Q6B and can be accepted. The specifications proposed for Direct and Indirect potency at batch release of AS and FP are given in % Functional activity and as Specific activity in Unit/mg. For the release and shelf life specification of reference material identical ranges/limits as for the commercial material are established.The purification process of andexanet alfa includes several steps for inactivation/removal of enveloped viruses. The effectiveness of these steps has been sufficiently demonstrated.

Finished product

Available real-time stability data (obtained from long-term, accelerated and stressed storage) is considered sufficient to confirm the shelf life of 2 years claimed for the andexanet alfa 200 mg strength final product, when stored at 2-8°C.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Sufficiently detailed data and documents have been provided indicating that the product can be reproducibly manufactured and is adequately controlled. The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC.

Based on the review of the quality data provided, the CHMP considers that the application to the marketing authorisation for Ondexxya is approvable from the quality point of view.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended some points for further investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

This is a centralised marketing authorisation application for the recombinant version of human Factor Xa (fXa) Andexanet alfa (andexanet; PRT064445), with a molecular weight of ~ 41 kDa that has been modified to render it enzymatically inactive. Andexanet was developed as a specific antidote for both direct and indirect fXa inhibitors.

2.3.2. Pharmacology

Andexanet is characterized in non-clinical in vitro and in vivo studies. The non-clinical in vitro pharmacology program was designed to confirm the mechanism of action of andexanet including binding to both direct and indirect inhibitors, reversal of anticoagulant activity by measuring anti-fXa activity, restoration of thrombin generation and absent pro-coagulant or anti-coagulant activity.

Non-clinical animal models of blood loss (rodent tail transection and rabbit liver laceration) were used to confirm the ability of andexanet to reverse anticoagulation as measured by anti-fXa activity and restore hemostasis as measured by coagulation markers, which correlated with a decrease in blood loss.

Primary pharmacodynamic studies

The *in vitro* and *in vivo* studies carried out by the applicant are indicative of efficacy of the recombinant version of human fXa which was designed to restore haemostasis and mitigate blood loss due to the anticoagulant effects of both indirect and direct fXa inhibitors.

In the pharmacology program, anti-fXa activity has been identified as a reliable marker of anticoagulation. Anti-fXa activity is a direct measure of the inhibition of the enzymatic activity of fXa anticoagulants and correlates 1:1 with the plasma concentrations of rivaroxaban, apixaban, and edoxaban (e.g., 100 ng/mL of plasma apixaban = 100 ng/mL anti-fXa activity of apixaban). Increases in anti-fXa activity correlate with decreases in thrombin generation. The anti-fXa activity also correlates with blood loss in animal models of bleeding.

The *in vitro* characterization indicates that Andexanet displays high affinities ((Kd) ranging from 0.5-1.5 nM.) to rivaroxaban, apixaban, betrixaban, and edoxaban (direct fXa inhibitors). The molecule has also displayed high binding affinity to complexes with ATIII-dependent inhibitors as enoxaparin and fondaparinux with dissociation constant of aproximately 53 nm. Andexanet dose-dependently reversed the anti-fXa activity of both enoxaparin and fondaparinux by inhibiting and reversing completely direct fXa inhibitor-induced inhibition of thrombin generation. Andexanet also reversed completely betrixaban activity in a dose dependent manner. Andexanet did not show apparent catalytic activity to the peptidyl substrate of fXa or its substrates prothrombin and fVII, and it does not display discernible effects in the activation of human platelets, leucocytes, or endothelial cells *in vitro*. *In vitro* studies also revealed that no relevant interaction with mayor protein plasma proteins and inhibitors was described but for TFPI. Andexanet binds to TFPI (Kd) with high affinity albeit slightly lower than the affinity of fXa-TFPI (Ki). Its relevance has to be addressed in a clinical scenario.

In vivo studies were carried out as well with andexanet in order to characterize the pharmacology of the molecule. Andexanet effect on the recovery of coagulation was assessed in animal models including mice, rats, and rabbits. Andexanet administration to anticoagulated animals results in dose-dependent reductions in blood loss in a variety of scenarios that included trauma, mimicking emergency surgery or in a prophylactic administration prior to surgery/trauma. The pharmacological effect in blood loss

diminishing reported following andexanet administration is concomitant with reversal in markers such as activated partial thromboplastin time (aPTT), anti-fXa activity, INR and prothrombin time. Andexanet reversed apixaban anticoagulation as measured by INR or PT at a molar ratio of plasma andexanet:total apixaban of ~1.2:1. For betrixaban, molar ratios of andexanet of ~2:2 (4.4 µM andexanet:2.2 µM betrixaban) were shown to reverse the 2-fold increase in INR.

The product did not reduce blood loss in anti-coagulated rabbits with a direct thrombin inhibitor, Angiomax and did not demonstrate any pro – or anticoagulant effects when administered alone, data indicative of its selectivity for fXa inhibitors. The effect of andexanet in fVIII-Deficient Mice in a Bleed Time and Blood Loss Model was assessed and also in the rat Wessler venous stasis thrombosis model. These nonclinical data could suggest that andexanet does not have pro- or anticoagulant activity when administered alone and only up to concentrations of 3 µM. Similar findings were reported in rat models. Although dose-dependent increases in aPTT and PT prolongation were seen following EGR-Xa administration, andexanet coadministration did not result promotion of procoagulant or anticoagulant effects. Andexanet but not rfVIIa or PCC reverses rivaroxaban-induced anticoagulation as seen by reduction in blood loss in a rabbit liver laceration model. Andexanet activity results into binding to the anticoagulant, resulting in a lowered free fraction and anti-fXa levels to reverse anticoagulation. Data from the rabbit liver laceration model show that andexanet reduced blood loss, anti-fXa, PT, aPTT, an plasma levels of the unbound circulating direct fXa inhibitors.

Secondary pharmacodynamic studies

Despite the lack of justification it was agreed that due to the nature of the product and the target of the molecule no secondary pharmacodynamics are expected from the administration of the product.

Safety pharmacology programme

Respiratory safety pharmacology of andexanet

A GLP-compliant respiratory function study using head-out plethysmography was performed in 8 male Crl:CD (SD) rats per group given a single intravenous bolus dose of vehicle control article or 3, 10, or 30 mg/kg andexanet at a dose volume of 10 mL/kg that was administered over 3 minutes. Data on the tidal volume, respiration rate and minute volume were collected on a day prior to dosing, immediately after the IV bolus dose administration, and then again at 24 hours post-dose. Administration of a single dose of andexanet had no effect on mortality, clinical observations or respiratory function assessed by measurement of tidal volume, respiration rate, and minute volume for up to 24 hours post-dose.

Central nervous system safety pharmacology

Neurological function was assessed in 6 male Crl:CD (SD) rats per group given a single dose of the vehicle control article or 3, 10, or 30 mg/kg andexanet via intravenous bolus injection at a dose volume of 10 mL/kg. Assessment of neurological effects was based on observations collected pre-dose and at 5 minute and 1, 2, 4, and 24 hours post-dose. All animals were subjected to a modified Irwin observational battery designed to detect potential effects on the central and peripheral nervous systems. Administration of a single dose of andexanet had no effect on mortality, clinical signs, or any component of the modified Irwin observational battery (home cage, hand-held, open-field, or elicited behaviour) up to 24 hours post-dose.

Cardiovascular safety pharmacology

Cardiovascular safety parameters were evaluated as part of the 14-day cynomolgus monkey toxicology study. In this study andexanet was administered at 6, 20, and 60 mg/kg/day by intravenous bolus

injection split into two equal doses BID every 3rd day over a 2 minute time span for a total of 10 administrations during the study. Multilead ECG data on anesthetised cynomolgus monkeys was obtained pre-dose and approximately one hour after the first administration on Day 10 of the dosing phase (Groups 1 through 8. Each group contained 10 monkeys, 5 male and female). In addition, ECG evaluations from free-moving conscious animals, by jacketed external telemetry (JET) were obtained on Study Day 7 (Groups 1 through 4), and blood pressure measurements, by Cardell cuff monitor were also obtained on Day 7 (Group 1 through 4), and blood pressure measurements, by Cardell cuff monitor were also obtained on Day 7. Results were compared to vehicle control animals. Assessments on Day 7 were performed immediately before and during the administration of andexanet and for 24 hours following administration. There were no blood pressure or ECG abnormalities detected in cynomolgus monkeys dosed with andexanet at 6, 20, or 60 mg/kg/day.

Pharmacodynamic drug interactions

Not applicable.

2.3.3. Pharmacokinetics

The PK studies performed had two objectives: to define PK parameters of andexanet and to assess the potential effect of andexanet on the PK of direct factor Xa (fXa) inhibitors. Therefore, the PK of andexanet was evaluated in single dose PK studies in rats and monkeys (both rhesus and cynomolgus). In one study in rats the PK of andexanet were determined following a single IV bolus over 2 minutes of 3 mg/kg PRT064445 to four groups of male Sprague-Dawley rats that had no surgery (control), underwent sham operation, or underwent unilateral or bilateral nephrectomy. In an additional study in rats sequential multiple bolus injections of andexanet were administered after the oral administration of rivaroxaban in order to study the effect of andexanet on rivaroxaban PK. Toxicokinetic (TK) assessment was done as part of toxicity studies.

Type of Study	Test System	Method of Administration (Lot Used)	Bioanalysis Method	Testing Facility	Report Number
Pharmacokinetics					
Single Dose	Rat	IV (Research Lot 4)	ELISA	Portola Pharmaceuticals, Inc.	NC-12-0442-R0001
	Rat	IV (Engineering Lot H5043)	ELISA	Portola Pharmaceuticals, Inc.	NC-12-0443-R0001
	Cynomolgus Monkey	IV (Engineering Lot DEV 11-16, GMP Lot No. 1:1-FIN-1281, GMP Lot 2: 12-0018)	Electrochemi-luminescent MSD	Covance	NC-12-0469-R0001
	Rhesus Monkey	IV (Research Lot 9)	ELISA	UC Davis and Portola Pharmaceuticals, Inc.	NC-12-0441-R0001
Other					
PK Interaction with fXa Inhibitor	Rat	IV (Research Lot 6)	ELISA	Portola Pharmaceuticals, Inc.	NC-12-0440-R0001
PK Interaction with fXa Inhibitor	Cynomolgus Monkey	IV Lots J7101A1, 1231-59-A, and 123-59B	Electrochemi-luminescent MSD	Covance	NC-12-0470-R0001

2.3.4. Toxicology

Single dose toxicity and Repeat dose toxicity

The non-clinical safety program for andexanet was designed to support single intravenous (IV) dose administration in humans. The toxicology of andexanet was evaluated in both rats and monkeys and assessments of the impact on coagulation biomarkers that were considered potential safety concerns were included. Because the intent is to administer andexanet to reverse the anticoagulant effect of fXa inhibitors and thereby restore normal haemostasis, studies in monkeys were conducted with andexanet administered alone as well as co-administered with fXa inhibitors. To maximize the exposure, andexanet was administered twice daily (BID), approximately 4 hours apart throughout the 14-day repeat dose studies up to the maximum feasible dose (MFD) of 60 mg/kg/day.

Furthermore, the immunogenicity of andexanet was evaluated as well as the potential for pro- and anticoagulant effects of andexanet.

Evaluation of reproductive and developmental toxicity was not conducted.

Study Type and Duration	Portola Study Number	fXa Inhibitor Co-administered	Route of Administration	GLP Compliant	Species
Single-dose Toxicity	NC-12-0472	None	IV	No	monkey
Single-day Toxicity (2 doses)	NC-13-0545	None	IV	Yes	monkey
Repeat-dose Toxicity					
2-week	NC-11-0397	None	IV	Yes	rat
2-week	NC-11-0394	enoxaparin, rivaroxaban	IV	Yes	monkey
2-week	NC-12-0417	apixaban, betrixaban	IV	Yes	monkey

In the course of the product development, changes were made to the manufacturing process resulting in andexanet alfa (Gen 2) with a lower level of impurities as determined by the previous standard analytical testing methodologies. Therefore, an additional non-clinical study (NC-16-0757) was designed to compare the PK and PD of the 2 materials (Gen 1 and Gen 2) and additionally assess the toxicity of the material produced using this modified manufacturing process.

Genotoxicity

No genotoxicity studies were performed with adexanet. Consistent with ICH S6, Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals, genotoxicity studies were not considered appropriate. Andexanet is a standard biotechnology-derived protein without any organic linkers that would be a cause for concern for a standard pharmaceutical product. This was agreed by the CHMP.

Carcinogenicity

No carcinogenicity studies were performed with andexanet. A carcinogenic risk assessment for andexanet was provided based on available data and literature information on the pathways involved in the mechanism of action of fXa. Based on the information provided on aspects like dose and duration of exposure, pharmacology risk, structural risk and toxicity risk, andexanet is considered to pose a low carcinogenic risk and the non-clinical evaluation of carcinogenicity potential is considered unnecessary in accordance with ICH Guideline S1A and S6.

Reproduction Toxicity

No reproductive/developmental toxicity studies were conducted with andexanet alfa based on the following:

1) andexanet is intended for single-dose administration and therefore has limited potential for reproductive or developmental toxicity; 2) neither andexanet nor fX crosses the placental barrier and is further unlikely to affect reproductive physiology; 3) andexanet is a biotechnology-derived protein that is a modification of an endogenous protein in the coagulation cascade (fXa); 4) andexanet has a very short half-life (1-2 hour effective half-life). Furthermore, there were no findings on reproductive organs observed in the 2-week toxicity studies performed. This was accepted by the CHMP.

Local Tolerance

Local tolerance was assessed in each toxicology study with no adverse events noted at the IV injection sites. In the repeat dose study in rats (NC-11-0397) microscopic evaluation of the injection sites was evaluated in the dosing and recovery phases of the studies. The microscopic observations were similar among control and andexanet-dosed animals and were consistent with sequela to the intravenous dosing procedure.

In the initial repeat dose study in monkeys (NC-11-0394) no microscopic observations were noted at the injection site. In the second repeat dose study (NC-12-0417) at the terminal euthanasia time point haemorrhage and/or inflammation were observed at intravenous injection sites for all animals, including the animals that received apixaban and betrixaban alone, as well as those animals that had andexanet administered together with apixaban and betrixaban. This perivascular haemorrhage at the intravenous injection sites was considered most likely associated with the pharmacologic effects of apixaban or betrixaban, or procedure-related, since this occurred in all monkeys and was not associated solely with andexanet administration. The omission of studies to evaluate local tolerance at unintended injection sites was considered to be adequately justified.

Other toxicity studies

No additional toxicity studies were conducted. Specific immunotoxicity studies were not conducted as native fXa does not have immunological effects. In addition, no andexanet-specific inflammatory reactions were seen at the injection sites during the standard toxicology studies that would indicate a stimulatory response.

2.3.5. Ecotoxicity/environmental risk assessment

The active substance, andexanet alfa, is a recombinant equivalent of the human factor Xa, a naturally occurring protein and therefore no environmental risk assessment studies have been submitted, in line with guidelines. There are no excipients of human or animal origin and the drug product does not contain any genetically modified organism. The product contains only standard excipients that comply with current European Pharmacopoeia requirements.

Therefore, the drug product is unlikely to result in a significant risk to the environment arising from its use, storage or disposal. As such, andexanet alfa powder for solution for infusion is exempted from the requirement of environmental risk assessment.

2.3.6. Discussion on non-clinical aspects

Pharmacology

The ability of andexanet to bind and neutralise fXa inhibitors was tested in a series of in vitro experiments for rivaroxaban, apixaban, betrixaban, and edoxaban in a buffered system using purified human fXa and a fXa peptidyl substrate, Spectrozyme-fXa (CH3O-CO-D-CHG-Gly-Arg-pNA.AcOH). It could be demonstrated that andexanet dose-dependently and completely (compared to the control without inhibitor) reverses inhibition of fXa by rivaroxaban, apixaban, betrixaban as well as edoxaban. Analysis of these kinetic profiles yields the binding affinity of andexanet to each fXa inhibitor (Kd), which range from 0.5-1.5 nM. Additionally, the interaction of andexanet with ATIII-dependent inhibitors as fondaparinux and enoxaparin has been investigated in vitro. The results demonstrated that andexanet preferentially binds to the ATIII-fondaparinux complex, resulting in dose-dependent reversal of the inhibition of fXa, and has a minimal effect on fXa inhibition by ATIII alone.

Studies have been performed to investigate the reversal of anti-fXa activity of fXa inhibitors in human plasma. Using the modified anti-fXa chromogenic assay in human plasma, andexanet dose-dependently and completely reverses the anti-fXa activity of direct fXa inhibitors (rivaroxaban, apixaban, betrixaban and edoxaban). In a similar assay, andexanet also dose-dependently reverses the anti-fXa activity of a LMWH, enoxaparin, as well as fondaparinux in human plasma.

Using two different thrombin generation assays the reversal of fXa inhibitor-induced inhibition of thrombin generation has been studied. In an in-house thrombin generation assay in human plasma, andexanet dose-dependently and completely (compared to the control without inhibitor) reverses the inhibition of thrombin generation by direct fXa inhibitors rivaroxaban, apixaban, and betrixaban, while andexanet alone has minimal effect in the absence of an inhibitor. Similarly, andexanet also dose-dependently and completely reverses inhibition of thrombin generation mediated by the ATIII-dependent indirect fXa inhibitors enoxaparin and fondaparinux.

In addition to binding to direct and indirect fXa inhibitors, the potential of andexanet to interact with other major plasma coagulation proteins, compared with native fXa, was characterised using a Biacore system. The binding analysis data indicate that andexanet has no significant interaction with other plasma coagulation proteins (II, FV, FVII, FX) or plasma inhibitors (ATIII, α-1-antitrypsin, α-2-macroglobulin), except for TFPI. Therefore, the interaction of andexanet with TFPI was further characterized. In a fXa enzymatic assay using human fXa purified from plasma and recombinant TFPI, andexanet dose-dependently reverses the inhibition of fXa activity by TFPI. Analysis of kinetic data yields binding affinity of andexanet-TFPI that is comparable to fXa-TFPI.

One of the primary physiologic functions of TFPI is to down-regulate the activity of the fVIIa/TF complex. Therefore, the effect of the andexanet-TFPI interaction on fVIIa/TF activity was also determined. In the enzymatic assay, fVIIa/TF activity was dose-dependently and completely inhibited by the fXa-TFPI complex, as expected. In contrast, the andexanet-TFPI complex does not inhibit the fVIIa/TF activity, possibly due to a lack of the Gla-domain in andexanet. When andexanet is co-incubated with rivaroxaban, the binding of andexanet to TFPI can be dose-dependently and completely blocked by the fXa inhibitor at 3 μM, suggesting potential competition between TFPI and rivaroxaban for binding to andexanet in the presence of an excess amount of a fXa inhibitor. The competitive interaction of andexanet with TFPI and fXa inhibitors could enhance reversal of anticoagulation in patients at clinically relevant andexanet doses/regimens for fXa inhibitors.

In summary, the *in vitro* studies demonstrate that andexanet binds to both direct and indirect fXa inhibitors. Andexanet has no significant interaction with other major plasma coagulation proteins, except for TFPI. Andexanet-TFPI interaction may enhance reversal of fXa inhibitor-induced inhibition of

thrombin generation while it has minimal effect on thrombin generation in the absence of a fXa inhibitor. In addition, andexanet lacks either pro- or anti-coagulant activity on its own.

The series of in vivo studies demonstrate that rapid reversal of fXa inhibitor-induced anticoagulation with andexanet can restore haemostasis and mitigate blood loss due to the anticoagulant effects of both indirect and direct fXa inhibitors, without promoting pro- or anticoagulant effects in several animal models of bleeding and thrombosis. Importantly, the PK and PD markers of anticoagulation have correlated with reduction of blood loss in animal models using multiple fXa inhibitors.

Comparisons of andexanet with other proposed reversal agents for fXa inhibitors in a rabbit model of bleeding, i.e., recombinant factor VIIa (rfVIIa), 3-factor and 4-factor prothrombin complex concentrates, and PER977 in the rabbit liver laceration model demonstrated that only andexanet significantly reduced blood loss, anti-fXa, PT, aPTT, and the unbound plasma levels of the circulating direct fXa inhibitors.

There were no adverse findings in male rat CNS and respiratory safety pharmacology studies up to, and including, the maximum dose considered feasible, 30 mg/kg, when administered by IV bolus. Andexanet was evaluated for cardiovascular safety as a component study of the 14-day repeat IV bolus administration to cynomolgus monkeys. No effects were found on ECG parameters and blood pressure.

Pharmacokinetics

The PK of andexanet was evaluated in single and multiple dose studies in male rats and monkeys (both rhesus and cynomolgus). In one study rats were administered a series of successive doses of andexanet after oral administration of rivaroxaban. The objective of combination studies was to determine the effect of andexanet on the PK of rivaroxaban and the effect of rivaroxaban on andexanet PK.

The exposure is close to dose proportional over the dose range studied (from 1 to 10 mg/kg), and the elimination is bi-exponential in both the non-clinical species examined. Consistent dose proportional PK was also seen in the toxicokinetic portion of the toxicity studies in the rat and the monkey. The volume of distribution is relatively small, approximately equivalent to the blood volume plus the extracellular space. The distribution half-life is quite short, while the elimination half-lives across species and studies were variable. However, the drop in concentrations during the distribution half-life demonstrated removal of over 99% of the drug from the vascular compartment during that distribution phase. The rapid elimination is also seen in the toxicity studies and is consistent with the complete lack of accumulation of andexanet.

When administered as intended, in the presence of the fXa inhibitor rivaroxaban, andexanet PK becomes more complex. A 1 mg/kg dose of andexanet appeared to be affected by rivaroxaban and have higher plasma concentrations and exposure than in the absence of rivaroxaban. However, this effect largely disappeared at the 5 mg/kg dose of andexanet and it was postulated that this effect may be due to an interaction with tissue factor pathway inhibitor (TFPI) on the surface of endothelial cells that can sequester a portion of andexanet. Rivaroxaban and other fXa inhibitors may disrupt or decrease this interaction, restoring the sequestered andexanet to the circulating plasma concentration.

The largest effect observed in PK studies was the effect of andexanet on the PK of rivaroxaban. Two studies, one in rats and one in monkeys, examined the effect of andexanet on total and unbound rivaroxaban in the presence and absence of andexanet. In rats the total rivaroxaban concentration increased up to 2-fold as small repeated successive IV bolus 1 mg/kg doses of andexanet were administered (after an initial 2 mg/kg bolus dose). These increases in total rivaroxaban concentrations coincided with decreases in the unbound levels to 0.1 ng/mL. The effect of the 5 mg/kg andexanet

dose in monkeys resulted in a more pronounced increase (5.5-fold) in the total rivaroxaban plasma concentration in monkeys, with a concomitant decrease in unbound rivaroxaban concentration of 93%. The unbound concentration correlates directly with the anti-fXa activity and is therefore a surrogate marker for the anti-fXa activity of fXa inhibitors. The dose-related effect of andexanet on the PK of rivaroxaban is evident from these studies.

The results of the PK study in nephrectomised rats that underwent sham operation, or underwent unilateral or bilateral nephrectomy indicate that renal clearance is a significant pathway in the elimination of andexanet in rats.

In summary, andexanet PK is predictable in non-clinical species. After IV bolus administration the elimination is biphasic, with a rapid elimination phase and a longer terminal elimination phase. The concentrations increase dose-dependently in both rats and monkeys. The volume of distribution is relatively small, equivalent to the blood plus the extracellular volume for both the rat and the monkey. While andexanet has a large effect on the PK of one of its target molecules, rivaroxaban, those molecules have very little effect on andexanet PK at exposure levels comparable to therapeutic dose levels. These results indicate that andexanet can be administered by bolus intravenous injection with resulting predictable exposure and elimination. The effects observed on the PK of rivaroxaban are transient, due to the rapid elimination of andexanet.

Toxicology

The non-clinical safety of andexanet was evaluated in one repeat dose study in rats and two single and two repeat dose studies in monkeys, as monkeys were the more relevant species based on genetic similarity of coagulation biomarkers. An additional toxicology study in monkeys was performed to compare the PK and PD of the 2 materials from the two manufacturing processes (Gen 1 and Gen 2) and additionally assess the toxicity of the material produced using this modified manufacturing process.

Andexanet is intended to be administered as a single dose to reverse uncontrolled bleeding that is due to the presence of either direct or indirect fXa inhibitors. Studies of two weeks duration in both species allowed evaluation of the potential safety issues of andexanet anticipated after a single dose administration in both the presence and absence of fXa inhibitors. Three different daily dose levels of andexanet were evaluated: 6, 20, and 60 mg/kg/day administered as two equal bolus IV injections separated by 4 hours. Evaluation of toxicity at the highest feasible daily dose of 60 mg/kg/day, was done with or without both direct and indirect fXa inhibitors. Evaluation of toxicity in the presence of these fXa inhibitors was important because andexanet is intended to be administered as an antidote to these inhibitors (i.e., in the presence of these inhibitors). Administration of andexanet in the presence of fXa inhibitors did not exacerbate any toxicity observed after andexanet administration. The highest feasible total daily dose of 60 mg/kg/day was also the NOAEL for all studies. The average Cmax in monkeys of 530,000 ng/mL is ~2.3-fold higher than the highest Cmax observed (235,000 ng/mL) in human clinical studies after administration of the highest selected dose for treatment of bleeding, 800 mg bolus dose followed by an 8 mg/min infusion for 120 minutes. The average AUC observed after the 60 mg/kg/day dose was 1,020,682 ng*hr/mL was more than 2-fold higher than the average AUC (429,000 ng*hr/mL) observed after the same 800 mg bolus/ 8 mg/min infusion dose in humans.

No safety issues were observed in any of the non-clinical studies that would suggest that andexanet cannot be used as intended for the treatment of uncontrolled bleeding. In rats, the only observation was that PT times were increased by less than 1 sec, which was dose-dependent and statistically significant. However, this small increase in PT would not be expected to increase the risk of bleeding if PT prolongation of 1 sec occurred in humans. Transient increases were observed in monkeys in a number of coagulation-related biomarkers that have been associated with thrombotic events: TAT and

D-dimer. These increases were less when andexanet was administered in the presence of fXa inhibitors. These transiently increased TAT and D-dimer values did not lead to any increase in clinical observations, or histologically detected intravascular thrombi.

The incidence of thrombi formation was not higher in andexanet-treated animals than vehicle-treated animals and the overall incidence was quite low. Anti-drug antibodies were observed in both rats and monkeys after multiple dose administration due to repeat dose administration of a foreign protein to animals. The incidence of anti-drug antibody formation was dose-related, with a higher incidence at increasing doses of andexanet. These antibodies did not affect the PK of andexanet in rats or monkeys. This result is expected and not considered an adverse effect or predictive of human immunogenicity.

From the results of the additional study NC-16-0757 it could be concluded that administration of andexanet (Gen 2) by IV bolus injection to cynomolgus monkeys on Days 1, 4, 7, 10, and 13, at a dose level of 60 mg/kg/dose day (30 mg/kg twice daily) either alone or in combination with 0.75 mg/kg/dose day apixaban was well tolerated, and all animals survived for the intended study duration. Andexanet pharmacodynamic activity (near complete reversal of apixaban anti-fXa activity) was demonstrated within 5 minutes following the andexanet dose on both days evaluated (Days 1 and 13). Definitive andexanet (Gen 2)-related effects were limited to mild postdose increases in D-dimer and TAT complexes in all treatment groups that trended toward baseline or approximated baseline or controls 3 days following dosing. Thrombi in the lungs of animals given andexanet (Gen 2) with and without apixaban have been observed and were considered a potential andexanet (Gen 2)-related effect. Nevertheless, the single thrombi were not definitively attributed to andexanet, due to the sporadic incidence of these findings. Furthermore, no thrombi were observed in recovery animals in any of the toxicity studies. Therefore, the no-observed-adverse-effect-level (NOAEL) for andexanet (Gen 2) remained unchanged and was considered to be 60 mg/kg/day when given alone or in combination with apixaban.

In summary, andexanet was well-tolerated in both rats and monkeys in these studies. Testing at a defined maximum-feasible dose did not elucidate any serious adverse effects in the presence or absence of fXa inhibitors. Coagulation parameters were evaluated and showed increased levels of D-dimer and TAT in monkeys, both of which were attenuated by co-administration with a fXa inhibitors. The increase in these biomarkers of coagulation activity did not correlate with any increased histopathologically observed intravascular thrombi after andexanet treatment compared to vehicle-treated animals. Cardiovascular evaluation did not elucidate any adverse observation in either of the 2-week monkey studies. Overall, andexanet appears to be well-tolerated at an exposure (measured by Cmax and AUC) that is 2- to 3-fold higher than that observed with the highest dose intended for human clinical use.

The results submitted with the additional study NC-16-0757 are indicative of andexanet (Gen2) PD activity measured as reversal of apixaban anti-fXa activity. The results are also indicative of comparability between Gen 1 and Gen 2 in terms of toxicity, confirming thrombi reported in a previous study (NC-11-0394) with a comparable distribution (small arterioles) and size. The results of this study do not show additional safety concerns with Gen 2 compared to Gen 1 when animals are dosed for two weeks and PD, PK and coagulation markers data are also comparable.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical *in vitro* pharmacology program confirmed the mechanism of action of andexanet including binding to both direct and indirect inhibitors, reversal of anticoagulant activity by measuring anti-fXa activity, restoration of thrombin generation and absent pro-coagulant or anti-coagulant activity. The non-clinical animal models of blood loss (rodent tail transection, rabbit liver laceration and trauma model in pigs) confirmed the ability of andexanet to reverse anticoagulation as measured by

anti-fXa activity and restore haemostasis as measured by coagulation markers, which correlated with a decrease in blood loss.

The pharmacokinetic studies define PK parameters of andexanet and demonstrate its dose-dependent effect on the PK of its target molecule rivaroxaban. Rivaroxaban and other fXa inhibitors may disrupt or decrease the interaction of andexanet with TFPI, restoring the sequestered andexanet to the circulating plasma concentration. Although there is a slight difference in the binding affinity of andexanet for the different direct FXa inhibitors and only rivaroxaban has been tested in the PK study, a difference within this range is not sufficient to expect a serious effect on the PK of apixaban and edoxaban and no separate studies are considered to be conductive. The missing non-clinical data can be compensated by already existing clinical data.

The results of the PK study in nephrectomised rats indicate that renal clearance is a significant pathway in the elimination of andexanet in rats. In summary, sufficient results of non-clinical pharmacokinetic studies are provided.

The safety of andexanet has been characterized in rats and monkeys at a maximum dose of 60 mg/kg/day. The results of the presented toxicology studies reveal no concerns.

In conclusion, from the non-clinical perspective, type and amount of studies investigating pharmacology, pharmacokinetics and toxicology of andexanet in different species and several animal models were considered sufficient and appropriate to support the marketing authorisation.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1 Tabular Overview of the Completed/Ongoing Studies

Type of Study; Location of Study Report	**Study Identifier**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s)**	**Dosage Regimen; Route of Admin.**	**Number of Subjects**	**Healthy Subjects or Diagnosis of Patients**	**Duration of Study**	**Study Status; Type of Report**
BA 5.3.1.1 Bioavailability Study Reports	**11-501**	A Phase 1, Randomized, Double-Blind, Placebo-Controlled Single Ascending Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Intravenously Administered PRT064445, a Factor Xa (FXa) Inhibitor Antidote	Randomized (3:1 andexanet:placebo), Double-Blind, Placebo-Controlled, Single Ascending Dose	andexanet	andexanet doses: 30 mg 90 mg 300 mg 600 mg IV Bolus over 10-30 minutes	N=32 (24 andexanet, 8 placebo) [2]	Healthy subjects	Up to ~8 weeks [1]	**Completed;** CSR Final
PK 5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports	**14-506**	A Phase 1, Open-Label Study of the Pharmacokinetics of Andexanet Alfa in Younger and Older Healthy Subjects Receiving Apixaban	Single Center, Open-Label 2 parallel groups of 10 subjects each of whom received apixaban 2.5 mg PO q12 hours x 7 doses: Group 1: healthy subjects ages 18-45 Group 2: healthy subjects ages > 65 Uncontrolled	andexanet	apixaban: 2.5 mg PO q12 hr for 7 doses. andexanet: 400 mg IV bolus	N=20	Healthy subjects	Up to ~7 weeks [1]	**Completed;** CSR Final

Type of Study; Location of Study Report	**Study Identifier**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s)**	**Dosage Regimen; Route of Admin.**	**Number of Subjects**	**Healthy Subjects or Diagnosis of Patients**	**Duration of Study**	**Study Status; Type of Report**
PD-PK 5.3.4.1 Healthy Subject PD and PK/PD Study Reports	**12-502**	A Phase 2, Randomized, Double-Blind, Vehicle-Controlled Multiple Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Intravenously Administered PRT064445 After Dosing to Steady State with One of Four Direct/Indirect FXa Inhibitors in Healthy Volunteers	Randomized (2:1 andexanet: placebo), Double-Blind, Placebo-Controlled, Cohort Dose Escalation	andexanet	**Module 1** apixaban 5 mg orally BID for 5.5 days. Andexanet doses: 90 mg bolus 210 mg bolus 420 mg bolus 420 mg bolus + 4 mg/min for 45 minutes (180 mg) 420 mg bolus + 180 mg bolus 420 mg bolus + 4 mg/min for 120 minutes (480 mg)	N=54 (36 andexanet, 18 placebo) [2]	Subjects	~7 weeks [1]	**Completed;** CSR Final
PD-PK 5.3.4.1 Healthy Subject PD and PK/PD Study Reports	**12-502** (Cont'd)				**Module 2** rivaroxaban 20 mg orally QD for 6 days. Andexanet doses: 210 mg bolus 420 mg bolus 600 mg bolus 720 mg bolus + 4 mg/min for 60 minutes (240 mg) 800 mg bolus + 8 mg/min for 120 minutes (960 mg)	N=45 (30 andexanet, 15 placebo) [2]	Healthy subjects	Up to 8 weeks [1]	**Completed;** CSR Final

Type of Study; Location of Study Report	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s)	Dosage Regimen; Route of Admin.	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Study	Study Status; Type of Report
PD-PK 5.3.4.1 Healthy Subject PD and PK/PD Study Reports	**12-502** (Cont'd)				**Module 3** enoxaparin 40 mg SQ QD for 6 days Andexanet doses: 210 mg bolus (2 cohorts at this dose) 420 mg bolus	N=27 (18 andexanet, 9 placebo) [2]	Healthy subjects	Up to ~8 weeks [1]	**Completed;** CSR Final
PD-PK 5.3.4.1 Healthy Subject PD and PK/PD Study Reports	**12-502** (Cont'd)				**Module 4** edoxaban 60 mg orally QD for 6 days. andexanet doses: 600 mg bolus 800 mg bolus + 8 mg/min for 60 minutes (480 mg) 800 mg bolus	N=28 (19 andexanet, 9 placebo) [2]	Healthy subjects	Up to ~8 weeks [1]	**Completed;** CSR Final
PD-PK 5.3.4.1 Healthy Subject PD and PK-PD Study Reports	**15-507**	A Phase 2, Randomized, Double-blind, Placebo-Controlled Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Intravenously Administered Andexanet After Dosing to Steady-State with Oral Betrixaban in Healthy Subjects	Randomized (2:1 Andexanet:placebo), Double-blind, Placebo-Controlled in healthy subjects	andexanet	betrixaban 80 mg orally QD for 7 days. andexanet up to 4 cohorts: 800 mg bolus 800 mg bolus + 8 mg/min for 120 minutes (960 mg)	9 subjects/ cohort	Healthy subjects	Up to ~8 weeks [1]	**Ongoing**

Type of Study; Location of Study Report	**Study Identifier**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s)**	**Dosage Regimen; Route of Admin.**	**Number of Subjects**	**Healthy Subjects or Diagnosis of Patients**	**Duration of Study**	**Study Status; Type of Report**
5.3.4.1 Controlled clinical study pertinent to claimed indication (Efficacy and Safety Studies	**16-508**	A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics/Pharmacodynamics of Andexanet Alfa Administered to Healthy Japanese and Caucasian Patients	Randomized (2:1 andexanet: placebo), Double-blind, Placebo-Controlled	andexanet	Oral FXa Direct Inhibitors: apixaban (5 mg BID), rivaroxaban (15 mg BID), and endoxaban (60 mg BID) Low dose andexanet: 400 mg bolus + 4 mg/min for 120 minutes (480 mg) High dose andexanet: 800 mg bolus + 8 mg/min for 120 minutes (960 mg)	Part 1 = 51 (34 andexanet, 17 placebo) Part 2 with up to 5 additional cohorts	Healthy subjects	36 days	**Ongoing**
5.3.4.1 Controlled clinical study pertinent to claimed indication (Efficacy and Safety Studies)	**16-512 Direct Inhib.**	A Phase 1, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of Second Generation Andexanet Alfa Administered to Healthy Subjects	PK-PD comparability study comparing Generation 1 and Generation 2 andexanet Generation 2 cohorts Placebo-controlled	andexanet (Gen 1, Process 2, Gen 1 Process 3, Gen 2)	**Direct Inhibitors**: apixaban (5 or 10 mg BID), rivaroxaban (10 or 20 mg BID), edoxaban (60 mg BID) Low dose andexanet: 400 mg bolus + 4mg/min infusion for 120 minutes (480 mg) High dose andexanet: 800 mg bolus + 8 mg/min infusion for 120 minutes (960 mg)	98 andexanet, 20 placebo	Healthy Subjects	37 days	**Completed; CSR Final**

Type of Study; Location of Study Report	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s)	Dosage Regimen; Route of Admin.	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Study	Study Status; Type of Report
5.3.4.1 Controlled clinical study pertinent to claimed indication (Efficacy and Safety Studies)	**16-512 Indirect Inhib.**	A Phase 1, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of Second Generation Andexanet Alfa Administered to Healthy Subjects	PK-PD comparability study comparing Generation 1 and Generation 2 andexanet Generation 2 cohorts Placebo-controlled	andexanet (Gen1, Process 2, Gen 1 Process 3, Gen 2)	**Indirect Inhibitors:** enoxaparin 1 mg/kg SC Low dose andexanet: 400 mg bolus + 4mg/min infusion for 120 minutes (480 mg) High dose andexanet: 800 mg bolus + 8 mg/min infusion for 120 minutes (960 mg)	24 andexanet, 6 placebo	Healthy Subjects	37 days	**Ongoing**
5.3.5.1 Controlled clinical study pertinent to claimed indication (Efficacy and Safety Studies)	**14-503**	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study in Older Subjects to Assess Safety and the Reversal of Apixaban Anticoagulation with Intravenously Administered Andexanet Alfa	Randomized (3:1 andexanet: placebo), Double-Blind, Placebo-Controlled Study in Older Subjects ages 50-75	apixaban andexanet	apixaban 5 mg orally BID for 3.5 days. Part 1: 400 mg bolus Part 2: 400 mg bolus + 4 mg/min infusion for 120 minutes (480 mg)	Part 1 = 33 (24 andexanet, 9 placebo) Part 2 = 32 (24 andexanet, 8 placebo) [2]	Healthy subjects	Up to ~6 weeks [1]	**Completed;** CSR Final
5.3.5.1 Controlled clinical study pertinent to claimed indication (Efficacy and Safety Studies)	**14-504**	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study in Older Subjects to Assess Safety and the Reversal of Rivaroxaban Anticoagulation with Intravenously Administered Andexanet Alfa	Randomized,(2:1 andexanet: placebo) Double-Blind, Placebo-Controlled Study in Older Subjects ages 50-75	rivaroxaban andexanet	rivaroxaban 20 mg orally QD for 4 days Part 1: 800 mg bolus Part 2: 800 mg bolus + 8 mg/min infusion for 120 minutes (960 mg)	Part 1 = 41 (27 andexanet, 14 placebo) Part 2 = 39 (26 andexanet, 13 placebo) [2]	Healthy subjects	Up to ~6 weeks [1]	**Completed;** CSR Final

Type of Study; Location of Study Report	**Study Identifier**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s)**	**Dosage Regimen; Route of Admin.**	**Number of Subjects**	**Healthy Subjects or Diagnosis of Patients**	**Duration of Study**	**Study Status; Type of Report**
5.3.5.1 Controlled clinical study pertinent to claimed indication (Efficacy and Safety Studies)	**14-505**	A Phase 3b/4, Prospective, Open-Label Study of Andexanet Alfa in Patients Receiving a Factor Xa Inhibitor who have Acute Major Bleeding	Multicenter, Open-Label	andexanet	FXa inhibitors (apixaban, rivaroxaban, edoxaban, enoxaparin) as prescribed Low dose andexanet: 400 mg bolus + 4mg/min infusion for 120 minutes (480 mg) High dose andexanet: 800 mg bolus + 8 mg/min infusion for 120 minutes (960 mg)	N= 352	Patients with acute major bleeds	37 days	**Ongoing**

2.4.2. Pharmacokinetics

Analytical methods

The validation of the electrochemiluminescent (ECL) analytical method used to quantify the concentration of andexanet in human plasma and urine samples were submitted. For both methods, plasma and urine samples, the validation of the method included assessment of precision and accuracy of the standard curve, the assay range (defined by the LLOQ and ULOQ), intra-assay precision and accuracy, inter-assay precision and accuracy, selectivity, specificity, dilutional linearity, minimum required dilution, pro-zone effect, and short-term and freeze/thaw stability.

The electrochemiluminescent method is suitable for the quantification of PRT064445 in human plasma and urine. The minimum required dilution (MRD) for the assay in human plasma and urine is 2-fold and 5-fold for plasma and urine, respectively.

The range of the assay for PRT064445 in neat human urine was 15.0 to 4500 ng/mL (3.00-900 ng/mL at the MRD) and the range of the assay for PRT064445 in neat citrated human plasma was 12.0 to 1800 ng/mL.

Both assays were selective in human plasma and urine diluted 2-fold and 5-fold, respectively, and was specific for PRT064445 in the presence of a 1-fold and 5-fold molar excess of human FX and FXa, rivaroxaban, enoxaparin (Lovenox), betrixaban and apixaban. However, recoveries in human plasma were outside the acceptable limits in the presence of betrixaban at 5-fold molar excess in samples spiked with PRT064445 at mid and high levels.

Linearity was observed at a dilution of 1000-fold in citrated human plasma samples and urine samples spiked with PRT064445 above the ULOQ and diluted in standard diluent and pro-zone effect was not observed at concentrations up to 100x the ULOQ in both matrices.

PRT064445 was stable through three cycles of being frozen at -80 ºC ± 15 ºC and thawed at room temperature, overnight storage at 1-8°C for plasma samples and for approximately 22 hours in urine samples, and storage at room temperature for approximately 4 hours and 4.5 hours for plasma and urine samples, respectively.

Long term storage for up to three months at -20 ºC ± 10°C and -80 ºC ± 15°C was demonstrated in human plasma. The applicant has submitted also the long-term stability for three months in urine at -20 ºC and -80 ºC. Parallelism for urine samples was not being conducted as there were no study samples with concentrations above the LLOQ. Since robotic liquid handling systems were not used in the andexanet bioanalysis carry-over effect experiments were not conducted and it is considered acceptable in accordance with the Guideline on bioanalytical method validation.

Several methods have been validated for the extraction (liquid liquid extraction [LLE]) and quantification (HPLC/MS/MS; LC/MS/MS) of FXa. HPLC/MS/MS has been validated for the quantification of FXa inhibitors rivaroxaban, edoxaban, and apixaban in plasma and urine samples.

A liquid-liquid extraction (LLE) and HPLC/MS/MS were used to determine the total concentration of apixaban and rivaroxaban from human sodium citrate plasma (also human K2EDTA for rivaroxaban) and human urine. The applicant has submitted also the validation reports for apixaban and rivaroxaban in human plasma and urine. In general, the pre-study validations of the bioanalytical methods were consistent and demonstrated an adequate precision and accuracy (both intra- and inter-day) within the calibrated range, which showed an adequate selectivity, matrix effect and carry-over.

Enoxaparin PK was quantified using an anti-fXa activity assay performed on a STA-Compact analyser (Diagnostica Stago, Inc.) using the STA Rotachrom Heparin kit per the manufacturer's instruction. This

test is not suitable for evaluating the reversal activity of andexanet due to the high plasma dilution factor utilised in this clinical assay that would dilute out the effect of andexanet.

The plasma concentration of edoxaban and D21-2393 was quantified using a standard LC/MS/MS. This method was submitted and is suitable for determination of edoxaban and D21-2393. In addition, edoxaban in urine samples was conducted using a validated method (Turbo Ion Spray LC/MS/MS)..

A 96-well Micro-Equilibrium Dialysis Device from HighThroughPut Dialysis (HTDialysis, Gales Ferry, NC) was utilised to determine the protein binding of apixaban, rivaroxaban, and edoxoban in human plasma. The applicant has submitted the requested validation reports utilised to determine the protein binding of apixaban, rivaroxaban, and edoxoban in human plasma. The validations of the analytical methods are satisfactory. The methods met the acceptance criteria for all the validation parameters evaluated, demonstrating acceptable performance.

Phase II studies of andexanet alfa suggest that andexanet has a slightly less than dose proportional linear pharmacokinetics over the dose range evaluated for both Cmax and area under the curve (AUC).

Table 2 Summary of Noncompartmental Plasma PRT064445 Pharmacokinetic Parameters Following PRT064445 IV Bolus Administration in Cohort 1 (Without the 0 Hour Concentration Value of one Subject) Through Cohort 4

Study 11-501 Variables	30 mg, 3 mg/mL IV formulation [J7101A1]	Andexanet alfa 90 mg	Andexanet alfa 300 mg	Andexanet alfa 600 mg
	Mean Parameters (± SD)			
C_{max} (ng/L)	3,080 ± 389	10,800 ± 4,110	52,800 ± 1,3200	93,300 ± 14,200
T_{max} (hours) *	0.21 (0.17, 0.29)	0.23 (0.18, 0.29)	0.26 (0.17, 0.34)	0.51 (0.42, 0.52)
$AUC_{0-\infty}$ (ng/L x hr)	4,710 ± 508	12,600 ± 3,450	61,400 ± 15,400	118,000 ± 17,300
$t_{1/2}$ (hours)	7.25 ± 2.14	7.38 ± 2.21	7.46 ± 1.58	6.40 ± 1.88
CL (L/hr)	6.30 ± 0.681	6.24 ± 0.92	5.13 ± 1.16	5.18 ± 0.639
Vss (L)	25.0 ± 5.58	14.8 ± 4.16	8.27 ± 2.40	7.82 ± 1.81

* T_{max} values are mean (min, max).

An additional 990 mg dose-level was targeted, originally. However, the Sponsor opted not to proceed to 990 mg dose after completion of the 600 mg dose level due to a dose-dependent increase in coagulation markers F1+2, TAT and D-dimer that appeared to be inconsistent with prior results from GLP toxicology study in cynomolgus monkeys.

Table 3 Andexanet PK Parameters Observed after IV Bolus Dose Administration (study 12-502)

Pharmacokinetic Parameters	Andexanet Dose, Mean ± SD (N = 6/Cohort)		
	210 mg (O)	210 mg (L)	420 mg (O)
C_{max} (ng/mL)	32,000 ± 7,320	42,700 ±14,400	55,800 ± 6,050
t_{max} [a] (hours)	0.18 (0.16, 0.35)	0.17 (0.17, 0.19)	0.29 (0.27, 0.54)
$AUC_{0-\infty}$ (ng*hr/mL)	33,600 ± 4,280	40,900 ± 12,300	63,900 ± 8,880
$t_{1/2}$ (hours)	5.28 ± 1.99	8.36 ± 7.46	6.11 ± 2.34
λ_z (1/hr)	0.142 ± 0.0358	0.130 ± 0.0686	0.130 ± 0.0517
CL (L/hr)	6.34 ± 0.870	5.56 ± 1.76	6.69 ± 0.991
V_{ss} (L)	9.86 ± 2.61	9.69 ± 4.16	9.62 ± 1.13

L = lyophilised and reconstituted formulation; O = original liquid formulation

[a] t_{max}: median (min, max).

Two formulations were used during PK studies. The lyophilised drug product (Generation 1, process 2) contained similar excipients to the initial liquid formulation (Generation 1, process 1), with the

exception of the addition of mannitol which was added to improve the stability of the lyophilised cake. This change in stabiliser does not affect the bioavailability and the "*in vitro*" comparability data suggests that the stability of the drugs is not affected. Therefore it is considered that both formulations are equivalent.

The Vd for andexanet alfa lyophilised formulation is about 9.69 L (study 12-502). However, disposition kinetics, protein binding and percentage of extravascular distribution has not been established and needs to be further clarified. This is particularly important to anticipate potential secondary untoward effects linked to permanence of the drug bound to proteins/membranes/cells.

Table 4 **AUC0-∞** for Study 11-501 and 12-502, Module 3 with Calculated Values for Dose-Normalized $AUC_{0-\infty}$ ($NAUC_{0-\infty}$)

Study Number	Dose mg	$AUC_{0-\infty}$ ng*hr/mL	CV %	$NAUC_{0-\infty}$ ng*hr/mL/mg
11-501	30	4,713	10.8%	157.1
	90	12,622	27.3%	140.2
	300	61,429	25.1%	204.8
	600	117,713	14.7%	196.2
12-502, Module 3	210 (O)	33,630	12.7%	160.1
	420 (O)	63,881	13.9%	152.1
	210 (L)	40,926	30.1%	194.9

Study 11-501 used Process 1 material and Study 12-502, Module 3 compared the original (O) liquid formulation to the (L) lyophilised formulation.

From the studies 11-501 and 12-502, it was observed a generally low inter-subject variability in AUC (Table 9). The inter-subject variability was also low (≤40.0%) for the other PK parameters.

Clearance (L/hr) for the andexanet alfa lyophilised formulation is approximately 5.56 L/hr (study 12-502). Renal involvement in elimination is uncertain. On the one hand, non-clinical studies suggest a renal elimination, but PK studies did not detect andexanet in urine samples. The elimination half-life is about 8.36 hours (study 12-502).

No radiolabeled mass balance studies have been conducted. There is no information in the clinical dossier about metabolic pathways: biodegradation, catabolism (i.e.: proteolytic catabolism in the kidneys, hepatic metabolism, etc). There is no sufficient information about elimination pathways (renal, biliar, other). This is important to ascertain whether dose-adjustments may be needed in patients with renal or hepatic impairment.

In a study comparing andexanet alfa pharmacokinetics in elderly (≥ 65 years) and younger (18 to 45 years) healthy subjects who had received apixaban, the pharmacokinetics of andexanet alfa in the elderly subjects were not statistically different than that in the younger subjects with respect to AUC and Cmax.

Table 5 Plasma Andexanet Pharmacokinetic Parameters (PK/PD Population)

Parameter Statistic[1]	Younger Subjects (18-45 Years) (N = 10)	Older Subjects (≥ 65 Years) (N = 10)	Ratio of Younger Subjects to Older Subjects
$AUC_{(0-\infty)}$ (H*NG/ML) Geometric Mean 90% CI	90425.76 (79948.63, 102275.9)	91594.84 (80982.26, 103598.2)	0.987 (0.829, 1.175)
$AUC_{(0-t)}$ (H*NG/ML) Geometric Mean 90% CI	90028.58 (79574.69, 101855.8)	91312.55 (80709.57, 103308.5)	0.986 (0.828, 1.174)
C_{max} (NG/ML) Geometric Mean 90% CI	69645.65 (61030.31, 79477.17)	63754.40 (55867.82, 72754.28)	1.092 (0.906, 1.317)

[1] Geometric means and confidence intervals obtained from a model with a fixed effect for age group

There is no information in the clinical dossier about metabolic pathways: biodegradation, catabolism (i.e.: proteolytic catabolism in the kidneys, hepatic metabolism, etc). There is no information about elimination pathways (renal, biliar, other). No formal studies have been conducted to investigate the pharmacokinetics of andexanet alfa in renally impaired patients or in patients with hepatic impairment. The applicant was requested to submit an appropriate summary and discussion about available and unavailable data on the influence of intrinsic factors in the PK/PD characteristics of andexanet alfa (i.e.: impaired renal function, impaired hepatic function, gender, race, weight). It should be discussed whether these populations might require dose-adjustment (i.e.: based on body-weight, renal function, hepatic impairment, etc.). The applicant has submitted an updated PK/PD analysis (Report NC-17-0810-R0001) based on data available with andexanet-rivaroxaban (in studies 501, 502 and 504; n = 149), but not with apixaban or edoxaban. All data included in the updated PK and PK/PD analyses in this report were from healthy (young and elderly) subjects. While healthy volunteers may exhibit some differences in PK and PK/PD behaviour relative to patients, they provide information that is not feasible to obtain in patients. For example, it is not possible to collect additional blood samples for measurement of andexanet concentrations in patients already suffering severe bleeding events. Therefore, the only option for characterizing andexanet PK is to study it in healthy volunteers. Additionally, the most robust estimates of apixaban and rivaroxaban PK parameter dependencies on key covariates will likely be those gleaned from the literature rather than estimated from the andexanet clinical study data, as the former were based on a much larger sample size. In the next stage of modeling, the population PK/PD model for apixaban and rivaroxaban (as well as for edoxaban) will be updated to include patient data from study 14-505. Specifically, when the patient data become available, simulations will be performed using the current model to predict anti-fXa activity and/or percent change from baseline in patients from study 14-505, based on the enrolment information and patient-level or summary covariates and dosing information. Congruence between model predictions and observed anti-fXa activity data in patients will be assessed, summarized, and visualized both for the overall population and by subgroups defined by the covariates. Based on these evaluations, the current PK/PD model will be refined to achieve better agreement with the patient data.

The mechanism of action of andexanet is based on an interaction with the factor Xa inhibitors. Although theoretically no other drug-drug interactions are expected, the applicant was requested to discuss about this issue. The company has discussed about potential for interactions between andexanet and other drugs, as requested. As andexanet is unlikely to be distributed intra-cellulary and

therefore unlikely to interact with cellular transporters or CYP45 enzymes. In addition, as it is administered directly into the vasculature, it would thus have limited exposure to any transporters.

The applicant was also requested to send all available data and discussion about tThe relationship between andexanet concentrations and adverse effects was. The company has included in the analysed for a total of 146 healthy subjects that were exposed to andexanet across the three PK trials with bolus doses ranging from 90 mg to 800 mg, and the total administered dose ranging from 90 mg. The median exposures were similar between subjects with AEs or IRRs (infusion-related reactions) and subjects without presenting these events. Exposure-response relationship could be defined for either parameter (p = 0.66 and 0.31, respectively). Therefore, no exposure-adverse event relationship was found for andexanet, probably because IRRs, which is the large majority of adverse events reported, are more likely to be related to the infusion procedure itself than to the product infused.

Finally, the pharmacokinetics of andexanet alfa has not been studied in paediatric patients. This is acceptable, as a PIP including deferral has been agreed with the EMA.

Special populations

Table 6 Enrolment of Andexanet Clinical Trials by Age Group

	Age < 65 (younger subjects number/total number)	**Age 65–74 (older subjects number/total number)**	**Age 75–84 (older subjects number/total number)**	**Age 85 + (older subjects number/total number)**
Efficacy/Safety Trials	15/101	26/101	41/101	19/101
PK Trials	216/247	31/247	0/247	0/247

Note: Number andexanet-treated subjects in specified age range/total number of andexanet-treated subjects.

2.4.3. Pharmacodynamics

Mechanism of action

The predominant mechanism of action is the binding and sequestration of the FXa inhibitor, although there may be a minor contribution from the inhibition of tissue factor pathway inhibitor (TFPI) activity through binding to TFPI. The interaction between andexanet alfa and TFPI has not been fully characterized. Andexanet alfa binds direct FXa inhibitors with high affinity, making them unavailable to exert their anticoagulant effects.

Primary and Secondary pharmacology

Four studies (11-501, 12-502, 14-506 and 16-512) as well as a PK/PD model, are relevant to establish the PD effects of andexanet alfa. From these studies it may be concluded that the predominant mechanism of action of andexanet alfa is binding and sequestration of the FXa inhibitor.

- Study 11-501:
  - This first-in-human Phase 1 study (11-501) evaluated the safety, tolerability, PK, and PD properties of andexanet alfa in healthy human subjects. The study was a single centre, double-blind, randomised, placebo-controlled, ascending, single dose study of andexanet or its matching placebo.
- Study 12-502:

- The ability of andexanet to reverse the anticoagulation of fXa inhibitors was evaluated in a PK PD study in healthy subjects. The study was conducted in separate modules for each fXa inhibitor: apixaban (Module 1), rivaroxaban (Module 2), enoxaparin (Module 3), or edoxaban (Module 4).

Clinical data from Study 12-502 was used to develop a PK-PD model that provided the basis to select a dosing regimen for reversal of anticoagulation for all the direct fXa inhibitors. A second modelling exercise provided information that allowed for selection of the andexanet dose to reverse anticoagulation due to administration of low molecular weight heparins such as enoxaparin.

- Study 14-506:
  - This study compared the PK and PD of andexanet administered to healthy elderly vs. younger healthy subjects anticoagulated with apixaban.
- Study 16-512:
  - The objectives of Part 1 of 16-512 were to demonstrate PK and PD comparability between andexanet manufactured by the Generation 1 and Generation 2 processes, and to evaluate the safety of Generation 2 process andexanet compared to placebo, in healthy subjects dosed to steady state with apixaban and rivaroxaban. Parts 2 and 3 expanded the evaluation of the PK, PD and safety of the Generation 2 process andexanet compared to placebo in healthy subjects dosed to steady state with enoxaparin, or edoxaban, in addition to apixaban and rivaroxaban at dose levels not previously assessed in healthy subjects, in order to demonstrate PD dose linearity of andexanet.

Study 11-501

This first-in-human Phase 1 study evaluated the safety, tolerability, PK, and PD properties of andexanet alfa in healthy human subjects. The study was a single centre, double-blind, randomised, placebo-controlled, ascending, single-dose study of andexanet or its matching placebo, administered as a single IV bolus over either 10 minutes for the 30, 90, and 300 mg dose, while the 600 mg dose was administered over 20 minutes. Within each dosing cohort, 6 subjects received andexanet and 2 received placebo. After non-clinical confirmation (in cynomolgus monkeys) the Sponsor opted not to proceed to the 990 mg dose level.

The PK was close to dose proportional. The clearance (CL) values were similar across the doses, ranging from 5.1 to 6.3 L/hr. The volume of distribution at steady-state (V_{ss}) decreased with increasing andexanet doses.

Peak and total exposure (Cmax and AUC) to andexanet increased with increasing andexanet doses. The increases were relatively dose proportional when the andexanet dose increased from 30 to 90 mg but more than dose proportional when the dose increased from 90 to 300 mg, and 600 mg doses.

Furthermore, PK-results of study 11-501 (andexanet in healthy volunteers) differ from the results studies where andexanet was administered in healthy volunteers taking NOAs although it has been stated that “FXa inhibitors did not affect andexanet alfa pharmacokinetics”. The applicant interpreted the differences of PK-behaviour of andexanet in Healthy volunteers versus andexanet in Healthy volunteers with test-anticoagulants as a dose-effect with no evidence of interference. This interpretation derives from the PK-modelling and seems to be highly theoretical. Physiological background and justification of such dose cut-off of 100mg for PK-behaviour (increase of clearance of 24% and increase of distribution volume of 7% for every 100mg) was discussed. An assumed mechanism of TFPI inhibition up to a certain saturation which is meant to be 100 mg Andexanet was agreed, although it was not supported by compelling PD-data. However, as the “breaking” dose is

below the doses recommended for andexanet treatment, the point was considered to be solved.Table 7 Summary of Noncompartmental Plasma PRT064445 Pharmacokinetic Parameters Following PRT064445 IV Bolus Administration in Cohort 1 (Without the 0 Hour Concentration Value of one Subject) Through Cohort 4

	Cohort 1 (N = 6)	Cohort 2 (N = 6)	Cohort 3 (N = 6)	Cohort 4 (N = 6)
Pharmacokinetic Parameters	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
C_{max} (ng/mL)	3078.35 ± 389.220	10779.47 ± 4113.716	52785.92 ± 13160.802	93288.30 ± 14212.071
t_{max}[a] (hr)	0.214 (0.17, 0.29)	0.227 (0.18, 0.29)	0.260 (0.17, 0.34)	0.506 (0.42, 0.52)
AUC_{0-24} (ng*hr/mL)	4564.204 ± 472.51849	12472.89 ± 3492.4875	61030.90 ± 15438.452	117230.5 ± 17385.398
AUC_{0-last} (ng*hr/mL)	4508.725 ± 471.64143	12463.56 ± 3474.0231	61037.41 ± 15439.284	117246.9 ± 17384.605
$AUC_{0-\infty}$ (ng*hr/mL)	4712.788 ± 507.68220	12621.60 ± 3445.4374	61428.90 ± 15442.566	117712.9 ± 17276.645
$t_{1/2}$ (hr)	7.250 ± 2.1400	7.378 ± 2.2142	7.460 ± 1.5821	6.403 ± 1.8788
λ_z (1/hr)	0.1028 ± 0.030034	0.1087 ± 0.059644	0.09592 ± 0.017299	0.1142 ± 0.024816
CL (L/hr)	6.303 ± 0.68095	6.241 ± 0.91761	5.126 ± 1.1629	5.175 ± 0.63863
V_d (L)	65.27 ± 17.614	67.29 ± 23.052	55.39 ± 19.891	48.49 ± 18.463
V_{ss} (L)	24.95 ± 5.5773	14.80 ± 4.1589	8.272 ± 2.3977	7.818 ± 1.8110

Cohort 1 = Administration of 30 mg PRT064445 IV Bolus (Cohort 1)
Cohort 2 = Administration of 90 mg PRT064445 IV Bolus (Cohort 2)
Cohort 3 = Administration of 300 mg PRT064445 IV Bolus (Cohort 3)
Cohort 4 = Administration of 600 mg PRT064445 IV Bolus (Cohort 4)
[a]t_{max} is presented as Median (Minimum, Maximum)
Source: Tables 14.2.1.1.5 through 14.2.1.1.8

Whereas in the animal studies, renal clearance was a significant elimination pathway for andexanet, no urinary andexanet could be detected in the current human study, suggesting that renal clearance may not be a major route of elimination in humans.

Study 14-506

This study was designed for comparing PK-, PD- and Safety-profiles of younger and older age-groups under apixaban-treatment. The mean plasma concentration of andexanet reached its peak at 2 minutes post-dose in both age cohorts in Study 14-506. Cmax was slightly higher in the younger subjects. This difference may be explained by the higher mean body weight of the older subjects, 75.1 ± 10.9 kg vs. 70.7 ± 10.1 kg for the younger subjects. Indeed, a correlation was detected between body weight and Cmax as well as between body weight and AUC in this study. Earlier studies of andexanet had narrower weight ranges and no such correlation could be established. After adjusting for body weight, the 90% CI for AUC0-∞, AUC0-tau, and Cmax were all contained within the equivalence boundaries (0.80, 1.25), indicating comparable exposure. The PK of andexanet and the PD effects on anti-fXa activity and thrombin generation in older and younger subjects were similar.

Study 12-502

The ability of andexanet to reverse the anticoagulation of fXa inhibitors was evaluated in a randomized, double-blind, placebo-controlled dose-escalation study in healthy volunteers. The study was conducted in separate modules for each fXa inhibitor: apixaban (Module 1), rivaroxaban (Module 2), enoxaparin (Module 3), or edoxaban (Module 4). The fXa inhibitor was dosed to steady state and following the last dose of the fXa inhibitor, andexanet was administered such that each andexanet bolus dose ended at the approximate Tmax for the specific fXa inhibitor. In this way the maximum required dose of andexanet for each fXa inhibitor could be determined by evaluating the PD response across the range of andexanet doses tested. PK-parameters were calculated using non-compartmental analysis methods. For each parameter, summary statistics, including arithmetic mean, standard deviation (SD), standard error of the mean (SEM), sample size (N), minimum, maximum, median, and coefficient of variation [CV (%)] were calculated by cohort. In addition, geometric mean and geometric CV (%) were calculated for AUCs and Cmax. BLQ values were treated as zero before the first quantifiable concentration and as (1/2) LOQ for the calculations of the summary statistics.

Results study 12-502:

Module 1 (apixaban)

The anti-fXa activity decreased as the andexanet bolus dose increased from 90 to 420 mg, with the end of bolus activity levels similar for all cohorts that had initial bolus doses of 420 mg (Cohorts 3-6). Decreases were also observed in unbound apixaban concentrations for the same cohorts. Among the placebo-treated subjects, 17 out of 18 subjects had thrombin generation levels below the baseline range. The 420 mg bolus dose alone (Cohort 3), as well as the same bolus dose with follow on bolus or infusion doses resulted in nearly all subjects having thrombin generation levels restored to within baseline levels (within 1 SD of the mean value prior to apixaban dose administration on Day 1). The key parameter in attaining reversal of fXa inhibition is having a molar excess of andexanet relative to the fXa inhibitor.

Table 8 Key Pharmacodynamic Measurements at the End of Andexanet Bolus Dose Administration in Apixaban-Anticoagulated Subjects (Study 12-502, Module 1)

Cohort (N=6)	Dose	Molar Ratio Andexanet : Apixaban Mean ± SD	Anti-fXa Activity (ng/mL) Mean ± SD	% Decrease Baseline Mean ± SD	Unbound Apixaban (ng/mL) Mean ± SD	%Decrease Baseline Mean ± SD	Number of Subjects Restored to Baseline Thrombin Generation
1	90 mg bolus	1.37 ± 0.23	50.4 ± 19.1	68 ± 8	3.83 ± 1.2	51 ± 12	4 (N=6)
2	210 mg bolus	1.74 ± 0.30	43.8 ± 24.6	79 ± 4	4.53 ± 2.6	54 ± 7	5 (N=6)
3	420 mg bolus	2.87 ± 0.63	7.35 ± 3.48	95 ± 1	2.25 ± 0.92	72 ± 7	6 (N=6)
4	420/4 x 45	2.37 ± 0.39	11.4 ± 2.87	94 ± 2	1.88 ± 0.21	79 ± 6	6 (N=6)
5	420/180	2.26 ± 0.20	13.9 ± 2.75	93 ± 2	1.10 ± 0.11	89 ± 3	5 (N=6)
6	420/4 x 2 hr	2.87 ± 1.11	11.0 ± 1.79	93 ± 1	1.17 ± 0.31	84 ± 6	6 (N=6)
Placebo (N=18)	NA	NA	160 ± 38.0	7 ± 11	8.37 ± 1.43	5 ±14	1 (N=18)

Notes: Andexanet bolus dose administration was at 30 mg/minutes for all dose cohorts; 420/4 x 45 is a 420 mg andexanet IV bolus over 14 minutes (30 mg/min) followed immediately by a 180 mg continuous IV infusion (4 mg/min over 45 minutes); 420/180 45 is a 420 mg andexanet IV bolus over 14 minutes (30 mg/min) followed after 45 minutes by a second bolus of 180 mg over 6 minutes (30 mg/min); 420/4 x 2 hours is a 420 mg andexanet IV bolus over 14 minutes (30 mg/min) followed immediately by a 480 mg continuous IV infusion (4 mg/min over 2 hours).

The addition of a second bolus (Cohort 5) or a continuous infusion (Cohorts 4 and 6) following the initial bolus maintained the reduction in anti-fXa activity observed with the 420 mg bolus alone. The PD response was similar between the two cohorts. The only notable difference was that the cohort with the second bolus (Cohort 5) had only 5 out of 6 subjects restored to baseline thrombin generation

(within 1 SD). The anti-fXa activity levels at the end of the second doses (either second bolus or infusion) were similar: 15.0 ± 1.72 ng/mL and 12.8 ± 3.69 ng/mL for Cohorts 4 and 5, respectively.

Module 2 (rivaroxaban)

The PD measurements at the end of the bolus doses for each of the 5 cohorts are provided in Table 14. The anti-fXa activity levels and unbound rivaroxaban levels decreased consistently with increasing andexanet doses, in spite of the relatively flat molar ratios. At the lowest dose of andexanet, 210 mg, none of the subjects attained baseline levels of thrombin generation. Restoration to baseline levels of thrombin generation was achieved by all six subjects at a bolus dose of 720 mg andexanet, but not at lower bolus doses. A 4 mg/min infusion rate did not maintain the reversal of fXa inhibition observed after the 720 mg bolus dose, while an 8 mg/min was able to maintain the fXa inhibition reversal brought about by the 800 mg bolus dose.

Table 9 Key Pharmacodynamic Measurements at the End of Andexanet Bolus Dose Administration in Rivaroxaban-Anticoagulated Subjects (Study 12 502, Module 2)

Cohort (N=6)	Andexanet Dose	Molar Ratio Andexanet: Rivaroxaban Mean ± SD	Anti-fXa Activity (ng/mL) Mean ± SD	% Decrease Baseline Mean ± SD	Unbound Rivaroxaban (ng/mL) Mean ± SD	% Decrease Baseline Mean ± SD	Number of Subjects Restored to Baseline Thrombin Generation
1	210 mg bolus	0.80 ± 0.14	198 ± 46.6	18 ± 24	14.5 ± 3.06	34 ± 22	0 (N=6)
2	420 mg bolus	1.22 ± 0.38	105 ± 42.3	51 ± 22	9.42 ± 2.91	52 ± 18	2 (N=6)
3	600 mg bolus	1.26 ± 0.87	63.6 ± 57.6	75 ± 19	6.02 ± 5.25	75 ± 16	3 (N=6)
4	720 mg/ 240 mg CI	1.06 ± 0.11	25.6 ± 15.9	89 ± 6	7.28 ± 5.68	67 ± 24	6 (N=6)
5	800 mg/ 960 mg CI	1.34 ± 0.33	15.1 ± 7.57	93 ± 3	5.08 ± 3.32	80 ± 12	6 (N=6)
Placebo (N=15)	NA	NA	269 ± 81.9	22 ± 42	24.3 ± 5.88	NA	0 (N=15)

Notes: Andexanet bolus dose administration was at 30 mg/min for all dose cohorts; 720 mg bolus IV dose over 24 minutes followed immediately by a 240 mg continuous IV infusion (4 mg/min over 60 min); 800 mg andexanet IV bolus over 27 minutes (30 mg/min) followed immediately by a 960 mg continuous IV infusion (8 mg/min over 2 hours).

Module 3 (enoxaparin)

In Study 12-502, Module 3, 40 mg of enoxaparin was administered subcutaneously QD for 5 days. The three cohorts were andexanet bolus doses of: 1) 210 mg frozen liquid formulation; 2) 420 mg of the frozen liquid formulation; and 3) 210 mg of the lyophilised formulation.

Table 10 Key Pharmacodynamic Measurements at the End of Andexanet Bolus Dose Administration in Enoxaparin-Anticoagulated Subjects (Study 12-502, Module 3)

Cohort (N=6)	Andexanet Dose	Molar Ratio Andexanet:Enoxaparin * Mean ± SD	Anti-fXa Activity (IU/mL) Mean ± SD	% Decrease Baseline Mean ± SD	Number of Subjects Restored to Baseline Thrombin Generation
1	210 mg bolus (O)	1.06 ± 0.41	0.112 ± 0.037	71 ± 7	6 (N=6)
2	420 mg bolus (O)	1.89 ± 0.42	0.129 ± 0.0273	61 ± 8	6 (N=6)
3	210 mg bolus (L)	1.41 ± 0.19	0.104 ± 0.0466	70 ± 7	5 (N=6)
Placebo (N=8)	NA	NA	0.335 ± 0.0505	4 ± 13	0 (N=8)

Notes: Andexanet bolus dose administration was at 30 mg/min for all dose cohorts; O stands for the original frozen liquid formulation and L stands for the lyophilised formulation. * Enoxaparin molar concentration calculated using average MW of 4,500 Da.

The anti-fXa activity observed at the end of the andexanet bolus dose was close to the lower limit of quantitation (0.1 IU/mL) for all three cohorts, indicating that the lowest dose (210 mg) was sufficient to reverse the anti-fXa activity of this low prophylatic dose of enoxaparin (40 mg QD). In addition, all three dose cohorts restored thrombin generation to within one standard deviation of the mean baseline level, except for a single subject in the 210 mg dose cohort using the lyophilised formulation.

The Rotachrom anti-fXa assay, which was used to evaluate enoxaparin PK required a high sample dilution. This assay was not useful for measuring the anti-fXa levels on Day 6 because the anti-fXa activities were too dilute to be accurately quantified. Therefore, the applicant stated that the Day 6 enoxaparin PK parameters using the results from the Rotachrom anti-fXa assay are not interpretable.

Module 4 (edoxaban)

Prior to andexanet administraiton 60 mg of edoxaban was administered QD for 5 days. The first two cohorts were designed such that the bolus dose of andexanet ended at 3 hours after the last dose of edoxaban (~Tmax): Cohort 1 a 600 mg bolus and Cohort 2 an 800 mg bolus dose followed by a 60 minute infusion at a rate of 8 mg/min. In Cohort 3, the 800 mg bolus dose of andexanet was administered at 5 hours after the last dose of edoxaban. Edoxaban has a human specific metabolite, D21-2393, which is approximately equipotent in the fXa activity assay, and is present at 5 to 8% of the total edoxaban levels at all time points. This metabolite was quantified for both total and unbound concentrations. Because the relative changes were similar, the values are not presented in the summary table or discussed separately.

At the lowest andexanet dose, a 600 mg bolus-only dose, the anti-fXa activity level decreased by ~52% compared to the pre- andexanet levels. An 800 mg bolus dose followed by an 8 mg/min (480 mg over 60 min) continuous infusion reduced the anti-fXa activity to 50.9 ± 27.2 ng/mL, which was

72.6% below the predose anti-fXa activity levels; this resulted in restoration of thrombin generation for 6 out of 6 subjects, indicating that this level of reversal is consistent with normalising haemostasis. The cohort 3 dose of andexanet ended at 5 hours after the last edoxaban dose, which resulted in a decrease of the anti-fXa activity to 16.9 ± 6.2 ng/mL, an 82% decline from the pre-andexanet level.

Table 11 Key Pharmacodynamic Measurements at the End of Andexanet Bolus Dose Administration in Edoxaban-Anticoagulated Subjects (Study 12-502, Module 4)

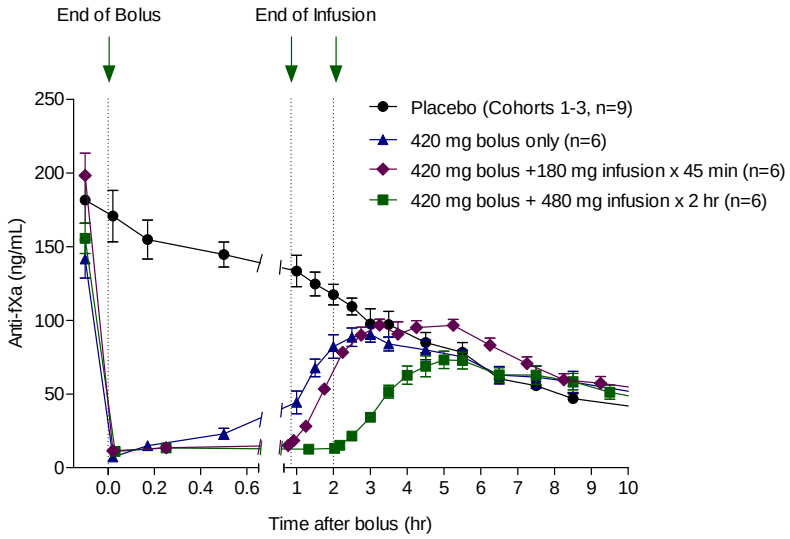
Cohort (N=6)	Andexanet Dose	Molar Ratio Andexanet: Edoxaban (+ D21-2393) Mean ± SD	Anti-fXa Activity (ng/mL) Mean ± SD	% Decrease Baseline Mean ± SD	Unbound Edoxaban (ng/mL) Mean ± SD	% Decrease Baseline Mean ± SD	Number of Subjects Restored to Baseline Thrombin Generation
1	600 mg bolus	1.05 ± 0.13	109.4 ± 76.2	51.7 ± 16.0	59.6 ± 33.1	55.5 ± 7.0	1 (N=6)
2	800/8 x 60 min	1.41 ± 0.36	50.9 ± 27.2	72.6 ± 8.3	41.1 ± 19.7	66.2 ± 9.4	6 (N=6)
3	800 mg bolus *	2.32 ± 1.01	16.9 ± 6.2	82.0 ± 6.7	15.1 ± 7.5	75.6 ± 12.6	6 (N=6)
Placebo ** (N=8)	NA	NA	155.2 ± 69.2	20.6 ± 11.5	103.1 ± 55.4	18.2 ± 15.3	0 (N=8)

Notes: Andexanet bolus dose administration was at 30 mg/min for all dose cohorts; Cohort 2 was an 800 mg IV bolus dose administered over 27 minutes followed immediately by an 8 mg/min IV infusion for 60 minutes. * Andexanet administered at 5 hours post the last edoxaban dose. ** Placebo values for anti-fXa activity and unbound levels are from Cohorts 1 and 2 only with N=5.

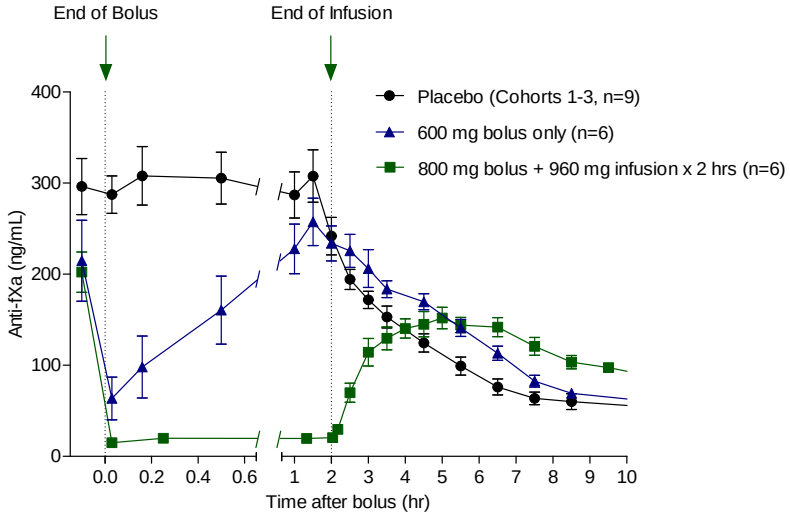
Anti-fXa Activity

Anti-fXa activity is considered the most relevant PD marker for demonstration of reversal of anticoagulation based on the similarity between the fXa inhibitors and the correlation between fXa inhibitor concentration, anti-fXa activity and increased bleeding risk observed in the registration enabling studies with fXa inhibitors. Administration of andexanet resulted in a rapid (i.e., within 2 minutes after the end of bolus dose) decrease in anti-fXa activity relative to pre-dose values. The magnitude and duration of decrease in anti-fXa activity following andexanet administration were dose- and dose-regimen dependent. Following a rapid decrease, the effect on mean anti-fXa activity was sustained (relative to placebo) when followed by a continuous infusion.

A. Apixaban (Study 12-502, Module 1)



B. Rivaroxaban (Study 12-502, Module 2)



C. Edoxaban (Study 12-502, Module 4)

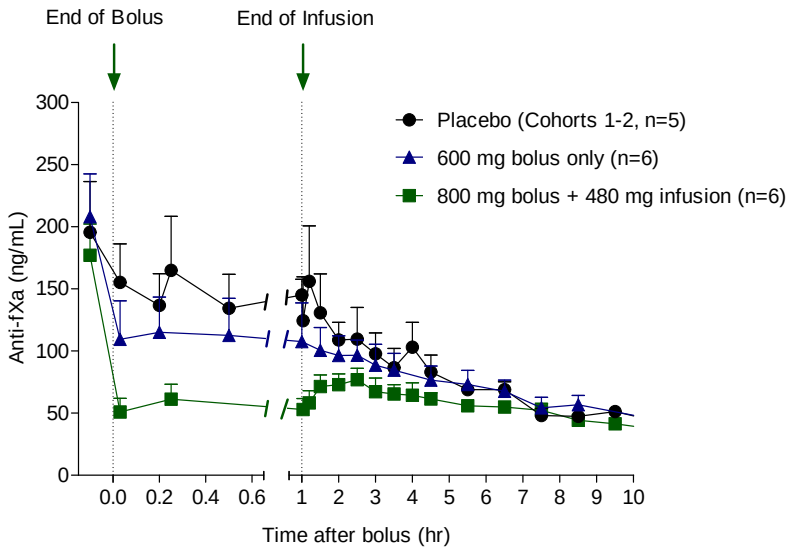
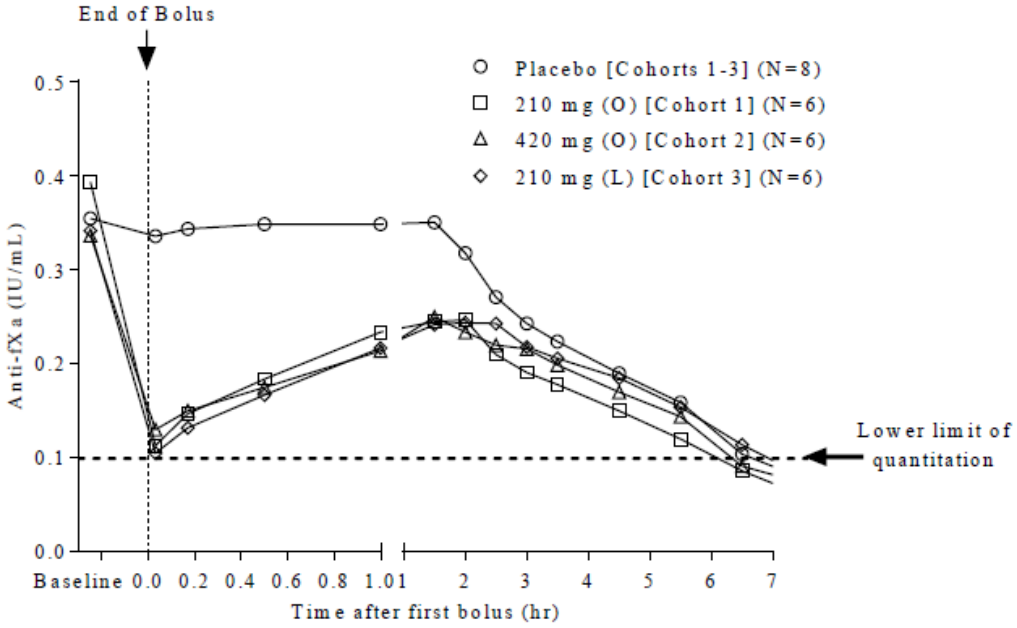


Figure 2 Rapid Reduction of Apixaban, Rivaroxaban, and Edoxaban Anti-fXa Activity



Source Tables 14.2.3.2.2.10.1 through 14.2.3.2.2.10.4. Module 3: enoxaparin 40 mg SC QD on Days 1 through 6. "Baseline" is defined as the time immediately prior to andexanet/placebo administration, which was administered such that the first bolus dose ended at 3 hours following the enoxaparin dose on Day 6. Baseline values following 210 mg (O), 420 mg (O), 210 mg (L) and pooled placebo groups were 0.39, 0.34, 0.34 and 0.35 ng/mL IU/mL, respectively. Each data point represents mean value. Mean values for placebo groups were manually calculated. O: original: L: lyophilized. Refer to Table 2 for andexanet dose notations.

Figure 3 Arithmetic Mean Anti-fXa Activity (IU/mL) Versus Time Following Andexanet/Placebo Administration

Unbound Concentrations of Direct fXa inhibitors

While the total plasma concentrations of fXa inhibitors increase with increasing andexanet dose levels, the unbound levels decrease, along with the anti-fXa activity. At steady state in the absence of andexanet, the unbound apixaban concentration at Cmax was ~8.4 ng/mL. After a 90 mg andexanet

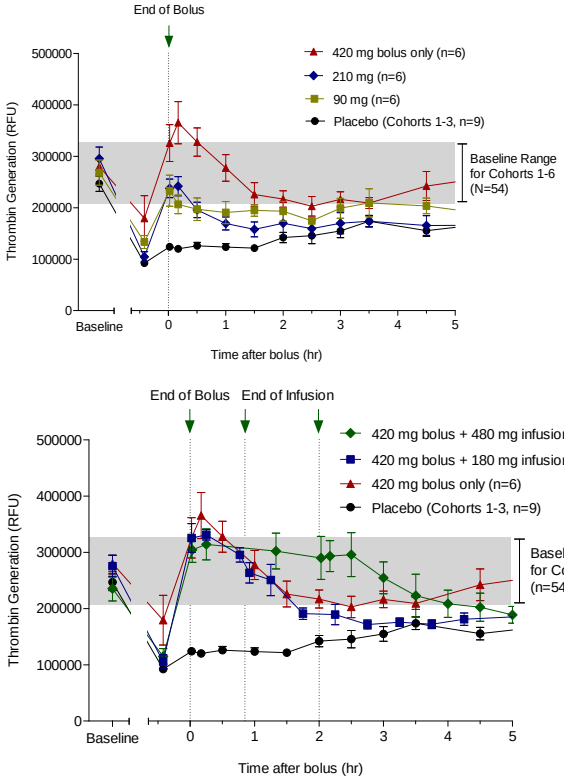
bolus, the unbound concentration decreased by approximately 50% to ~4 ng/mL. At the end of a 420 mg bolus, the unbound concentration was generally less than 2 ng/mL, below the estimated no effect level of 3.5 ng/mL. The steady state Cmax unbound concentration of rivaroxaban was higher, with a mean value of 24.3 ± 5.9 ng/mL. A bolus dose of 800 mg was required to decrease the mean unbound concentration to 5.1 ± 3.3 ng/mL. The higher andexanet dose required for rivaroxaban than apixaban is due to both the initial higher unbound concentration at Cmax as well as the higher volume of distribution for rivaroxaban compared to apixaban. Edoxaban has the highest unbound concentration of any of the fXa inhibitors (due to the lowest level of plasma protein binding) and the mean unbound edoxaban concentration at three hours after a 60 mg dose at steady state was 128.8 ± 47.4 ng/mL in subjects receiving a 600 mg IV andexanet bolus. This 600 mg dose decreased the unbound concentration by 55.5%, to 59.6 ± 33.1 ng/mL; an 800 mg bolus decreased it by ~66% to 41.1 ± 19.7 ng/mL. Thus, these findings feedback to results of PK-PD modelling and andexanet dosing recommendations.

In the comparability study (16-512), all subjects in the low dose cohorts (1, 3, and 4) were anticoagulated using the 5 mg apixaban BID dose. Free apixaban values were similar at baseline, the nadir, and by percent changes from baseline to nadir, consistent with the primary PD endpoint.

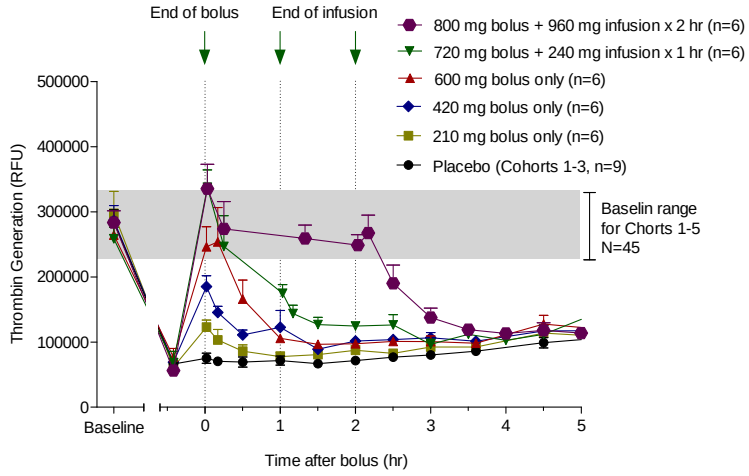
Thrombin Generation

Thrombin generation results from cleavage of prothrombin to thrombin by fXa in the prothrombinase complex. Thrombin is the last protease in the coagulation cascade to convert fibrinogen to fibrin and determines the ability of blood to clot. Therefore, thrombin generation was used as an additional PD marker to determine if the reversal of anticoagulation by andexanet was able to restore haemostasis. Following administration, andexanet restored thrombin generation to baseline levels (the mean ± 1 SD of the level observed prior to anticoagulation). The magnitude and duration of thrombin generation restoration following andexanet administration were dose- and dose-regimen dependent. The reversal of anti-fXa activity correlated with normalisation of thrombin generation in a dose and dose regimen-dependent manner for all three direct fXa inhibitors. For apixaban at steady state levels (5 mg BID dose) a dose of 420 mg followed by a 4 mg/min infusion restored all subjects to baseline levels of thrombin generation and that restoration was maintained throughout the duration of the infusion. For rivaroxaban at steady state levels after the 20 mg QD dose, a 600 mg bolus dose restored thrombin generation to pre-anticoagulant levels, but only transiently. A 720 mg bolus dose with the 4 mg/min infusion also restored thrombin generation to baseline levels, but this restoration was also transient, in spite of the infusion. However, an 800 mg andexanet bolus followed by an 8 mg/min infusion restored and maintained thrombin generation to/at pre-baseline levels for the duration of the infusion. Thrombin generation was restored to baseline levels for both edoxaban cohorts administered 800 mg andexanet and the follow-on 8 mg/min infusion maintained the same level of thrombin generation during the 60 minute infusion.

A. Apixaban



B. Rivaroxaban



C. Edoxaban

Legend: Restoration of thrombin generation by andexanet in Study 12-502 with apixaban, rivaroxaban, and edoxaban.

A. With apixaban, andexanet was administered as a 90 mg, 210 mg, 420 mg IV bolus; a 420 mg bolus + 180 mg continuous infusion (45 minutes at 4 mg/min); or a 420 mg bolus + 480 mg continuous infusion (120 minutes at 4 mg/min).

B. With rivaroxaban, andexanet was administered as a 210 mg, 420 mg, 600 mg IV bolus; a 720 mg IV bolus + 240 mg continuous infusion (60 minutes at 4 mg/min); or a 800 mg IV bolus + 960 mg continuous infusion (120 minutes at 8 mg/min).

C. With edoxaban, andexanet was administered as a 600 mg IV bolus; an 800 mg IV bolus + 480 mg continuous infusion (60 minutes at 8 mg/min); or an 800 mg IV bolus administered at 5 hours after the last edoxaban dose. Data are shown as mean ± standard error of the mean (SEM). Baseline range was based on thrombin generation (mean ± standard deviation (SD) on Day 1 prior to dosing of anticoagulant.

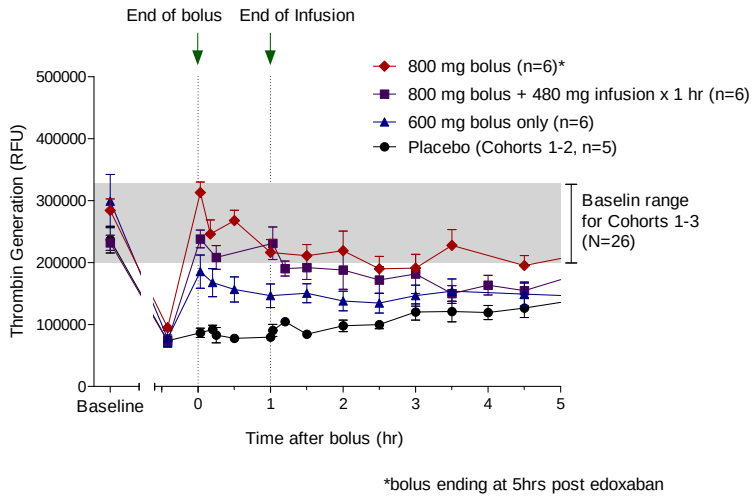
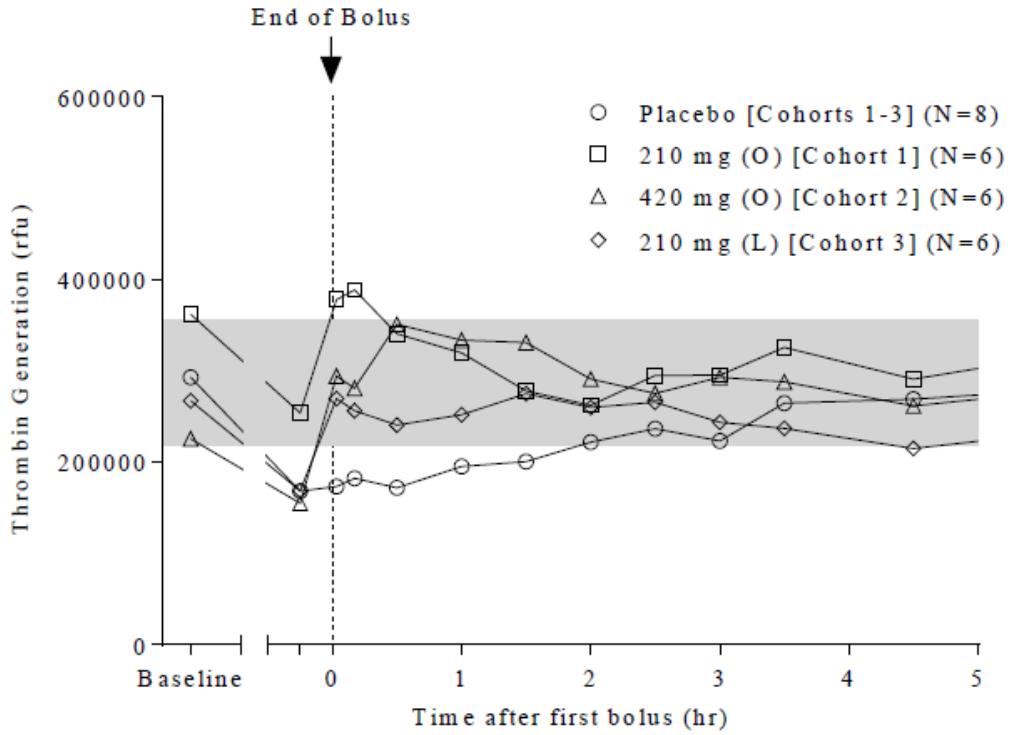


Figure 4 Thrombin Generation Levels During Phase 2 Studies with Apixaban, Rivaroxaban, and Edoxaban

For enoxaparin, the percent of subjects achieving restoration of thrombin generation at 2 minutes after the end of bolus dose in Cohorts 1- 3 was 83% to 100%.

A prolonged restoration of thrombin generation starting immediately (within 2 minutes post bolus dose) and extending for 2-3 hours following the bolus dose was observed for Cohorts 1-3. In the pooled placebo subjects, mean thrombin generation levels were restored at approximately 2.0 hours after the bolus dose, following plasma clearance of enoxaparin.



Source Tables 14.2.3.2.2.16.1 through 14.2.3.2.2.16.4. Module 3: enoxaparin 40 mg SC QD on Days 1 through 6. "Baseline" is defined as the time immediately prior to enoxaparin administration on Day 1 (Mean ± SD of 287562 ± 68957 rfu, N = 27). Day 1 Mean ± SD baseline value (prior to enoxaparin) was manually calculated using individual subject data enrolled in this module (Table 14.2.3.2.1.16.1 through 14.2.3.2.1.16.4).
Shaded region represents Day 1 pre-enoxaparin (Mean ± 1SD) values, i.e. 218605 to 356519 rfu.
Andexanet/placebo was administered such that the bolus dose ended at 3 hours following the enoxaparin dose on Day 6. Each data point represents mean value. Mean values for placebo groups were manually calculated.
O: original: L: lyophilized. Refer to Table 2 for andexanet dose notations.

Figure 5 Arithmetic Mean Thrombin Generation (rfu) Versus Time Following Andexanet/Placebo Administration

Secondary TFPI-mediated effects:

Study 11-501 showed some transient but important increases in coagulation biomarkers of D-dimer (during 24 hours post dose), F1+2 (up to 7 days) and TAT (up to 24 hours) compared to placebo-treated subjects, and a decrease in the TFPI endogenous anticoagulant (up to 24 hours). This trend was confirmed in study 12-502, in which there were transient increases in D-dimer and F1+2 levels and decreased levels of TFPI with andexanet administration in all four study modules for at least one of these markers, as well as in ANNEXA-A and ANNEXA-R phase 3 studies (see also efficacy section). Andexanet binds to TFPI in the plasma and possibly also to TFPI bound to the endothelium. These mechanisms may contribute to the reversal of the anticoagulated state (i.e., fXa inhibition). However, the binding to TFPI may also explain the observed dose-dependent transient increase in D-dimer, F1+2 and TAT with simultaneous decrease in TFPI. As in study 11-501 and 12-502, transient but important elevations in D Dimer and F1+2 occurred following andexanet exposure were observed in the majority of subjects in study 11-506, with longer durations observed in the elderly group (aged >65 years). The magnitude of the effects of andexanet in increasing in D-dimer and F1+2 levels and decreasing levels of TFPI in the study 12-502, in which andexanet was given in anticoagulated non-elderly healthy volunteers, was of a lesser magnitude than those observed when andexanet was administered in the absence of a fXa inhibitor in humans (Study 11-501). However, the study 14-506 in elderly volunteers

vs. non-elderly also showed that the increases in D-dimer and F1+2 levels and decreased levels of TFPI, which were more prolonged in elderly subjects, who are the target population for andexanet. Furthermore, the biomarker findings are consistent with the presence of fibrinolysis (i.e.: indirect evidence of some degree of thrombus formation). These findings are consistent with those obtained in primates, as D-dimer and TAT levels in plasma samples from primates that received both apixaban and andexanet were attenuated in magnitude relative to primates treated with andexanet alone [NC-12-0417].

The single clinical study in patients (Annexa-4 study interim analysis submitted 13 November 2018 [data cut July 09, 2018]) has shown evidence of thrombotic events in 10.3% of patients (see clinical safety section). Whether these thrombotic events are due to the underlying risk of thrombosis of these patients, due to neutralisation of the anticoagulation (thrombosis due to success of neutralisation), due to the pro-thrombotic effect of andexanet (thrombosis due to pro-thrombotic effect of andexanet), or a combination of all, cannot be established with confidence. However, it does not deny that there is a risk of thrombosis associated with the use of andexanet. Therefore, an increased risk of thrombotic events, particularly in elderly subjects, cannot be ruled out.

PK-PD Modelling

The required doses of andexanet have been modelled based on the PK and PD properties of the anticoagulants. The reversal of the anticoagulant activity of both direct and indirect fXa inhibitors (enoxaparin) has been investigated. No predictive PK-PD model for enoxaparin has been established. Therefore, no dosage recommendation is available from such a model, currently.

This mechanistic PK-PD model for direct fXa inhibitors has been further expanded and adapted for rivaroxaban data and literature-based covariates. Following this, PK-PD models regarding apixaban has been developed. No PK-PD model regarding edoxaban has been provided. Further analyses and validation will be required to render the model(s) more appropriate to explain patient data from Study 14-505 and healthy subjects from study 16-512 and to draw firm model-based conclusions on the appropriateness of the envisaged posology.

Study 16-512 – Comparability of Generation 1 and 2

Two different presentations of Generation 1 were evaluated at the low dose: Generation 1, Process 3, the U.S. approved commercial manufacturing process, and Generation 1, Process 2, which was evaluated in studies in healthy subjects during the course of andexanet clinical development. Co-primary PK and PD endpoints were selected for evaluation of the comparability: the primary PK endpoint was the andexanet AUC(0-∞) and the primary PD endpoint was the reversal of the anti-fXa activity. Secondary PK objectives were AUC(0-last), Cmax, Tmax, t1/2, CL, Vss, and λz. The secondary PD endpoints were reversal of FXa inhibitor anticoagulation as measured by free fraction and thrombin generation. Additional exploratory PD endpoints included the effects on change in clotting activity as measured by PT, aPTT and ACT. Safety endpoints included assessment of thrombotic events, bleeding events and immunogenicity. Co-primary endpoints of the ratio of the Geometric Mean (GM) of the andexanet AUC(0-∞) and percent change in anti-fXa activity of Generation 2 andexanet were compared to Generation 1 andexanet by cohorts of 10-12 healthy subjects. The 90% CIs of the ratio of the GM values of AUC0-∞ were within 80.00% and 125.00% for the low andexanet dose comparison of Cohort 4 (Generation 2, fXa inhibitor apixaban) and Cohort 1 (Generation 1 Process 3, fXa inhibitor apixaban) but the CIs for the high andexanet dose cohorts (fXa inhibitor rivaroxaban) were outside the 90% CI limits (see table below). Of note, no andexanet PK comparison without pre-administration of fXa inhibitor has been conducted.

Results Study 16-512:

Parameter	Statistic	Cohort 4 vs. Cohort 1	Cohort 4 vs. Cohort 3	Cohort 5 vs. Cohort 2
	N1/N2	10/11	10/11	10/11
$AUC_{(0-\infty)}$	Geometric Mean Ratio	1.04	1.40	1.30
(hr*ng/mL)	90% CI	(0.94, 1.14)	(1.22, 1.61)	(1.17, 1.45)
Anti-fXa Activity (Percent Change from Baseline to Nadir)	Geometric Mean Ratio	1.04	1.01	0.99
(ng/mL)	90% CI	(0.96, 1.11)	(0.99, 1.02)	(0.98, 1.01)

CI = Confidence interval; N1/N2 = Number of observations in the first cohort/Number of observations in the second cohort.

Note: Baseline is the value collected at Day 4, prior to Andexanet/Placebo bolus dosing. If this value is missing, then baseline is the value at Day 3, post FXa inhibitor dose. Only subjects with both a baseline and a post-baseline assessment are presented in the table.

§ Geometric Mean Ratios (GMR) and the corresponding confidence intervals are presented as the ratio of geometric means of Cohort X/Cohort Y. For the low dose comparisons, the GMR is calculated from a one-way ANCOVA model with body weight as a covariate for log-transformed data for Cohort 1, 3, and 4. The high dose comparison is based on a similar ANCOVA model for Cohort 2 and 5 respectively. All GMRs (and the corresponding CI) are calculated by exponentiating the model-based mean differences between cohorts.

Source Tables: Study 16-512 14.2.1.3A and 14.3.1.2A.

The andexanet AUC(0-∞) values had greater variability (>15% CV) than the co-primary endpoint of change in anti-fXa activity or the secondary PD endpoints of change in unbound FXa inhibitor concentration and thrombin generation levels. In Parts 2 and 3 of the study, the PK and PD were calculated for each cohort but inter-cohort comparisons were not made. Dose linearity for PK was assessed as per the statistical analysis plan by dose normalization for the low and high dose AUC(0-∞) values followed by subsequent evaluation of the GMR and the 90% CI of that GMR. The table below shows that the point estimate was higher than unity (1.19) and that the Generation 2 process andexanet was in the range of dose-proportionality.

Parameter	Andexanet High Dose (N=22) Geometric Mean 95% CI	Andexanet Low Dose (N=22) Geometric Mean 95% CI	High Dose vs. Low Dose Geometric Mean Ratio § 90% CI
Dose Normalized $AUC_{0-\infty}$ (h*ng/mL) [1]	268.08	226.13	1.19
	(238.88, 300.84)	(201.51, 253.77)	(1.03, 1.36)

N1 = Number of observations in the low dose cohort; N2 = Number of observations in the high dose cohort

[1] Dose normalization was performed by dividing the exposure by total dose since we are using actual dose instead of planned dose.

§ Geometric Mean Ratios (GMR) and the corresponding confidence intervals are presented as the ratio of geometric means of High dose/Low dose. The comparison is based on calculation based on a one-way ANCOVA model with body weight as a covariate for log-transformed data. The GMR (and the corresponding CI) is calculated by exponentiating the mean difference between doses.

Source: Study 16-512 Listing 16.2.5.2.2 and Table 14.2.1.3B.

2.4.4. Discussion on clinical pharmacology

No radiolabeled mass balance studies have been conducted. Based on the available PK data for andexanet in humans that andexanet has little to no renal clearance, and thus would not require dose adjustment for patients with renal impairment. Based on what is known about the disposition kinetics of native FXa, it is likely that andexanet is rapidly broken down in plasma by endogenous proteases, consistent with its relatively short effective half-life.

No formal studies have been conducted to investigate the pharmacokinetics of andexanet alfa in renally impaired patients or in patients with hepatic impairment. The applicant discussed the available and unavailable data on the influence of intrinsic factors in the PK/PD characteristics of andexanet alfa (i.e.: impaired renal function, impaired hepatic function, gender, race, weight). No dose adjustment is recommended for patients with impaired hepatic or renal functions. The applicant has submitted an updated PK/PD analysis based on data available with andexanet-rivaroxaban (in studies 501, 502 and 504; n = 149), but not with apixaban or edoxaban. All data included in the updated PK and PK/PD analyses in this report were from healthy (young and elderly) subjects. While healthy volunteers may exhibit some differences in PK and PK/PD behaviour relative to patients, they provide information that is not feasible to obtain in patients. For example, it is not possible to collect additional blood samples for measurement of andexanet concentrations in patients already suffering severe bleeding events. Therefore, the only option for characterizing andexanet PK is to study it in healthy volunteers. Additionally, the most robust estimates of rivaroxaban PK parameter dependencies on key covariates will likely be those gleaned from the literature rather than estimated from the andexanet clinical study data, as the former were based on a much larger sample size. It was agreed that no dose adjustment is required in elderly patients.

In the next stage of modelling, the population PK/PD model for rivaroxaban and for apixaban was further updated to include among the others some patient data from study 14-505 and to be validated with data from healthy subjects collected from study 16-512. Further updates to PK/PD model are expected in the post-authorisation phase as part of the specific obligations (SO 4). A PK-PD model for edoxaban is planned to be developed. With more patient data becoming available, modelling will be annually updated and validated. Simulations will be performed to predict anti-fXa activity and/or percent change from baseline in patients from study 14-505, based on the enrolment information and patient-level or summary covariates and dosing information. Congruence between model predictions and observed anti-fXa activity data in patients will be assessed, summarized, and visualized both for the overall population and by subgroups defined by the covariates. Based on these evaluations, the current PK/PD models will be refined to achieve better agreement with the patient data.

Finally, the pharmacokinetics of andexanet alfa has not been studied in paediatric patients. This is acceptable, as a PIP including deferral has been agreed with the EMA.

Study 11-501

PK-values are considered to be dose-proportional. However, increases of plasma levels for higher doses might be above average. This point should be taken into account for dosage recommendation.

8 subjects were included in each cohort. Renal elimination has been suggested to be low as no urinary andexanet was detected. However, database for a respective statement included initially in section 5.2 of the SmPC (“Clearance (L/hr) for andexanet alfa is approximately 4.3 L/hr with low renal involvement”) was considered to be limited and the statement was subsequently modified to: “Clearance (L/hr) for andexanet alfa is 4.4 ± 1.2 L/hr with low renal elimination”. Furthermore, PK-results of study 11-501 differ from PK/PD studies included in the SmPC although it has been stated in section 5.2 of the SmPC that “FXa inhibitors did not affect andexanet alfa pharmacokinetics at therapeutic levels”.

Responses of thrombin generation might point to a thrombophilic potential above average with increasing doses. This point should be considered for safety evaluation and dosage-recommendations. Infusion related reactions have been documented.

Study 14-506

This study was designed for comparing PK-, PD- and safety-profiles of younger and older age-groups under apixaban-treatment. However, the final age-groups are not too far apart (65-69 versus 26-42 years) with respect to essential differences of physical health. Main target population of anticoagulation (and the antidote) might be assumed to be a considerably “older” age group (around 80 years of age) with definitely changed metabolism and health as compared to younger patients. Thus, the documentation of only marginal differences for plasma concentrations between the chosen age-groups is not surprising. Furthermore, dosage of apixaban was reduced to 50% for feasibility reasons – again challenging the results of this study. Elevations and persistence of D-dimers and F1+2 fragments were noticeable and they might represent a safety issue (risk of thrombosis or DIC) and should be put in correlation with higher plasma andexanet levels being linked with high thrombin generation.

From Study 14-506, a correlation of andexanet exposure with body weight became visible. Subjects with higher body weight (mean body weight: 75 kg) showed lower exposure than subjects with lower body weight (70 kg). The analysis and overall magnitude of influence of body weight on andexanet PK was unclear. Therefore the applicant conducted a covariate analysis including body weight. In the first step of this analysis body size measures (body weight and BMI) have only been investigated on the andexanet volume of distribution. Body weight effect on clearance was introduced in the andexanet PK model after the second covariate selection process. These were the only remaining relationships that were both statistically significant and clinically relevant. The estimated coefficient of body weight effect on volume is 0.579, indicating that subjects at the 10th percentile (65.5 kg) and 90th percentiles (89.5 kg) of body weight in the current PK dataset were predicted to have central volume values that were 96.2% and 115% that of a 70 kg subject. These volume differences translate to Cmax values at the 10th and 90th percentiles that are 103.9% and 86.7% those of a 70 kg subject, respectively. The estimated coefficient of body weight effect on clearance was 0.492, indicating that subjects at the 10th and 90th body weight percentiles were predicted to have clearance values that are 96.8% and 112.9% that of a 70 kg subject. Of note, the 10th and 90th percentiles indicate a rather balanced distribution of body weight among the investigated healthy subjects, with no subjects at extreme body weight values. Of note, the reference value for covariate body weight in the PK-PD model (rivaroxaban) was different (59 kg).

Study 12-502

Overall, the study presents PK-and PD-results of andexant bolus and continuous infusion administration in healthy subjects to reverse anticoagulation of 1 of 4 direct and indirect fXa-inhibitors. The different Modules followed a similar course to assess relevant PK- and PD-marker like anti-fXa activity and thrombin generation.

A randomized, double-blind, placebo-controlled study design was chosen to minimize bias. Because the study population was healthy volunteers without acute bleeding, placebo is considered as an appropriate control for reversal of anticoagulation. Conducting the study in healthy volunteers allowed standardization of the anticoagulant dose, the timing of andexanet relative to the Cmax of the anticoagulant, accurate timing of sample collection, and avoidance of use of confounding medications.

Andexanet exhibited dose-proportional PK for both Cmax and AUC with a mean terminal t½ of approximately 5 to 7 hours and an effective (biological) t½ of approximately 1 hour.

In accord with its mechanism of action, administration of andexanet was associated with a rapid decrease in unbound apixaban, rivaroxaban, and edoxaban concentration that was dose-dependent, with the greatest effect observed at the highest bolus doses tested (420 mg dose for apixaban, and 800 mg dose for rivaroxaban and edoxaban). The effect of andexanet on plasma unbound apixaban, rivaroxaban and edoxaban was immediate (i.e., within 2 minutes following completion of andexanet administration).

When andexanet was administered as a bolus followed by a 180 mg infusion administered over 45 minutes, or a 480 mg infusion over 120 minutes, the decrease in unbound apixaban concentrations was sustained for the duration of the infusion and increased slowly thereafter. A continuous infusion of andexanet (960 mg infusion over 120 minutes) resulted in a sustained decrease in unbound rivaroxaban. Similarly, a continuous infusion of andexanet (480 mg infusion over 60 minutes) resulted in a sustained decrease in unbound edoxaban.

More males than females and more Hispanic or Latino subjects than other ethnicities were recruited to the study. The higher percentage of males in a study with healthy volunteers is commonly accepted. The higher proportion of Hispanic or Latino subjects has no impact on the results as has been discussed by the applicant. Urine andexanet concentrations for all subjects were BLQ at all time intervals, suggesting that renal clearance is not a major route of elimination for andexanet in humans. Elimination of andexanet has been described. Respective references have been provided.

Regarding the posology, the applicant proposed two dosing regimens based on the type/dose of the anticoagulant taken and the elapsed time from last anticoagulant dose. Although this attempt seems to be easy to understand for the prescriber, it was regarded to be challenging and even misleading: non-compliance with the prescribed dosage-regimen for the anticoagulant, older age and uncontrolled circumstances, potential of renal/hepatic impairment causing unintended overdose might be of higher significance for bleeding risk than prescribed dose and assumed elapsed time may pretend. Furthermore, monitoring antifXa-activity is not suggested for respective factor Xa anti-coagulants. The determination of the andexanet dose for different dose regimen in Modules 1-4 has been clarified by the applicant. The dose of andexanet selected for each cohort was based on data from the Phase 1 Study 11-501. The concern of a dose of andexanet more than 600 mg was addressed with the hypothesis that andexanet must be in stoichiometric excess to the FXa inhibitor to reverse the anticoagulant activity of that FXa inhibitor. Most relevant to address the concern is the clarification that a portion of the extravascular compartment of the direct FXa inhibitors was redistributed to the vascular compartment and was bound to andexanet.

Secondary TFPI-mediated effects: study 11-501 showed some transient but important increases in coagulation biomarkers of D-dimer (during 24 hours post dose), F1+2 (up to 7 days) and TAT (up to 24 hours) compared to placebo-treated subjects, and a decrease in the TFPI endogenous anticoagulant (up to 24 hours). This trend was confirmed in study 12-502, in which there were transient increases in D-dimer and F1+2 levels and decreased levels of TFPI with andexanet administration in all four study modules for at least one of these markers, as well as in ANNEXA-A and ANNEXA-R phase 3 studies (see also efficacy section). Andexanet binds to TFPI in the plasma and possibly also to TFPI bound to the endothelium. These mechanisms may contribute to the reversal of the anticoagulated state (i.e., fXa inhibition). However, the binding to TFPI may also explain the observed dose-dependent transient increase in D-dimer, F1+2 and TAT with simultaneous decrease in TFPI. Transient but important elevations in D Dimer and F1+2 occurred following andexanet exposure were also observed in the majority of subjects in study 11-506, with longer durations observed in the elderly group (aged >65 years), who are the target population for andexanet. Furthermore, the biomarker findings are consistent with the presence of fibrinolysis (i.e.: indirect evidence of some degree of thrombus formation). These findings are consistent with those obtained in primates, as D-dimer and TAT levels in plasma samples from primates that received both apixaban and andexanet were attenuated in magnitude relative to primates treated with andexanet alone [NC-12-0417]. The single clinical study in patients (Annexa-4 study interim report) has shown evidence of thrombotic events in 10.3% of patients (based on interim analysis with the cut off of 13 Nov 2018; see clinical safety section). Whether these thrombotic events are due to the underlying risk of thrombosis of these patients, due to neutralisation of the anticoagulation (thrombosis due to success of neutralisation), due to the pro-

thrombotic effect of andexanet (thrombosis due to pro-thrombotic effect of andexanet), or a combination of all, couldnot be established with confidence. It was agreed that based on the data available, there would not be any anticipated difference in PD response to andexanet based on differences in TFPI genes. There is no consistent evidence that low levels of TFPI, naturally occurring or due to TFPI inhibition would result in increased thrombotic risks. However, it has been demonstrated for enoxaparin and other LMWHs that induction of TFPI release (natural anticoagulant), is a secondary mechanism of action resulting in enhanced antithrombotic effect in addition to FXa inhibition, as included in the SmPC of Clexane. Whether TFPI inhibition by andexanet may increase thrombotic risk is unknown. It was agreed that thrombotic events detected in clinical trials with andexanet were within expected range for patients at high risk of thrombosis included in ANNEXA-4 and may be manageable within the RMP. Furthermore, additional data regarding the risk of thromboses and thromboembolic events will be provided as part of the specific obigations.

Study 12-502

Module 1 (apixaban)

Plasma andexanet pharmacokinetic parameters on Day 6 are considered to be dose-proportional. Mean total exposure (AUC0-∞) to andexanet increased with increasing andexanet doses in a dose proportionate manner. Mean t1/2 of andexanet ranged from 4.35 to 6.45 hours and mean systemic CL ranged from 3.93 to 4.70 L/hr across cohorts. Mean apparent volume of distribution at steady-state (Vss) of andexanet decreased with increasing dose with values ranging from 6.97 L following 90 mg bolus (Cohort 1) to 4.01 L following 420 mg bolus/4 mg per min infusion over 2 hours (Cohort 6).

However, PK-results of this study at subtherapeutic levels differ from those in study 11-501 (first-in-human Phase 1 study). The applicant was asked to explain the difference between the PK-values of andexanet in both studies and to discuss the potential impact of apixaban (and other fXa inhibitors) on the results. It was clarified that this difference is believed to be due to the saturable high affinity binding of andexanet to TFPI, which is disrupted by binding to FXa inhibitors that bind to the same site on TFPI as andexanet.

Administration of andexanet led to an immediate, dose-dependent decrease in unbound apixaban plasma concentrations. The decrease occurred within 2 minutes after the end of bolus dose and produced up to approximately 90% decrease in unbound apixaban relative to baseline and placebo values. Simultaneously, there was a dose-dependent increase in total apixaban concentration. These findings likely reflect a shift in steady-state concentrations of apixaban from extravascular or tissue-bound drug to the intravascular compartment following binding of plasma apixaban by andexanet. The duration of decrease in unbound apixaban plasma concentrations was dose- and dose-regimen dependent with the longest duration of effect (3 hours) observed when andexanet was administered as a 420 mg bolus followed by a 480 mg infusion (Cohort 6).

Andexanet decreased both the total oral and renal clearance of apixaban on Day 6 in a dose-dependent manner by up to approximately 55% compared to both the Day 5 and placebo values as anticipated. Reduction in clearance was likely due to the binding of unbound apixaban to andexanet, temporarily lowering the amount of apixaban available for elimination. The percent apixaban dose excreted in urine was similar between all groups and within each group on Days 5 and 6.

Administration of andexanet resulted in a rapid (i.e., within 2 minutes after the end of bolus dose) decrease in anti-fXa activity relative to baseline values in each active group. It is agreed that the greatest effect of andexanet on anti-fXa activity (>90% decrease in anti-fXa activity relative to baseline) was observed following the 420 mg bolus dose followed by a 480 mg continuous infusion (Cohorts 6). This near-complete reversal of the anti-fXa activity of apixaban (>90% decrease following

the 420 mg bolus) was achieved with a >1:1 molar ratio of andexanet to total plasma apixaban (the actual molar ratio was ~2.3:1 to 2.9:1). The unbound apixaban plasma concentrations and percent unbound apixaban corresponding to the >90% reversal of anti-fXa activity ranged between 1.10 to 2.25 ng/mL.

Similar to the rapid decrease, an increase of anti-fXa activity and free apixaban is observed within 30 minutes or immediately after stopping infusion. The increase after infusion comes up to an anti-fXa activity level which is higher than the placebo level. The applicant has explained possible reasons for this apparent “rebound” effect. The most likely explanation despite the redistribution of residual FXa inhibitor from the extravascular compartment into the intravascular compartment is a reduction in the rate of elimination of the FXa inhibitor during andexanet treatment. Moreover, once a clot is formed, any “rebound” increase in anti-fXa activity will not affect the structural integrity of the hemostatic plug. This was endorsed by the CHMP. In addition, a thorough discussion of the “rebound” effect in the clinical study with patients (ANNEXA-4) was provided.

As can be seen from the non-clinical study provided, a transient reversal of anticoagulation appears to be sufficient to allow for normal haemostatic mechanisms to take hold and bleeding to be greatly reduced. Moreover, a bolus alone of andexanet was as effective at reducing blood loss and promoting survival as the bolus plus 2 hour infusion. Even in clinical studies, andexanet was effective in normalising thrombin generation with both the bolus plus infusion and the bolus only dosing regimens. However, it will be difficult to differentiate whether it is necessary to treat with bolus alone or with bolus plus infusion. Therefore the applicant was asked to clarify this issue. At the end it was agreed andexanet alfa is to be administered as an intravenous bolus over 15 minutes (low dose) or 30 minutes (high dose), followed by administration of a continuous infusion of for 120 minutes as reflected in the SmPC.

It can be concluded that a prolongation of FXa inhibitor elimination would not be expected to affect haemostatic efficacy and the rebound-effect is insufficient to result in re-bleeding.

Restoration of thrombin generation following andexanet treatment was dose- and dose regimen dependent. The percent of subjects achieving restoration of thrombin generation at 2 minutes after the end of bolus dose in Cohort 1, Cohort 2 and Cohorts 3-6 were 67%, 83% and 83% - 100%, respectively. In contrast, thrombin generation was restored in only 6% of pooled placebo subjects at the end of bolus.

The mean D-dimer level and Prothrombin fragments F1 +2 increased in a dose dependent manner following andexanet doses. These significant findings are relevant for all Modules. Some healthy volunteers had clinically meaningful transient elevations (e.g. Cohort 2 of Module 4). The clinical relevance of elevation in the relevant patient group has been discussed by the applicant. Clinical relevance in the target population (patients with uncontrolled or life-threatening bleeding who are anticoagulated due to high to very high risk of thrombosis) is unknown as also reflected in the SmPC.

Module 2 (rivaroxaban)

Administration of andexanet led to an immediate, dose-dependent decrease in unbound rivaroxaban plasma concentrations. The decrease occurred within 2 minutes after the end of bolus dose and produced up to 80% decrease in unbound rivaroxaban (Cohort 5) relative to baseline and placebo values. Simultaneously, there was a dose-dependent increase in total rivaroxaban concentrations. The duration of decrease in unbound rivaroxaban plasma concentrations was dose and dose-regimen dependent with the longest duration of effect (3.5 hours) observed when andexanet was administered as a 800 mg bolus followed by a 960 mg infusion over 120 min (8 mg/min infusion rate) [Cohort 5]. Near-complete reversal of anti-fXa activity (≥89% decrease) was achieved with a ~1:1 to 1.3:1 molar

ratio of andexanet to total plasma rivaroxaban. The unbound rivaroxaban plasma concentrations and percent unbound rivaroxaban corresponding to the ≥89% reversal of anti-fXa activity ranged between 5.08 to 7.28 ng/mL.

The magnitude and duration of thrombin generation restoration following andexanet administration were dose- and dose-regimen dependent. The percent of subjects achieving restoration of thrombin generation at 2 minutes after the end of 210 mg (Cohort 1), 420 mg (Cohort 2), 600 mg (Cohort 3), 720 mg (Cohort 4) and 800 mg (Cohort 5) andexanet bolus doses were 0%, 33%, 50%, 100% and 83%, respectively.

For rivaroxaban, thrombin generation was not restored in subjects receiving 210 mg- 600 mg bolus andexanet. The Applicant has provided a detailed discussion with regards to different dosing regimens of andexanet. Andexanet must be in stoichiometric excess to the FXa inhibitor to reverse the anticoagulant activity of that FXa inhibitor. Therefore, the use of approximately one-half of the andexanet dose (i.e., 400 mg), after half of the rivaroxaban has been eliminated, is supported by the respective PK properties of rivaroxaban and andexanet.

Module 3 (enoxaparin)

Andexanet was administered intravenously using two different formulations (original liquid [O] or reconstituted lyophilized powder [L]) at the same dose (210 mg bolus) and using only one formulation at the higher dose (420 mg bolus). Andexanet pharmacokinetics were not similar between the original liquid (Cohort 1) and reconstituted lyophilized (Cohort 3) formulations. The mean exposure [Cmax, AUC] to andexanet following the lyophilized formulation (Cohort 3) was slightly higher than the original formulation and the mean elimination half-life value (t1/2) of andexanet for Cohort 3 was ~40% higher than the value estimated for Cohort 1. No final conclusion can be drawn regarding PK differences between the two formulations due to the small number of subjects in each cohort. Therefore, it is not possible to compare different formulations at different dose regimens.

Moreover, the applicant didn't present enoxaparin PK parameters post-andexanet administration because the results from the Rotachrom anti-fXa assay are not interpretable, although two anti-fXa assays were used in this study. The Applicant justified the missing results from the Rotachrom anti-fXa assay. Concerning the lack of relevant enoxaparin PK-data post-andexanet administration, the applicant stated that the presence of andexanet does not alter the PK due to the distribution of LMWHs is limited to the vascular space. It is agreed that the enoxaparin PK results in the presence of andexanet can be inferred from the enoxaparin PK results in the absence of andexanet.

In general, administration of andexanet resulted in a rapid (i.e., within 2 minutes after the end of bolus dose) decrease in anti-fXa activity relative to baseline values (maximum ~70%) in each active group. But as not expected the maximum decrease in anti-fXa activity relative to baseline values was found in cohort 1 (210 mg bolus) and not in cohort 3 (420 mg). The unexpected difference in the anti-fXa activity between the two doses should have been explained by the applicant. Any excess of andexanet beyond a molar ratio of ~1 is not expected to result in any further dose response as assessed by anti-fXa activity. However, both doses (210 mg and 420 mg) decreased the anti-fXa activity close to the lower limit of quantitation of the assay (0.100 IU/mL). The benefit of the higher dose is questionable. As requested the applicant discussed the difference in the anti-fXa activity between the two doses. The applicant points out that any excess of andexanet beyond a molar ratio of ~1 is not expected to result in any further dose response as assessed by anti-fXa activity. This is accepted with regard to the same dosing regimen for enoxaparin (40 mg SC daily) in each cohort. The issue was considered resolved, but the benefit of the higher dose remained questionable.

Moreover, a bolus dose of more than 420 mg and the option of continuous infusion were not investigated. Therefore, the recommended high dosing regimen of 800 mg andexanet as stated in the SmPC followed by continuous infusion in both dosing regimens are not supported by PK data. The applicant has discussed the option of continuous infusion for enoxaparin. The argumentation that a continuous infusion is sufficient to maintain the concentration at the peak levels and should maintain the pharmacodynamic effect for as long as the compound is infused could be followed. Nevertheless, the applicant didn't presented relevant PK-data for enoxaparin, an indirect fXa-inhibitor and has only referred to rivaroxaban, a direct FXa-inhibitor. These inconsistencies, coupled with the lacking benefit of the higher dose of andexanet don't support the option of continuous infusion.

The percent of subjects achieving restoration of thrombin generation in Cohorts 1 and 2 were similar. However, more subjects achieved restoration of thrombin generation in Cohort 1 (original liquid formulation) than in Cohort 3 (lyophilized formulation).

Andexanet reverses both the Xa-ase activity and II-ase activity. A statement regarding the mode of action of andexanet on FactorIIa has been presented by the Applicant.

The andexanet bolus dose proposed for neutralisation of enoxaparin (andexanet 800 mg bolus for enoxaparin 1 mg/kg and 400 mg bolus for enoxaparin 40 mg) is based in that leading to concentrations that are in molar equivalence of the average plasma concentration of ATIII. The applicant estimated that an andexanet 210 mg dose is sufficient to reverse a 40 mg dose of enoxaparin. However, in the proposed SmPC, a 400 mg andexanet "low dose" (which seems in fact quite high, almost double of the dose predicted to be effective) was recommended for enoxaparin. On the contrary, the applicant estimated that approximately 600 mg andexanet bolus dose will neutralise a concentration of ATIII 3 microM associated with a enoxaparin treatment dose of 1.5 mg/kg/OD or 1 mg/kg/BID, but proposes a 800 mg high dose, thus resulting in an overestimation of the andexanet dose needed. These inconsistencies, coupled with the fact that there are very few clinical data with enoxaparin in patients with bleedings from ANNEXA-4, as well as the availability of protamine as antidote for heparins, results in insufficient data and no unmet clinical need precluding from running the risk of exposing patients with enoxaparin-related bleeding to a new active substance like andexanet. An indication for enoxaparin-treated subjects was not supported and enoxaparin was removed from the indication claimed during the procedure.

Module 4 (edoxaban)

D21-2393 is an equipotent and active metabolite of edoxaban in humans. The contribution of this metabolite to anticoagulation activity is significantly lower compared to edoxaban since exposure to this metabolite is <10% of edoxaban. The effects on andexanet on the metabolite concentrations were similar to its effect on the parent unbound edoxaban.

Administration of andexanet led to an immediate, dose-dependent decrease in unbound anticoagulant (edoxaban and D21-2393) plasma concentrations. The decrease occurred within 2 minutes after the end of bolus dose and produced up to approximately 76% decrease in unbound (edoxaban and D21-2393) concentrations relative to baseline and placebo values. Simultaneously, there was a dose-dependent increase in mean total anticoagulant (edoxaban and D21-2393) plasma concentration.

The effect of andexanet on PD markers (anti-fXa activity and thrombin generation) was immediate (i.e., within 2 minutes following completion of andexanet bolus dose) and dose-dependent. The greatest effect of andexanet on PD markers (maximal ~73% to 82% decrease in anti-fXa activity relative to baseline and restoration of thrombin generation in all subjects at the end of bolus dose) was observed when the 800 mg bolus was administered at 3 hours [Cohort 2] or 5 hours [Cohort 5] following the edoxaban dose. The effect of andexanet was observed to be sustained (up to 2 hours

following bolus dose for both anti-fXa activity and thrombin generation) when the 800 mg bolus dose was followed by a 480 mg continuous infusion (8 mg/min for 60 minutes) [Cohort 2].

For edoxaban, thrombin generation was not restored in subjects receiving 600 mg bolus andexanet and in addition the difference in the mean change from baseline in anti-fXa activity between the andexanet and placebo groups was no longer significant at 2 minutes.

The company acknowledges that there is no strict correlation between the level of neutralisation of anti-Xa activity and restoring thrombin generation. While neutralisation of edoxaban's anti-Xa activity at the andexanet doses tested was significantly lower than the corresponding activity of apixaban and rivaroxaban, thrombin generation was restored to a similar degree. Therefore, it was endorsed that proposed bolus dose (800 mg bolus) may be appropriate in patients. On the other hand, this finding supports that thrombin generation maybe a more clinically relevant PD marker than anti-Xa activity. One major drawback was the duration of the test (several hours), which makes it not suitable for emergency cases. On the other hand the assay is not standardized for broad clinical use, which still hampers its approval as a routine clinical tool.

Transient elevations in both D-dimer and F1+2 were seen in Cohort 2, when the 800 mg bolus dose was followed by a 480 mg continuous infusion. The clinical relevance of elevation in the relevant patient group remains open. The applicant has discussed the significance of the increased D-dimer and prothrombin activation fragment 1+2 (F1+2) levels observed in Study 12-502, particularly within the context of the clinical diagnosis of DVT, PE, and DIC in elderly patients. The response provided by the applicant is satisfactory.

Changes to Activated Clotting time (ACT), Prothrombin Time (PT) and activated partial thromboplastin time (aPTT) have been documented. Values are different in subjects on apixaban and rivaroxaban. Prior to andexanet/placebo dosing, apixaban had little effect on PT and aPTT levels, therefore, no dose response in PT and aPTT levels were observed following andexanet administration. There was a modest (up to ~31%), dose-dependent decrease in mean ACT values at 2 minutes following the end of bolus dose in all andexanet-treated groups relative to just prior to andexanet dosing. The effect of rivaroxaban on PT and aPTT was relatively small (~20-40% increase) compared to its effect on ACT (~80-100% increase). Post-andexanet, there was a large dose-dependent decrease in mean PT, aPTT and ACT values at 2 minutes following the end of bolus dose in all andexanet-treated groups. Edoxaban increased PT and aPTT (maximal ~22-25% increase), and ACT (maximal ~100% increase), but post-andexanet no dose response in aPTT levels and a small (maximal ~7%) and modest (maximal ~27%), dose-dependent decrease in mean PT and ACT values were observed.

The applicant presented a clarification of the different changes of Activated Clotting time (ACT), Prothrombin Time (PT) and activated partial thromboplastin time (aPTT) during anticoagulation prior to andexanet treatment and afterwards. The DOACs have irrelevant effects on aPTT and PT. However, they can significantly prolong ACT at therapeutic doses at different degrees. In studies with andexanet, ACT prolongation after DOAC admnistration ranged from 30% (apixaban) to 90-100% (rivaroxaban and edoxaban). In practice, it is difficult to measure plasma concentrations and effects of the DOACs. Therefore, the achievement of a normal ACT could help physicians to guide against re-administration (e.g. normal ACT levels may indicate a complete reversal and therefore no need for additional dosing), while the maintenance of a prolonged ACT and persistence of bleeding may indicate residual anticoagulation and need for additional dosing.

As a consequence of the above discussed factors, edoxaban has been omitted from the indication claimed during the procedure.

Comparability of Generation 1 and Generation 2 andexanet

Co-primary PK and PD endpoints were selected for evaluation of the comparability between the Generation 1 and Generation 2 andexanet: the primary PK endpoint was the andexanet AUC0-∞ and the primary PD endpoint was the reversal of the anti-FXa activity.

The low dose of Generation 2 andexanet vs. Generation 1 Process 3 andexanet met the pre-specified statistical criteria for AUC0-∞, while for the high dose cohort and the low dose of Generation 2 andexanet vs. Generation 1 Process 2 geometric mean ratio (GMR) and the 90% CIs were outside the pre-specified criteria. High variability as an explanation cannot be followed, based upon the submitted data. In this line, a 2-compartment model could not be fitted although there was a clear bi-phasic decline in andexanet PK data. This is particularly not understood as the established andexanet PK model itself is a 2-compartment model. Instead, data were analysed using NCA and no update of or validation by the established andexanet PK model occurred although it would have been possible based on the PK data available. Consequently, bioequivalence based upon PK has not been demonstrated. However, PD endpoints were supportive. PD-linearity between high and low doses of Gen 2 was confirmed.

Immunogenicity assessments showed similar rates to previous studies with Generation 1 andexanet of low-titer, non-neutralizing antibodies, with no post-dose anti-andexanet antibodies detected in subjects receiving Generation 2 andexanet. As in previous studies, no cross-reacting and/or neutralizing antibodies against FX or FXa were detected in any subject.

PK-PD Model for direct fXa inhibitors

The PK-PD model for direct fXa inhibitors was used to estimate the required andexanet bolus dose and maintenance infusion to achieve and maintain an 80% to 90% reduction in anti-fXa activity, fXa inhibitor trough levels of anti-fXa activity, and 20 ng/ml anti-fXa activity. From this, dose recommendations for andexanet have been concluded. In addition, timing of fXa inhibitor last dose (< or ≥ 8h) has been investigated. Separate PK-PD models are developed for rivaroxaban and apixaban.

Model structure and assumptions: The PK-PD models for andexanet plasma concentrations, fXa inhibitor total and free plasma concentrations, and anti-Xa activity were built jointly because the objective was to quantify the impact of the PD interaction between andexanet and fXa inhibitor on the PK of the fXa inhibitor. The PK-PD model parameters for each of the three andexanet and fXa inhibitor combinations were estimated separately. This was endorsed. The mechanistic PK/PD model contains three compartments for direct fXa inhibitors: Vc, and two peripheral tissues (one fast equilibrating with Vc and one slow equilibrating). The introduction of a fast equilibrating compartment has been deemed essential to render the model capable to explain the rapid rise in total fXa concentrations seen after andexanet administration ended. It represents the fXa inhibitor being redistributed to the plasma site by andexanet from rapidly equilibrating tissue sites. These peripheral compartments itself seem justified as fXa inhibitors show volume of distribution of 50 L (rivaroxaban), 21 L (apixaban) and 107 L (edoxaban), greater than Vc, however, estimated volumes of compartments highly differed from these PK properties. In addition to Vc (~4.5L), a second tissue compartments for andexanet is included in the model (~0.5 L). According to the applicant, andexanet mainly remains in Vc. This is opposed with large a large volume of distribution that was calculated for Phase 1 Study data. PK of andexanet is assumed not to be affected by the fXa inhibitor. However, this is not supported by comparing data from Studies 12-502 and 11-501. In summary, the model comprises four compartments being connected via a range of parameterized rates baring a source of over-parameterization. Estimated compartment volumes enormously differed from physiological values. The condition number for the andexanet PK model was estimated to 528.6 which is, like ETA shrinkage, in an acceptable range. However in total, the model structure seems much designed rather than systematically built and should be updated and validated appropriately with PK data from study 16-512

to incorporate all available information and variability also regarding the new Generation 2 andexanet. Parameter estimates: Regarding the andexanet module, estimated andexanet clearance (4.35-4.44 L/hr) slightly differed from values resulting from study 11-501 (5.1-6.3 L/hr). Estimated values for Vc (4.07 – 4.67 L) and peripheral compartment for andexanet (0.5 – 0.713 L) were much lower than those observed in the Phase 1 study (Vss: 24.95 – 7.81 L; Vd: 67 – 48 L). Comparing PK parameter estimates with PK values in modules 1, 2, 4 (Study 12-502), the deviations were decreased; however observed Vss values in apixaban module (4-7L) were slightly higher than the estimated one. From this it also becomes apparent that the PK of andexanet may be influenced by the administered fXa inhibitor. The k_off rate was fixed to the apixaban k_off constant (0.232 1/hr) for the rivaroxaban and edoxaban models which is highly approximate and the choice of value remains unclear. For edoxaban, additionally the capacity for saturable binding site andexanet was fixed to the corresponding apixaban value (0.115).

Regarding the full model, estimates of the fraction unbound of all three inhibitors as well as the fixing bioavailability factors to the value in label are acceptable. Other parameters for characterizing the dynamic behaviour of fXa inhibitors differ from known PK properties:

The source and validity of absorption rates Ka remain unknown.

Estimated Kd values were calculated to 2.0 nM (0.2-2.5; 95% CI) for apixaban, 1.4 nM (0.0-2.9) for rivaroxaban, and 4.1 nM (0.0-11) for edoxaban. These values may critically influence the simulation results (especially Cxfree) but cannot be precisely estimated out of the data. Estimated Kds were moderately comparable with values resulting from kinetic measurements (rivaroxaban: 1.53 nM vs 1.4 nM, apixaban: 0.58 nM vs 2nM and edoxaban: 0.95 nM vs 4.1 nM). Thus, the model assumes that apixaban is 20 fold more likely to bind fXa compared to andexanet. For edoxaban, Kd/Ki relation rises to 33, for rivaroxaban it remained the same (~4). Estimated clearance of free and bound fXa inhibitor drastically differed from known PK properties of rivaroxaban (10 L/hr), apixaban (3.3 L/hr), and edoxaban (22 L/hr). For rivaroxaban CL(free) and CL(bound) were estimated to 94.7 and 2.82 L/hr; for apixaban 35.4 and 0.5 L/hr and for edoxaban 42.7 and 2.5 L/hr, respectively.
fXa inhibitors show volumes of distribution of 50 L (rivaroxaban), 21 L (apixaban) and 107 L (edoxaban), respectively. The estimated volumes of distribution for all three fXa inhibitors differ enormously from these PK properties of direct inhibitors. The distribution volume is composed of the central volume and the volumes of the two peripheral compartments Vslow and Vfast. Rivaroxaban: 50 L vs. 593.33 L (Vc + Vslow, Vfast), apixaban: 21 L vs. 274.95 L (Vc + Vslow, Vfast) and edoxaban: 107 L vs. 364.44 L (Vc + Vslow, Vfast).

Model simulations and evaluations: The PK-PD model was simulated to test its ability to explain observed data. In general, as also shown by graphical “goodness-of-fit” plots, simulations and data were in acceptable concordance. The relationship between free fXa inhibitor concentrations and anti-fXa activity was also evaluated. This set of graphs showed that the mean predicted outcomes matched the mean observed outcome and general dynamic behaviour. Besides graphical goodness-of-fit plots, no other diagnostic plots were provided.

The PK-PD model for direct fXa inhibitors was used to estimate the required andexanet bolus dose and maintenance infusion to achieve and maintain an 80% to 90% reduction in anti-fXa activity, fXa inhibitor trough levels of anti-fXa activity, and 20 ng/ml anti-fXa activity. From this, dose recommendations have been concluded. In addition, timing of fXa inhibitor last dose (< or ≥ 8h) has been investigated.

The applicant admitted that the previous model was not adequate to derive valid dose recommendations for andexanet to achieve efficient reversing of rivaroxaban, apixaban and edoxaban-

mediated anticoagulant effects. The applicant now uses a two stage modelling approach. The interaction between andexanet and rivaroxaban or alternatively, the interaction between andexanet and apixaban for the andexanet-apixaban model, and anti-FXa activity, the andexanet PK data were modelled independently using a structural model consistent with the prior analysis. The individual parameter estimates from the andexanet PK model were then used to inform the PK/PD models for both rivaroxaban and apixaban.

The final population andexanet PK model used for the two stage approach tested the influence of andministered fXa inhibitors formally. The respective covariate was not introduced in the final model. This process was further clarified. However the validation with data from study 16-512 cannot be followed. Andexanet PK model should be adequately updated and validation should be reported in line with current guidelines. This was agreed to be done as part of the specific obligations in the post authorisation phase.

The applicant updated the andexanet PK model and the PK-PD model which is now strongly adapted to the rivaroxaban case and includes literature-based covariates. Covariate inclusion for apixaban PKPD model is still missingI. Simulations showed that regarding the andexanet bolus predictions, the 80% CI for these median values are predicted rather precise, in contrast to the estimates for the slow infusion rates, where the 80% confidence intervals are comparatively wide. This shows the limits of precise predictions for the rivaroxaban model and a thorough comparison with rivaroxaban data collected from patients (study 14-505) is still missing.

A similar PK-PD model has been developed for apixaban, using only one unpublished study for covariate selection but inclusion to the final apixaban PKPD model is still missing. Simulations and comparison of predicted percent reduction of anti-FXa activity showed differential effects regarding the inhibitors rivaroxaban and apixaban which is expected from considerations regarding unbound fXa inhibitor concentrations. In addition, estimated Kd values that are provided for the updated PK-PD models for rivaroxaban and apixaban are estimated to 0.00165 µM (apixaban) and 0.00133 µM. These are not fully in line with in vivo-derived binding affinity. Sensitivity analysis indicated however only a minor impact of the detected difference in in vivo- and in vitro-derived Kd constants on %reversal of anti-fXa activity.

There are two andexanet clinical trials that were ongoing during the procedure: the Phase 3b/4 study ANNEXA-4 (14-505) in patients with acute major bleeding and a Phase 2 PK-PD study in healthy volunteers (Study 16-512) evaluating the PK, PD, and safety of andexanet produced by an improved manufacturing process (i.e., Generation 2 andexanet). At the current stage, the rather complex PK/PD models serving as predictor for appropriate dosing are highly adapted to the respective inhibitor, built on data from healthy subjects only and suffering from over-parameterization and broad confidence intervals for forecasted slow infusion doses. This renders the model not appropriate for valid predictions. More complete PK-PD data became available from both healthy volunteers and especially from bleeding patients during the procedure. A more detailed analysis comparing model predictions with observed data was provided including additional validation for the all direct inhibitor models. Some preliminary model validation approaches have been conducted but results and approaches were only poorly reported and are thus not properly assessable. No re-estimated PK or PK/PD model parameters have been shown. Model refinement and evaluation using upcoming data should account for patient population differences including plausible covariates, special characteristics of the respective fXa inhibitor, as well as differences of the andexanet formulation.

A detailed model analysis including sensitivity and identifiability analyses to identify any intrinsic or extrinsic factors that potentially merit an andexanet dose adjustment is currently being conducted and

is expected to be provided regarding all developed PK/PD models with the upcoming updates, which should be reported in accordance to current guidelines.

Model-based predictions regarding the therapeutic window (margin of percentage of reduction in anti-FXa activity) should be compared among the different fXa inhibitors using the updated PK and PK/PD models. The applicant is still asked to conduct sensitivity analyses regarding model parameters to determine the potential source of detected deviations among fXa inhibitors.

These analyses to be provided as specific obligation are still remaining and are indispensable to determine optimal dosing regarding the direct fXa inhibitors.

As part of the Specific Obligations (SO 4) in the context of conditional MA the applicant agreed to submit an updated PK-PD model using all previously incorporated data (from studies 11-501, 12-502, 14-503, 14-504, and 14-506) as well as newly incorporated data from Study 16-512 (PK-PD study of Generation 2 andexanet vs. Generation 1), Study 16-508 (PK-PD study of andexanet in individuals of Japanese ethnicity), and Study 14-505 (ANNEXA-4).

PK-PD Model for indirect fXa inhibitors

No mathematical model was built to support the andexanet dose selection necessary to reverse the activity of enoxaparin, an indirect fXa inhibitor. Instead, assumptions were provided to roughly estimate a dose recommendation to achieve efficient sufficient reversal of anti-coagulation effects in healthy subjects.

Fondaparinux neutralisation:

The real unmet clinical need for neutralisation of indirect FXa inhibitors is for fondaparinux, which lacks an antidote. However, the applicant has not generated sufficient data to support the use of andexanet for reversal of fondaparinux and to establish an appropriate dosing regimen. In the mean time, the indication could not be approved for indirect FXa inhibitors (fondaparinux and LMWH). The applicant was requested to propose appropriate studies before an indication and dosing recommendation for neutralisation of indirect FXa inhibitors could be granted.

2.4.5. Conclusions on clinical pharmacology

Andexanet has a slightly less than dose proportional linear pharmacokinetics over the dose range evaluated for both Cmax and area under the curve (AUC). The Vd for andexanet alfa lyophilised formulation is about 9.69 L (study 12-502).

The mechanism of action of andexanet alfa is binding and sequestration of the FXa inhibitor.

In addition, relevant anti-TFPI (tissue factor pathway inhibitor) effects point to a general pro-coagulative effect of andexanet - independent from anti-FXa-sequestration. It has been shown that andexanet-administration to healthy subjects or bleeding patients on direct fXa inhibitors results in immediate short-term drop of free drug levels and antiFXa activity. Anti-TFPI-levels drop immediately but remain low for a prolonged interval of 72 hours for apixaban and 93 hours for rivaroxaban with a 24 hours shift for low versus high dose andexanet. At therapeutic doses, andexanet rapidly saturates the available TFPI, reducing TFPI activity to undetectable levels. It seems that the contribution of this interaction to the immediate reversal of the anticoagulant effects of FXa inhibitors is minimal, while it may play a role in increasing and maintaining thrombin generation within the normal range after the discontinuation of andexanet. In terms of safety, TFPI inhibition runs in parallel with increase in D-dimer and F1+2. The significance of this activity has yet to be fully elucidated. Notwithstanding, the contribution of TFPI inhibition to total thrombotic events (12% of patients) seems limited to those events occurring within 2 days after andexanet administration, which is only a minority of thrombotic

events occurred in the ANNEXA-4 (6 of 23 total thrombotic events). Important etiologic factors include the increased background thrombotic risk, the coagulopathy associated with major bleeding, the severity and acuity of illness, and delayed re-anticoagulation. While changes in coagulation biomarkers such as D-dimer, F1+2, and TFPI have been noted over the first 96 hours after andexanet treatment in healthy volunteers, most thrombotic events in ANNEXA-4 have occurred after this timeframe, suggesting that these biomarker abnormalities are not significant contributors to the pathogenesis of these events.

Enoxaparin:

Currently available data-base was considered to be insufficient and consequently enoxaparin was removed from the proposed indication. PK/PD-study 16-512 in Healthy Volunteers was ongoing and submitted for assessment during current procedure. No satisfactory PK/PD model was available for enoxaparin. Furthermore, laboratory evaluation for enoxaparin-reversal was challenging as the (low) amounts of anti-fXa-activity are not in the range of the anti-fXa-assay currently used.

Fondaparinux:

Andexanet has not been administered to individuals anticoagulated with fondaparinux, be they healthy volunteers or bleeding patients. Likeliness of similarity with enoxaparin was not considered sufficient and consequently fondaparinux was removed from the proposed indication.

Regarding apixaban- and rivaroxaban-reversal currently available dosage recommendation rely on PK/PD-modelling, which still requires improvement and it was agreed to provide it as part of the Specific Obligation 4. In addition, model simulations indicate differential effects regarding the reduction in anti-FXa activity when comparing predictions regarding rivaroxaban and apixaban. This becomes also apparent by investigating unbound concentrations of the direct fXa inhibitors. While the total plasma concentrations of FXa inhibitors increase with increasing andexanet dose levels, the unbound levels decrease, along with the anti-fXa activity. At steady state in the absence of andexanet, the unbound apixaban concentration at Cmax was ~8.4 ng/mL. After a 90 mg andexanet bolus, the unbound concentration already decreased by approximately 50% to ~4 ng/mL which is close to the estimated no effect level of 3.5 ng/mL. At the end of a 420 mg bolus, the unbound concentration was generally less than 2 ng/mL < 3.5 ng/mL.

Bolus strengths of andexanet alfa necessary to achieve mean unbound apixaban (400 mg bolus) and unbound rivaroxaban concentrations (800 mg bolus) below the anticipated respective threshold for no anticoagulant effect were twice as high for rivaroxaban (20 mg QD) compared to apixaban (5 mg BID). This PD effect is mainly driven by the differential direct FXa-inhibitors' PK characteristics. This is to some extent reflected in the andexanet alfa graded dose recommendations.

Valid transfer of such data from healthy volunteers to the targeted patient group based on PK/PD modelling still remains open until full CSR of study 14-505 is assessed and efficacy evaluated for certain dosages, certain bleeding episodes, and certain FXa-Inhibitors.

Concerns during assessment regarding andexanet PK and PK/PD models have to be properly addressed by the applicant and are to be provided as part of SO 4. Derived PK/PD models and their detailed analysis and validation which are crucial regarding adequate dosing recommendations for all fXa inhibitors remain to be provided and updated. All modelling updates and model validations should be reported according to the current guidelines.

This includes an appropriate update of the andexanet PK model with data from 16-512 and 16-508 and all PK/PD models with current and newly recruited data from healthy subjects and patients. In this line, comparability of Generation 1 and Generation 2 was not established with respect to PK parameters.

Besides further clarification on this, data from study 19-514 should be included in the PK model to incorporate this degree of variability.

Study 16-512 did not solely compare the PK of andexanet Genaration 1 and 2 but also the PD-effect under medication of the anti-coagulants apixaban and rivaroxaban, in different dosages. It could not be ruled out that this pre-treatment has an effect on the results. For maintaining the clinical data package, the applicant agreed to compare plain andexanet Gen1 with Gen2 - not mediated through the PD-marker for presenting comparison of -PK of Gen1 used in clinical studies with Gen2 for the European market.

It was concluded that PK comparability of Generation 2 to both Process 2 and 3 for Generation 1 has not been demonstrated although PD-parameters support similarity, challenging the integrity of the clinical data–package. The applicant provided an assignment of the clinical studies to the respective manufacturing processes. As all PK studies have been conducted with former andexanet alfa of Generation 1 and comparability with the to-be-marketed Genereation 2 failed, PK comparability should be proven as soon as possible. As long as PK comparability is not proven, this uncertainty remains reflected in the SmPC and study results should be interpreted stratified by the different andexanet alfa generations.

In summary, the final andexanet PK and PK/PD models development for apixaban and rivaroxaban were considered not complete. The proposed andexanet posology for reversing anti-fXa activity is mainly based on PK/PD modelling on the basis of healthy subjects. The incorporation of patients' characteristics was considered still not sufficient in addition to differences in andexanet PK (Generation 2 vs Generation 1). The update and proper validation with data from healthy subjects and with patient data is still missing. In order to further confirm the posology of Ondexxya, the applicant should submit the results of a comparative PK study with Generation 1, and Generation 2 material (study 19-514). The study should be based on an agreed protocol. This was agreed to be provided as part of the Specific Obligation 2 (Section 4) and is expected by 3Q 2019.

In detail, the modelling update is expected to provide:

- A proper and more exigent external model evaluation including graphical assessment (including mean tendency and variability) of model predictions versus observations from Study 16-512 together with numerical/graphical assessment of PK/PD endpoints such as AUC, Cmax, % decrease in Anti-fXa activity, as essential basis to accept the validity of external model evaluation and therefore, the administration schedule proposed .
- The andexanet PK model is being updated with andexanet concentration data as well as the FXa inhibitor concentrations (total and unbound) and anti-fXa activity from Studies 16-512 (PK-PD study of Generation 2 andexanet) and 16-508 Part 1 (PK-PD study of andexanet in individuals of Japanese ethnicity). The update and validation should be reported according to current EMA guidelines.
- As long as PK comparability is not shown, validation of andexanet PK and PK/PD models should be stratified by the different Generation and Processes regarding the andexanet variation administered. In this line, a covariate is to be introduced to account for PK differences in andexanet formulation when updating the PK andexanet model. Formerly tested covariates including "fXa inhibitor" and "race" on andexanet PK should be re-checked during updating the andexanet PK model.
- the missing detailed reporting of approach (i) the reporting of approach (ii) using data from Study 16-512 are completed with the information regarding final parameter estimates of the models using base and expanded datasets for andexanet PK/PD

models (rivaroxaban and apixaban) including results for both cases and reported according to current EMA guidelines .

- updated PK/PD models will use all previously incorporated data (11-501, 12-502, 14-503, 14-504, and 14-506) as well as newly incorporated data from Studies 16-512 (PK-PD study of Generation 2 andexanet) and 16-508 Part 1 (PK-PD study of andexanet in individuals of Japanese ethnicity). The covariates for the three drugs involved in the modelling (andexanet, rivaroxaban, and apixaban) are adequately selected, justified and analysed.
- the requested covariate analyses will be conducted and reported in line with current guidelines and are deemed adequate to mimic the target population; detailed information on statistics for data analysis and thresholds for clinical relevance applied are clearly stated.

The CHMP considers the following measures necessary to address the issues related to pharmacology:

- In order to further confirm the posology of Ondexxya, the MAH should submit the results of a comparative PK study with Generation 1, process 2 and 3, and Generation 2 material (study 19-514). The study should be based on an agreed protocol.
- In order to further confirm the efficacy and safety, the MAH should submit an updated PK/PD model using all previously incorporated data (from studies 11-501, 12-502, 14-503, 14-504, and 14-506) as well as newly incorporated data from study 16-512 (PK-PD study of Generation 2 andexanet versus Generation 1), study 16-508 (PK-PD study of andexanet in individuals of Japanese ethnicity), and study 14-505 (ANNEXA-4).

2.4.6. Clinical efficacy

2.4.6.1. Dose response studies and main clinical studies

The above described PK/PD studies provide significant information on efficacy as anti-FXa-activity as surrogate parameter represents the co-primary efficacy endpoint. In addition, two dose-response studies in healthy volunteers have been submitted: study 14-503 regarding apixaban and study 14-504 regarding rivaroxaban. Study 14-505 represents a study in patients with acute major bleeding. An interim analysis (submitted 13 November 2018 [data cut July 09, 2018]) has been assessed. Full study results will be provided as Specific Obligation 1 in 2Q 2019.

Summary of main efficacy results

5.3.5.1 Controlled clinical study pertinent to claimed indication (Efficacy and Safety Studies)	**14-503**	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study in Older Subjects to Assess Safety and the Reversal of Apixaban Anticoagulation with Intravenously Administered Andexanet Alfa	Randomized (3:1 andexanet: placebo), Double-Blind, Placebo-Controlled Study in Older Subjects ages 50-75	Apixaban Andexanet	Apixaban 5 mg orally BID for 3.5 days. Part 1: 400 mg bolus Part 2: 400 mg bolus + 4 mg/min for 120 minutes (480 mg)	Part 1: = 33 (24 andexanet, 9 placebo) Part 2 = 32 (24 andexanet, 8 placebo) [2]	Healthy subjects	Up to ~6 weeks [1]	**Completed;** CSR Final
5.3.5.1 Controlled clinical study pertinent to claimed indication (Efficacy and Safety Studies)	**14-504**	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study in Older Subjects to Assess Safety and the Reversal of Rivaroxaban Anticoagulation with Intravenously Administered Andexanet Alfa	Randomized,(2:1 andexanet: placebo) Double-Blind, Placebo-Controlled Study in Older Subjects ages 50-75	Rivaroxaban Andexanet	Rivaroxaban 20 mg orally QD for 4 days Part 1: 800 mg bolus Part 2: 800 mg bolus + 8 mg/min for 120 minutes (960 mg)	Part 1 = 41 (27 andexanet, 14 placebo) Part 2 = 39 (26 andexanet, 13 placebo) [2]	Healthy subjects	Up to ~6 weeks [1]	**Completed;** CSR Final

The primary efficacy analysis compared the active and the placebo groups by means of an exact Wilcoxon rank-sum test (separately for each part of the studies). The Hodges-Lehman estimate of shift and a 95% Hodges-Lehman confidence interval were constructed for the difference in percentage change from baseline between andexanet and placebo. Secondary endpoints were analysed using an exact Wilcoxon rank-sum test (percent change) or Fisher's Exact Test (dichotomous outcomes).

Study 14-503

This single-site, randomized, double-blind, placebo-controlled, Phase 3 study evaluated the safety and efficacy of andexanet in reversing apixaban-induced anticoagulation in healthy volunteers, ages 50 to 68 years. Efficacy was evaluated using biomarker endpoints, with anti-fXa levels as the primary efficacy measure. Secondary endpoints included plasma levels of free unbound apixaban and ETP, a measure of thrombin generation.

The study consisted of 2 parts. After being treated with apixaban 5 mg BID for 3.5 days, a total of 34 subjects were randomized into part 1 of the trial receiving either a single andexanet bolus (400 mg, 25 subjects) or placebo (9 subjects). Further 32 subjects were randomized into part 2 of the trial receiving either an andexanet bolus (400 mg) followed by a continuous infusion (480 mg over 120 minutes, 24 subjects) or placebo (8 subjects).

Change (%) from baseline in anti-fXa activity at a nadir (after bolus for Part 1 or during infusion for Part 2) was evaluated as the primary endpoint

Currently, it is unknown what degree of reversal of anti-fXa activity is required to impact bleeding in subjects receiving fXa inhibitors. However, the specific threshold for reduction in anti-fXa activity to ≥80% of baseline was chosen for the key secondary endpoint in this study based on data from the Phase 2 study (Study 12-502): Analysis of the anti-fXa activity and thrombin generation (endogenous thrombin potential) data from all subjects dosed with apixaban (5 mg twice daily [BID]) for 5.5 days showed that normalization of hemostasis (as measured by a thrombin generation assay) was achieved when circulating anti-fXa activity was <37 ng/mL. This corresponds to an approximate 75% reduction of peak (just prior to andexanet administration) anti-fXa activity. In these subjects anticoagulated with apixaban, average anti- fXa activity from 4 separate cohorts (n=6/cohort) at 2 minutes after the 420 mg intravenous (IV) bolus of andexanet ranged from 6.3 ng/mL to 11.9 ng/mL, well below the level at which thrombin generation was normalized (<37 ng/mL). This decrease represents an average 94% reduction of peak (just prior to andexanet administration) anti-fXa activity.

Efficacy results:

Primary Endpoint: In Part 1 (bolus), the mean percent change from baseline in anti-fXa activity at the nadir was -93.86% (±1.650%) for the andexanet group and -20.71% (±8.559%) for the placebo group (p<0.0001).

In Part 2 (bolus+c.i.), the mean percent change from baseline in anti-fXa activity at the nadir was -92.34% (±2.809%) for the andexanet group and -32.70% (±5.578%) for the placebo group (p<0.0001):

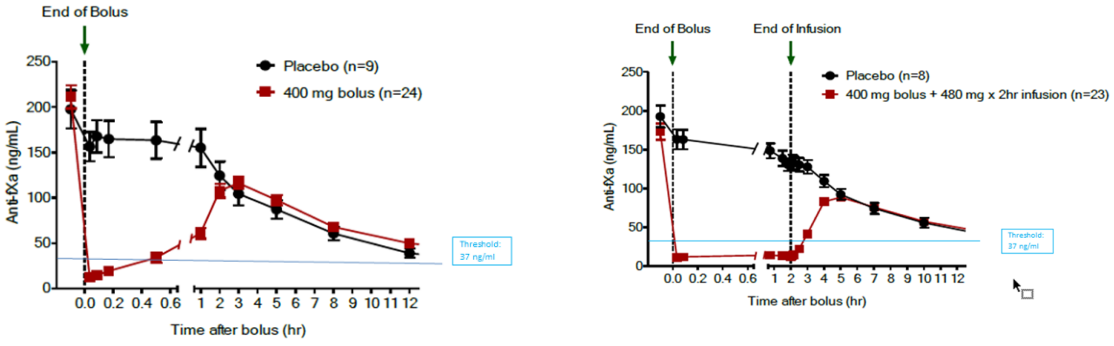


Figure 6 Time Course of anti-fXa activity following Andexanet Bolus/Placebo (Part 1) and Bolus+Infusion/Placebo (Part 2)

Secondary endpoints:

The occurrence of ≥80% reduction in anti-fXa activity from baseline was met in 100% of patients in the andexanet group and no subjects in the placebo group (p<0.0001) in both Part 1 and Part 2.

Coincident with andexanet administration, the total apixaban concentrations increased. The increase occurred within 2-5 minutes after the end of bolus dose and produced up to ~3-fold increase in total apixaban concentrations relative to placebo values. Mean total apixaban plasma concentrations peaked at 2-30 minutes postbolus (Part 1) and 45 minutes after the start of infusion (Part 2) and declined slowly thereafter to near placebo levels. Free apixaban curves proceeded reciprocally:

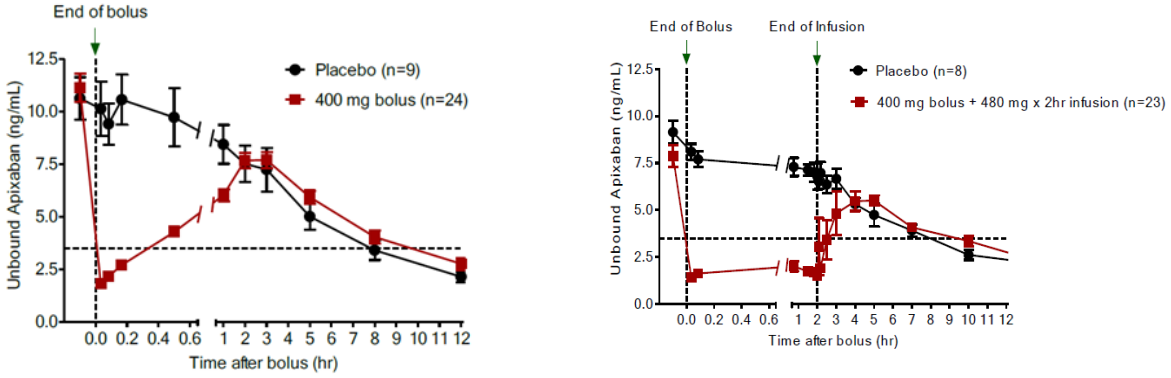


Figure 7 Time Course of free apixaban following Andexanet Bolus/Placebo (Part 1) and Bolus+Infusion/Placebo (Part 2) [–––no-effect-level (3.0 ng/ml) for Apixaban]

Thrombin generation (ETP) from baseline to its peak increased significantly more in subjects who received andexanet than in subjects who received placebo (p<0.0001), in both Part 1 and Part 2 in the mITT Population, with levels increasing for all subjects in the andexanet group and for 1 (Part 1) and 2 (Part 2) subjects in the placebo group.

In addition to the PD parameters that comprised the primary and secondary endpoints, the PD markers of PT, aPTT, and ACT were analyzed.

Study 14-504

This study was similarly designed as study 14-503 with rivaroxaban as the fxa inhibitor.

The study consisted of 2 parts. After being treated with 20 mg rivaroxaban once daily for 4 days, a total of 41 subjects were randomized into part 1 of the trial receiving either a single andexanet bolus (800 mg, 27 subjects) or placebo (14 subjects). Further 39 subjects were randomized into part 2 of the trial receiving either an andexanet bolus (800 mg) followed by a continuous infusion (960 mg over 120 minutes, 26 subjects) or placebo (13 subjects).

Change (%) from baseline in anti-fXa activity at a nadir (after bolus for Part 1 or during infusion for Part 2) was evaluated as the primary endpoint

Currently, it is unknown what degree of reversal of anti-fXa activity is required to impact bleeding in subjects receiving fXa inhibitors. However, the specific threshold for reduction in anti-fXa activity to ≥80% of baseline was chosen for the key secondary endpoint in this study based on data from the Phase 2 study (Study 12-502). Analysis of the anti-fXa activity and thrombin generation (endogenous thrombin potential) data from all subjects dosed with rivaroxaban (20mg daily) for 6 days showed that normalization of hemostasis (as measured by a thrombin generation assay) was achieved when circulating anti-fXa activity was <16 ng/mL. However, in the presence of andexanet in these subjects anticoagulated with rivaroxaban, average anti-fXa activity from 2 separate cohorts (n=6/cohort) at 2 minutes after the 720 mg intravenous (IV) bolus or 800 mg IV bolus of andexanet ranged from 55.7 ng/mL to 64.6 ng/mL. This represents an average 78-81% reduction of peak (just prior to andexanet administration) anti-fXa activity but it resulted in thrombin generation activity within the normal range.

Efficacy results:

Primary Endpoint: In Part 1, the mean percent change from baseline in anti-fXa activity at the nadir was -92.22% (±10.697%) for the andexanet group and -18.39% (±14.662%) for the placebo group (p<0.0001).

In Part 2, the mean percent change from baseline in anti-fXa activity at the nadir was -96.72% (±1.838%) for the andexanet group and -44.75% (±11.749%) for the placebo group (p<0.0001).

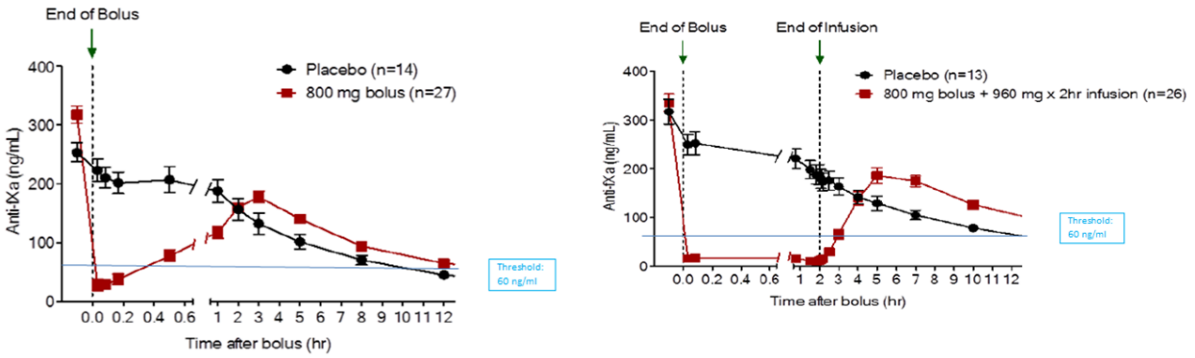


Figure 8 Time Course of anti-fXa activity following Andexanet Bolus/Placebo (Part 1) and Bolus+Infusion/Placebo (Part 2)

Secondary endpoints:

The occurrence of ≥80% reduction in anti-fXa activity from baseline was met in 96.3% of patients in the andexanet group in Part 1, in 100% of patients in the andexanet group in Part 2, and in no subjects in the placebo group in either Part 1 or Part 2 (p<0.0001 within each part).

Coincident with andexanet administration, the total rivaroxaban concentrations increased. The increase was observed at the first measurement, 2 minutes after the end of bolus dose, and produced up to 4- to 5-fold increase in total rivaroxaban concentrations. Mean total rivaroxaban plasma concentrations peaked at 5 minutes post bolus for both Part 1 and Part 2) and declined slowly thereafter to near placebo levels. Free rivaroxaban curves proceeded reciprocally:

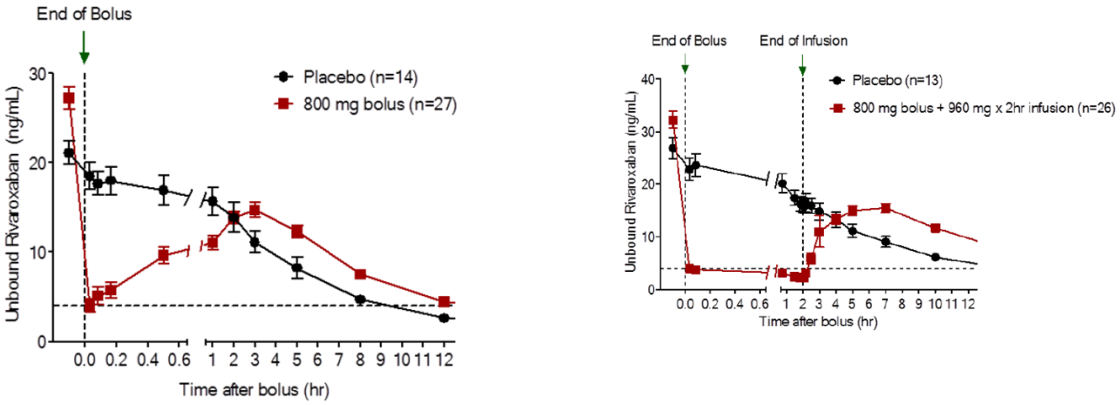


Figure 9 Time Course of free rivaroxaban following Andexanet Bolus/Placebo (Part 1) and Bolus+Infusion/Placebo (Part 2)[–––no-effect-level (4.0 ng/ml) for Rivaroxaban]

Thrombin generation (ETP) from baseline to its peak increased significantly more in subjects who received andexanet than in subjects who received placebo ($p<0.0001$), in both Part 1 and Part 2 in the mITT Population, with levels increasing for all subjects but 1 in the andexanet group and for 1 subject in the placebo group in Part 1 and for all subjects in Part 2.

In addition to the PD parameters that comprised the primary and secondary endpoints, the PD markers of PT, aPTT, and ACT were analyzed.

The main efficacy study, study 14-505 introduces "hemostatic efficacy" as co-primary endpoint and is ongoing, yet:

5.3.5.1 Controlled clinical study pertinent to claimed indication (Efficacy and Safety Studies)	**14-505**	A Phase 3b/4, Prospective, Open-Label Study of Andexanet Alfa in Patients Receiving a Factor Xa Inhibitor who have Acute Major Bleeding	Multicentre, Open-Label	Andexanet	400 mg bolus + 4 mg/min for 120 min (480 mg) All patients receiving apixaban and those patients who received rivaroxaban or edoxaban > 7 hours ago 800 mg bolus + 8 mg/min for 120 min (960 mg). Patients who received enoxaparin or edoxaban or a dose of rivaroxaban within ≤ 7 hours or at an unknown time	162 evaluable (up to 250 enrolled)	Patients with acute major bleeds	37 Days	**Ongoing** Summary Report

This is an ongoing multicenter, prospective, open-label study of andexanet in patients presenting with acute major bleeding who have recently received one of the following fXa inhibitors: apixaban, rivaroxaban, or enoxaparin. The definition of major bleeding was based on the ISTH definition.

At least 162 efficacy evaluable patients were planned to be enrolled.

Initially data on 57 patients have been presented with 36 subjects having received andexanet and meeting bleeding entry criteria. During the procedure: Data on 352 patients have been presented to date, with 167 patients meeting criteria for inclusion in the efficacy analysis set (see discussion on clinical efficacy and safety).

Primary efficacy endpoints were anti-fXa activity and achievement of hemostatic efficacy of stopping a major bleed at 12 hours from end of andexanet infusion

Secondary Efficacy Endpoint was to assess the relationship between the two primary endpoints to establish change in anti-fXa activity as a predictor of achievement of haemostatic efficacy.

Exploratory efficacy endpoints will be analyzed as exploratory at the completion of the study and cover decrease in the free fraction of the fXa inhibitor following andexanet treatment for patients receiving apixaban, edoxaban or rivaroxaban, use of red blood cells transfusions and use of other blood products and haemostatic agents; all-cause mortality through Day 30.

Dose selection: Patients received one of two dose-regimens of andexanet based on the anticoagulant taken and on timing of the last dose:

(1) 400 mg IV bolus followed by 480 mg infusion (4 mg/min) for all patients receiving apixaban and for patients who received rivaroxaban >7 hours previously

(2) 800 mg IV bolus followed by a 960 mg infusion (8 mg/min) for all patients who received enoxaparin, edoxaban or a dose of rivaroxaban within ≤ 7 hours.

Of note, besides other – minor – modifications, the following two changes in amendment 1 have been documented:

- The primary efficacy objective and primary efficacy endpoint were modified to include changes in anti-fXa activity. The two primary efficacy endpoints will be tested sequentially, with the proportion achieving haemostatic efficacy tested only if the change in anti-fXa activity is first demonstrated.
- Eliminated the original Study Day 1 24-hour study data point and updated time points to Day 1 8-hour and Day 1 12-hour data points.

The planned sample size is based on the achievement of hemostatic efficacy at 12 hours from the end of the andexanet infusion, rated by the independent Endpoint Adjudication Committee (EAC) as excellent or good. A sample size of 162 efficacy evaluable patients will provide 80% power for a 2-sided 95% confidence interval (CI) that is completely above 50%. This is based on an anticipated response rate of 61%. To account for approximately 30% of the subjects with andexanet anti-fXa activity of <75 ng/mL (0.5 IU/mL for patients receiving enoxaparin) leading to exclusion from the primary efficacy analysis and 5% of subjects not be evaluable for reasons unrelated to andexanet a total of up to 250 patients may have to be treated to achieve the requisite number of efficacy evaluable patients. In amendment 4, the sample size was increased to 350 patients to accommodate additional patients with intracranial haemorrhage.

Biostatistics: All analyses in the context of the interim analysis were descriptive only and no inferential testing was performed.

As of 09 June 2016, 110 patients had been enrolled. Three analyses populations were defined:

- The Efficacy Population (N=38) included all enrolled patients who received any amount of andexanet treatment and were determined by the EAC to meet the bleeding entry criteria.
- The ‘Complete’ Efficacy Population (N=36) included all enrolled patients form the efficacy population who had complete follow-up and demographic data as of the data cut-off date (June 20, 2016)
- The Exploratory Efficacy Assessment Population (N=54) included all enrolled patients who received any amount of andexanet treatment and were determined by the EAC to meet the bleeding entry criteria. Patients in this population were evaluated for both primary endpoints regardless of their level of anti-fXa at baseline.

Categorical data were summarized by providing absolute and relative frequencies, continous data were summarised by mean, median, standard deviation, minimum and maximum. 95%-CIs were used to describe the precision of the observed efficacy parameter.

Results

Demography: Patients were predominately white (4657/57) and not Hispanic or Latino, and had a median body mass index (BMI) of 28 kg/m^2. Approximately 28/57 were males and 2929/57 were females and had a median age of 81 years (range 47 to 95 years). Patients had a median weight of 77.5 kg (range 45.4 to 145.2 kg).

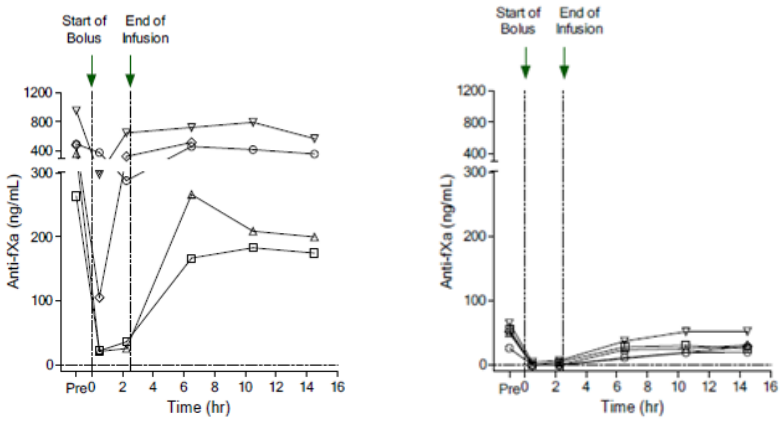
Most patients were administered the fXa inhibitors apixaban (2757/57; 47.4%) or rivaroxaban (2457/57; 42.1%); approximately 10.5657% (6/57patients were given enoxaparin. However, efficacy population (38 patients) includes only 1 patient on enoxaparin, 16 on apixaban and 21 on rivaroxaban.

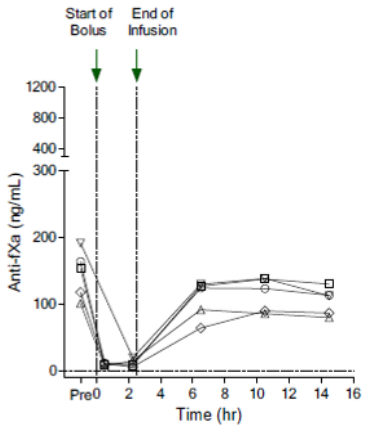
Primary Endpoints:

Anti-fXa Activity: For the efficacy population, a median decrease from baseline in anti-fXa activity of 92.18% (95% CI -94.2%, -87.2%) to the nadir was observed.

Time-course-profiles as graphs have been presented in the summary report, covering up to 5 individuals, each. Time-points cover pre-dose, end of bolus, end of infusion, 4, 8, and 12 hours post infusion.

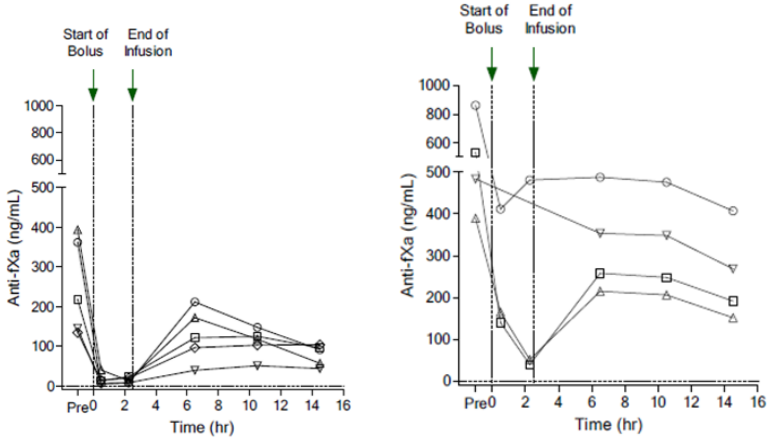
Apixaban: Submitted figures show apixaban patient-profiles with baseline anti-fXa ≥75 ng/mL (N=13); patients with the highest baseline levels of anti-fXa (N=5); patients with baseline levels of anti-fXa <75 ng/mL (N=7); and patients with the baseline levels of anti-fXa <4.0 ng/mL or unknown (N=2).





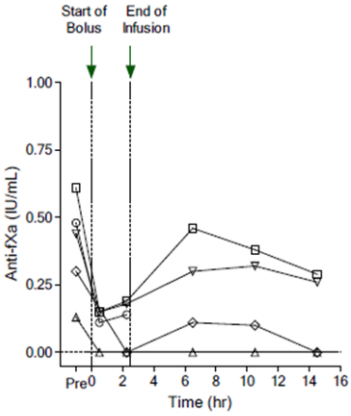
Patients with baseline anti fXa ≥ 75ng/ml, exp Patients with highest baseline anti fXa-levels Patients with baseline anti fXa < 75ng/ml, exp

Rivaroxaban: Submitted figures show rivaroxaban patient-profiles with baseline anti-fXa ≥75 ng/mL (N=17); patients with the highest baseline levels of anti-fXa (N=4); and patients with the baseline levels of anti-fXa <4.0 ng/mL (N=4).



Patients with baseline anti fXa ≥ 75ng/ml, exp Patients with highest baseline anti fXa-levels

Enoxaparin: Submitted figures show enoxaparin patient-profiles with baseline detectable anti-fXa levels (N=5); and patients with the baseline levels of anti-fXa <0.10 IU/mL (N=1).



Patients with detectable baseline anti fXa-levels

The time course profiles of anti-fXa activity in patients before and after andexanet treatment demonstrated a reduction in anti-fXa activity. Of note, a number of patients presented with higher than expected levels of anti-fXa activity at baseline (therapeutic range: > 75ng/ml for apixaban and rivaroxaban; > 0.5 IU/ml for enoxaparin). As the anti-fXa activity and free-fraction of the fXa inhibitors are directly correlated, this indicates that the exposures for the fXa inhibitors were also higher than expected.

Despite the high baseline anti-fXa levels, all the patients had large absolute decreases in anti-fXa activity ranging from 211 to 653 ng/mL. This decrease in anti-fXa activity appears to correlate with haemostatic response even though only 4 of the patients had levels of anti-fXa activity considered subtherapeutic (<60 ng/mL) after andexanet treatment.

It will be important to monitor whether the magnitude of drop in anti-fXa activity – and not just the anti-fXa activity nadir – continues to correlate with haemostatic efficacy in the patients beyond these initial patients.

Haemostatic efficacy results for the second primary enpoint for patients in the 'Complete' Efficacy Population (N=36) demonstrated that 29 patients (80.6%) achieved either excellent or good hemostasis following andexanet treatment.

Secondary endpoints:

Median (min;max) percent decrease in anti-fXa activity for excellent hemostatic efficacy was -92,53 (-98.1; -41.7), for poor hemostatic efficacy it was -91.82 (-95.1; 0).

Median (min;max) absolute change in anti-fXa activity for excellent hemostatic efficacy was -157.1 (-493.2; -0.5), for poor hemostatic efficacy it was -111.9 (-337.2; 0).

Median (min;max) at the end of andexanet administration (NADIR) of anti-fXa activity for excellent hemostatic efficacy was 13.5 (0.2; 411.4), for poor hemostatic efficacy it was 14.4 (5.8; 483.4), see table, below.

Table 12 Comparing Amount of Anti-fXa Activity at the End of Andexanet Administration (NADIR)

Efficacy Analysis Population (N=38)							
	n	Mean	Median	Std. Dev.	Minimum	Maximum	Non Parametric 95% Exact Confidence Interval for Median Difference*
Excellent/Good Hemostatic Efficacy (n=31)	31	52.20	13.50	91.104	0.2	411.4	
Poor/None Hemostatic Efficacy (n=7)	7	83.60	14.40	177.019	5.8	483.4	-13.9, 10.4

Exploratory endpoints:

Time course of Thrombin Generation

The time course profiles of thrombin generation (ETP) demonstrate the restoration and maintenance of thrombin generation to within baseline ranges that were established for healthy volunteers from the Phase 3 studies. Poor responders, however, show similar graphs with normal thrombin generation as excellent responders.

Summary of main studies

The following tables summarise 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 13 Summary of efficacy for phase III trials

Title: A Phase 3 Randomized, Double-blind, Placebo-controlled Study in Older Subjects to Assess Safety and the Reversal of Apixaban Anticoagulation with Intravenously Administered Andexanet Alfa			
Study identifier	14-503		
Design	Randomized, Double-blind, Placebo-controlled Study.		
	Duration of main phase: 6 weeks.		
Hypothesis	To compare reversal of apixaban anticoagulation between andexanet alfa (andexanet) and placebo as measured by anti-Factor Xa (fXa) activity, both after a bolus and after a bolus followed by a continuous infusion.		
Treatments groups	Andexanet alfa Part 1: 400 mg bolus Part 2: 400 mg bolus + 4 mg/min for 120 minutes (480 mg)		Placebo
Endpoints and definitions	Primary endpoint: anti-Factor Xa (fXa) activity	The percent change from baseline in anti-fXa activity at the nadir, when nadir was defined as the smaller value for anti-fXa activity at the +2-minute or +5-minute time point after the completion of the andexanet bolus.	
	Secondary endpoints	- Percent change from baseline in anti-fXa activity at the nadir after the bolus. - Occurrence of ≥ 80% reduction in anti-Xa activity from its baseline to nadir. - Change from baseline in free apixaban concentration at nadir. - Change in thrombin generation (EPT) from baseline to its peak. - Thrombin generation above the lower limit of the normal range at its peak.	

Results and Analysis

Primary endpoint. Percent change from baseline in anti-fXa activity at the nadir

Percent Change from Baseline at the Nadir [a]	Part 1 (n=33)		Part 2 (n=32)	
	Andexanet n=24	Placebo n=9	Andexanet n=23	Placebo n=8
Mean (± SD)	-93.86 (1.650)	-20.71 (8.559)	-92.34 (2.809)	-32.70 (5.578)
Median (range)	-94.43 (-96.3, -89.7)	-18.95 (-31.6, -9.3)	-92.73 (-96.3, -83.4)	-33.01 (-40.1, -24.1)
Hodges-Lehman estimate of shift (95% CI)	-74.55 (-78.39, -66.28)		-59.50 (-64.10, -55.17)	
p-value	< 0.0001 [b]		< 0.0001 [b]	

CI = Confidence interval; mITT = Modified intent-to-treat; SD = Standard deviation

[a] Nadir for Part 1 is the smaller value for anti-fXa activity at the +2 minute or +5 minute time point after the completion of the andexanet bolus for each subject. Nadir for Part 2 is the smallest value for anti-fXa activity at the 110 minute (10 minutes prior to the end of the infusion) time point, 2 minute time point before completion of the infusion, or the 5 minute time point after the completion of the infusion for each subject.

[b] P-value obtained from a 2-sided exact Wilcoxon rank-sum test.

Notes: Baseline is the last assessment obtained prior to the bolus of andexanet or placebo. Only subjects with both a baseline and a post-baseline assessment are presented in the table.

Source: Study 14-503, Table 14.2.2.1a & Table 14.2.2.1b.

Secondary endpoints

	Part 1 (n=33)			Part 2 (n=31)		
	Andexanet n=24	Placebo n=9	p-value	Andexanet n=23	Placebo n=8	p-value
Percent change from baseline in anti-fXa activity at the nadir [a] after the bolus, mean (± SD), %	NA	NA	NA	-93.49 (1.525)	-16.73 (4.104)	< 0.0001
Occurrence of ≥ 80% reduction in anti-fXa activity from its baseline to nadir [b], n (%)	24 (100.0)	0	< 0.0001	23 (100.0)	0	< 0.0001
Change from baseline in free apixaban concentration at nadir [b], mean (± SD), ng/mL	-9.338 (3.2043)	-1.854 (1.6152)	< 0.0001	-6.480 (2.7814)	-2.964 (1.1567)	0.0002
Change in thrombin generation (ETP) from baseline to its peak, mean (± SD), nmol/min	1,323.180 (335.4321)	88.182 (125.7621)	< 0.0001	1,193.060 (263.3471)	189.409 (184.7842)	< 0.0001
Thrombin generation above the lower limit of the normal range at its peak [c], n (%)	24 (100.0)	1 (11.1)	< 0.0001	23 (100.0)	2 (25.0)	< 0.0001

ETP = Endogenous thrombin potential; fXa = Factor Xa; mITT = Modified intent-to-treat; NA = Not applicable; SD Standard deviation

[a] For Part 2, nadir is the smaller value for anti-fXa activity at the +2 minute or +5 minute time point after the completion of the Andexanet bolus.

[b] For Part 1, nadir is the smaller value for anti-fXa activity at the +2 minute or +5 minute time point after the completion of the andexanet bolus. For Part 2, nadir is the smaller value for anti-fXa activity between the 110 minute time point (10 minutes prior to the end of the continuous infusion) and the 5 minute time point after the end of the continuous infusion (inclusive).

[c] For Part 1, peak is the largest value for thrombin generation at the +2 minute or +10 minute time point after the completion of the andexanet bolus for each subject. For Part 2, is the largest value for endogenous thrombin potential at the 110 minute (10 minutes prior to the end of the continuous infusion) time point, 2 minute time point before completion of the andexanet infusion, or the 5 minute time point after the completion of the andexanet infusion for each subject.

Source: Study 14-503, Table 14.2.2.1b, Table 14.2.3.1a & Table 14.2.3.1b, Table 14.2.4.1a & Table 14.2.4.1b, Table 14.2.5.1a & Table 14.2.5.1b, Table 14.2.2.3b, Table 14.2.3.1b, Table 14.2.4.1b, Table 14.2.5.1b, Table 14.2.6.1a & Table 14.2.6.1b.

Title: A Phase 3 Randomized, Double-blind, Placebo-controlled Study in Older Subjects to Assess Safety and the Reversal of Rivaroxaban Anticoagulation with Intravenously Administered Andexanet Alfa			
Study identifier	14-504		
Design	Randomized, Double-blind, Placebo-controlled Study.		
	Duration of main phase: 6 weeks.		
Hypothesis	To compare reversal of rivaroxaban anticoagulation between andexanet alfa (andexanet) and placebo as measured by anti-Factor Xa (fXa) activity, both after a bolus and after a bolus followed by a continuous infusion.		
Treatments groups	Andexanet alfa Part 1: 800 mg bolus Part 2: 800 mg bolus + 8 mg/min for 120 minutes (960 mg)		Placebo
Endpoints and definitions	Primary endpoint: anti-Factor Xa (fXa) activity	The percent change from baseline in anti-fXa activity at the nadir, when nadir was defined as the smaller value for anti-fXa activity at the +2-minute or +5-minute time point after the completion of the andexanet bolus.	
	Secondary endpoints	- Percent change from baseline in anti-fXa activity at the nadir after the bolus. - Occurrence of ≥ 80% reduction in anti-Xa activity from its baseline to nadir. - Change from baseline in free rivaroxaban concentration at nadir. - Change in thrombin generation (EPT) from baseline to its peak. - Thrombin generation above the lower limit of the normal range at its peak.	

Results and Analysis

Primary endpoint: Percent change from baseline in anti-fXa activity at the nadir

Percent Change from Baseline in Anti-fXa Activity at the Nadir [a]	Part 1 (n=40)		Part 2 (n=39)	
	Andexanet n=27	Placebo n=14	Andexanet n=26	Placebo n=13
Mean (± SD)	-92.22% (10.697)	-18.39% (14.662)	-96.72% (1.838)	-44.75% (11.749)
Median (range)	-94.28% (-97.0, -39.4)	-24.43% (-36.7, 12.3)	-96.62% (-100.0, -91.0)	-45.46% (-68.3, -27.8)
Hodges-Lehman estimate of shift (95% CI)	-70.14 (-85.43, -65.91)		-51.87 (-57.95, -47.03)	
P-value	< 0.0001 [b]		< 0.0001 [b]	

CI = Confidence interval; mITT = Modified intention to treat; SD = Standard deviation

[a] For Part 1, nadir is the smaller value for anti-fXa activity at the +2 minute or +5 minute time point after the completion of the andexanet bolus for each subject. For Part 2, nadir is the smallest value for anti-fXa activity at the 110 minute (10 minutes prior to the end of the infusion) time point, 2 minute time point before completion of the infusion, or the 5 minute time point after the completion of the infusion for each subject.

[b] P-value obtained from a 2-sided exact Wilcoxon rank-sum test.

Notes: Baseline is the last assessment obtained prior to the bolus dose of andexanet or placebo. Only subjects with both a baseline and a post-baseline assessment are presented in the table.

Source: Study 14-504, Table 14.2.2.1a & Table 14.2.2.1b.

Secondary endpoints

	Part 1 (n=41)			Part 2 (n=39)		
	Andexanet n=27	Placebo n=14	*P*-value	Andexanet n=26	Placebo n=13	*P*-value
Percent change from baseline in anti-fXa activity at the nadir [a], mean (± SD)	NA	NA	NA	-96.72 (1.838)	-44.75 (11.749)	< 0.0001
Occurrence of ≥ 80% reduction in anti-fXa activity from its baseline to nadir [a,b], n (%)	26 (96.3)	0 [c]	< 0.0001	26 (100)	0	< 0.0001
Change from baseline in free rivaroxaban concentration at nadir [a,b], mean (± SD), ng/mL	-23.347 (6.2229)	-4.155 (2.8914)	< 0.0001	-30.296 (8.1451)	-12.063 (5.2510)	< 0.0001
Change in thrombin generation (ETP) from baseline to its peak [d], mean (± SD), nm•min	1314.193 (331.1670)	173.861 (104.2528)	< 0.0001	1510.368 (344.7691)	264.424 (140.6792)	< 0.0001
Thrombin generation (ETP) above the lower limit of the normal range at its peak [d], n (%)	26 (96.3)	1 (7.1)	< 0.0001	26 (100)	0	< 0.0001

ETP = Endogenous thrombin potential; mITT = Modified intention to treat; NA = Not applicable; SD = Standard deviation

[a] In Part 2, nadir is the smallest value for anti-fXa activity at the 110 minute (10 minutes prior to the end of the continuous infusion) time point, 2 minute time point before completion of the andexanet infusion, or the 5 minute time point after the completion of the andexanet infusion for each subject.

[b] In Part 1, nadir is the smaller value for anti-fXa activity at the +2 minute or +5 minute time point after the completion of the andexanet bolus for each subject.

[c] 13 subjects in the placebo group had the requisite number of readings to be included.

[d] In Part 1, the peak was defined as the largest value for thrombin generation between the +2 minute time point +5 minute, or the +10 minute time point after the completion of the andexanet bolus. In Part 2, the peak was defined as the largest value for endogenous thrombin potential at the 110 minute (10 minutes prior to the end of the continuous infusion) time point, 2 minute time point before completion of the andexanet infusion, or the 5 minute time point after the completion of the andexanet infusion for each subject.

Notes: Baseline was the last assessment obtained prior to the bolus dose of andexanet or placebo. Only subjects with both a baseline and a post-baseline assessment are presented in the table.

Source: Study 14-504, Table 14.2.2.1b, Table 14.2.3.1a & Table 14.2.3.1b, Table 14.2.4.1a & Table 14.2.4.1b, Table 14.2.5.1a & Table 14.2.5.1b, Table 14.2.6.1a & Table 14.2.6.1b.

Title: Prospective, Open-label Study of Andexanet Alfa in Patients Receiving a Factor Xa Inhibitor Who Have Acute Major Bleeding.			
Study identifier	14-505 (ANNEXA-4)		
Design	Prospective, Open-label Study		
	Duration of main phase:		30 days
Hypothesis	Exploratory		
Treatments groups	andexanet		400 mg bolus + 4 mg/min for 120 min (480 mg). All patients receiving apixaban and those patients who received rivaroxaban or edoxaban > 7 hours ago. 800 mg bolus + 8 mg/min at an unknown time for 120 min (960 mg). Patients who received enoxaparin or edoxaban or a dose of rivaroxaban within ≤ 7 hours or.
Endpoints and definitions	Primary endpoint		Change in anti-Xa activity
	Co-primary endpoint		Effective haemostasis
Database lock	Interim analysis submitted 13 November 2018 [data cut July 09, 2018]		

Primary endpoint: Change in anti-Xa activity

Variable	Statistics	Apixaban (ng/mL)	Rivaroxaban (ng/mL)	Enoxaparin (IU/mL)
Baseline	No. Patients	83	70	13
	Mean (Std)	183.4 (143.91)	240.7 (149.33)	0.56 (0.21)
	Median	147.3	207.9	0.48
	Range	76.5, 950.0	75.0, 862.4	0.30, 1.02
	Median 95% CI	132.6, 164.2	163.4, 253.9	0.41, 0.61
Nadir	No. Patients	83	70	13
	Mean (Std)	24.7 (52.84)	63.0 (115.83)	0.15 (0.07)
	Median	10.1	14.0	0.11
	Range	4.0, 297.2	4.0, 570.6	0.10, 0.32
	Median 95% CI	8.0, 11.6	9.7, 25.3	0.10, 0.21
Percent Change	No. Patients	83	70	13
	Mean (Std)	-89.5 (13.01)	-77.6 (31.40)	-71.74 (15.81)
	Median	-93.1	-92.0	-75.41
	Range	-99.5, 0.0	-98.4, 34.0	-83.61, -21.95

Variable	Statistics	Apixaban (ng/mL)	Rivaroxaban (ng/mL)	Enoxaparin (IU/mL)
	Median 95% CI	-94.2, -91.6	-94.1, -88.0	-79.41, -66.67

Based on data transfer from 09JUL18. All patients who received any amount of andexanet, met clinical bleeding criteria, and have anti-fXa level of at least 75 ng/mL (0.25 IU/mL for patients receiving enoxaparin) are included. Values >950 were replaced with 950 the ULQ. Values <4 (or <0.10 for Enoxaparin) were replaced with 4 or 0.1 then BLQ.
One patient who received Edoxaban was excluded from the summary.
Study: ANNEXA-4 (14-505), Source: Table 14.2.1.1.rtf, Date: 22AUG2018

Co-primary endpoint: Effective Haemostasis at 12 h post –andexanet administration

'Complete' Efficacy Analysis Population (N=167)		
Number of Patients	Number of Patients and Proportion who Achieved Excellent or Good Hemostasis*	Binomial Exact 95% Confidence Interval
165	133 (0.806)	0.737, 0.863

Based on data transfer from 09JUL18. All patients who received any amount of andexanet, met clinical bleeding criteria, and have anti-fXa level of at least 75 ng/mL (0.25 IU/mL for patients receiving enoxaparin) are included. Patients 011008 and 206004 were not adjudicated and excluded from the analysis. Six Patients adjudicated as non-evaluable for hemostatic efficacy are included in the analysis and were considered as having Poor/None hemostatic efficacy.
Study: ANNEXA-4 (14-505), Source: Table 14.2.2.1.rtf, Date: 30AUG2018

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

Pooling or integration of efficacy data was not considered appropriate due to differences in anticoagulant therapy, andexanet doses, study designs, and time-points of efficacy evaluation.

Clinical studies in special populations

Elderly

Introduction, disease epidemiology

Andexanet is intended for use in all adult age-groups. However, it is assumed that elderly subjects will form the main target population as respective anticoagulation is applied for underlying diseases most often seen in the elderly. On the other hand, postoperative anticoagulation, e.g., after orthopaedic surgery might include a patient collective with lower age. Safety evaluation in the target patient group points to a significantly increased mortality and risk of thrombosis in the patient group >75 years of age. It is not clear if co-morbidities, risks of the previous anti-coagulant treatment or andexanet itself account for this finding.

Pharmacokinetics and Pharmacodynamics

Study 11-501

This first-in-human Phase 1 study evaluated the safety, tolerability, PK, and PD properties of andexanet alfa in healthy human subjects. Of 32 subjects, 24 received single-dose andexanet, and 8 received placebo. None of the subjects was above 42 years of age.

Study 14-506

This study was designed for comparing PK-, PD- and Safety-profiles of younger and older age-groups under apixaban-treatment. Age-groups were 65-69 versus 26-42 years. Only marginal differences in PK-data were observed.

Clinical efficacy

Clinical efficacy in the elderly population will be further addressed within the ongoing at the time of the marketing authorisation application study 14-505 and updated within the conditional approval procedure.

Clinical safety

Adverse Events

Refer to Table delineating adverse events by age in section 4.6.

Conclusion Elderly

The Elderly Population has not been addressed sufficiently within the currently available documentation as mainly studies in healthy volunteers have been provided. Safety and Efficacy data will be supplemented with submission of the final study report of the on-going study 14-505.

Evaluation of ADR-incidences in the elderly-subgroup within study 14-505 points to higher thrombo-embolic risks, and risk of death in this subgroup. Annual updates should accompany conditional approval. A dedicated PK study was conducted in elderly, otherwise healthy volunteers (study 14-506; see PK section). However, no dedicated efficacy studies have been conducted in elderly patients.

Supportive study(ies)

N/A

2.4.7. Discussion on clinical efficacy

Design and conduct of clinical studies

The above described PK/PD studies provide significant information on efficacy as anti-FXa-activity as surrogate parameter represents the co-primary efficacy endpoint. In addition, two pivotal studies have been submitted: study 14-503 regarding apixaban and study 14-504 regarding rivaroxaban. The main efficacy study, study 14-505 introduces “hemostatic efficacy” as co-primary endpoint .

Study 14-503

Overall, the study presents comprehensible results regarding surrogate laboratory parameters as a function of andexant bolus and continuous infusion administration. Anti-fXa activity – similar to free apixaban – drops within minutes after andexanet administration. It remains open if the degree of this drop (to about 12 ng/ml) is adequate in the light of 37 ng/ml being the lower level of reaching normal hemostasis. Defined therapeutic levels of anti-fXa activity might be essential in the context of dosage recommendation.

Similar to the rapid decrease, an increase of anti-fXa activity and free apixaban is observed within 30 minutes or even less. For therapeutic use rapid onset of the intended effect is acknowledged. However, with respect to serious bleeds (e.g. ICH) or emergency surgery 2 hours of continuous infusion while achieving therapeutic conditions is considered to be limited as half-life of apixaban is 12 to 13 hours. Furthermore, as reversal for bleeding prophylaxis under surgery is intended, effects beyond the applied dosage of 400 plus 420 mg and 2 hours require documentation and evaluation.

Activated Clotting time (ACT), Prothrombin Time (PT) and activated partial thromboplastin time (aPTT) have been documented. Values changed during anticoagulation prior to Andexanet treatment and afterwards. Levels and course of these parameters might be relevant with respect to treatment-monitoring.

Study 14-504

Study 14-504 follows a similar course as study 14-503. However, the following significant differences have been observed:

Andexant dosage for a reversal of rivaroxaban has been chosen to be 800+960mg (compared with 400+720mg for Apixaban). Justification derives from study 12-502.

Threshold-levels for reversal of anticoagulation from study 12-502 module 1 and 2 have been transferred to study 14-504. However, data do not correspond to each other: For rivaroxaban, threshold of 16 ng/ml anti-fXa-activity has been specified in absence of andexanet to allow for thrombin generation. In presence of andexanet, threshold of 55.7 to 64.6 ng/ml anti-fXa-activity (and a drop of 78-81%) was correlated with normal thrombin generation (according to CSR study 14-504 p 23/138). In CSR of study 12-502, threshold in presence of andexanet has been identified to be 26 ng/ml for achieving 89% drop of anti-FXa-activity. This applies to edoxaban and enoxaparin, similarly.

Levels of anti-fXa activity increase rapidly after the end of bolus/infusion. This increase exceeds the levels under placebo, significantly. This finding has been explained by “redistribution-effects”. This phenomenon might be dose-dependent as it is documented less pronounced for apixaban.

Activated Clotting time (ACT), Prothrombin Time (PT) and activated partial thromboplastin time (aPTT) have been documented. Values changed during anticoagulation prior to andexanet treatment and afterwards. Levels and course of these parameters might be relevant with respect to treatment-monitoring.

Study 14-505

The ongoing at the time of the evaluationof this application Phase 3b/4 open-label, single arm study (ANNEXA-4) is evaluating andexanet alfa for reversal of FXa inhibitors in patients with major bleeding. An interim report with 57 patients was initially submitted within this MAA (dated on 22 July 2016) which was amended by data from 20 Sept 2016 reflecting 74 patients and further amended by data from interim analysis submitted 13 November 2018 with data cut July 09, 2018.

In the last submitted interim analysis, of the 352 patients enrolled, 167 were efficacy-evaluable, defined as meeting bleeding entry criteria, having anti-FXa activity in a pre-specified baseline of ≥75 ng/mL anti-FXa activity and having post-baseline anti-FXa activity and haemostatic efficacy outcome data. For the efficacy population, the median decrease from baseline to nadir in anti-FXa activity observed for rivaroxaban was -92.0% (95% CI -94.1%, -88.0%) and for apixaban was -93.1% (95% CI -94.2%, -91.6%). Of the 167 efficacy-evaluable patients, 159 patients were evaluable for haemostatic efficacy, of whom 133 patients (83.6%) were assessed as having excellent (113 patients) or good (20 patients) haemostasis by the endpoint adjudication committee. However, there are aspects of this analysis that still remain challenging:

It has been shown that andexanet-administration to healthy subjects or bleeding patients on direct fXa inhibitors results in immediate drop of free drug levels and antiFXa activity. For supporting these surrogate parameters, it was considered to be desirable that well-confirmed thresholds for anti-coagulation and reversal are available for each anticoagulant. From the currently available non-clinical and clinical data, threshold levels for anti fXa activity are not clearly defined, are not congruent between the studies and do not correspond with an assumed “general therapeutic” anti-coagulative level of 75 ng/ml. For evaluation of efficacy of andexanet – and potentially improved dosage-recommendation clinical confirmation in the bleeding target population remains target of further evaluation within the frame of Conditional Approval.

In Phase 2 study 12-502, unbound fraction of apixaban decreased from 10 ng/ml to 1.5 ng/ml (no-effect-level is 3.5 ng/ml), and unbound fraction of rivaroxaban decreased from 24.5 ng/ml to 5.1

ng/ml, demonstrating sequestration of rivaroxaban. From studies 14-503 and 14-504 we learned, that for anti-fXa, which is directly correlated with free NOAC a threshold of 37 ng/ml for subjects on apixaban and a threshold of 60 ng/ml for subjects on rivaroxaban have been established. Edoxaban and enoxaparin have not been addressed for study 14-505, in this context. However, from study 14-505 clinical relevance of these thresholds regarding recommended dosage and clinical outcome will be further investigated.

Required dosages for the respective NOACs have been chosen at 400 plus 480 mg and 800 plus 960mg. However, respective PK/PD-modelling as a justification for choosing these doses and clinical confirmation based upon laboratory parameters (surrogate) is to be submitted post authorisation with the updated PK-PD model.

Correlation between the co-primary efficacy parameters “anti-fXa-activity” and “hemostatic efficacy” was considered to be challenging: target levels of anti-fXa-activity together with respective percent changes from baseline have been elaborated from Phase 2 and Phase 3 studies (12-502, 14-503 and 14-504). Such levels should correlate either with poor or with excellent response. However, even high anti-fXa activities – far beyond what was defined to be “therapeutic level” – resulted in excellent responses and vice versa. This finding remains challenging with respect to the value of the surrogate. It was concluded that the correlation of anti-FXa activity and haemostatic efficacy has not been established.

Table 14.2.13c from the CSR correlates poor and excellent responders with anti-fXa activities. Similar median (min;max) nadir anti-fXa activities for poor (14.4 [5.8;483.4] ng/ml) versus excellent (13.5 [0.2; 411.4] ng/ml) response have been documented. The numbers do not show a difference for excellent versus poor responders regarding anti-fXa-activities. However, an update of 20Sep2016 shows medians of 11.95 ng/ml in 56 excellent outcome patients and 22.0 ng/ml in 13 poor outcome patients.

The link between healthy subjects on anti-coagulation and actively bleeding subjects with respect to the thrombin-generation results remains to be challenging: thrombin generation might be increased in bleeding subjects irrespective of andexanet effects. Available thrombin-generation-profiles (pre-, 8h, 12h, and 72h post dose) do not show conclusive correlation for excellent versus poor hemostatic response, see figure below. Thrombin-generation data at the time of andexanet effect (immediately after bolus and after infusion) are not available.

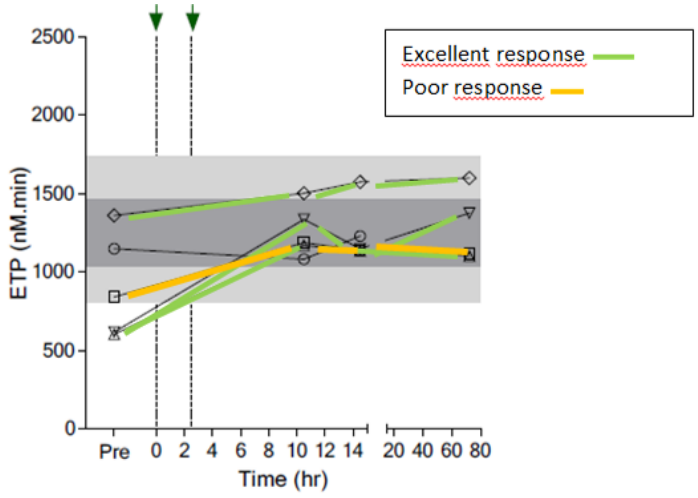


Figure 10 Patients with Rivaroxaban (6-10), exp.

For enoxaparin, the chosen primary endpoint of anti-fXa-activity was considered to be challenging as there is no validated assay for unbound enoxaparin and consequently no documented correlation of unbound enoxaparin and anti-fXa-levels. As, consequently, no threshold for an effect of andexanet was available, clinical efficacy of andexanet for enoxaparin-treated patients could not be demonstrated.

Study amendment 1 introduces a "sequential testing of haemostatic efficacy to be tested only if a change in anti-fXa-activity is first demonstrated". As both, surrogate and clinical endpoint are relevant for evaluation of efficacy and correlation of anti-fXa-activity and hemostatic efficacy is to be evaluated, this approach is not supported.

In the interim report of the ANNEXA-4, 36 (10.3%) patients experienced a total of 42 thromboembolic events and of the patients in the safety population completing 30-day follow up (N=351), 54 patients (15.4%) died, although the issue of causality relationship with andexanet is difficult to be solved without a controlled study.

Dosage recommendation in the SmPC references to the last dosage and timing of the anticoagulant. This recommendation is not supported by the dosage recommendations of the ongoing study where low dose received all patients on apixaban and those patients on rivaroxaban who received their last dose >7 hours previously. High dose regimen was restricted to patients on rivaroxaban < 7hours, enoxaparin or edoxaban. Andexanet dose-recommendation based upon previous NOAC-dose, anti-fXa level, or plasma-drug-level was not evaluated in study 14-505. The Applicant was asked to justify further their dose recommendation. Furthermore, dosage recommendation for surgical intervention has not been confirmed in clinical studies.

The following dosing recommendation was finaly agreed to be included in the SmPC: The recommended dose regimen of Ondexxya is based on the dose of apixaban (or rivaroxaban) the patient is taking at the time of anticoagulation reversal, as well as on the time since the patient's last dose of apixaban. The dosing recommendation might be further refined post authorisation as further support for dosing recommendation is to be provided as part of the specific obligations.

Responder Analysis

Within the 2nd Day 180 response, the Applicant presented a responder analysis for supporting the correlation of the surrogate antiFXa-activity and haemostatic efficacy. 77 patients treated with apixaban and 68 patients on rivaroxaban (N=68) fromn study 14-505 were included. The Applicant stated that these analyses identified the log of nadir of anti-fXa activity as a predictor of clinical efficacy. However, the AUC ROC (0.67, 95%-CI: (0.55, 0.79)) indicates that the log of nadir is at best a modest indicator for clinical efficacy. Furthermore, this 'indicator' was determined posthoc, and a confirmation based on the outstanding data remains open.

Additional efficacy data needed in the context of a conditional MA

The CHMP considered that for the development to be considered comprehensive additional efficacy (and safety) data in bleeding patients will need to be provided and the applicant committed to submit as part of the specific obligations the full clinical data from ANNEXA-4 study, further confirmation of the posology of Ondexxya, further clinical data from RCT in patients with ICH and update to the PK/PD model (see Conclussions on the clinical efficacy).

2.4.8. Conclusions on the clinical efficacy

Final conclusions on haemostatic efficacy remains challenging: (1) Hemostatic efficacy requires further evaluation from the study 14-505 (ANNEXA-4); (2) A valid surrogate parameter has not been

identified: target anti-fXa-level, nadir value, extent of reduction, percentage or absolute reduction, difference in influence between different FXa-inhibitors, baseline anti-fXa-activity might all be relevant. Correlation with haemostatic efficacy has not been confirmed; (3) Furthermore, treatment monitoring is an open issue which has not been addressed in the clinical setting; (4) Dosage recommendation derives from anti-FXa levels in healthy volunteers. PD-modelling was used for recommending dosage – bolus plus c.i. - and elapsed time from previous DOAC-treatment. However, PK/PD-modelling was still considered insufficient and uncertainties regarding posology remain.

However, given the assumed mechanism of action, the reversal data in healthy volunteers, the available data in bleeding patients (ANNEXA-4) and the high unmet medical need the CHMP agreed that the benefit of andexanet outweights its risks but that further data would still need to be provided postauthorisation, therefore granted a conditional marketing authorisation.

The CHMP considered the following measures necessary to address the missing efficacy data in the context of a conditional MA:

(Specific Obligation 1) In order to further substantiate correlation of the biomarker (antiFXa-activity) with haemostatic efficacy and clarify the risk of thromboses and thromboembolic events, the MAH should submit the results of ANNEXA-4, an interventional non-randomized, multicentre, prospective, open-label, single-group study in patients with acute major bleeding.

(Specific Obligation 2) In order to further confirm the posology of Ondexxya, the MAH should submit the results of a comparative PK study with Generation 1, process 3, and Generation 2 material (study 19-514). The study should be based on an agreed protocol.

(Specific Obligation 3) In order to substantiate correlation of the biomarker (antiFXa-activity) with haemostatic efficacy and clarify the risk of thromboses and thromboembolic events, the MAH should submit the results of a global randomised controlled clinical trial to investigate the use of andexanet versus standard of care treatment in patients with intracranial haemorrhage (ICH) taking apixaban, rivaroxaban, or edoxaban (study 18-513).

2.4.9. Clinical safety

Patient exposure

The table, below, summarizes subjects in completed studies:

Table 14 Number of Subjects in Completed Studies

Type of Study	Total Number of Subjects (N=444)	Number of Subjects Administered Anticoagulant (N=439)	Number of Subjects Administered Placebo (N=116)	Number of Subjects Administered Andexanet (N=321)
Portola 12-502 (Phase 2)	157	152	50	102
Portola 14-503 (Phase 3)	65	65	17	48
Portola 14-504 (Phase 3)	80	80	27	53
Portola 14-506 (Phase 1)	20	20	0	20
Portola 16-512 (Phase 1)	122	122	22	98

In Study 12-502: 5 subjects had missing treatment information.
In Study Portola 16-512 (Direct Inhibitors Only): Actual Treatment is used for number of subjects administered andexanet.
Study: ISS, Program: Table_3_4_7_1.sas, Output: Table_3_4_7_1.rtf, Date: 15JAN2019

Of 32 healthy subjects in study 11-501, 24 received andexanet, and 8 received placebo. Subjects (24) were randomized to single-dose cohorts of 30, 90, 300 or 600 mg Andexanet with 6 subjects in each cohort.

In study 14-506, 20 healthy subjects received andexanet together with apixaban.

Study 12-502:

In Module 1, 36 of 54 healthy subjects on apixaban received one of 6 dosages of andexanet; 18 subjects received apixaban and placebo.

In Module 2, 30 of 45 healthy subjects on rivaroxaban received one of 5 dosages of andexanet; 15 received rivaroxaban and placebo.

In Module 3, 18 of 27 healthy subjects on enoxaparin received one of 3 dosages of andexanet; 8 subjects received enoxaparin and placebo.

In Module 4, 18 of 28 healthy subjects on edoxaban received one of 3 dosages of andexanet; 10 subjects received edoxaban and placebo.

Study 14-503:

In Part 1, 33 subjects received all 7 doses of apixaban. Of these 33 subjects, 24 subjects received a single IV bolus of andexanet, and 8 subjects received a single IV bolus of placebo. In Part 2, 32 subjects received all 7 doses of apixaban and 32 subjects received a single IV bolus and a continuous infusion of andexanet or placebo.

Study 14-504:

In Part 1, 41 subjects received 4 doses of rivaroxaban. Of these, 27 subjects received a single IV bolus of andexanet, and 14 subjects received a single IV bolus of placebo.

In Part 2, 39 subjects received all 4 doses of rivaroxaban and 26 subjects received a single IV bolus of andexanet 800 mg or placebo, and a continuous infusion of andexanet 960 mg or placebo

Study 14-505:

As of 09 June 2016, 110 patients had been enrolled and treated in the trial. At the summary analysis, data from 57 patients were available and included in the safety population.

Dosages:

Dosages of andexanet administered in the 4 pooled studies (Studies 12-502 Modules 1, 2, 3, and 4; 14-503 Parts 1 and 2; and 14-504 Parts 1 and 2; and Study 14-506) are presented, below:

Table 15 Subjects Treated with Andexanet in Phase 1, Phase 2, and Phase 3 Completed Studies

Dose Regimens		FXa Inhibitor				Total
		Apixaban	Rivaroxaban	Edoxaban	Enoxaparin	
Bolus Only	90 mg	6				6
	210 mg	6	6		12	24
	400 mg [a]	44 [b]				44
	420 mg	6	6		6	18
	600 mg	6 [d]	6	6		18
	800 mg [a]		27	6		33
Bolus + Infusion	600 mg	6				6
	880 mg [a]	56 [e]	10	12		78
	900 mg	6				6
	960 mg		6			6
	1280 mg			6		6
	1760 mg [a]	10	53[c]	13		76
Total subjects dosed		146	114	43	18	321

[a] Doses in Phase 3 studies (14-503 and 14-504)

[b] 24 subjects from Study 14-503 and 20 subjects from Study 14-506

[c] 26 subjects from Study 14-504, 6 subjects from Study 12-502 and 21 subjects from Study 16-512

[d] 420 mg bolus + 180 mg bolus from study 12-502 Module 1

[e] 24 subjects from Study 14-503 and 32 subjects from Study 12-512

The table includes only completed studies.

The safety population includes all subjects randomized and treated with study medication (andexanet or placebo).

The safety summary is based on integrated data from Studies 12-502, 14-503, 14-504, 14-506, and 16-512 studies in healthy volunteers.

Study: ISS, Program: Table_3_4_7_2.sas, Output: Table_3_4_7_2.rtf, Date: 11JAN2019

Adverse events

Study 11-501:

In vivo PD evaluation of the subjects in this study revealed a transient dose-dependent decrease in TFPI activity with reciprocal elevations in F1+2, D-dimer, and TAT (consistent with thrombin generation and fibrinolysis), with a peak effect at 24 hours postdose for D-dimer and approximately 3 hours postdose for TAT and F1+F2.

In 1 subject of the 90 mg group an infusion-related reaction resulted in premature discontinuation of the infusion, and in 1 subject of the 600 mg group an infusion-related reaction resulted in a reduction in the infusion rate from 10 to 5 ml/min.

One subject in the active group was believed to have had a spontaneous abortion.

Comparison of AEs between placebo- and active group shows similar overall frequency of AEs in both groups. With placebo, vessel puncture and catheter-related AEs, upper respiratory tract infection and an accident are documented. With verum, gastrointestinal disorders, vessel puncture and catheter-related AEs pneumonia, infusion-related reactions, laboratory changes, muscoloskeletal, CNS and gynecology (see above: abortion) were affected.

Study 14-506

Andexanet was similarly well tolerated in both age cohorts. Three subjects experienced transient, non-treatment requiring, mild infusion-related reactions (flushing or tingling) that resolved despite ongoing treatment with andexanet. One subject had an unexplained transient elevation of ALT and AST less than three times the ULN that started prior to administration of andexanet.

There was no apparent effect of andexanet on clinical laboratory, ECG, vital signs, oxygen saturation, or physical examination findings.

Study 14-502

Module 1

In total 34 (63%) subjects had a TEAE during this study, 20 (56%) subjects in the active groups and 14 (78%) subjects in the placebo group.

Among the active groups, TEAEs occurred in all of the treatment groups: 3 (50%) subjects in Cohort 1, 3 (50%) subjects in Cohort 2, 5 (83%) subjects in Cohort 3, 4 (67%) subjects in Cohort 4, 2 (33%) subjects in Cohort 5, and 3 (50%) subjects in Cohort 6.

In the active groups, 9 subjects (25%) had adverse events related to andexanet and 4 (11.1%) had events related to both andexanet and anticoagulant. Treatment-related events were reported in 4 placebo subjects (22.2%); events related to both andexanet/placebo treatment and anticoagulant were reported in 1 subject (5.6%).

The overall incidence of treatment-emergent adverse events was lower in active subjects (56%) than in placebo (78%) subjects. Infusion-related reactions were observed in 9 subjects dosed with andexanet and 2 placebo subjects; no clear dose response was observed. The most frequently reported symptoms reported as infusion-related reactions included flushing (3 subjects), non-productive cough (3 subjects), dyspnea (2 subjects) and abnormal taste during infusion (2 subjects). Transient dyspnea lasting ≤ 4 minutes was reported in 2 subjects receiving active treatment; there was no association with clinically significant changes in blood pressure, heart rate, or physical examination findings.

For both andexanet/placebo and anticoagulant treatment-emergent events, the majority were mild in severity. All AEs resolved without sequelae. There were no severe, serious, or life-threatening or thrombotic events reported; there were no subject deaths during the study.

Module 2

Overall, 34 (76 %) subjects reported one or more AE. Of subjects with AEs, 22 (73% of group) were in the active group and 12 (80% of group) were in the placebo group. There was no apparent dose-response for any adverse events.

The most common system organ class (SOC) of TEAEs (>15%) were injury, poisoning, and procedural complications (18 subjects, 40%), nervous system disorders (13 subjects, 29%), skin and subcutaneous tissue disorders (9 subjects, 20%), and general disorders and administration site conditions (9 subjects, 20%). The most frequently reported AEs (≥ 7% of subjects) were infusion-related reaction (11 subjects, 24%), headache (8 subjects, 18%), dizziness postural (6 subjects, 13%), post-procedural hematoma (6 subjects, 13%), procedural site reaction (3 subjects, 7%), and dermatitis contact (3 subjects, 7%).

In the active treatment groups, TEAEs were most frequently (>7%) reported in the injury, poisoning and procedural complications (12 subjects, 40%), nervous system disorders (7 subjects, 23%), general disorders and administration site conditions (7 subjects, 23%), skin and subcutaneous tissue disorders (3 subjects, 10%), infections and infestations (4 subjects, 13%), and gastrointestinal disorders (3 subjects, 10%) SOC. The most frequently reported AEs (> 7% of subjects) were infusion-related reaction (10 subjects, 33%), post –procedural hematoma (3 subjects, 10%), headache (5 subjects, 17%) and dizziness postural (4 subjects, 13%).

The frequency of individual adverse events was generally similar between the active and placebo groups. Adverse events for which there was a >10% difference between the active and placebo groups were as follows: infusion-related reactions (33% and 7%, respectively), and dermatitis contact (0% and 20%, respectively). Post-procedural hematomas and one event of wound dehiscence were all associated with the protocol skin punch biopsies.

Module 3

Among andexanet-treated subjects, TEAEs were observed with similar frequencies in all cohorts.

Of the 18 subjects with adverse events, 8 (44.4%) subjects had events classified as andexanet/placebo treatment-related, 3 (16.7%) related to anticoagulant, and 7 (38.9%) unrelated to treatment. Andexanet-related events in 4 subjects were classified as infusionrelated events.

For the active groups, the most common SOCs of TEAEs (2 or more subjects, ≥11%) were gastrointestinal disorders (4 subjects, 22%), injury, poisoning and procedural complications (10 subjects, 56%), nervous system disorders (3 subjects, 17%), musculoskeletal and connective tissue disorders (2 subjects, 11%), respiratory, thoracic and mediastinal disorders (2 subjects, 11%) and skin and subcutaneous system disorders (2 subjects, 11%). The most frequently reported preferred terms (≥11%) were infusion related reactions (4 subjects, 22%), procedural site reactions (4 subjects, 22%), dry mouth (2 subjects, 11%), nausea (2 subjects, 11%), post procedural hematoma (2 subjects, 11%), procedural pain (2 subjects, 11%) and dizziness (2 subjects, 11%).

The majority of andexanet/placebo-emergent adverse events were mild in severity; only 3 subjects reported moderate events.

In the active groups, 7 of the 13 subjects who reported events (53.8% of active subjects) had events related to andexanet treatment, 2 (15.4%) had anticoagulant-related events and 4 (30.8%) had

events unrelated to treatment. The andexanet-related events included dizziness (1 subject), dry mouth (2 subjects), infusion-related reactions (4 subjects), muscle spasm (1 subject), nausea (1 subject) and thirst (1 subject).

Module 4

Overall, 14 (54%) subjects [11 (61%) active subjects; 3 (38%) placebo subjects] experienced one or more adverse events.

There were no subject deaths, no SAEs, no severe adverse events, no thrombotic events and no major bleeding events during the study.

Among subjects treated with andexanet, TEAEs were observed in 83% of the 600 mg bolus cohort and 50% each of the 800/8x60min and 800 mg bolus cohorts.

No apparent dose-response was observed for overall adverse events or for individual adverse event preferred terms. Of the 14 subjects with adverse events, 4 (28.6%) had events classified as andexanet/placebo treatment-related, 3 (21.4%) had events considered related to anticoagulant, and 7 (50.0%) had events classified as unrelated to treatment. Adverse events occurring during or soon after treatment with andexanet/placebo in 4 subjects (3 active; 1 placebo) were classified as infusion-related events.

Overall, the most common (≥ 15%) system organ classes (SOCs) of TEAEs were general disorders and administration site conditions (5 subjects, 19%), injury, poisoning and procedural complications (4 subjects, 15%), and musculoskeletal and connective tissue disorders (4 subjects, 15%). The most frequently reported adverse events, experienced by 2 or more subjects (≥8%) were vessel puncture site hematoma (2 subjects, 8%), infusion-related reaction (4 subjects, 15%), decreased appetite (2 subjects, 8%), headache (2 subjects, 8%), presyncope (2 subjects, 8%), and pruritus (2 subjects, 8%).

Study 14-503

One specifically analyzed group of Adverse Events was “Infusion-related reactions”. An event occurring during or shortly after the bolus or infusion was to be labeled as an “Infusion-Related Reaction—specific sign or symptom” unless the Investigator judged that the event was unrelated to study drug administration.

The following Table shows the distribution of documented Infusion-related reactions:

Table 16 Infusion related Reactions after Apixaban

Infusion Reaction Verbatim Coded to MedDRA Preferred Term and SOC	Part 1		Part 2	
SOC MedDRA Preferred Term Infusion-Related Reaction Verbatim Term	**Andexanet N=24 n (%)**	**Placebo N=9 n (%)**	**Andexanet N=24 n (%)**	**Placebo N=8 n (%)**
Subjects with ≥1 Infusion-Related Reaction TEAE	3 (12.5)	0	4 (16.7)	2 (25.0)
Cardiac Disorders	0	0	1 (4.2)	0
Sinus Tachycardia Infusion Reaction - Sinus Tachycardia	0	0	1 (4.2)	0
Eye Disorders	1 (4.2)	0	0	1 (12.5)
Lacrimation Increased Infusion Reaction - Watery eyes	0	0	0	1 (12.5)
Ocular Hyperaemia Infusion Reaction - Ocular Hyperemia, Bilateral	1 (4.2)	0	0	0
Gastrointestinal Disorders	2 (8.3)	0	1 (4.2)	1 (12.5)
Dysgeusia Infusion Reaction - Dysgeusia Infusion Reaction - Taste Disturbance	2 (8.3)	0	1 (4.2)	0
Nausea Infusion Reaction - Nausea	0	0	0	1 (12.5)
General Disorders and Admin Site Conditions	4 (16.7)	0	5 (20.8)	1 (12.5)
Chest Discomfort Infusion Reaction - Chest Discomfort, Non-cardiac	0	0	1 (4.2)	0
Face Oedema Infusion Reaction - Facial Oedema	1 (4.2)	0	0	0
Feeling Hot Infusion Reaction - Sensation of Warmth Infusion Reaction - Sensation of Warmth Chest Infusion Reaction - Sensation of Warmth Face	1 (4.2)	0	2 (8.3)	1 (12.5)
Flushing Infusion Reaction - Facial Flushing Infusion Reaction - Flushing chest	2 (8.3)	0	2 (8.3)	0
Immune System Disorders	0	0	1 (4.2)	0
Urticaria Infusion Reaction - Exacerbation of Generalized Erythematous Hives	0	0	1 (4.2)	0
Nervous System Disorders	0	0	0	1 (12.5)
Dizziness Infusion Reaction - Dizziness	0	0	0	1 (12.5)
Respiratory, Thoracic and Mediastinal Disorders	2 (8.3)	0	0	0
Parosmia Infusion Reaction - Smell Disturbance	1 (4.2)	0	0	0
Sinus Pressure	1 (4.2)	0	0	0
Infusion Reaction - Nasal/Sinus Pressure	1 (4.2)	0	0	0
Skin and Subcutaneous Tissue Disorders	0	0	0	1 (12.5)
Papular Rash Infusion Reaction - Exacerbation of Erythematous Papular Patch Forehead	0	0	0	1 (12.5)

Reference: Table 19, CSR 14-504 p102/142

Study 14-504

One specifically analyzed group of Adverse Events was “Infusion-related reactions”. An event occurring during or shortly after the bolus or infusion was to be labeled as an “Infusion-Related Reaction—specific sign or symptom” unless the Investigator judged that the event was unrelated to study drug administration.

The following Table shows the distribution of documented Infusion-related reactions:

Table 17 Infusion related Reactions after Rivaroxaban

Infusion Reaction Verbatim Coded to MedDRA Preferred Term and SOC	Part 1 (n=41)		Part 2 (n=39)	
SOC MedDRA Preferred Term Infusion-Related Reaction Verbatim Term	Andexanet n=27 n (%)	Placebo n=14 n (%)	Andexanet n=26 n (%)	Placebo n=13 n (%)
Subjects with ≥1 Infusion-Related Reaction TEAE	5 (18.5)	0	0	0
General Disorders and Admin Site Conditions	2 (7.1)	0	0	0
Flushing	2 (7.1)	0	0	0
Infusion Reaction—Flushing	2 (7.1)	0	0	0
Immune System Disorders	1 (3.7)	0	0	0
Urticaria	1 (3.7)	0	0	0
Infusion Reaction—Hives	1 (3.7)	0	0	0
Musculoskeletal and Connective Tissue Disorders	1 (3.7)	0	0	0
Neck Pain	1 (3.7)	0	0	0
Infusion Reaction—Neck Throbbing	1 (3.7)	0	0	0
Skin and Subcutaneous Tissue Disorders	2 (7.1)	0	0	0
Pruritus	1 (3.7)	0	0	0
Infusion Reaction—Itching	1 (3.7)	0	0	0
Rash Erythematous	1 (3.7)	0	0	0
Infusion Reaction—Left Lower Extremity Rash Erythematous	1 (3.7)	0	0	0

Reference: Table 19, CSR 14-504 p98/138

Study 14-505

As of 09 June 2016, 110 patients had been enrolled and treated in the trial. Data from 57 patients were included in the safety population as they received a bolus and an infusion of andexanet. The size of the Safety Population (57 subjects) is too small to allow for appropriate characterization of AEs by patient age or sex.

Adverse Events: In safety population,30 patients experienced a total of 71 TEAEs. Eight patients died, and 7 patients had fatal TEAEs reported.

The most frequently reported AEs (occurring in ≥2% of subjects) by preferred term were deep vein thrombosis in 4 patients (7.02%); pneumonia, headache, and respiratory failure in 3 patients each (5.26%); and cardiogenic shock, sepsis, and pulmonary embolism in 2 patients each (3.51%).

Serious adverse event/deaths/other significant events

Studies 11-502, 14-506, 12-502, 14-503, 14-504

There were no severe, serious, or life-threatening or thrombotic events reported; there were no subject deaths during the study.

Study 14-505

Deaths

8 Deaths were reported – all but one assessed to be not related with the andexanet treatment:8 Deaths were reported – all but one assessed to be not related with the andexanet treatment:

One patient presented with a traumatic ICH under rivaroxaban, received high-dose andexanet and died from subdural hematoma preceded by thrombotic stroke. This was the only death assessed to be probably related with andexanet.

Serious AEs: Thirty-six (36) SAEs were reported for 18 (31.58%) of the 57 patients in the Safety Analysis Population. Events covered cardiac, cerebral, vascular and other incidents.

AEs of special interest (reported within 24 hours):

Embolic and thrombotic events: 8 subjects experienced thrombotic and/or embolic events. Only 2 patients were re-anticoagulated prior to the event.

Re-bleeding/Bleeding events: In the Phase 3b/4 study thus far there is also no evidence of andexanet-induced bleeding. With respect to withdrawal of andexanet, it is mechanistically possible that rebleeding could occur. Andexanet efficiently binds the fXa inhibitor in the bloodstream. As the fXa inhibitor in the intravascular compartment is bound by andexanet, there is a re-equilibration of the unbound fXa inhibitor from the extravascular compartment into the bloodstream where it can also be bound by andexanet. As andexanet is cleared, with a terminal half-life of approximately 5 hours, the fXa inhibitor is released where it can then function as an anticoagulant until it is cleared from the bloodstream through its usual metabolic and excretory processes. If the residual anticoagulant remaining after andexanet clears is still sufficiently high, it could theoretically result in re-bleeding.

Thrombin Generation: Thrombin generation – as a marker of normalized coagulation was tested at baseline, 8 and 12 and 72 hours and post andexanet. The following table presents the results.

Table 18 Endogenous Thrombin Potential in Patients with Thrombotic Events vs No Events (Bleeding Patient Studies)

		Safety Population (N = 351)			Efficacy Population (N = 167)		
Assessment Time	Statistics	TE	No TE	P-Value	TE	No TE	P-Value
Baseline	No. Patients	21	189		15	139	
	Mean (Std)	954.5 (349.61)	849.7 (276.98)		911.5 (391.17)	804.7 (282.39)	
	Median	897.5	877.0	0.1674	881.7	817.0	0.3372
	Median 95%CI	807.0, 1163.8	832.0, 915.9		630.4, 1222.9	753.7, 888.1	
EI + 8 hrs	No. Patients	21	188		14	140	
	Mean (Std)	1113.9 (228.32)	1107.8 (245.20)		1146.9 (254.80)	1103.7 (231.91)	
	Median	1113.3	1100.4	0.9985	1074.3	1103.5	0.6448
	Median 95%CI	915.6, 1252.7	1056.8, 1125.6		915.6, 1431.0	1043.2, 1128.3	
EI + 12 hrs	No. Patients	22	193		15	143	
	Mean (Std)	1155.0 (195.71)	1093.2 (245.00)		1195.6 (222.16)	1086.8 (249.18)	
	Median	1118.0	1072.5	0.2024	1206.3	1072.5	0.0885
	Median 95%CI	1050.8, 1264.3	1044.5, 1129.1		1000.3, 1407.3	1029.1, 1129.1	
Day 3	No. Patients	20	177		15	129	
	Mean (Std)	1151.0 (287.80)	1074.5 (284.01)		1231.1 (279.21)	1084.5 (295.26)	
	Median	1110.0	1080.2	0.4814	1158.0	1086.8	0.1142
	Median 95%CI	931.9, 1233.8	1022.9, 1118.6		969.3, 1552.1	1013.2, 1130.6	

Based on data transfer from July 9 2018. All patients who received any amount of andexanet are included in safety population. The efficacy population included all patients in the safety population who met clinical bleeding criteria, and have anti-fXa level of at least 75 ng/mL (0.25 IU/mL for patients receiving enoxaparin) are included.
This table excludes patients without ETP data whether or not they had a TE.
P-values are based on a non-parametric test to compare two medians. The 95% CI for the median are based on distribution free method.
Study: ANNEXA-4 (14-505), Program: T_3-4-7-5-JULY'09.sas, Output: Table 3_4_7_5_July9.rtf, Date: 25FEB2019

Infusion Reactions: Infusion reactions were reported in 2 patients.

Laboratory findings

Study 11-501

In vivo PD evaluation of the subjects in this study revealed a transient dose-dependent decrease in TFPI activity with reciprocal elevations in F1+2, D-dimer, and TAT (consistent with thrombin generation and fibrinolysis), with a peak effect at 24 hours postdose for D-dimer and approximately 3 hours postdose for TAT and F1+F2.

There were no remarkable findings observed in the safety assessments for vital signs, ECGs, physical examinations, or in clinical laboratory trends. All 32 subjects completed the study.

Study 14-506

D-dimer and F1+2 increased transiently following andexanet exposure in most subjects at 1 or more time points during the study, peaking at 14.5 hours post-andexanet dose completion on Day 4 and typically decreasing starting on Day 6. Longer durations of D-dimer elevations and F1+2 were more common in the elderly group. Higher plasma andexanet concentrations were observed concurrently with higher thrombin generation levels. Andexanet binds to tissue factor pathway inhibitor (TFPI) in the plasma and possibly also to TFPI bound to the endothelium. The binding to TFPI may also explain the observed dose-dependent transient increase in D-dimer and F1+2 with simultaneous decrease in TFPI. The clinical relevance of these findings is unknown. There was no clinical evidence of thrombotic events in this study and the clinical relevance of these findings is unknown.

Study 12-502

The mean D-dimer level and Prothrombin fragments F1 +2 increased in a dose dependent manner following andexanet doses. These significant findings are relevant for all Modules. Some healthy volunteers had clinically meaningful transient elevations.

Study 14-503

There were transient elevations observed in D-dimer and F1+2 levels in Part 1 and Part 2, most often observed on Day 4 following andexanet and resolving within 24 to 96 hours postdose. Three subjects had either increase of D-Dimer or F1+2 levels >ULN for 11 days that started immediately following treatment with andexanet (ie, Days 4-15).

Of note, no subject in the placebo group had respective elevations of D-Dimers or F1+2.

Vital signs: In Part 1, low SBP and DBP (Systolic and Diastolic Blood Pressure) and high HR (Heart Rate)were reported in 12 of 24 (50%) of the subjects in the andexanet group and low and high DBP and low HR (Heart Rate) were reported in 4 of 9 (44%) of the subjects in the placebo group. In Part 2, low or high SBP and DBP and high HR (Heart Rate)were reported in 19 of 24 (79%) of the subjects in the andexanet group and low and high DBP were reported in 2 of 8 (25%) of the subjects in the placebo group.

Study 14-504

There were transient elevations observed in D-dimer, and F1+2 levels, most often observed following andexanet administration on Day 4 and resolving within 24 to 96 hours postdose. Two subjects had D-Dimer and/or F1+2 levels >2× the ULN on Day 43.

Vital signs: In Part 1, low (high) SBP and DBP (Systolic and Diastolic Blood Pressure) and low SBP or DPP were reported in 16 of 27 (59%) of the subjects in the andexanet group and low DBP or SBP were reported in 6 of 14 (43%) of the subjects in the placebo group. In Part 2, low or high SBP and DBP and high HR (Heart Rate)were reported in 17 of 26 (65%) of the subjects in the andexanet group and in 9 of 14 (75%) of the subjects in the placebo group.

Study 14-505

Clinical Laboratory evaluation and evaluation of vital signs has been presented in (preliminary) summary tables and within patient profiles. No conclusive findings are available, yet.

Clinical safety data from the pooled andexanet analysis set were evaluated by the following intrinsic factors:

- Age groups: 19 to 29 years, 30 to 39 years, 40 to 49 years, 50 to 59 years, 60 to 69 years, 70 to 79 years, where age is defined based on the date of informed consent and birth date.
- Sex: Male, Female.
- Ethnicity groups: American Indian or Alaska Native, Asian, Black or African American, Native White, Other.

Tables summarising incidence by analysis set are provided.

The initially provided safety population of 35 patients in the Phase 3b/4 study (14-505) in acutely bleeding patients was too small to support complete characterisation of AE's by race, gender or age.

Overall Summary (integrated safety population)

No clinically meaningful trends or safety concerns for TEAEs, TEAEs by severity, or TEAEs related to study drug in the pooled andexanet analysis set were identified with respect to intrinsic factors of age, gender, or race.

Ongoing 3b/4 Study 14-505 (ANNEXA-4):

The initially provided safety population in the Phase 3b/4 study (14-505) of 35 patients was too small to characterize adverse events by age, sex, or race. The full safety database of patients from ANNEXA-4 contains data from 351 patients.

Age

Adverse Events by Age Category

The incidence of subjects with ≥ 1 TEAE among age groups is shown in Table 49. In the pooled andexanet analysis set, there was no obvious trend in the incidence of subjects with ≥ 1 TEAE among age groups (range 33.3-74.3%), given the small subgroup sizes. The most common preferred term was infusion-related reaction in each age group in the andexanet analysis set. The incidence of subjects with ≥ 1 TEAE was generally similar in the pooled andexanet analysis set and pooled placebo analysis set for each age groups.

The incidence of subjects with ≥ 1 TEAE was generally similar between the combined bolus and combined bolus plus infusion analysis sets and between the dosing regimen analysis sets for each age group, given the small subgroup sizes, and no trends were observed.

Note that small samples sizes (most subgroups < 20 subjects and many subgroups < 10 subjects) results in imprecise estimates in the percentage of subjects with ≥ 1 TEAE for some subgroups.

The following table presents age-related AE-analysis: Although age-categories are slightly different and subjects are split into small patient subgroups, the pooled analysis does not point to considerable differences – at least up to the age of 69 years. Of note, AEs from healthy volunteer studies and from patients with haemorrhages are pooled which might be challenging.

Table 19 Treatment-Emergent Adverse Events by Age Category (Healthy Volunteer Studies)

	Andexanet Bolus Only			Andexanet Bolus Plus Infusion				
	400-420 mg (N=62)	600-800 mg (N=51)	Combined Bolus Only (N=113)	400-420 mg plus Infusion (N=90)	720-800 mg plus Infusion (N=88)	Combined Bolus plus Infusion (N=178)	Pooled Andexanet All Doses (N=321)	Pooled Placebo (N=114)
Number of Subjects, N1								
All Patients	62	51	113	90	88	178	321	114
19-29 Years	11	7	18	17	15	32	57	18
30-39 Years	11	6	17	24	28	52	85	25
40-49 Years	6	11	17	16	10	26	50	22
50-59 Years	11	25	36	24	24	48	84	36
60-69 Years	21	2	23	5	10	15	38	12
70-79 Years	2	0	2	4	1	5	7	1
Subjects with TEAE, n/N1(%)								
All Patients	34 (54.8%)	27 (52.9%)	61 (54.0%)	44 (48.9%)	51 (58.0%)	95 (53.4%)	174 (54.2%)	60 (52.6%)
19-29 Years	10 (90.9%)	4 (57.1%)	14 (77.8%)	10 (58.8%)	9 (60.0%)	19 (59.4%)	37 (64.9%)	8 (44.4%)
30-39 Years	6 (54.5%)	3 (50.0%)	9 (52.9%)	12 (50.0%)	19 (67.9%)	31 (59.6%)	51 (60.0%)	15 (60.0%)
40-49 Years	4 (66.7%)	8 (72.7%)	12 (70.6%)	8 (50.0%)	7 (70.0%)	15 (57.7%)	30 (60.0%)	14 (63.6%)
50-59 Years	3 (27.3%)	11 (44.0%)	14 (38.9%)	9 (37.5%)	10 (41.7%)	19 (39.6%)	33 (39.3%)	18 (50.0%)
60-69 Years	11 (52.4%)	1 (50.0%)	12 (52.2%)	3 (60.0%)	6 (60.0%)	9 (60.0%)	21 (55.3%)	5 (41.7%)
70-79 Years	0	0	0	2 (50.0%)	0	2 (40.0%)	2 (28.6%)	0

TEAE = Treatment emergent adverse event. Percentages are the proportion of patients in each age group within event.
The safety population includes all subjects randomized and treated with study medication (andexanet or placebo). The safety summary was based on integrated data from 12-502, 14-503, 14-504, 14-506, and 16-512 studies in healthy volunteers.
Study: ISS, Program: Table_3_4_7_6.sas, Output: Table_3_4_7_6.rtf, Date: 11JAN2019

(Ref: Table 2.7.4-29, Clinical Summary)

Adverse Events by Age Categotry and Severity

The incidence of subjects with ≥ 1 TEAE among age groups is shown by maximum severity (mild, moderate or severe) in Table 50. Most TEAEs were of mild severity.

There were no severe AEs in the pooled andexanet analysis set. In the pooled andexanet analysis set, the incidence of subjects with ≥ 1 moderate TEAE (range 2.9-14.3%) was lower than subjects with ≥ 1 mild TEAE (range 35.7-60%) for most age groups. In the pooled placebo analysis set, the incidence of subjects with ≥ 1 moderate TEAE (range 10.5-16.7%) was lower than subjects with ≥ 1 mild TEAE (range 40.0-57.9%) for most age groups.

In the pooled andexanet analysis set, the incidence of subjects with ≥ 1 moderate TEAE was generally similar among age groups (range 2.9-14.3%), given the small subgroup sizes, and no trends were observed. The incidence of subjects with ≥ 1 moderate TEAE was generally similar between the pooled andexanet analysis set and pooled placebo analysis set for each age group. The incidence of subjects with ≥ 1 moderate TEAE was generally similar between the combined bolus and combined bolus plus infusion analysis sets and between the dosing regimen analysis sets for each age group, given the small subgroup sizes, and no trends were observed. In the pooled andexanet analysis set, the incidence of subjects with ≥ 1 mild TEAE was generally similar among age groups (range 35.7-60%), given the small subgroup sizes, and no trends were observed. The most common preferred term was infusion-related reaction or headache in each age group in the andexanet analysis set. The incidence of subjects with ≥ 1 mild TEAE was generally similar between the pooled andexanet analysis set and pooled placebo analysis set for each age group. The incidence of subjects with ≥ 1 mild TEAE was generally similar between the combined bolus and combined bolus plus infusion analysis sets and between the dosing regimen analysis sets for each age group, given the small subgroup sizes, and no trends were observed.

Note that small samples sizes (most < 20 subjects and many < 10 subjects per subgroup) resulted in large variations in the percentage of subjects with ≥ 1 TEAE for some subgroups.

Table 20 Treatment-Emergent Adverse Events by Age Category and Severity (Healthy Volunteer Studies)

	Andexanet Bolus Only			Andexanet Bolus Plus Infusion				
	400-420 mg (N=62)	600-800 mg (N=51)	Combined Bolus Only (N=113)	400-420 mg plus Infusion (N=90)	720-800 mg plus Infusion (N=88)	Combined Bolus plus Infusion (N=178)	Pooled Andexanet All Doses (N=321)	Pooled Placebo (N=114)
Number of Subjects, N1								
All Subjects	62	51	113	90	88	178	321	114
19-29 years	11	7	18	17	15	32	57	18
30-39 years	11	6	17	24	28	52	85	25
40-49 years	6	11	17	16	10	26	50	22
50-59 years	11	25	36	24	24	48	84	36
60-69 years	21	2	23	5	10	15	38	12
70-79 years	2	0	2	4	1	5	7	1
Subjects with TEAE, n/N1 (%)								
Severe TEAEs	0	0	0	0	0	0	0	0
Moderate TEAEs								
All Subjects	3 (4.8%)	4 (7.8%)	7 (6.2%)	12 (13.3%)	7 (8.0%)	19 (10.7%)	29 (9.0%)	10 (8.8%)
19-29 years	1 (9.1%)	1 (14.3%)	2 (11.1%)	2 (11.8%)	3 (20.0%)	5 (15.6%)	7 (12.3%)	2 (11.1%)
30-39 years	0	1 (16.7%)	1 (5.9%)	4 (16.7%)	1 (3.6%)	5 (9.6%)	9 (10.6%)	4 (16.0%)
40-49 years	1 (16.7%)	2 (18.2%)	3 (17.6%)	2 (12.5%)	1 (10.0%)	3 (11.5%)	6 (12.0%)	3 (13.6%)
50-59 years	0	0	0	3 (12.5%)	1 (4.2%)	4 (8.3%)	4 (4.8%)	1 (2.8%)
60-69 years	1 (4.8%)	0	1 (4.3%)	0	1 (10.0%)	1 (6.7%)	2 (5.3%)	0
70-79 years	0	0	0	1 (25.0%)	0	1 (20.0%)	1 (14.3%)	0
Mild TEAEs								
All Subjects	34 (54.8%)	27 (52.9%)	61 (54.0%)	40 (44.4%)	50 (56.8%)	90 (50.6%)	169 (52.6%)	58 (50.9%)
19-29 years	10 (90.9%)	4 (57.1%)	14 (77.8%)	8 (47.1%)	8 (53.3%)	16 (50.0%)	34 (59.6%)	8 (44.4%)
30-39 years	6 (54.5%)	3 (50.0%)	9 (52.9%)	10 (41.7%)	19 (67.9%)	29 (55.8%)	49 (57.6%)	15 (60.0%)
40-49 years	4 (66.7%)	8 (72.7%)	12 (70.6%)	8 (50.0%)	7 (70.0%)	15 (57.7%)	30 (60.0%)	12 (54.5%)

	Andexanet Bolus Only			Andexanet Bolus Plus Infusion				
	400-420 mg (N=62)	600-800 mg (N=51)	Combined Bolus Only (N=113)	400-420 mg plus Infusion (N=90)	720-800 mg plus Infusion (N=88)	Combined Bolus plus Infusion (N=178)	Pooled Andexanet All Doses (N=321)	Pooled Placebo (N=114)
50-59 years	3 (27.3%)	11 (44.0%)	14 (38.9%)	9 (37.5%)	10 (41.7%)	19 (39.6%)	33 (39.3%)	18 (50.0%)
60-69 years	11 (52.4%)	1 (50.0%)	12 (52.2%)	3 (60.0%)	6 (60.0%)	9 (60.0%)	21 (55.3%)	5 (41.7%)
70-79 years	0	0	0	2 (50.0%)	0	2 (40.0%)	2 (28.6%)	0

TEAE = Treatment emergent adverse event. Percentages are the proportion of patients in each age group within event.
The safety population include all subjects randomized and treated with study medication (andexanet or placebo).
The safety summary is based on integrated data from 12-502, 14-503, 14-504, 14-506, and 16-512 studies in healthy volunteers.
Study: ISS, Program: Table_3_4_7_7.sas, Output: Table_3_4_7_7.rtf, Date: 14JAN2019

Adverse Events by Age Category and Relationship to Study Drug

The incidence of subjects with ≥ 1 TEAE related to study drug was similar among age groups (Table 51).

In the pooled andexanet analysis set, the incidence of subjects with ≥ 1 TEAE related to study drug was generally similar among age groups (range 15.7-45.7%), given the small subgroup sizes, and no trends were observed. The most common preferred term was infusion-related reaction in each age group in the andexanet analysis set. The incidence of subjects with ≥ 1 TEAE related to study drug was generally higher in the pooled andexanet analysis set compared to the pooled placebo analysis set for most age groups.

The incidence of subjects with ≥ 1 TEAE related to study drug was generally similar between the combined bolus and combined bolus plus infusion analysis sets and between the dosing regimen analysis sets for each age group, given the small subgroup sizes, and no trends were observed.

Note that small samples sizes (most subgroups < 20 subjects and many subgroups < 10 subjects) resulted in large variations in the percentage of subjects with ≥ 1 related to study drug was TEAE for some subgroups.

In the Phase 3b/4 Study 14-505, a total of 31 (8.8%) patients experienced at least one adverse event that was assessed as related to andexanet.

Table 21 Treatment-Emergent Adverse Events by Age Category (Bleeding Patient Studies)

	Age Category (Years)								
Number (%) Patients	19-29 N=1 (n%)	30-39 N=2 (n%)	40-49 N=5 (n%)	50-49 N=15 (n%)	60-69 N=40 (n%)	70-79 N=122 (n%)	80-89 N=136 (n%)	90-99 N=30 (n%)	Andexanet Total N=351 (n%)
All Patients									
Total Number of Patients	1	2	5	15	40	122	136	30	351
Total Number of Events	1	2	10	38	61	251	317	64	744
Number of Patients with at Least One TEAE	1 (100.0)	1 (50.0)	4 (80.0)	6 (40.0)	22 (55.0)	87 (71.3)	100 (73.5)	25 (83.3)	246 (70.1)
Related to the Study Drug	1 (100.0)	0	1 (20.0)	1 (6.7)	2 (5.0)	11 (9.0)	11 (8.1)	4 (13.3)	31 (8.8)
Thrombotic Events	0	0	0	1 (6.7)	6 (15.0)	13 (10.7)	11 (8.1)	5 (16.7)	36 (10.3)
Infusion Reactions	0	0	0	0	0	0	1 (0.7)	1 (3.3)	2 (0.6)
TEAEs Leading to Premature Discontinuation of Drug	0	0	0	0	0	0	2 (1.5)	0	2 (0.6)
Serious TEAEs	0	1 (50.0)	1 (20.0)	3 (20.0)	14 (35.0)	45 (36.9)	59 (43.4)	17 (56.7)	140 (39.9)
Serious Related TEAEs	0	0	1 (20.0)	0	2 (5.0)	6 (4.9)	5 (3.7)	2 (6.7)	16 (4.6)
Fatal TEAEs	0	0	0	0	3 (7.5)	10 (8.2)	23 (16.9)	10 (33.3)	46 (13.1)
Deaths	0	0	0	1 (6.7)	4 (10.0)	10 (8.2)	27 (19.9)	12 (40.0)	54 (15.4)

Based on data transfer from 09JUL18. All patients that received andexanet, died or completed day 30 follow-up visit are included.
Study: ANNEXA-4 (14-505), Source: Table 14.3.1.4b.rtf, Date: 14AUG2018

Gender

Adverse Events by Gender

The incidence of subjects with ≥ 1 TEAE among males and females is shown in Table 52. In the pooled andexanet analysis set, the incidence of subjects with ≥ 1 TEAE was lower among males (48%) compared to females (65

%). The most common preferred term was infusion-related reaction for both males and females in the andexanet analysis set. In the pooled placebo analysis set, the incidence of subjects with ≥ 1 TEAE among males and females was 56.1% and 60.7%, respectively.

The incidence of males and the incidence of females with ≥ 1 TEAE was generally similar between the combined bolus and combined bolus plus infusion analysis sets and between the dosing regimen analysis sets.

	Andexanet Bolus Only			Andexanet Bolus Plus Infusion				
	400-420 mg (N=62)	600-800 mg (N=51)	Combined Bolus Only (N=113)	400-420 mg plus Infusion (N=36)	720-800 mg plus Infusion (N=44)	Combined Bolus plus Infusion (N=80)	Pooled Andexanet All Doses (N=223) [a]	Pooled Placebo (N=94)
Number of Subjects, N1								
All Subjects	62	51	113	36	44	80	223	94
Male	40	30	70	26	31	57	151	66
Female	22	21	43	10	13	23	72	28
Subjects with ≥ 1 TEAE, n/N1 (%)								
All Subjects	34 (54.8%)	27 (52.9%)	61 (54.0%)	17 (47.2%)	24 (54.5%)	41 (51.3%)	120 (53.8%)	54 (57.4%)
Male	19 (47.5%)	12 (40.0%)	31 (44.3%)	12 (46.2%)	15 (48.4%)	27 (47.4%)	70 (46.4%)	37 (56.1%)
Female	15 (68.2%)	15 (71.4%)	30 (69.8%)	5 (50.0%)	9 (69.2%)	14 (60.9%)	50 (69.4%)	17 (60.7%)

TEAE = Treatment-emergent adverse event

[a] Study 11-501 (N=24 administered andexanet; N=8 placebo) was not pooled as discussed in Section 2.7.4.1.1.2.4.4.

Source: ISS Table 4.2a, ISS Table 4.2b; ISS Table 4.

Table 22 Treatment-Emergent Adverse Events by Gender (Healthy Volunteer Studies)

	Andexanet Bolus Only			Andexanet Bolus Plus Infusion				
	400-420 mg (N=62)	600-800 mg (N=51)	Combined Bolus Only (N=113)	400-420 mg plus Infusion (N=90)	720-800 mg plus Infusion (N=88)	Combined Bolus plus Infusion (N=178)	Pooled Andexanet All Doses (N=321)	Pooled Placebo (N=114)
Number of Subjects, N1								
All Subjects	62	51	113	90	88	178	321	114
Male	40	30	70	61	54	115	209	79
Female	22	21	43	29	34	63	112	35
Subjects with TEAE, n/N1 (%)								
All Subjects	34 (54.8%)	27 (52.9%)	61 (54.0%)	44 (48.9%)	51 (58.0%)	95 (53.4%)	174 (54.2%)	60 (52.6%)
Male	19 (47.5%)	12 (40.0%)	31 (44.3%)	29 (47.5%)	29 (53.7%)	58 (50.4%)	101 (48.3%)	40 (50.6%)
Female	15 (68.2%)	15 (71.4%)	30 (69.8%)	15 (51.7%)	22 (64.7%)	37 (58.7%)	73 (65.2%)	20 (57.1%)

TEAE = Treatment emergent adverse event. Percentages are the proportion of patients in each sex group within event.
The safety population include all subjects randomized and treated with study medication (andexanet or placebo).
The safety summary is based on integrated data from 12-502, 14-503, 14-504, 14-506, and 16-512 studies in healthy volunteers.
Events are counted as one per subject if more than one same event
Study: ISS, Program: Table_3_4_7_9.sas, Output: Table_3_4_7_9.rtf, Date: 11JAN2019

Adverse Events by Gender and Relationship to Study Drug

The incidence of subjects with ≥ 1 TEAE related to study drug was lower among males compared to females for both the pooled andexanet analysis set (23.2% vs. 48.6%) and the pooled placebo analysis set (16.7% vs. 39.3%). The most common preferred term was infusion-related reaction for both males and females in the andexanet analysis set.

Race

Adverse Events by Race

The incidence of subjects with ≥ 1 TEAE is shown for each race group in Table 2.7.4-35. In the pooled andexanet analysis set, the incidence of subjects with ≥ 1 TEAE was generally similar among race groups, given the small subgroup sizes, and no trends were observed. The most common preferred term was infusion-related reaction for each race (except American Indian or Alaska native) in the andexanet analysis set. The incidence of subjects with ≥ 1 TEAE was generally similar in the pooled andexanet analysis set and pooled placebo analysis set for each race groups. The incidence of subjects with ≥ 1 TEAE was generally similar between the combined bolus and combined bolus plus infusion analysis sets and between the dosing regimen analysis sets for each race group, given the small subgroup sizes, and no trends were observed. Note that small samples sizes (most subgroups < 10 subjects) resulted in large variations in the percentage of subjects with ≥ 1 TEAE for some subgroups.

Pregnancy and Lactation

Andexanet is an emergency use treatment for patients experiencing a major bleeding episode while on an anti-fXa medication. No human or animal studies have investigated the potential effects of andexanet during pregnancy and lactation.

No pregnant subjects were enrolled. One woman experienced a transient chemical pregnancy after participating in the study, an event which was labeled “spontaneous abortion”. The Principal Investigator considered this AE possibly/probably related to study drug. No other subjects became pregnant during any andexanet clinical study.

Immunological events

Analytical methods:

An electrochemiluminescence method was developed and validated under GLP conditions in order to detect and quantify antibodies against andexanet (NC-15-0643-R0001). Screening for antibodies was conducted in 3 stages. Plasma samples that had a positive result in the initial assay were tested in a confirmatory assay in which the degree of inhibition of the response after the addition of a high concentration of the protein in question was measured. The initial cut point (baseline signal) above which samples were deemed to be positive was a floating cut point based on the baseline from negative control samples in a particular set. This cut point could vary significantly from plate-to-plate. The second step, confirmation, required that the signal decrease by 36% (or greater) in the presence of an excess of andexanet. Confirmation for antibodies against fX and fXa required larger decreases of 51.8% and 65.9% in the signals in the presence of excess of levels of the two proteins, respectively. The last step in the initial 3-step process was measurement of the titre in which the abundance of the antibody was estimated by determining the number of serial 2-fold dilutions required to decrease the signal to below the established cut point. An additional assay was conducted on all samples from subjects for whom antibodies against andexanet were confirmed. Samples from these subjects were tested for the presence of neutralising antibodies (i.e., antibodies that interfere with the functional activity of andexanet) (NC-15-0620-R0001 and NC-15-0621-R0001).

Study 11-502:

None of the subjects receiving andexanet or placebo had positive results for antibodies to andexanet, fX, or fXa.

Study 14-506:

No subjects developed antibodies to fX or fXa. Three subjects developed low-titer non-neutralizing antibodies to andexanet.

Study 12-502

Samples were collected to test for antibodies to test article (ATA) (i.e., andexanet), fX, and fXa at 4 time points.

No subject developed antibodies to fX, or fXa. Two subjects developed low-titer non-neutralizing antibodies to andexanet in Module 1.

In Module 3, Antibodies to andexanet were detected and confirmed in 4 subjects [210 mg (L)] on Day 34: Subject (titer was below the minimum required dilution of 1:10 and is reported as MRD), Subject (Day 34 [1:10 titer]), Subject (1:40 titer) and Subject (titer was below the minimum required dilution of 1:10 and is reported as MRD); in 1 subject on Day 48: Subject (210 mg (L), 1:640 titer). However, functional activity testing of andexanet antibody (i.e., effect on anti-fXa with vs. without andexanet) for Subjects confirmed a lack of neutralizing activity towards andexanet.

Study 14-503

Antibody testing: Confirmed antibodies to fX or to fXa were not present in any subjects in Part 1 or Part 2.

Antibody testing was performed for anti-andexanet, anti-fX, and anti-fXa antibodies. None of the detected antibodies were considered to be neutralizing.

In Part 1, 3/25 (12.0%) subjects in the andexanet group had anti-andexanet antibodies, in Part 2, 7/24 (29.2%) subjects in the andexanet group had anti-andexanet antibodies.

Study 14-504

Antibody testing: Confirmed antibodies to fX or to fXa were not present in any subjects in Part 1 or Part 2.

Antibody testing was performed for anti-andexanet, anti-fX, and anti-fXa antibodies. None of the detected antibodies were considered to be neutralizing.

In Part 1, 4/27 (14.8%) subjects in the andexanet group had anti-andexanet antibodies detected, in Part 2, 2/26 (7.7%) subjects in the andexanet group had anti-andexanet antibodies.

Study 14-505:

Antibody testing was performed for anti-andexanet, anti-fX, and anti-fXa antibodies.

As per interim analysis provided during the procedure (data cut July 09, 2018) 345 andexanet alfa-treated healthy subjects were tested for antibodies cross reacting with andexanet alfa and antibodies to factor X and FXa. Treatment-emergent, non-neutralizing antibodies to andexanet alfa were detected in approximately 10% (35/345). These antibodies were generally low titre, and no clinical consequences were observed. No neutralising antibodies or antibodies to factor X or FXa were detected. To date, the occurrence of positive, non-neutralizing antibodies to andexanet alfa following

treatment in patients in the ANNEXA-4 study (8.5% or 20/236 patients) has been similar to that observed in healthy subjects.

Safety related to drug-drug interactions and other interactions

No human or animal studies have investigated the potential effects of drug-drug, or food-drug interactions with andexanet.

Discontinuation due to adverse events

Study 14-503

There was 1 subject in the andexanet group in Part 2 who prematurely discontinued study drug because of an AE (subject, urticaria). Overall incidences of TAEs did not show any signals.

Study 14-504

In Part 2, there were 2 subjects, both in the andexanet treatment group, who did not complete the study: Subject withdrew from the study on Day 33, and Subject was lost to follow-up Study Day 15.

2.4.10. Discussion on clinical safety

Studies 11-501, 14-506, 12-502, 14-503 and 14-504

In the study population of healthy volunteers, andexanet doses were well tolerated, and there were no significant safety findings. No deaths, serious adverse events, severe adverse events, adverse events resulting in early termination, thrombotic events or major bleeding events occurred during the study. The overall incidence of adverse events was higher in placebo subjects than in the active groups, and there was no apparent dose-response relationship for any adverse event.

Infusion-related reactions were observed in all studies and considered to be possibly/probably related to andexanet. Infusion-related reactions generally resolved without treatment.

No adverse events of venous thromboembolism were reported following treatment with andexanet in healthy volunteers.

Studies 14-503 and 14-504:

Evaluation of adverse events is mainly reduced to AEs “related” to andexanet. Potential allergic symptoms (including e.g. flushing, urticaria, all kinds of “rashes”, face edema, itching etc) and gastrointestinal symptoms (including taste and smell disturbance) are considered to be noticable. However, in the context of the target population receiving andexanet only once, these symptoms are considered to be of minor relevance.

Rise of D-Dimers and prothrombin fragments F1+2 is considered to reflect a significant finding of this study as it points to coagulation activation. For diagnosis of deep vein thrombosis (DVT), pulmonary embolism (PE) or disseminated intravascular coagulation (DIC) elevations above 500µg/l are taken as significant. Although not all of the subjects show an increase, others do have significant and clinically meaningful elevations.

Changes of vital signs (Blood pressure, Heart Rate) are considered to be noticeable for the andexanet group. However, clinical relevance is considered to be low.

Study 14-505

Update of the safety analysis has been provided:_Of the 351 patients in the Safety Population (N=352) who completed the 30-day safety follow up, a total of 744 Treatment-Emergent Adverse Events (TEAEs) were reported by 246 (70.1%) patients (Section 12.2.2). Rate of TEAES were similar with Andexanet generation 1 and 2.

There were 54 deaths (15.4%). The numbers of cardiovascular and non-cardiovascular deaths were each 27 (50.0% of the total deaths each).

In post hoc subgroup analyses, there were significant higher mortality rates in elderly patients >75 yrs (20.1% vs. 7.5% in patients aged <75 yrs) and in patients recruited in the European Union (22.1% vs. 10.9% in patients recruited in North-America). The higher mortality rate according to age is not unexpected; reason for significant difference between geographical regions remains open.

In interim analysis of ANNEXA-4 (submitted 13 November 2018 [data cut July 09, 2018]), there were 42 thromboembolic events (TE) identified in 351 patients from ANNEXA-4 study. Identified factors which might contribute to TEs are high-dose versus low-dose andexanet (14.8% vs 9.4%), lower dose anti-coagulant treatment, and patients on rivaroxaban vs apixaban (11.0% vs 8.2). Risk of thrombosis in view of not established posology and increased laboratory markers for thrombosis (D-Dimers, F1+F2, TAT) from healthy volunteers justifies recommendation of re-anticoagulation as soon as possible. Further clinical evaluation of these findings was considered necessary and it will be done as part of the assessment of data to be provided as specific obligations in the context of conditional MA.

Results on CHO-antibody testing do not show increased risk. However, data-base is limited and requires extension. 345 andexanet alfa-treated healthy subjects were tested for antibodies cross reacting with andexanet alfa and antibodies to factor X and FXa. Treatment-emergent, non-neutralizing antibodies to andexanet alfa were detected in approximately 10% (35/345). These antibodies were generally low titre, and no clinical consequences were observed. No neutralising antibodies or antibodies to factor X or FXa were detected. To date, the occurrence of positive, non-neutralizing antibodies to andexanet alfa following treatment in patients in the ANNEXA-4 study (8.5% or 20/236 patients) has been similar to that observed in healthy subjects.

There have been no reports of medication errors during the clinical trial programme. Risk of medication errors is considered to be low as andexanet alfa is reconstituted and prepared by a healthcare professional/pharmacist in a hospital setting.

The potential for off label use was acknowledged. The typical population on fXa inhibitors is comprised of adults (which is the primary target population) not children, or women who are pregnant or currently lactating. The prescribing information clearly outlines that there are potential risks to children, pregnant or lactating females, and their respective offspring, since these groups of individuals have not been studied. Situations where the product could intentionally be used outside the authorised indication have been adequately reflected in the RMP. To minimize the potential off-label use in patients treated with anticoagulants other than as indicated, routine risk minimisation measures were put in place. Target population is clearly reflected in the agreed SmPC (Sections 4.1, 4.2, 4.4 and 5.1) including respective warnings. It is indicated that andexanet alfa is not suitable for pre-treatment of urgent surgery, use for edoxaban- or enoxaparin-reversal is not recommended due to lack of data and that andexanet alfa will not reverse the effects of non-FXa inhibitors. Restricted medical prescription applies.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Additional safety data needed in the context of a conditional MA.

The CHMP considered that for the development to be considered comprehensive additional safety (and efficacy) data in bleeding patients will need to be provided and the applicant committed to submit it as part of specific obligations the full clinical data from ANNEXA-4 study and further clinical data from RCT in patients with ICH (see Conclusions on the clinical safety).

2.4.11. Conclusions on the clinical safety

Incidence of thromboses and thromboembolic events is considered to be relevant and requires additional clinical evaluation. Noticeable safety data from healthy volunteers are “infusion-related-reactions”, significant rise of D-dimers and prothrombin fragments F1+2 and development of ADAs. Relevance for the target population and identified risk factors (high-dose andexanet, previous anticoagulant, and previous lower-dose anticoagulant) was considered as subject to further evaluation in post-authorisation phase as part of the specific obligations.

Timing and dosage for re-introduction of anticoagulation after andexanet remains challenging, as available laboratory understanding mainly derives from healthy volunteers. Preliminary evaluation in the target patient group points to a recommendation of early re-anticoagulation, especially for Gen-2 andexanet. Further clinical data were considered to be necessary and are to be provided post-authirisation as part of specific obligations.

The CHMP considers the following measures necessary to address the missing safety data in the context of a conditional MA:

(Specific Obligation 1) In order to further substantiate correlation of the biomarker (antiFXa-activity) with haemostatic efficacy and clarify the risk of thromboses and thromboembolic events, the MAH should submit the results of ANNEXA-4, an interventional non-randomized, multicentre, prospective, open-label, single-group study in patients with acute major bleeding.

(Specific Obligation 2) In order to further confirm the posology of Ondexxya, the MAH should submit the results of a comparative PK study with Generation 1, process 3, and Generation 2 material (study 19-514). The study should be based on an agreed protocol.

(Specific Obligation 3) In order to substantiate correlation of the biomarker (antiFXa-activity) with haemostatic efficacy and clarify the risk of thromboses and thromboembolic events, the MAH should submit the results of a global randomised controlled clinical trial to investigate the use of andexanet versus standard of care treatment in patients with intracranial haemorrhage (ICH) taking apixaban, rivaroxaban, or edoxaban (study 18-513).

(Specific Obligation 4) In order to further confirm the efficacy and safety, the MAH should submit an updated PK/PD model using all previously incorporated data (from studies 11-501, 12-502, 14-503, 14-504, and 14-506) as well as newly incorporated data from study 16-512 (PK-PD study of Generation 2 andexanet versus Generation 1), study 16-508 (PK-PD study of andexanet in individuals of Japanese ethnicity), and study 14-505 (ANNEXA-4).

2.5. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Thrombotic events Antibody formation
Important potential risks	Medication error Off-label use in patients treated with anticoagulants other than as indicated Re-bleeding
Missing information	Use in patients who receive (pre-treatment) vitamin K antagonist, PCC products, recombinant FVIIa, whole blood or plasma fractions; or planned administration of these products within 12 hours of andexanet alfa treatment Use in pregnant or lactating patients Use in children

Pharmacovigilance plan

Study/status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 2 - imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Prospective open-label study ANNEXA-4 (14-505) Ongoing *	To confirm safety and efficacy in patients with acute major bleeds	Thrombotic events Antibody formation Re-bleeding	Interim study reports Final study report	August 2016, September 2017, January 2018 and September 2018 30 June 2019

Study/status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Randomised Controlled Trial (18-513) Planned	This study aims to evaluate the safety and effect of andexanet versus usual care in oral FXa inhibitor-treated patients with acute intracranial bleeding	Thrombotic events Antibody formation Re-bleeding	Protocol submission Enrolment begins Interim study reports Blinded pooled data) in DSUR/PSURStudy complete Final study report	18 February 2019 31 March 2019 DSUR Annually PSUR every 90 days 31 December 2022 30 June 2023
Bioequivalence PK Study 19-514 Planned	To evaluate the PK comparability of Generation 1 process 3 andexanet and Generation 2 andexanet	Thrombotic events Antibody formation Re-bleeding	Protocol submit to CHMP Enrolment begins Study complete Final study report	31 March 2019 30 June 2019 30 June 2019 30 September 2019
PK Modeling Update	PK/PD model using all previously incorporated data (from studies 11-501, 12-502, 14-503, 14-504, and 14-506) as well as newly incorporated data from study 16-512 (PK-PD study of Generation 2 andexanet versus Generation 1), study 16-508 (PK-PD study of andexanet in individuals of Japanese ethnicity), and study 14-505 (ANNEXA-4).	None	Final Modeling Report	30 September 2019
Category 3 – required additional pharmacovigilance activities				
Paediatric Protocol Planned	Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of Andexanet in Paediatric Patients Undergoing an Elective Invasive Procedure or Surgery Following Enoxaparin Treatment	Use in children	Protocol submission Interim study updates in DSUR/PSUR Final study report	31 December 2019 Annually 30 June 2025

* Study 14-505 is considered complete, though an extension to accrue additional patients taking edoxaban and Japanese patients has been initiated

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Thrombotic events	Routine risk minimisation measures: – SmPC sections 4.2, 4.4, 4.8, and 5.1 – PL section 4 Re-introduction of anticoagulation treatment recommendation provided in SmPC section 4.4 Restricted medical prescription	Additional pharmacovigilance activities: – prospective open-label study ANNEXA-4 (14-505) – randomised controlled trial (18-513) – Bioequivalence PK Study 19-514
Antibody formation	Routine risk minimisation measures: – SmPC section 5.1 – PL section 4 Restricted medical prescription	Additional pharmacovigilance activities: – prospective open-label study ANNEXA-4 (14-505) – randomised controlled trial 18-513 – Bioequivalence PK Study 19-514
Medication error	Routine risk minimisation measures: – SmPC sections 4.2, 4.9, and 6.6 – PL section 3 Restricted medical prescription	Additional pharmacovigilance activities: – None
Off-label use in patients treated with anticoagulants other than as indicated	Routine risk minimisation measures: – SmPC sections 4.1, 4.2, 4.4, and 5.1 – PL sections 1 and 2 Restricted medical prescription	Additional pharmacovigilance activities: – None
Re-bleeding	Routine risk minimisation measures: – SmPC section 4.2 – PL section 3 Restricted medical prescription	Additional pharmacovigilance activities: – prospective open-label study ANNEXA-4 (14-505) – randomised controlled trial 18-513 – Bioequivalence PK Study 19-514
Use in patients who receive (pre-treatment) vitamin K antagonist, PCC products, recombinant FVIIa, whole blood or plasma fractions; or planned administration of these products within 12 hours of andexanet alfa treatment	Routine risk minimisation measures: – SmPC section 4.4 Restricted medical prescription	Additional pharmacovigilance activities: – None
Use in pregnant or lactating patients	Routine risk minimisation measures: – SmPC sections 4.6 and 5.3 – PL section 2 Restricted medical prescription	Additional pharmacovigilance activities: – None
Use in children	Routine risk minimization	Additional pharmacovigilance

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	measures: SmPC section 4.2 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Breastfeeding should be discontinued as stated in SmPC section 4.6 Restricted medical prescription	activities: - Paediatric Study

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 03.05.2018. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.7. New Active Substance

The applicant declared that andexanet alfa has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers andexanet alfa to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

The QRD Group accepted to have only the minimum particulars printed on the vial label (20 ml) based on the fact that this product is to be used in hospital only. The QRD Group requested to have the storage conditions printed on the vial as it does not have to be stored in the outer carton. In order to fit the latter information, omission of reference to the package leaflet as well as MAH details and MA number were suggested.

2.8.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Ondexxya (andexanet alfa) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU and is approved under a conditional marketing authorisation.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Target population for andexanet alfa includes patients needing reversal of a FXa inhibitor due to a severe/life-threatening bleeding. As per initially applied indication the target population also included patients in need of urgent surgery/procedure.

Severe/life-threatening bleeding comprises about half of all major bleedings and occurs at yearly rate of 1-2% with the DOACs and warfarin in patients with atrial fibrillation (AF). Based on data available from the idarucizumab study, approximately 90% of severe bleedings with DOACs will occur in the AF indication and 10% in other indications (i.e.: mainly VTE), while the localisation of the severe bleeding will be intracranial in 40% of cases, gastrointestinal in another 40% of cases, 10% will occur in trauma patients and 10% in other localisations (i.e.: retroperitoneal, pericardial, etc). Given that LMWHs and fondaparinux are not used in AF, severe bleedings with these compounds will mainly occur during thromboprophylaxis in surgical patients, as well as with the use of high doses in the context of treatment of VTE and acute coronary syndromes (ACS). The localisation of the severe bleeding will depend on the indication, with most cases being excessive wound bleedings in surgical patients and intracranial and/or gastrointestinal in patients with VTE or ACS.

With respect to the second part of the initially applied indication, annually 10% of patients taking antithrombotic agents undergo surgery/procedure that requires temporary discontinuation of therapy. Only 1 in 10 surgeries/procedures is considered to be urgent. In anticoagulated patients who have an urgent surgery/procedure, rates of thromboembolism range between 7% and 16%, rates of major bleeding between 17% and 23%, and mortality rate between 2%-6%. Rates of these outcomes are multi-fold higher in patients having an urgent rather than an elective surgery/procedure.

3.1.2. Available therapies and unmet medical need

Various new oral anticoagulants have been marketed in the last decade: The direct thrombin inhibitor dabigatran etexilate, and the direct inhibitors of activated factor X (FXa) rivaroxaban, apixaban and edoxaban. These direct oral anticoagulants (DOAC) are authorized for use in various indications related to the prophylaxis and treatment of VTE and the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF). The relatively short half-life of DOACs (between 11 and 17 h in patients with normal renal function) can be seen as an advantage in case of bleeding, as their anticoagulant activity quickly decline between 12 and 24 h after their administration. However, the absence of a specific antidote and well as standardized tools for the measurement of the anticoagulant effect in any emergency laboratory has caused some concern. Current treatment of bleeding associated with DOAC is based on the interruption of antithrombotic medication and the establishment of supportive care (local haemostasis, transfusion, activated charcoal, dialysis in the case of dabigatran, etc.). In the absence of specific antidotes, unspecific procoagulant agents have been used (prothrombin complex concentrates and recombinant factor VIIa) in the case of severe bleeding, but without approval in this indication. Mortality after severe bleeding with DOAC, although not being higher than with VKA remains significant, ranging between 10% for non-intracranial severe bleeding to 35–50% for ICH. Therefore, up to now, the availability of an antidote for direct FXa inhibitors is an unmet medical need.

The unmet clinical need holds also true for the indirect FXa inhibitor fondaparinux. Overdose associated with bleeding complications should lead to treatment discontinuation and initiation of supportive therapy (surgical haemostasis, blood replacements, fresh plasma transfusion, plasmapheresis). Routine coagulation tests cannot be used to determine the degree of anticoagulation, making it more challenging to determine when the anticoagulant effect has resolved. For enoxaparin, the more widely prescribed LMWH, the anticoagulant effects can be largely neutralised by protamine, but even with high doses of protamine, the anti-Xa activity of enoxaparin sodium is never completely neutralised (maximum about 60%). Decisions regarding the necessity and dose of subsequent protamine injections should be based on clinical response rather than measurement of anti-Xa or anti-IIa results.

In summary, andexanet would be an addition to the available treatment options for bleeding events in patients treated with DOACs and fondaparinux. The unmet clinical need is less robust for neutralisation of LMWHs, for which an antidote (protamine) already exists. Of note, a further molecule (ciraparantag) is under development which is intended to monovalently bind to NOACs.

3.1.3. Main clinical studies

PK and PD of andexanet were investigated in the following 3 studies:

- Study 11-501:
    - This first-in-human Phase 1 study (11-501) evaluated the safety, tolerability, PK, and PD properties of andexanet alfa in healthy human subjects. The study was a single centre, double-blind, randomised, placebo-controlled, ascending, single-dose study of andexanet or its matching placebo.
- Study 12-502:
    - The ability of andexanet to reverse the anticoagulation of fXa inhibitors was evaluated in a PK-PD study in healthy subjects. The study was conducted in separate modules for each fXa inhibitor: apixaban (Module 1), rivaroxaban (Module 2), enoxaparin (Module 3), or edoxaban (Module 4).

- Study 14-506:
    - This study compared the PK and PD of andexanet administered to healthy elderly vs. younger healthy subjects anticoagulated with apixaban.

Clinical data from Study 12-502 was used to develop a PK-PD model that provided the basis to select a dosing regimen for reversal of anticoagulation for all direct fXa inhibitors. The mechanistic PK-PD model for direct fXa inhibitors has been further expanded and specifically adapted to rivaroxaban data and literature-based covariates. This model was further expanded for apixaban but the model was considered insufficient to reliably predict PK-PD and dosing recommendations for edoxaban. No modelling exercise provided information that would allow for selection of the andexanet dose to reverse anticoagulation due to administration of low molecular weight heparins such as enoxaparin. Dose selection was solely based on historical literature around the PK of enoxaparin and the known pharmacology of indirect FXa inhibitors.

Efficacy

Two phase 3 studies in healthy volunteers have been submitted: study 14-503 regarding apixaban and study 14-504 regarding rivaroxaban (14-504). They were considered as pivotal efficacy studies in the current applicationThese pivotal studies were conducted according to similar protocols. Study 14-505 (ANNEXA-4), currently the only study in patients, should validate the results.

- Study 14-503
    - This single-site, randomized, double-blind, placebo-controlled, Phase 3 study evaluated the safety and efficacy of andexanet in reversing apixaban-induced anticoagulation in healthy volunteers, ages 50 to 68 years. Efficacy was evaluated using biomarker endpoints, with anti-fXa levels as the primary efficacy measure. Secondary endpoints included plasma levels of free unbound apixaban and ETP, a measure of thrombin generation.
- Study 14-504
    - This study was similarly designed as study 14-503 with respect to rivaroxaban.

In addition, during the procedure, study 16-512 was provided.

- Study 16-512
    - Phase 1 randomized double blind, placebo-controlled study to evaluate the pharmacokinetics, safety, and tolerability of 2nd generation andexanet alfa administered to healthy subjects.

Main phase 3b/4 study in patients, study 14-505 (ANNEXA-4) was ongoing at the time the marketing authorisation procedure started. The data from the interim analysis were submitted during the procedure (dated 13 November 2018 [data cut-off: July 09, 2018]):

- Study 14-505
    - This is a multicenter, prospective, open-label study of andexanet in patients presenting with acute major bleeding who have recently received one of the following fXa inhibitors: apixaban, rivaroxaban, or enoxaparin. The two primary endpoints were: a) percent change in anti-FXa activity from baseline to the nadir between five minutes after the end of the bolus up until the end of the infusion; and b) rate of good or excellent (compared to poor or none) haemostatic efficacy within 12 hours after infusion, as rated by an independent endpoint adjudication committee ..

3.2. Favourable effects

- Phase 2 study 12-502: The effect of andexanet alfa in reversing the anticoagulant effect of three direct and one indirect fXa-inhibitor has been investigated in a pharmacokinetic (PK)/pharmacodynamics (PD) study in 154 healthy subjects. The subjects were pre-treated with the appropriate anticoagualant to steady state over 5 to 6 days. Subsequent administration of andexanet alfa led to an immediate, dose-dependent decrease in unbound direct fXa-inhibitor plasma concentrations. The decrease occurred within 2 minutes after the end of bolus dose. Simultaneously, there was a dose-dependent increase in total fXa-inhibitor concentration. The duration of decrease in unbound fXa-inhibitor plasma concentrations was dose- and dose-regimen dependent with the longest duration of effect observed when andexanet was administered as a bolus followed by an infusion. The reversal of anti-fXa activity correlated with normalisation of thrombin generation in a dose and dose regimen-dependent manner for all three direct fXa inhibitors. For apixaban a dose of 420 mg followed by a 4 mg/min infusion restored all subjects to baseline levels of thrombin generation and that restoration was maintained throughout the duration of the infusion. For rivaroxaban an 800 mg andexanet bolus followed by an 8 mg/min infusion restored and maintained thrombin generation to/at pre-baseline levels for the duration of the infusion. Thrombin generation was restored to baseline levels for both edoxaban cohorts administered 800 mg andexanet and the follow-on 8 mg/min infusion maintained the same level of thrombin generation during the 60 minute infusion. For the indirect fXa-inhibitor enoxaparin, administration of andexanet also resulted in a rapid (i.e., within 2 minutes after the end of bolus dose) decrease in anti-fXa activity relative to baseline values (maximum ~70%) in each active group. A prolonged restoration of thrombin generation starting immediately (within 2 minutes post bolus dose) and extending for 2-3 hours following the bolus dose was observed. In the pooled placebo subjects, mean thrombin generation levels were restored at approximately 2.0 hours after the bolus dose, following plasma clearance of enoxaparin.

- Phase 3 Study 14-503: This randomised, double-blind, placebo-controlled trial in healthy volunteers anticoagulated with apixaban demonstrated that andexanet (400 mg IV bolus) rapidly sequestered the unbound fXa inhibitor apixaban, thus reversing the anticoagulant effect of fXa inhibition, restoring thrombin generation, and normalising haemostasis. Following the bolus in Part 1, anti-fXa activity immediately decreased to sub-therapeutic levels, but then increased over time, returning to levels observed in the placebo group within 180 minutes post bolus. In Part 2, reversal of anticoagulation following the bolus was maintained during a continuous infusion of 4 mg/min over 120 minutes. Following the end of the infusion, anti-fXa activity increased over time, returning to levels observed in the placebo group within 300 minutes post infusion. Furthermore, thrombin generation was restored to and remained within the normal baseline range for all time points after the end of the infusion, i.e., through 24 hours up to 40 days.

- Phase 3 Study 14-504: This randomised, double-blind, placebo-controlled trial in healthy volunteers anticoagulated with rivaroxaban demonstrated that andexanet (800 mg IV bolus) rapidly sequestered the unbound fXa inhibitor, thus reversing the anticoagulant effect of fXa inhibition, restoring thrombin generation, and normalising haemostasis. Furthermore, reversal of anti-fXa activity was maintained during a continuous infusion of 8 mg/min over 120 minutes (but increased to placebo levels afterwards). Thrombin generation was restored to and remained within the normal baseline range for all time points after the end of the infusion, i.e., through 24 hours up to 40 days.

- Phase 3b/4 study 14-505 (ANNEXA-4): In the the preliminary report of this cohort study (data cut July 09, 2018) in 352 patients with acute major bleeding associated with the use of factor Xa inhibitors, andexanet rapidly reversed anti–factor Xa activity. For the efficacy population, the median decrease from baseline to nadir in anti-FXa activity observed for rivaroxaban was

-92.0% (95% CI -94.1%, -88.0%) and for apixaban was -93.1% (95% CI -94.2%, -91.6%). Of the 167 efficacy-evaluable patients, 159 patients were evaluable for haemostatic efficacy, of whom 133 patients (83.6%) were assessed as having excellent (113 patients) or good (20 patients) haemostasis by the endpoint adjudication committee.

In summary, the studies 14-503 and 14-504 taken together, indicate that andexanet, at the dosing tested, is effective for reversal of anti-Xa activity of apixaban and rivaroxaban and restoration of thrombin generation. In addition, in the ongoing uncontrolled study ANNEXA-4, there was a 92% change (decrease) in anti-Xa activity after the administration of andexanet compared to baseline levels. The results of the preliminary evaluation of the ongoing study in the respective patient population suggest a potential favourable effect of andexanet alfa with regards to restoration of haemostasis. Effective hemostasis was achieved 12 hours after an infusion of andexanet in approximately 80% of the patients, irrespectively of the anticoagulant neutralised (apixaban, rivaroxaban or enoxaparin).

3.3. Uncertainties and limitations about favourable effects

Biomarker

It remains unclear which level of decrease in anti-fXa activity and unbound fraction of the direct inhibitor (apixaban, rivaroxaban) is necessary to reverse the effect of fXa-inhibitor. Therefore, the clinical relevance of these thresholds regarding dosage and clinical outcome remains open. Similar to the rapid decrease, an increase of anti-fXa activity is observed within 30 minutes or immediately after stopping of infusion. The increase after infusion comes up to an anti-fXa activity level which is higher than the placebo level, in the sense of a “rebound” effect. The clinical relevance of this effect with respect to the unknown therapeutic level of anti-fXa activity remains open.

The following biomarkers (surrogates) were chosen and studied: anti-fXa-levels, thrombin generation (“ETP”) and unbound NOAC-levels. However, a reliable surrogate parameter has not ben identified: target anti-fXa-level, nadir value, extent of reduction, percentage or absolute reduction, difference in influence between different FXa-inhibitors, baseline anti-fXa-activity – might all be relevant. In addition, laboratory testing in patients remains challenging.

Although in patients with major bleeds (based on ANNEXA-4), clinical outcome and surrogate have been evaluated, convincing correlation between t the biomarker of anti-FXa-activity and haemostatic efficacy was not established. According to current publications, determination anti-FXa-levels in emergency situations is increasingly recommended for patients on DOACs. However, dosage recommendation of andexanet cannot presently adequately address such levels.

Relevant anti-TFPI (tissue factor pathway inhibitor) effects correlate with D-dimer, F1+F2, and TAT-increase, and point to a general pro-coagulative effect of andexanet.

Posology

Dosage-recommendation for apixaban and rivaroxaban is based upon PK-PD modelling. However, presented PK-PD modelling and validation is still inconclusive showing differing results for apixaban and rivaroxaban.

Comparison of both PK-PD models and simulations indicate a differential ability of andexanet to reduce the anti-FXa activity evoked by the respective fXa inhibitor rivaroxaban or apixaban. There is a trend of higher reduction in anti-FXa activity evoked by apixaban compared to rivaroxaban. This is already indicated in the differential dose of andexanet bolus needed to reduce unbound fXa of apixaban and rivaroxaban. Regarding model-based justification of the envisaged posology, simulations indicate that

600 mg bolus and 6 mg/min for 120 min infusion rate might be sufficient to achieve 90% reduction of anti-FXa activity regarding the higher dosing group in case of apixaban. On the other hand, an andexanet slow infusion dose of 8 mg/min might not be sufficient to achieve comparable reduction in anti-FXa activity in case of rivaroxaban. Simulations showed that with proposed dosage, anti-FXa activity of 80% of simulated patients treated with rivaroxaban would be reduced by 70% whereas the anti-FXa activity of 80% of simulated patients treated with apixaban would be reduced by 90%. In addition, the actual degree of reversal required to restore hemostasis in bleeding patients is yet unknown. This is of particular importance as andexanet high dose is to be administered in case of unknown last dose or kind of fXa inhibitor (apixaban or rivaroxaban). Full data from the study ANNEXA-4 will be needed to address this issue and to further confirm the selection and identification of covariates on fXa inhibitor and PK in the respective PK-PD models.

Preliminary model validations were conducted using a subset of data collected from study 14-505 as well as data from healthy subjects from study 16-512. Provided validation with patient data indicates an over-prediction of the magnitude of anti-fXa activity reversal after apixaban administration (bolus and infusion) and rivaroxaban (bolus) and over-prediction of the lower border of the 90% CI. Data from 16-512 were considered to be of greater variability than expected and the failed PK comparison of Generation 1 and Generation 2 andexanet adds further uncertainty. Preliminary validation with data from 16-512 indicates that the median and the 90% CI were similar and large, but an under-prediction of anti-fXa activity reversal for the rivaroxaban model at end-of-infusion (EOI) and an over-prediction at 1.5 hours post EOI, when the observed versus predicted anti-fXa activity reversal for rivaroxaban and apixaban was compared.

However, results and validation could not be assessed properly due to missing information regarding andexanet PK model and PK/PD modelling. No re-estimated model parameters or information about PK and PD data update have been provided.

As the andexanet PK model and PK/PD final model development for apixaban and rivaroxaban is still ongoing and the update and proper validation with data from healthy subjects (16-512) and with patient data (14-505) is in most parts preliminary, the concerns regarding the uncertainties in the proposed andexanet posology for reversing anti-fXa activity remain.

The proposed dosage-recommendation for edoxaban were not based upon the PK-PD model as PK-dataset are currently insufficient. The applicant decided for a lower dose (800mg bolus + 480mg c.i.) than theoretically calculated and assumes 75% decrease of anti-fXa-activity to be acceptable – as 2 healthy subjects on that dose responded positively. Adequate PK/PD-modelling (distinct models for each fXa inhibitor) and clinical confirmation remain open. Therefore edoxaban was removed from the final approved indication.

Enoxaparin PK/PD data have not been presented. The chosen primary endpoint of anti-fXa-activity is considered to be challenging as there is no validated assay for unbound enoxaparin and consequently no documented correlation of unbound enoxaparin and anti-fXa-levels. As, consequently, no threshold for an effect of andexanet is available, clinical efficacy of andexanet for enoxaparin-treated patients cannot be demonstrated. Therefore also enoxaparin was removed from the final approved indication.

Timing and dosage for re-introduction of anticoagulation after andexanet remains challenging as available laboratory understanding and PK/PD modelling derives from healthy volunteers and may not be transferred to the target population. However, preliminary analyses from ANNEXA-4 suggest early re-introduction of anticoagulation. The SmPC recommends antithrombotic therapy can be re-initiated as soon as medically indicated following treatment if the patient is clinically stable and adequate haemostasis has been achieved. Medical judgement should balance the benefits of anticoagulation with the risks of re-bleeding.

The contradictory findings of a short-term neutralisation of anti-Xa activity and a more prolonged effect, the increase in pro-thrombotic coagulation markers (i.e.: D-dimer and prothrombin F1+2), rapid and sustained restoration of thrombin-generation, and the pro-coagulatory effect of anti-TFPT-activity raises concerns about what is the optimal dose and treatment duration. Furthermore, dosage recommendations are based upon elapsed time and dose of DOAC in healthy volunteers and are not corresponding with the target population. As the PK/PD-modelling will be further developed, dosage recommendation might be adapted in the future and further clinical data are considered to be necessary. This was agreed to be provided as part of specific obligations.

The clinical effect of andexanet alfa therapy on reduction in morbidity or mortality (most notable bleeding complications) remains uncertain. The ongoing during the initial MAA Phase III b/ IV study ANNEXA-4 was not designed to detect a difference between andexanet treatment and a comparator population. The safety and efficacy of adexanet will be further studied in randomised controlled clinical trial to investigate the use of andexanet versus standard of care treatment in patients with intracranial haemorrhage (ICH) taking apixaban, rivaroxaban, or edoxaban (study 18-513). The results of these investigations will be provided as part of specific obligations.

The andexanet data in patients (ANNEXA-4) are mainly limited to treatment of life-threatening bleeding associated to rivaroxaban and apixaban, while very few data are available for enoxaparin and edoxaban and no data are available in this part of the indication for fondaparinux. In addition, no clinical data at all are available with andexanet in patients undergoing urgent surgery/invasive procedures. The uncertainties listed above led to the restriction of the initially proposed indication leaving out patients treated with edoxaban, enoxaparin and fondaparinux and also emergency surgery/urgent procedures.

3.4. Unfavourable effects

In the clinical studies in healthy volunteers, there were few adverse events. Andexanet was not associated with serious adverse events.

Infusion-related reactions were observed and considered to be possibly/probably related to andexanet. Infusion-related reactions generally resolved without treatment.

Treatment-emergent, non-neutralizing antibodies to andexanet alfa were detected in approximately 10% (35/345). These antibodies were generally low titre, and no clinical consequences were observed. No neutralising antibodies or antibodies to factor X or FXa were detected.

The mean D-dimer level and Prothrombin fragments F1 +2 increased in a dose dependent manner following andexanet doses. Healthy subjects did not show clinical symptoms. However, in the interim results of the ANNEXA-4- study (interim analysis submitted 13 November 2018 [data cut July 09, 2018]) 36 (10.3%) of patients experienced a total of 42 thromboembolic events. This high numbers of thrombo-embolic events was of concern. From ANNEXA-4, high-dose andexanet, previous anticoagulant, previous lower-dose anticoagulant, have been identified as potential risk-factors for thromboembolic events. Further evaluation of the risk of thromboses and thromboembolic events will be evaluated in expanded clinical data that will be provided in CSR of ANNEXA-4 and of study 18-513 (SO1 and SO3).

Timing and dosage for re-introduction of anticoagulation after andexanet remains to be challenging, as available laboratory understanding mainly derives from healthy volunteers. Preliminary evaluation in the target patient group points to a recommendation of early re-anticoagulation, especially for Generation 2 andexanet. Further data regarding Generation 2 andexanet will be provided post-

authorisation (SO2) .With respect to the short half-life of andexanet, it is mechanistically possible that re-bleeding could occur.

To minimize the potential off-label use in patients treated with anticoagulants other than as indicated, routine risk minimisation measures were put in place. Target population is clearly reflected in the agreed SmPC (Sections 4.1, 4.2, 4.4 and 5.1) including respective warnings. It is indicated that andexanet alfa is not suitable for pre-treatment of urgent surgery, use for edoxaban- or enoxaparin-reversal is not recommended due to lack of data and that andexanet alfa will not reverse the effects of non-FXa inhibitors. Restricted medical prescription is requested.

3.5. Uncertainties and limitations about unfavourable effects

Safety data from healthy volunteers differ significantly from the target population. Safety evaluation in the target patient group reveals a significantly increased mortality and risk of thrombosis in the patient group >75 years of age. It is not clear if co-morbidities, risks of the previous anti-coagulant treatment or andexanet itself account for this finding.

The clinical relevance of elevation of D-Dimers and Prothrombin fragments F1+2 has not been established. Correlation with typical diagnoses (deep vein thrombosis (DVT), pulmonary embolism (PE), disseminated intravascular coagulation (DIC) in the relevant patient groups, especially in the elderly population is considered to be significant. As in bleeding patients these markers may be elevated unspecifically, assumed increased risk of thromboses can only be addressed in a clinical study context.

The clinical relevance of antibodies to andexanet alfa is considered to be low, although available database is small.

There were more TEAEs with andexanet in women (69.4%) than in men (46.4%) in the integrated safety population.

There is a paucity of data in special populations. The main concern is the elderly and patients with concomitant diseases like renal or hepatic impairment.

3.6. Effects Table

Table 23 Effects Table for andexanet alfa based on completed studies in healthy volunteers and on study ANNEXA-4 in bleeding patients in line with the interim analysis submitted 13 November 2018 [data cut July 09, 2018]

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Unbound fXa-Inhibitor concentration	Rapid decrease 2 minutes after the end of bolus dose	ng/mL	Apixaban: 1.10-4.53 Rivaroxaban: 5.08-14.5	Placebo 8.37 24.3	Effect was immediate, dose-dependent; Decrease was sustained for duration of infusion; Determination of andexanet dose remains unclear;	Results of PK/PD studies in healthy volunteers.
Anti-fXa activity	Rapid decrease 2 minutes after the end of bolus dose	Ng/mL IU/mL	Apixaban: 11.0-50.4 Rivaroxaban: 15.1-198	Placebo 160 269	Effect was immediate, dose-dependent; Decrease was sustained for duration of infusion; Definition of lower level of reaching normal haemostasis is open	Results of PK/PD studies in healthy volunteers.
Thrombin generation	Restoration at 2 minutes after end of bolus	Percent of subjects restored to baseline	Apixaban: 67-100 Rivaroxaban: 0-100	Placebo 6 0	Effect was immediate, dose-dependent;	Results of PK/PD studies in healthy volunteers.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Hemostatic efficacy	stopping a major bleed at 12 hours from end of andexanet infusion	Percent of subjects	excellent or good hemostasis : 80.6	none	Correlation between anti-fXa-activity and Thrombin generation and hemostatic efficacy is considered to be challenging Significance of the evaluation time-point (12h) is open: According to immediate Surrogate-response, earlier evaluation time-points are of interest.	Interim data of phase 3b/4 study in patients (interim analysis submitted 13 November 2018 [data cut July 09, 2018])
Unfavourable Effects						
Thrombotic events		Number of patients (Percent of subjects)	36 (10,3%)	N/A	Possible Clinical relevance of elevations in both D-dimer and F1+2 remains open.	Interim data of phase 3b/4 study in patients
Re-bleeding potentail		Percent of patients	2.9%	N/A	Co-incidence of increasing anti-fXa-activity and start of bleeding event is visible	Interim data of phase 3b/4 study in patients (JAR 28 Nov 2018, CSR section 11.3.1.4))
Infusion		Number of subjects/pa	25	n/a	influence of the infusion rate	Results of PK/PD studies in healthy

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
reactions		tients				volunteers.
Hyper-sensitivity reaction					Hypersensitivity-related AEs have been documented in healthy volunteers; relevance for the target population is considered to be low	Safety section of AR

Abbreviations:

Notes:

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The approval of andexanet alfa is based on PK/PD studies in healthy volunteers anticoagulated with DOACs and preliminary clinical data in bleeding patients (interim results of ANNEXA-4 study [data cut July 09, 2018]). Theoretical background including stoichiometrial explanation, biological plausibility and evaluation in healthy volunteers support the idea of andexanet being an adequate reversal agent in subjects treated with direct fXa inhibitors as anti-coagulants.

PK/PD-modelling has been used to establish dosage recommendation. Separate PK-PD models were developed for rivaroxaban and apixaban using a common andexanet POP PK model. The PK/PD model has been highly adapted to rivaroxaban data and includes literature-derived covariate effects, rendering the model inappropriate to draw quantitative conclusions regarding other direct fXa inhibitors than rivaroxaban. Adaptation to apixaban has been further provided. Both model adaptations remain to be validated. Overall, PK and PK/PD modelling requires improvement and needs to be adapted to patients' data and data from healthy subjects as soon as available.

Biomarkers ("surrogates") that have been chosen to be used are: anti-fXa-levels, thrombin generation ("ETP") and unbound NOAC-levels. However, a reliable surrogate parameter has not been identified, yet: target anti-fXa-level, nadir value, extent of reduction, percentage or absolute reduction, difference in influence between different FXa-inhibitors, baseline anti-fXa-activity – might all be relevant. In addition, laboratory testing in patients remains challenging.

Correlation between the co-primary efficacy parameters "anti-fXa-activity" and "hemostatic efficacy" and the link between healthy subjects on anti-coagulation and actively bleeding subjects with respect to the thrombin-generation results was not established.

Desipte no thromboembolic events observed in studes with healthy volunteers, the increased risk of thrombo-embolic events (10.3%) was observed in the only study in bleeding patients and raises safety-concern.

3.7.2. Balance of benefits and risks

The uncertainties listed above led to the restriction of the initially proposed indication leaving out the reversal of antithrombotic activity with edoxaban, enoxaparin and fondparinux. Following the evaluation the CHMP agreed to grant the indication only for adult patients treated with a direct factor Xa (FXa) inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. The surgery/urgent procedure part of the indication was also removed from section 4.1 of the SmPC as there were no data available in this population of patients.

Granting an approval for reversal of antithrombotic activity with rivaroxaban and apixaban was agreed by the CHMP due to unmet medical need of reversal therapy for DOACs. Specific obligations in the context of conditional MA were agreed with the applicant and should address the following open issues:

(1) The concept of a FXa-decoy-molecule for reversing the anticoagulant effect of fXa-inhibitors has been investigated in pharmacokinetic (PK)/pharmacodynamics (PD) studies in healthy subjects pre-treated with anticoagulants. The results are promising. However, adequate dosage and differing effects for different anticoagulants remain to be challenging. Transfer into bleeding patients shows promising overall haemostatic efficacy at 12 hours post treatment (80.6%). However, this is challenged by lack of control population, rather long interval (12 hours) in correlation with the short half-life of the DOACs (about 12 hours) and no convincing correlation between the biomarker and haemostatic efficacy. PK/PD modelling for substantiating posology has not been successful. This is highly challenging in the light of contradictory biomarker-results (anti-fXa activity versus ETP) in healthy volunteers and lack of final posology. On the other hand, e.g. relevant anti-TFPI-(tissue factor pathway inhibitor) effects' point to a general pro-coagulative effect of andexanet - independent from anti-FXa-sequestration.

(2) Increased risk of thrombo-embolic events raises safety-concern (10,3% based on interim results of ANNEXA-4 study [data cut July 09, 2018]). High-dose andexanet, previous anticoagulant, previous lower-dose of anticoagulant, have been identified as potential risk-factors for TE. Safety evaluation in the target patient group, points to a significantly increased mortality and risk of thrombosis in the patient group >75 years of age. It is not clear if co-morbidities, risks of the previous anti-coagulant treatment or Andexanet itself account for this finding.

(3) Clinical comparability of the Generation 1 Andexanet as used in clinical studies and Generation 2 andexanet has not been established, sufficiently. Provided data are difficult to interpret because of different dosages of andexanet and different dosages of anti-coagulant. Confirmation of posology is requested within SO2.

3.7.3. Additional considerations on the benefit-risk balance

The initially proposed indication was significantly modified during the evaluation (see above section 3.7.2 Balance of benefits and rsks).

Medical need of a reversal therapy for anticoagulation with DOACs was acknowledged, as life-threatening bleeds under DOAC treatment are reported in similar frequency as under coumarines. Theoretical concept, data from healthy volunteers, and a 80% haemostatic effect in bleeding patients were considered promising. However in the interim results of the ANNEXA-4- study (interim analysis submitted 13 November 2018 [data cut July 09, 2018]) 36 (10.3%) of patients experienced a total of 42 thromboembolic events. This high numbers of thrombo-embolic events was of concern.

The currently submitted data are not considered comprehensive.

a. Correlation of the biomarker (anti-FXa-%change from baseline) with haemostatic efficacy is not convincing. As the clinical development concept is based upon anti-FXa-activity to represent the clinical effect for reversing anti-fXa effects induced by DOACs (mode of action), this is still of concern and further clinical evaluation is considered necessary.

b. Comparability of Generation1 and Generation2 Andexanet has not been established. This is of concern as all reference studies for dosage and efficacy in healthy volunteers have been conducted with Generation 1.
PK comparison of Generation 1 and Generation 2 based on Study 16-512 failed in showing PK comparability, but indicates unexplained differences between Generation1 and Generation2. Respective study-results might either be biased by differences between Generation 1 and Generation 2, or by yet ill-defined influence of the inhibitor (apixaban versus rivaroxaban), or by the andexanet dosage (high or low-dose). These gaps challenge the PD-modelling, and consecutive adequate dosage-recommendation.

c. A risk of thromboses and thromboembolic events has been identified with the treatment of andexanet. This potential risk may involve patients on high-dose andexanet, patients on rivaroxaban and patients on lower dose anti-coagulant-regimen prior to the bleeding event.

Given the high unmet medical need a conditional approval is acceptable with the following obligations:

Post-authorisation measure(s)	Motivation
Proposed post-authorisation measure 1 with proposed classification: category 2 (specific obligation in the context of conditional approval - ANNEX II condition)	
<u>Specific obligation 1:</u> In order to further substantiate correlation of the biomarker (antiFXa-activity) with hemostatic efficacy and clarify the risk of thromboses and thromboembolic events, the MAH should submit the results of ANNEXA-4, an interventional non-randomized, multicenter, prospective, open-label, single-group study in patients with acute major bleeding. Due date: Submission of final CSR : by 2Q 2019	Currently submitted data is not considered comprehensive as: I. Correlation of the biomarker (anti-FXa-%change from baseline) with haemostatic efficacy is not established. As the clinical development concept is based upon anti-FXa-activity to represent the clinical effect for reversing anti-fXa effects induced by DOACs (mode of action), this is still of concern and further evaluation is considered necessary. The log of nadir of anti-FXa activity cannot be interpreted as a validated indicator for clinical efficacy as no validation data are available. The applicant should validate the log of nadir of anti-FXa activity as indicator for clinical efficacy II. The risk of thromboses and thromboembolic events has been identified with the treatment of andexanet. This potential risk may involve patients on high-dose andexanet, patients on rivaroxaban and patients on lower dose anti-coagulant-regimen prior to the bleeding event. The CSR should include complete analysis of all 352 patients enrolled. Any discrepancy with recently published data (DOI: 10.1056/NEJMoa1814051) should be discussed.
Proposed post-authorisation measure 2 with proposed classification: category 2 (specific obligation in the context of conditional approval - ANNEX II condition)	

Post-authorisation measure(s)	Motivation
<u>Specific obligation 2:</u> In order to further confirm the posology of Ondexxya, the MAH should submit the results of a comparative PK study with Generation 1 process 3, and Generation 2 material (study 19-514). The study should be based on an agreed protocol. Due date: Submission of final CSR by 3Q 2019	Currently submitted data is not considered comprehensive as comparability of Generation 2 to Process 3 of Generation 1 has not been demonstrated although PD-parameters support similarity. All reference studies for dosage and efficacy in healthy volunteers have been conducted with Gen 1, Process 1 and 2. PK comparison of Gen 1 and Gen 2 based on Study 16-512 failed in showing PK comparability, but indicates unexplained differences between Gen1 and Gen2. Respective study-results might either be biased by differences between Gen 1 and Gen 2, or by yet ill-defined influence of the inhibitor (apixaban versus rivaroxaban), or by the andexanet dosage (high or low-dose). For addressing the open concerns, cross-over study with bolus only (plain andexanet, Gen2 vs Gen1 process 3, low and high dose) should be envisaged. The submission should include a proposal for addressing the influence of pre-dosed DOAC on Gen 2. Such proposal should cover sufficient data for dose recommendation and for an updated PK/PD modelling. The proposal might be based on the design of studies 14-503 and 14-504, reflecting the currently recommended doses. Final study report should be available for the PK/PD-modelling-update in Q3 2019 (see Specific Obligation 4 below)
Proposed post-authorisation measure 3 with proposed classification: category 2 (specific obligation in the context of conditional approval - ANNEX II condition)	

Post-authorisation measure(s)	Motivation
Specific obligation 3: In order to substantiate correlation of the biomarker (antiFXa-activity) with hemostatic efficacy and clarify the risk of thromboses and thromboembolic events, the MAH should submit the results of a global randomised controlled clinical trial to investiguate the use of andexanet vs. standard of care treatment in patients with intracranial haemorrhage (ICH) taking apixaban, rivaroxaban, or edoxaban (study 18-513). Due date: Submission of final CSR by 2Q 2023	Currently submitted data is not considered comprehensive as: I. Correlation of the biomarker (anti-FXa-%change from baseline) with haemostatic efficacy is not established. As the clinical development concept is based upon anti-FXa-activity to represent the clinical effect for reversing anti-fXa effects induced by DOACs (mode of action), this is still of concern and further evaluation is considered necessary II. A risk of thromboses and thromboembolic events has been identified with the treatment of andexanet. This potential risk may involve patients on high-dose andexanet, patients on rivaroxaban and patients on lower dose anti-coagulant-regimen prior to the bleeding event. Currently missing information relates to safety as regards the risk of thromboembolic events relative to a concurrent control population that does not receive andexanet. Given the uncontrolled nature of the ANNEXA-4 trial the applicant should commit to perform an additional data collection to construct relevant control data.
Proposed post-authorisation measure 4 with proposed classification: category 2 (specific obligation in the context of conditional approval - ANNEX II condition)	

Post-authorisation measure(s)	Motivation
Specific obligation 4: In order to further confirm the efficacy and safety, the MAH should submit an updated PK/PD model using all previously incorporated data (from studies 11-501, 12-502, 14-503, 14-504, and 14-506) as well as newly incorporated data from Study 16-512 (PK-PD study of Generation 2 andexanet vs. Generation 1), Study 16-508 (PK-PD study of andexanet in individuals of Japanese ethnicity), and Study 14-505 (ANNEXA-4) . Due date: Submission by 3Q 2019	Currently submitted data is not considered comprehensive as currently submitted PK/PD model did not incorporate data from studies: 16-512 (PK-PD study of Generation 2 andexanet vs. Generation 1), 16-508 (PK-PD study of andexanet in individuals of Japanese ethnicity), and 14-505 (ANNEXA-4). The following missing points should be addressed: I. Adequacy and validity of the PK/PD model: This comprises a proper and more exigent external model evaluation including graphical assessment (including mean tendency and variability) of model predictions versus observations from Study 16-512 together with numerical/graphical assessment of PK/PD endpoints such as AUC, Cmax, % decrease in Anti-fXa activity, as essential basis to accept the validity of external model evaluation and therefore, the administration schedule proposed. II. Update of the andexanet PK-model: The andexanet PK model has to be updated with andexanet concentration data as well as the FXa inhibitor concentrations (total and unbound) and anti-fXa activity from Studies 16-512 (PK-PD study of Generation 2 andexanet) and 16-508 Part 1 (PK-PD study of andexanet in individuals of Japanese ethnicity). The update and validation should be reported according to the current EMA guidelines. As long as PK comparability is not shown, validation of andexanet PK and PK/PD models should be stratified by the different Generation and Processes regarding the andexanet variation administered. In this line, a covariate is to be introduced to account for PK differences in andexanet formulation. Formerly tested covariates including “fXa inhibitor” and “race” on andexanet PK should be re-checked during update. III. The missing detailed reporting of approach using data from Study 16-512 should be completed with the information regarding final parameter estimates of the models using base and expanded datasets for andexanet PK/PD models (expected in 3Q 2019) including results for both cases and reported according to current EMA guidelines.

Post-authorisation measure(s)	Motivation
	IV. The covariates for the three drugs involved in the modelling (andexanet, rivaroxaban, and apixaban) should be adequately selected, justified and analysed. V. The Andexanet PK model and PK/PD model updates and validation should be conducted appropriately and the lack of PK comparability should be adequately accounted for in PK and PK/PD model updates. VI. The Model diagnostics and information on all assumptions should be adequately provided and reported according to current guidelines. VII. The requested covariate analyses should be conducted and reported in line with current guidelines and should be deemed adequate to mimic the target population; detailed information on statistics for data analysis and thresholds for clinical relevance applied should be clearly stated.

* Classification: category 1= Annex II D condition; category 2= Annex II E specific obligations; category 3 = All other studies reflected only in the RMP (non-clinical, PK, PASS)

Conditional marketing authorisation

As comprehensive data on the product are not available, a conditional marketing authorisation was requested by the applicant in the initial submission and agreed by the CHMP during the assessment.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning treatment of a life-threatening disease. Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed.
- It is likely that the applicant will be able to provide comprehensive data. New data will become available post-authorisation in 2019 (full results of ANNEXA-4, study 19-514 and update regarding PK-PD model supporting posology) and in 2023 (results of RCT [study 18-513] in patients with intracranial haemorrhage). Therefore the applicant committed to submit the final results of ANNEXA-4 by 2Q 2019. This was requested to further substantiate correlation of the biomarker (antiFXa-activity) with haemostatic efficacy and clarify the risk of thromboses and thromboembolic events. In addition the applicant committed as well to submit the results of a comparative PK study with Generation 1, process 3, and Generation 2 material (study 19-514) by3Q 2019. This was requested to confirm the posology of Ondexxya. The study will be based on an agreed protocol that will be also submitted for the assessment to the Agency in the postauthorisation phase. The submission was agreed to cover a proposal for addressing the influence of pre-dosed DOAC on Gen 2 with the aim of sufficient data for dose recommendation and for an updated PK/PD modelling. The proposal might be based on the design of studies 14-503 and 14-504, reflecting the currently recommended doses. Furthermore, the applicant agreed

to submit the results of a global randomised controlled clinical trial to investigate the use of andexanet versus standard of care treatment in patients with intracranial haemorrhage (ICH) taking apixaban, rivaroxaban, or edoxaban (study 18-513) by 3Q 2019. This was also requested to further substantiate correlation of the biomarker (antiFXa-activity) with haemostatic efficacy and clarify the risk of thromboses and thromboembolic events. Finally, the applicant committed to provide the an updated PK/PD model using all previously incorporated data (from studies 11-501, 12-502, 14-503, 14-504, and 14-506) as well as newly incorporated data from study 16-512 (PK-PD study of Generation 2 andexanet versus Generation 1), study 16-508 (PK-PD study of andexanet in individuals of Japanese ethnicity), and study 14-505 (ANNEXA-4) by 3Q 2019.

- Unmet medical needs will be addressed, as andexanet alfa will be first antidote for reversal of anticoagulation with direct factor Xa inhibitors apixaban and rivaroxaban. For direct FXa antagonists, no specific antagonist is available in contrast to PCCs and Vitamin K to reverse coumarin derivatives. Use of procoagulant reversal agents such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC), or recombinant factor VIIa (rfVIIa) may be considered, but have not been evaluated in clinical trials. There is urgent unmet medical need for a more targeted therapy specifically directed at the fXa inhibition with a better benefit/risk profile than coagulation factor infusions. The development of andexanet alfa aimed to fulfil these immediate, unmet medical needs.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. The CHMP agreed that there is a high unmet medical need in this field. Given the CHMP considered that according to the available data the benefit-risk balance is positive, immediate availability of an antidote for FXa-inhibitors was considered to be of significant impact for the target population and outweighted the risks related to the fact that additional data are still required to further assure safety and efficacy of this product. The company committed to provide missing additional data aspart of the specific obligations according to agreed deadlines.

3.8. Conclusions

The overall benefit risk balance of Ondexxya is positive and the applicant committed to provide additional data as part of agreed specific obligations listed in Annex II.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Ondexxya is favourable in the following indication:

For adult patients treated with a direct factor Xa (FXa) inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to further substantiate correlation of the biomarker (antiFXa-activity) with haemostatic efficacy and clarify the risk of thromboses and thromboembolic events, the MAH should submit the results of ANNEXA-4, an interventional non-randomized, multicentre, prospective, open-label, single-group study in patients with acute major bleeding.	Submission of the final CSR by 30 June 2019
In order to further confirm the posology of Ondexxya, the MAH should submit the results of a comparative PK study with Generation 1 process 3, and Generation 2 material (study 19-514). The study should be based on an agreed protocol.	Submission of the final CSR by 30 September 2019
In order to substantiate correlation of the biomarker (antiFXa-activity) with haemostatic efficacy and clarify the risk of thromboses and thromboembolic events, the MAH should submit the results of a global randomised controlled clinical trial to investigate the use of andexanet versus standard of care treatment in patients with intracranial haemorrhage (ICH) taking apixaban, rivaroxaban, or edoxaban (study 18-513).	Submission of the final CSR by 30 June 2023
In order to further confirm the efficacy and safety, the MAH should submit an updated PK/PD model using all previously incorporated data (from studies 11-501,	Submission by 30

Description	Due date
12-502, 14-503, 14-504, and 14-506) as well as newly incorporated data from study 16-512 (PK-PD study of Generation 2 andexanet versus Generation 1), study 16-508 (PK-PD study of andexanet in individuals of Japanese ethnicity), and study 14-505 (ANNEXA-4).	September 2019

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that andexanet alfa is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.