Clinical Study Report Synopsis	
Drug Substance	Andexanet Alfa
Study Code	18-513
Edition Number	1
Date	22 November 2023
EudraCT Number	2018-002620-17
NCT Number	NCT03661528

A Randomized Clinical Trial of Andexanet Alfa in Acute Intracranial Hemorrhage in Patients Receiving an Oral Factor Xa Inhibitor (ANNEXA-I)

Study dates: First patient enrolled: 06 June 2019
Last patient last visit: 09 August 2023

Phase of development: Therapeutic use (IV)

International Co-ordinating Investigator: [redacted]
Canada

Sponsor's Responsible Medical Officer: [redacted]
Clinical Development Sciences
Alexion Pharmaceuticals UK Ltd

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centers

This study was conducted at 131 centers across 23 countries in Europe and North America.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary efficacy	
• Evaluate the effect of andexanet versus usual care on the rate of effective hemostasis.	• Effective hemostasis 12 hours post randomization as determined by the blinded EAC.
Secondary efficacy	
• Evaluate the effect of andexanet versus usual care on anti-FXa activity.	• Percent change from baseline to nadir in anti-FXa activity during the first 2 hours post randomization.
Additional efficacy [a]	
• Assess the relationship between anti-FXa activity and the achievement of hemostatic efficacy.	• Correlation analysis between anti-FXa activity and the achievement of hemostatic efficacy.
Safety	
• Evaluate the occurrence of TEs at 30 days after randomization.	• Occurrence of TEs, confirmed by adjudication, through 30 days post randomization.
• Evaluate in-hospital and 30-day mortality (all-cause, CV, and bleeding).	• In-hospital mortality (during index hospitalization; all-cause, CV, and bleeding). • 30-day all-cause, CV, and bleeding related mortality (defined as any death within 72 h from randomization and not associated to the occurrence of an identified TE).
• Evaluate the occurrence of invasive intracranial procedures post randomization.	• Proportion of patients with invasive intracranial procedures performed post randomization to manage the intracranial hematoma and/or its complications.
• Evaluate the length of initial hospitalization for primary bleeding event.	• Length of initial hospitalization for primary bleeding event. • Total time admitted to the intensive care unit during the initial hospitalization.
• Evaluate the rate of re-hospitalization at 30 days after randomization.	• Proportion of re-hospitalizations, including total number of re-hospitalizations and total days re-hospitalized, at 30 days post randomization.
• Evaluate AEs and vital signs.	• AEs and vital signs.
• Evaluate the immunogenicity of andexanet.	• Antibodies to FX, FXa, and andexanet. • Neutralizing antibodies to FX, FXa, and andexanet.[b]

[a] Several additional efficacy objectives were pre-defined. The results for these objectives are not presented in this synopsis but can be found in the clinical study report.

[b] No data are currently available for neutralizing antibodies to andexanet. For information, see main clinical study report.

AE, adverse event; CV, cardiovascular; EAC, Endpoint Adjudication Committee; FX, Factor X; FXa, activated factor X; TE, thrombotic event.

Study design

The study was designed to determine the efficacy and safety of andexanet versus usual care in patients presenting with acute intracranial hemorrhage within 6 hours of symptom onset (from the baseline scan) and within 15 hours of taking an oral activated Factor X (FXa) inhibitor (from randomization). Usual care comprised any treatment(s) (including no hemostatic treatment) other than andexanet, initiated within 3 hours post randomization that the Investigator and/or other treating physicians considered to be appropriate.

Patients were randomized (1:1) to andexanet or usual care, stratified by intended usual-care-agent (plasma-derived coagulation factor concentrates vs other); and time from symptom onset to baseline imaging scan (< 180 minutes vs ≥ 180 minutes). Treatment was initiated as soon as possible after randomization. Cross-over between treatment groups was not permitted. Patients could be treated for bleeding with any unplanned rescue medications or intervention deemed to be clinically warranted, except andexanet in the usual care group.

Hemostatic efficacy was based on hematoma expansion, assessment of neurologic status determined by the National Institutes of Health Stroke Scale (NIHSS), and use of rescue therapy, and was adjudicated by an independent Endpoint Adjudication Committee (EAC). Hematoma expansion between baseline and 12 hours was assessed using serial brain imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) read by a blinded core laboratory, and clinical assessment performed by study personnel blinded to treatment allocation. The EAC also adjudicated all potential thrombotic events (TEs) which were an adverse event of special interest (AESI), and deaths. A Data Safety Monitoring Board (DSMB) was responsible for monitoring all efficacy and safety data, evaluating the interim analysis performed by the independent statistician, and for making recommendations for study modification or stopping for efficacy or safety reasons.

Given the numerous therapeutic options available for patients randomized to usual care, it was considered unfeasible to blind all study personnel directly involved in the care of an enrolled patient. Thus, the local Investigator and most of the local site study team were not blinded to the treatment allocation. Alexion and AstraZeneca remained blinded to adjudication outcomes and imaging results.

Target population and sample size

Key inclusion criteria: Provision of informed consent; acute intracranial bleeding episode (defined as an acute intracerebral bleeding episode with an estimated blood volume ≥ 0.5 to ≤ 60 mL) acutely observed radiographically within the cerebrum; CT or MRI scan demonstrating intracerebral bleeding within 2 h prior to randomization; treatment with an oral

FXa inhibitor (apixaban, rivaroxaban, or edoxaban)[1] ≤ 15 hours prior to randomization; time from bleeding symptom onset < 6 hours prior to baseline imaging scan; time of trauma (if applicable) or time last seen normal could be used as surrogates for time of symptom onset; NIHSS score ≤ 35 at the time of consent.

It was assumed that the rate of effective hemostasis in this study would be 70% and 80% for patients treated with usual care and andexanet, respectively. The 10% absolute difference represented a 33% risk reduction of not achieving effective hemostasis by andexanet compared to usual care, which was considered clinically meaningful. A total sample size of approximately 900 patients (ie, 450 patients per group) was estimated to have approximately 90% power to detect a 10% absolute difference in the rate of effective hemostasis at a 0.05 two-sided significance level.

Investigational product: dosage, mode of administration, and lot numbers

Andexanet was administered as intravenous (IV) bolus (over approximately 15 to 30 minutes) immediately followed by a continuous infusion (over approximately 120 minutes). Patients received 1 of 2 dosing regimens of andexanet based on the specific anticoagulant and dose taken, and timing of the last dose: Low dose (400 mg IV bolus followed by continuous infusion of 480 mg at 4 mg/min), or high dose (800 mg IV bolus followed by continuous infusion of 960 mg at 8 mg/min). Andexanet dosing was to be initiated no later than 30 minutes after randomization and preferably within 2 hours of the baseline brain imaging scan. Lot numbers: *1788637, 1793980, 1804903, 1804904, 1804905, GCS520010, GCS521016, GCS522571, J18-0815, J19-0281, J19-0706, J19-0933, J19-1177, J19-1614, J20-0247, J20-0893, J20-0955, J20-1240, J20-1407, J20-1408, J20-1409, N7197A9.*

Duration of study

The study duration for most patients was up to 37 days, and included 3 study periods as follows: Screening and Baseline Period (< 1 day [Day 1]), followed by a Treatment Period (< 1 day [Day 1]), and a Follow-up Period for all adverse events (AEs), survival, and antibodies (approximately 30 days [Day 1 to the Day 30 visit]). Patients with a positive anti-andexanet antibody response at Day 30 were to have an additional visit approximately 120 days post randomization, or within 30 days of when the positive test was made known to the Investigator, whichever was later.

Statistical methods

The primary endpoint was based on achievement of effective hemostasis, as determined by the blinded EAC based on pre-specified criteria. The treatment groups were compared using a

[1] Enoxaparin-treated patients were also considered eligible for the study in CSP Amendment 2, but this change was reversed in CSP Amendment 3.

Cochran-Mantel-Haenszel test stratified by time from symptom onset to baseline imaging scan (< 180 minutes vs ≥ 180 minutes). The difference in the proportion of patients with effective hemostasis between andexanet and the usual care group, the corresponding 95% confidence intervals (CIs) for the difference, and the p-value for the comparison were provided.

A pre-specified interim analysis on the primary endpoint was performed by the DSMB-associated statistician after approximately 50% of the anticipated patients had been adjudicated for hemostatic efficacy. If the primary efficacy objective was met at the interim analysis, the DSMB could recommend stopping the study early. If the study had continued to recruit patients after the interim analysis, a final analysis would have taken place.

The overall type I error for the interim and final analyses was controlled at 5% by employing the alpha spending function by Lan and DeMets based on Pocock boundaries. The study was considered to have met its primary objective if the proportion of patients with effective hemostasis in the andexanet group was statistically significantly higher than that in the usual care group (ie, $p < 0.0310$ at interim, or $p < 0.0277$ at a final analysis if the study had not stopped early following the DSMB recommendation after the interim analysis). Enrollment of patients continued without interruption from the first data cut-off (DCO) for the interim analysis until the stop decision was communicated and recruitment was closed. Thus, the second DCO captured the data from all patients who participated in the study.

The secondary efficacy endpoint was percent change in anti-FXa activity from baseline to nadir during the first 2 hours post randomization, where baseline was defined as the last assessment prior to randomization. Andexanet and usual care were compared by analysis of covariance on the ranked percent change from baseline to nadir 2 hours post randomization, adjusted for covariates of time from symptom onset to baseline imaging scan (< 180 minutes vs ≥ 180 minutes), and baseline anti-FXa activity. The relationship between change in anti-FXa activity and hemostatic efficacy was evaluated using logistic regression.

The safety data including deaths, AEs (including AESIs), laboratory data, vital signs, and hospitalizations were analyzed descriptively.

The primary efficacy population and the extended population refer to the intent-to-treat analysis set for efficacy based on the first and second DCOs, respectively. The safety analyses were based on the second DCO, the extended population.

Study population

In the primary efficacy population, 452 patients were enrolled and randomized: 224 to andexanet and 228 to usual care. Discontinuation from the study (27.7% overall) was balanced between the treatment groups. In the extended population, 530 patients were enrolled and randomized: 263 to andexanet and 267 to usual care; 29.6% discontinued from the study and the treatment groups were balanced. No patients were lost to follow-up.

The primary efficacy population was predominantly White (93.5%), the median age was 80.0 years, and 54.2% were male. Regarding FXa inhibitors received prior to study treatment, 60.8% of the patients had received apixaban, 28.5% had received rivaroxaban, and 10.0% had received edoxaban. The most common indications for FXa inhibitors were atrial fibrillation (84.7%), venous thromboembolism prevention (5.3%), and venous thromboembolism treatment (4.4%). The most common bleeding event location was intracerebral hemorrhage (91.6%) and median hematoma volume at baseline was 9.7 mL. Median time from symptom onset to baseline CT or MRI scan was 142 minutes. The demographic and baseline characteristics were consistent between the primary efficacy and extended populations, and they were also balanced between the treatment groups.

Summary of efficacy results

Based on the results of the pre-specified interim analysis of the primary endpoint, the DSMB recommended stopping the study early, at a meeting held on 31 May 2023. The study met its primary objective. Andexanet was superior to usual care in achieving effective hemostasis (excellent or good as adjudicated by the blinded EAC) at 12 hours post randomization (67.0% of patients in the andexanet group, 53.1% of patients in the usual care group, absolute difference: 13.4% [95% CI: 4.6%, 22.2%], $p = 0.0032$). This improvement was considered to be both clinically important and statistically significant. The results of sensitivity analyses, including the analysis of the extended population, were consistent with the primary analysis. When considering the 3 components that were part of the assessment of the primary endpoint (ie, hemostatic efficacy evaluated using only imaging parameters, proportion of patients with ≥ 7-point increase from baseline in NIHSS, and use of rescue therapy), there were numerical improvements in the andexanet group compared to the usual care group.

Andexanet was also superior to usual care on the secondary endpoint of reduction in anti-FXa activity from baseline to nadir during the first 2 hours post randomization (-94.4% median reduction in the andexanet group, -27.5% median reduction in the usual care group, $p < 0.0001$). There was a weak relationship between hemostatic efficacy and percentage change in anti-FXa activity: Odds ratio 0.9988, 95% CI [0.9952, 1.0024]; Area under the concentration-time curve (AUC) 0.56, 95% CI [0.51, 0.62].

Summary of safety results

In total, 262 patients received andexanet (203 at the low dose, 59 at the high dose). Andexanet was administered as expected per the prescribing information. Of the 265 patients treated with usual care, 230 received prothrombin complex concentrate, 2 received other treatments, and 33 received no treatment (ie, no hemostatic treatment of the ICrH; platelets or packed red blood cells were allowed).

The proportion of patients with treatment-emergent adverse events (TEAEs) was balanced between the treatment groups: 85.1% in the andexanet group and 82.6% in the usual care group. No TEAEs led to withdrawal of study drug in either treatment group.

The proportion of patients with treatment-emergent serious AEs (TESAEs) was higher in the andexanet group (120 [45.8%]) than the usual care group 96 [36.2%]). TESAEs were most frequently reported within Nervous system disorders: 18.7% in the andexanet group and 19.2% in the usual care group. Within this system organ class, TESAEs of ischemic stroke were more frequent in the andexanet group (13 patients [5.0%]) than in the usual care group (2 [0.8%]).

Overall mortality was balanced between treatment groups: 74 patients (28.2%) in the andexanet group died before the Day 30 visit vs 70 (26.4%) in the usual care group. In-hospital mortality was also balanced (23.3% in the andexanet group vs 21.5% in the usual care group). Bleeding-related death within 72 hours post-randomization (not associated with a TE) occurred in 14 patients (5.3%) in the andexanet group and 19 (7.2%) in the usual care group. Deaths due to TEAEs occurred in 64 patients (24.4%) in the andexanet group and in 54 (20.4%) in the usual care group; no marked differences were observed between treatment groups, as there were small numbers of patients reported for each preferred term.

The proportion of patients with TEs confirmed by adjudication was higher in the andexanet group (27 [10.3%]) than the usual care group (15 [5.7%]). There was a higher frequency of patients with events in the adjudication categories of ischemic stroke and myocardial infarction in the andexanet group: ischemic stroke 17 patients (6.5%) vs 4 (1.5%), and myocardial infarction 11 patients (4.2%) vs 4 (1.5%), for andexanet and usual care, respectively.

Vital signs were balanced between the andexanet and usual care groups during the study. Blood pressure control, a key factor in minimizing hematoma expansion in the first 24 hours, was balanced between the treatment groups. A decrease in median systolic blood pressure (SBP) from baseline (160.5 and 156.0 mmHg for the andexanet and usual care groups, respectively) was apparent from 1 hour (145.0 and 140.0 mmHg for the andexanet and usual care groups, respectively). This decrease was maintained, with median SBP < 140 mmHg from 6 hours (133 mmHg in both groups), and thereafter ≤ 140 mm Hg in both groups through the Day 30 visit. Similar findings were observed for diastolic blood pressure, which also showed a decrease from baseline, though at Day 30 in both treatment groups, it had increased slightly (74.0 and 75.5 mmHg, for andexanet and usual care groups, respectively).

There were no clinically significant differences in hematology or clinical chemistry parameters between the treatment groups.

In the andexanet group, 6.5% of patients had at least one invasive intracranial procedure, compared with 8.7% in the usual care group; the most common procedure in both treatment groups was burr hole for implanting ventricular catheter.

The median duration of initial hospitalization for the primary bleeding event was 11.0 days in each treatment group. The median time spent in an intensive care unit during initial hospitalization was 8.0 days in the andexanet group and 6.0 days in the usual care group. Eighteen patients in the andexanet group and 8 in the usual care group were re-hospitalized, and the median duration of total re-hospitalization was 5.0 days in the andexanet group vs 3.5 days in the usual care group.

No neutralizing antibodies to FX or FXa were detected at Day 30. No data are currently available for neutralizing antibodies to andexanet.

No new adverse drug reactions were identified for andexanet, and the frequency of known adverse drug reactions was unchanged.

Conclusions

- ANNEXA-I demonstrated that treatment with andexanet resulted in a statistically significant and clinically relevant improvement in effective hemostasis at 12 hours in acute ICrH in patients receiving a direct oral FXa inhibitor, when compared to usual care.
- The overall safety profile of andexanet in the ANNEXA-I population was consistent with the known safety profile of andexanet and no new safety concerns were identified.