Andexanet alfa (acute major bleeding)

Addendum to Project A25-87 (dossier assessment)[1]

ADDENDUM (DOSSIER ASSESSMENT)

Project: A25-141 Version: 1.0 Status: 28 Nov 2025 DOI: 10.60584/A25-141_en

[1] Translation of the addendum *Andexanet alfa (akute schwere Blutungen) – Addendum zum Projekt A25-87 (Dossierbewertung)*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Andexanet alfa (acute major bleeding) – Addendum to Project A25-87

Commissioning agency

Federal Joint Committee

Commission awarded on

11 November 2025

Internal Project No.

A25-141

https://doi.org/10.60584/A25-141_en

Address of publisher

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Siegburger Str. 237
50679 Köln
Germany

Phone:+49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Recommended citation

Institute for Quality and Efficiency in Health Care. Andexanet alfa (acute major bleeding); Addendum to Project A25-87 (dossier assessment) [online]. 2025 [Accessed: DD.MM.YYYY]. URL: https://doi.org/10.60584/A25-141_en.

Keywords

Andexanet alfa, Hemorrhage, Benefit Assessment, NCT03661528

IQWiG employees involved in the addendum

- Sebastian Meller
- Lukas Gockel
- Ulrich Grouven
- Daniela Preukschat

Table of contents

List of tables

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
DGHO	Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (German Society for Haematology and Medical Oncology)
DSG	Deutsche Schlaganfall-Gesellschaft (German Stroke Society)
FDA	Food and Drug Administration
FXa	factor Xa
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HCC	hepatocellular carcinoma
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NIHSS	National Institutes of Health Stroke Scale
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	summary of product characteristics
SVR	sustained virologic response

1 Background

On 11 November 2025, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for project A25-87 (Andexanet alfa – Benefit assessment according to §35a Social Code Book V) [1].

In its comments [2], the pharmaceutical company (hereinafter referred to as 'the company') presented analyses for the ANNEXA-I study, which went beyond the information provided in the dossier [3]. The commission comprised the assessment of the composite outcome 'effective haemostasis' and the assessment of the additional analyses on thrombotic events, taking into account the information in the dossier.

The responsibility for this assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

A subpopulation of the open-label randomized controlled trial (RCT) ANNEXA-I [4-8] was used for benefit assessment A25-87 [1] of andexanet alfa compared with the appropriate comparator therapy (ACT) in adult patients treated with a direct factor Xa (FXa) inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrollable bleeding. The subpopulation exclusively represented patients who were enrolled under ongoing treatment with apixaban and rivaroxaban. A detailed description of ANNEXA-I and of the subpopulation used can be found in dossier assessment A25-87.

In its dossier [3], the company presented results from the ANNEXA-I study for the primary outcome 'effective haemostasis', which was made up of 3 components. As justified in dossier assessment A25-87, the results on the primary outcome presented by the company were not used for the benefit assessment of andexanet alfa in comparison with the ACT, as the patient relevance of the individual components was unclear or not ensured. The 3 components and the main reasons for each were the following:

- No haematoma expansion > 35% 12 hours after randomization

  It was unclear to what extent an increase in haematoma volume represented tangible symptoms and thus how directly relevant it was for the patient.

- No rescue therapy between 3 and 12 hours after randomization

  It is not appropriate to distinguish between study medication and rescue therapy based solely on a time criterion.

- No neurological deterioration 12 hours after randomization

  In the given therapeutic indication, the period of 12 hours considered was too short to show any longer-term impairment of patients.

In the commenting procedure, the company subsequently submitted further data and information on the outcome 'effective haemostasis' to show, among other things, the association between effective haemostasis and a better clinical outcome. In addition, the company presented further analyses on the outcome of thrombotic events.

In the following, the data and analyses subsequently submitted by the company are assessed as commissioned.

Patient relevance of the primary outcome 'effective haemostasis' remained unclear

The suitability or patient relevance of the 3 components of the primary outcome 'effective haemostasis' are discussed below, taking into account the data and publications subsequently submitted in the commenting procedure.

Component 1: no haematoma expansion > 35% 12 hours after randomization

Dossier assessment A25-87 already cited publications that did not show a clear association (in terms of a surrogate outcome) between an effect on haematoma expansion and long-term impairment or survival of patients with intracerebral haemorrhage. This selection was perceived as biased and selective by a single commentator in the commenting procedure. The basic requirements for surrogate validation according to IQWiG are explained in detail below. It is also discussed why the data presented by the company and the publications referenced in the comments did not provide sufficient evidence overall to show that the primary outcome 'effective haemostasis' (or the individual component haematoma expansion) is a sufficiently valid surrogate for mortality or long-term neurological impairment.

A common, fundamental misunderstanding is the equation of a prognostic marker and a surrogate outcome. In terms of surrogate validation, it is not sufficient to demonstrate that an outcome has a prognostic character, because a prognostic marker only indicates that there is a higher probability of dying earlier or of the disease becoming more severe. However, this does not mean that an effect on the prognostic marker can simultaneously be quantitatively translated into or transferred to an effect on the clinically relevant outcome (see also Section 'Haematoma expansion is not directly patient-relevant' below).

Surrogate validation based on a validation study (RCT)

Surrogate outcomes are normally considered only if they have been validated by means of appropriate statistical methods based on a complete study pool [9]. For a validation study, the study pool must only contain studies of sufficiently high quality (RCTs) that recorded and reported the treatment effect on the surrogate outcome and the treatment effect on the outcome of interest in the relevant population (see rapid reports A10-05 [10] and A24-61 [11]). Consequently, cohort studies or analyses of RCTs in which patients from the different treatment arms are pooled are not suitable, for example.

Assessment of validity in the absence of a surrogate validation study

In special situations, validity can also be recognized without a validation study. For this, it is necessary that the relationship between the patient-relevant outcome and the surrogate outcome is biologically/medically clearly plausible and that one of the following criteria is met:

1) The occurrence of the surrogate outcome leads to a dramatically reduced risk (point estimate factor 1/10 or smaller) with regard to the actual outcome.
2) The occurrence of the surrogate outcome leads to a substantially reduced risk (point estimate factor 1/5 or smaller) with regard to the actual outcome. In addition, the risk with regard to the actual outcome reaches a minimal level, e.g., that of a non-diseased population.

3) The occurrence of the surrogate outcome immediately and inevitably also means the occurrence of the actual outcome.

For Cases 1 and 2, additional conditions must be met. For example, statistically significant results must be available, at least from cohort studies relating to patients undergoing treatment; data on the natural course of the disease are not sufficient. Narrow specificity of intervention and therapeutic indication is not required. In addition, the follow-up period must be sufficiently long to accurately assess the risk of the actual outcome occurring. Furthermore, at least a focused search should have been conducted to obtain the evidence base (Rapid Report A24-61 [11]).

An example of Case 2 is the surrogate outcome 'sustained virologic response (SVR)' for the patient-relevant outcome hepatocellular carcinoma (HCC) in the therapeutic indication hepatitis C (treatment-naive or treatment-experienced, without cirrhosis for various genotypes). The risk for the occurrence of HCC under SVR is notably lower than without SVR; the relative risk (RR) is 0.21. In addition, the risk of HCC under SVR is comparable to the risk of HCC in the non-diseased population [12].

Insufficient evidence on the validity of haematoma expansion as a surrogate

Neither the data subsequently submitted by the company nor the publications subsequently submitted in the commenting procedure constituted a validation study according to the criteria listed above in which a correlation between the treatment effect on haematoma expansion and the treatment effect on a patient-relevant outcome was investigated on the basis of RCTs.

There was also no alternative evidence in the absence of a validation study, as described above. In the present case, the question is: Is haematoma expansion > 35% within the first 12 hours a valid surrogate for mortality or outcomes of morbidity? However, some of the publications address other research questions. For example, the publication by Broderick [13] investigated whether different categories of haematoma volume (0 to 29 cm^3, 30 to 60 cm^3 and ≥ 61 cm^3) are associated with the clinical outcome, but not a relative or absolute change in haematoma volume. The publications by Al-Shahi Salman [14] and Morotti [15] addressed the question of which risk factors exist for haematoma expansion and how to prevent them. Gerner [16] investigated the extent to which outcomes in patients with intracerebral haemorrhage associated with vitamin K antagonists differ from those with direct oral anticoagulants. Such studies are therefore not suitable for answering the question at hand. However, several publications [17-24] have shown an association between haematoma expansion and a clinical outcome (mortality, neurological outcomes, grade of impairment). It will not be discussed in more detail at this point that there were often other operationalizations and other data collection periods both for haematoma expansion and for

the clinical outcomes, and therefore to what extent there was any comparability at all between the studies and versus the operationalizations and timepoints of recording defined by the company, as there were overarching problems.

One of the overarching problems was that none of these publications were based on a focused literature search and therefore did not have a sufficiently complete data basis. However, this is an important prerequisite in order that the data is not presented in a biased manner. For example, as described in A25-87, individual studies showed little or no correlation between haematoma expansion and the patient-relevant clinical outcomes. Other studies (possibly numerous studies, subsequently submitted in the comments as mentioned above) showed a notably higher correlation, but also a sometimes highly variable extent. As already mentioned, narrow specificity of intervention and therapeutic indication is not required in the alternative approach without a validation study, but to be able to address this variance in the results between the individual studies, a meta-analysis is needed, as in the above-mentioned dossier assessment A11-17 on the SVR [12]. Apart from this, none of these publications showed a risk reduction to the extent described above and fulfilled the criteria mentioned.

The same applied to the data subsequently submitted by the company on the basis of the ANNEXA-I study. The company presented analyses on survival or deterioration in neurological outcomes depending on the achievement of effective haemostasis independent of the treatment arm. This neither fulfilled the above-mentioned requirements for a validation study nor did it show a risk reduction to the extent described.

The argument that the intervention acted as an effect modification, and that studies/analyses as requested by IQWiG were therefore not suitable, was not appropriate in the context of surrogate validation. It is precisely the effect of a treatment that should be taken into account for a surrogate validation. The decisive factor is that a therapy that improves the surrogate also has a favourable influence on the clinical outcome (predictive of treatment effects). If both treatment arms are considered together, the information on the effect of the individual forms of therapy is lost. The company's approach of pooling the 2 treatment arms of ANNEXA-I to prove the validity of effective haemostasis as a surrogate outcome was therefore not appropriate. In addition, there was the fundamental question as to whether there is a need for a surrogate outcome at all in the given situation; see separate section in the text below.

Overall, the publications and data were therefore not suitable for demonstrating the validity of haematoma expansion as a surrogate for mortality or outcomes of morbidity.

Haematoma expansion is not directly relevant to the patient

The company also argued that haematoma expansion is directly relevant to the patient, as the expansion of further haemorrhage directly destroys brain tissue and that haematoma expansion should therefore not be classified as a surrogate. The fact that (further)

haemorrhage is harmful is undisputed and was not questioned. However, whether a reduction in further haemorrhage (haematoma expansion) has a direct impact on clinical outcomes such as mortality or neurological outcomes and is therefore directly patient-relevant is a different question. As mentioned above, such a reduction in haematoma expansion can have a prognostic character, which has also been shown in the publications mentioned above. In this case, this means that patients with a haematoma expansion of ≥ 35% may have a higher risk of death or neurological deterioration. However, this does not mean that an observed treatment effect on haematoma expansion necessarily translates into an effect on overall survival or morbidity (which does not appear to be the case, as there were no relevant differences in the patient-relevant outcomes, see A25-87). The German Stroke Society (DSG) also rated the primary outcome of the ANNEXA-I study as a clear surrogate outcome and not as a directly patient-relevant outcome [25,26]. The Food and Drug Administration (FDA) also found no clear clinically relevant benefit, i.e. it also did not consider the primary outcome 'effective haemostasis' to be directly patient relevant. In its overall assessment, the FDA did not grant a full marketing authorization [27,28]. Both the publications by Smith [29] and Buka [30] as well as the comments of the DSG critically discussed that although there was a significant effect in the primary outcome 'effective haemostasis', there were no effects in the clinically relevant outcomes. Furthermore, no clear subgroups could currently be identified that would have a clinical benefit from the improved haemostatic efficacy. Based on previous data and pathophysiological considerations, according to the DSG, patients at high risk of haematoma growth and at the same time a low risk of thromboembolic complications could theoretically benefit from andexanet alfa [25,26]. However, when asked in the oral hearing, the company did not indicate that further investigations are planned in the future to characterize such a subgroup [31].

In this context, it should be noted that analyses of the characteristic of andexanet alfa dose (high dose vs. low dose) were prepared for the FDA [27,32]. As the dose level was not determined prior to randomization (see also A25-87), it was determined for the control arm which patients in the control arm would have met the criteria for a high or low dose. Based on these results (see Appendix A, Table 2), the question arose as to what extent the higher dose of andexanet alfa tends to cause greater harm.

Necessity of a surrogate in this therapeutic indication questionable

Irrespective of the validity of haematoma expansion as a surrogate, it is questionable whether a surrogate is necessary at all in the therapeutic indication at hand, as the patient-relevant outcomes such as mortality and neurological outcomes can also be observed directly. Whether the relevant timepoint of recording these patient-relevant outcomes is then on Day 30 or Day 90, for example, as was usually the case in the publications listed above, is a secondary question in this context. It should be noted, however, that the FDA had also recommended the recording of the modified Rankin Scale or the Glasgow Outcome Score at

Day 90 as the primary outcome, but this was not implemented in the ANNEXA-I study [27]. This underlines the criticism described in A25-87, both of the observation period and of the suitability of the primary outcome.

The comments also stated that the first 72 hours were particularly relevant and that there was a 'survivorship bias' thereafter, which 'diluted' the data up to Day 30, as patients who were predisposed to late complications were accumulated. Such an effect is, in principle, plausible, but would primarily only be relevant if patients were only observed from a point in time after this critical initial phase of approximately 72 hours. In such a situation, the probability of survival (after the first 72 hours) may shift to the disadvantage of the intervention group, as more patients in a highly critical condition would have been included who could have died under the comparator treatment (if the intervention shows an effect in the early phase). However, since the patients in the ANNEXA-I study were observed from the start of treatment, a positive effect in the first 72 hours should also translate into an advantage in mortality after 30 days, at least to a possibly attenuated extent. The same applies to a deterioration in neurological symptoms, which will be discussed separately below. Particularly when potential advantages of the intervention become apparent right at the start of treatment, it is both sensible and feasible to assess the patient-relevant outcome, such as survival, directly. However, in the ANNEXA-I study, there were no statistically significant differences between the treatment arms at Hour 72 or at Day 30 (mortality rate: 5% versus 7% at Hour 72 and 28% versus 26% at Day 30). Even though this therapeutic indication is an emergency situation and andexanet alfa is only indicated in acute bleeding situations, an observation period beyond the treatment period and the first critical phase is still necessary for the benefit assessment. No added benefit for patients can be derived from a possible positive effect in the early phase up to 72 hours, which, however, already disappears by the medium-term observation on Day 30 or Day 90 (both typical observation periods, as described) or even turns into the opposite due to late complications. In order to assess this properly, the outcomes must be observed for a sufficiently long period. It is possible to cover such a period within the framework of an RCT. The recording of effective haemostasis as an outcome makes medical/scientific sense, but does not replace the recording of patient-relevant outcomes directly relevant to the benefit assessment over a sufficiently long period of time.

Component 2: no rescue therapy between 3 and 12 hours after randomization

In dossier assessment A25-87, the following points of criticism were addressed in particular: the fact that the distinction between study medication and rescue therapy or subsequent treatment based solely on a time criterion was not appropriate, particularly in the comparator arm; and the fact that a (repeated) administration of haemostatic treatment later than 3 hours after randomization was also to be considered part of the standard treatment in the comparator arm. The company did not address the 2 main points of criticism in its comments.

The outcome ‘no rescue therapy between 3 and 12 hours after randomization’ was therefore still not suitable for the benefit assessment.

Component 3: no neurological deterioration 12 hours after randomization

Dossier assessment A25-87 described that although the prevention of neurological deterioration was generally considered patient-relevant, the period of 12 hours taken into account was too short to represent a longer-term impairment of patients in the therapeutic indication in question. At the hearing, the German Society for Haematology and Medical Oncology (DGHO) also emphasized that the aim (in addition to survival) is to avoid long-term disability as far as possible. As described above, it also applies to this outcome that it is not sufficient for the benefit assessment to show a possible positive effect in the first 12 or 72 hours without being able to estimate whether this possible effect might not disappear or even reverse by Day 30, or even Day 90 (e.g. due to thrombotic events). The data on the National Institutes of Health Stroke Scale (NIHSS) at Hours 24 and 72 subsequently submitted as part of the comments were therefore not suitable for the benefit assessment.

Regardless of this aspect, the conclusion expressed by one commentator that patients in the intervention arm were in a notably better neurological condition than those in the control arm during the first 72 hours was not accepted. As shown in Module 4 A of the company, the proportion of patients without neurological deterioration (NIHSS score ≥ 7) 12 hours after randomization was almost the same (87.6% versus 86.3%), so that there was no statistically significant difference between the treatment arms ($p = 0.694$). As already shown in A25-87, there was also no relevant difference between the treatment arms in the period up to 72 hours after randomization. Consequently, the company itself did not derive any indication of an added benefit in Module 4 A.

In summary, the points of criticism addressed in A25-87 regarding the individual components of the primary outcome ‘effective haemostasis’ remained and the outcome was not used for the benefit assessment.

Appendix A, Table 3, provides a supplementary presentation of the outcome ‘effective haemostasis’ in compliance with the commission.

Thrombotic events

In dossier assessment A25-87, thrombotic events (serious adverse events [SAEs] up to Day 30) were used to derive the added benefit. A disadvantage of andexanet alfa was shown. The company argued in its comments that there was an increased incidence of any thrombotic events and of serious thrombotic events, particularly during the first 24 hours. After 72 hours, the incidence between the treatment arms was comparable, according to the company. In addition, the company argued that antithrombotic therapy can be resumed after the use of andexanet alfa as soon as this is indicated in the physician’s assessment. The company added

that in patients in the intervention arm in whom antithrombotic therapy was resumed before a thrombotic event, the incidence of thrombotic events was comparable to the incidence in the control arm (presented as supplementary information in Table 4). However, the early occurrence of thrombotic events in particular can make it difficult to resume antithrombotic therapy in time to prevent these early thrombotic events. According to the summary of product characteristics (SmPC) [33], antithrombotic therapy can be re-initiated if the patient is clinically stable and adequate haemostasis has been achieved. Balancing the benefits of anticoagulation against the risks of re-bleeding is extremely difficult and a specific time for re-initiation has not been established. Thus, no clearly defined subpopulation can be determined that benefits from a (timely) re-initiation of antithrombotic therapy. These results could therefore not be used for the benefit assessment.

The new analysis of thrombotic events presented by the company, which used an exact test procedure based on Fisher's exact test, a method which, according to the company, is preferred by IQWiG, was also not taken into account. Module 4 A presented the analyses based on the Cochran-Mantel-Haenszel method, which were used in A25-87 and which showed a significant difference between the treatment arms to the disadvantage of andexanet alfa. If the relative risk and p-value are calculated by IQWiG itself, an unconditional exact test using the convexity, symmetry, z-score (CSZ) method is usually used [34], which also showed a significant difference between the treatment arms to the disadvantage of andexanet alfa ($p = 0.047$). The new analyses presented by the company therefore did not appear consistent and were not informative overall. Irrespective of this, andexanet alfa, even using the Fisher's Exact Test, continued (as presented in A25-87) to show greater harm with the extent 'major' for the outcome ischaemic stroke (SAE).

The disadvantage described in A25-87 for andexanet alfa in serious thrombotic events remains.

2.1 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of andexanet alfa from dossier assessment A25-87.

The following Table 1 shows the result of the benefit assessment of andexanet alfa under consideration of dossier assessment A25-87 and the present addendum.

Table 1: Andexanet alfa – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients treated with a direct FXa inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrollable bleeding[b]	Individualized treatment[c, d] with a choice of: ▪ prothrombin complex concentrates ▪ BSC[e, f]	▪ Patients with intracerebral haemorrhage: hint of a lesser benefit[g] ▪ All other patients in the therapeutic indication: added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, it is assumed that patients in both arms received optimal intensive care.
c. The term 'individualized treatment' is used instead of previously used terms such as 'patient-specific therapy' or 'treatment of physician's choice'. This ensures consistency with the terms used in European health technology assessments (EU HTAs).
d. Both a single-comparator study with prothrombin complex concentrates and a multi-comparator study with a choice of the above-mentioned treatment options may be suitable for the implementation of the ACT. However, the choices should always include prothrombin complex concentrates. If the implementation takes the form of a multi-comparator study, the individualized treatment decision regarding the comparator therapy should be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons).
e. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
f. According to the G-BA, it is assumed that fluid replacement and the administration of plasma expanders or blood products, if indicated, are carried out as part of BSC in the event of severe or life-threatening bleeding. The location of the life-threatening or uncontrollable bleeding (e.g. cerebral haemorrhage, gastrointestinal haemorrhages) is also a criterion for the appropriate therapy in each case.
g. The subpopulation of the ANNEXA-I study relevant for this benefit assessment also includes a small proportion (9%) of patients with other intracranial haemorrhages.

ACT: appropriate comparator therapy; BSC: best supportive care; EU: European Union; FXa: Factor Xa; G-BA: Federal Joint Committee; HTA: health technology assessment

The G-BA decides on the added benefit.

3 References

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Andexanet alfa (akute schwere Blutungen); Nutzenbewertung gemäß § 35a SGB V (Ablauf Befristung); Dossierbewertung [online]. 2025 [Accessed: 07.10.2025]. URL: https://doi.org/10.60584/A25-87.

2. AstraZeneca. Stellungnahme zum IQWiG-Bericht Nr. 2088: Andexanet alfa (akute schwere Blutungen); Nutzenbewertung gemäß § 35a SGB V. [Soon available at: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1236/#stellungnahmen in the document "Zusammenfassende Dokumentation"].

3. AstraZeneca. Andexanet alfa (Ondexxya); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2025 [Accessed: 13.11.2025]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1236/#dossier.

4. Alexion Pharmaceuticals. Trial of Andexanet Alfa in ICrH Patients Receiving an Oral FXa Inhibitor [online]. 2024 [Accessed: 02.09.2025]. URL: https://clinicaltrials.gov/show/NCT03661528.

5. AstraZeneca. A Randomized Clinical Trial of Andexanet Alfa in Acute Intracranial Hemorrhage in Patients Receiving an Oral Factor Xa Inhibitor (ANNEXA-I); study 18-513; Clinical Study Report [unpublished]. 2023.

6. AstraZeneca. A Randomized Clinical Trial of Andexanet Alfa in Acute Intracranial Hemorrhage in Patients Receiving an Oral Factor Xa Inhibitor (ANNEXA-I); study 18-513; Clinical Study Report Addendum [unpublished]. 2024.

7. Connolly SJ, Sharma M, Cohen AT et al. Andexanet for Factor Xa Inhibitor-Associated Acute Intracerebral Hemorrhage. N Engl J Med 2024; 390(19): 1745-1755. https://doi.org/10.1056/NEJMoa2313040.

8. Portola Pharmaceuticals. A Phase 4 Randomized Clinical Trial of Andexanet Alfa (Andexanet Alfa for Injection) in Acute Intracranial Hemorrhage in Patients Receiving an Oral Factor Xa Inhibitor [online]. [Accessed: 02.09.2025]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2018-002620-17.

9. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 02.09.2025]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf.

10. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Aussagekraft von Surrogatendpunkten in der Onkologie; Rapid Report [online]. 2011 [Accessed: 11.07.2023]. URL: https://www.iqwig.de/download/a10-05_rapid_report_surrogatendpunkte_in_der_onkologie.pdf.

11. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Wissenschaftliche Ausarbeitung zu klinischen Studien im Therapiegebiet Wundbehandlung; finaler Rapid Report [online]. 2025 [Accessed: 09.05.2025]. URL: https://doi.org/10.60584/A24-61.

12. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Boceprevir – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2011 [Accessed: 11.07.2023]. URL: https://www.iqwig.de/download/a11-17_boceprevir_nutzenbewertung_gemaess_35a_sgb_v.pdf.

13. Broderick JP, Brott TG, Duldner JE et al. Volume of intracerebral hemorrhage. A powerful and easy-to-use predictor of 30-day mortality. Stroke 1993; 24(7): 987-993. https://doi.org/10.1161/01.str.24.7.987.

14. Al-Shahi Salman R, Frantzias J, Lee RJ et al. Absolute risk and predictors of the growth of acute spontaneous intracerebral haemorrhage: a systematic review and meta-analysis of individual patient data. Lancet Neurol 2018; 17(10): 885-894. https://doi.org/10.1016/S1474-4422(18)30253-9.

15. Morotti A, Boulouis G, Dowlatshahi D et al. Intracerebral haemorrhage expansion: definitions, predictors, and prevention. Lancet Neurol 2023; 22(2): 159-171. https://doi.org/10.1016/S1474-4422(22)00338-6.

16. Gerner ST, Kuramatsu JB, Sembill JA et al. Characteristics in Non-Vitamin K Antagonist Oral Anticoagulant-Related Intracerebral Hemorrhage. Stroke 2019; 50(6): 1392-1402. https://doi.org/10.1161/STROKEAHA.118.023492.

17. Davis SM, Broderick J, Hennerici M et al. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. Neurology 2006; 66(8): 1175-1181. https://doi.org/10.1212/01.wnl.0000208408.98482.99.

18. Delcourt C, Huang Y, Arima H et al. Hematoma growth and outcomes in intracerebral hemorrhage: the INTERACT1 study. Neurology 2012; 79(4): 314-319. https://doi.org/10.1212/WNL.0b013e318260cbba.

19. Dowlatshahi D, Demchuk AM, Flaherty ML et al. Defining hematoma expansion in intracerebral hemorrhage: relationship with patient outcomes. Neurology 2011; 76(14): 1238-1244. https://doi.org/10.1212/WNL.0b013e3182143317.

20. Abou Karam G, Chen MC, Zeevi D et al. Time-Dependent Changes in Hematoma Expansion Rate after Supratentorial Intracerebral Hemorrhage and Its Relationship with Neurological Deterioration and Functional Outcome. Diagnostics (Basel) 2024; 14(3). https://doi.org/10.3390/diagnostics14030308.

21. Fletcher-Sandersjoo A, Tatter C, Tjerkaski J et al. Time Course and Clinical Significance of Hematoma Expansion in Moderate-to-Severe Traumatic Brain Injury: An Observational Cohort Study. Neurocrit Care 2023; 38(1): 60-70. https://doi.org/10.1007/s12028-022-01609-w.

22. Dowlatshahi D, Butcher KS, Asdaghi N et al. Poor prognosis in warfarin-associated intracranial hemorrhage despite anticoagulation reversal. Stroke 2012; 43(7): 1812-1817. https://doi.org/10.1161/STROKEAHA.112.652065.

23. Morotti A, Boulouis G, Nawabi J et al. Association Between Hematoma Expansion Severity and Outcome and Its Interaction With Baseline Intracerebral Hemorrhage Volume. Neurology 2023; 101(16): e1606-e1613. https://doi.org/10.1212/WNL.0000000000207728.

24. Gulati AK, Ma T, Rolle I et al. Predictors and Outcomes of Hematoma Expansion and Neurological Decline in Intracerebral Hemorrhage; A Multisite Mobile Stroke Unit Study. Stroke: Vascular and Interventional Neurology 2025; 5(1): 1-12. https://doi.org/10.1161/SVIN.124.001546.

25. Steiner T, Huttner H, Köhrmann M. Stellungnahme der Deutschen Schlaganfallgesellschaft zu den Ergebnissen der ANNEXA-I Studie [online]. 2024 [Accessed: 17.11.2025]. URL: https://www.dsg-info.de/wp-content/uploads/2024/07/Stellungnahme-DSG-Annexa-I-FINAL.pdf.

26. Kuramatsu J, Beynon C, Schäbitz W-R. Stellungnahme der DSG zur Strategie der Aufebung einer Gerinnungshemmung bei Antikoagulanzien- assoziierten intrazerebralen Blutungen [online]. 2024 [Accessed: 17.11.2025]. URL: https://www.dsg-info.de/wp-content/uploads/2024/11/Stellungnahme-der-DSG-Aufhebung-einer-Gerinnungshemmung-bei-Antikoagulanzien-assoziierten-intrazerebralen-Blutungen.pdf.

27. Food and Drug Administration. Tissue, and Gene Therapies Advisory Committee Meeting; November 21, 2024; DCEH/OCE/OTP; Briefing Document [online]. 2024 [Accessed: 19.11.2025]. URL: https://www.fda.gov/media/183674/download.

28. Food and Drug Administration. Summary Minutes; 77th Cellular, Tissue, and Gene Therapies Advisory Committee Meeting; November 21, 2024 [online]. 2024 [Accessed: 19.11.2025]. URL: https://www.fda.gov/media/185461/download.

29. Smith WS, Hemphill JC. Reversing Oral Anticoagulation in Intracerebral Hemorrhage. N Engl J Med 2024; 390(19): 1815-1816. https://doi.org/10.1056/NEJMe2403726.

30. Buka RJ. Andexanet alfa: trials just leave us with more questions. Res Pract Thromb Haemost 2025; 9(1): 102628. https://doi.org/10.1016/j.rpth.2024.102628.

31. Gemeinsamer Bundesausschuss. Mündliche Anhörung gemäß § 35 a Abs. 3 Satz 2 SGB V des Gemeinsamen Bundesausschusses hier: (Andexanet alfa (D-1217); Stenografisches Wortprotokoll [online]. 2025 [Accessed: 25.11.2025]. URL: https://www.g-ba.de/downloads/91-1031-1236/2025-11-10_Wortprotokoll_Andexanet-alfa_D-1217.pdf.

32. Food and Drug Administration. Cellular, Tissue, and Gene Therapies Advisory Committee November 21, 2024 Meeting Announcement; Video Zeitpunkt 5:27:28, [online]. 2024 [Accessed: 25.11.2025]. URL: https://www.fda.gov/advisory-committees/advisory-committee-calendar/cellular-tissue-and-gene-therapies-advisory-committee-november-21-2024-meeting-announcement-11212024#event-information.

33. AstraZeneca. Ondexxya 200 mg Pulver zur Herstellung einer Infusionslösung [online]. 08.2025 [Accessed: 04.09.2025]. URL: https://www.fachinfo.de/fi/detail/023014/ondexxya-r-200-mg-pulver-zur-herstellung-einer-infusionsloesung.

34. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574. https://doi.org/10.1016/0167-9473(94)90148-1.

Appendix A Results

Table 2: Subgroups, supplementary presentation (mortality, side effects, effective haemostasis) – RCT, direct comparison: andexanet alfa vs. standard treatment

Study Outcome	andexanet alfa		Standard treatment		andexanet alfa vs. standard treatment
Characteristic Subgroup	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI][a]; p-value[b]
ANNEXA-I					
All-cause mortality (up to Day 30)					
Andexanet alfa dose regimen					
High dose[c]	53	21 (39.6)	49	13 (26.5)	1.49 [0.84; 2.65]; 0.172
Low dose[c]	186	46 (24.7)	183	48 (26.2)	0.94 [0.67; 1.34]; 0.808
Total				Interaction:	p-value[d] = 0.179
Thrombotic events[e] (AEs)[f] (up to Day 30)[g]					
Andexanet alfa dose regimen					
High dose[c]	53	11 (20.8)	49	4 (8.2)	2.54 [0.87; 7.46]; 0.079
Low dose[c]	186	24 (12.9)	183	12 (6.6)	1.97 [1.01; 3.82]; 0.042
Total				Interaction:	p-value[d] = 0.691
Effective haemostasis (at Hour 12)					
Andexanet alfa dose regimen					
High dose[c]	54	22 (40.7)	49	22 (44.9)	0.91 [0.58; 1.42]; 0.723
Low dose[c]	187	129 (69.0)	184	100 (54.3)	1.27 [1.08; 1.49]; 0.004
Total				Interaction:	p-value[d] = 0.163

a. RR and CI: Institute's calculation.
b. Institute's calculation, unconditional exact test (CSZ method according to [34])
c. High dose: 800 mg IV as a 30-minute bolus infusion, followed by 960 mg IV as a 120-minute infusion; low dose: 400 mg IV as a 15-minute bolus infusion, followed by 480 mg IV as a 120-minute infusion.
d. Institute's calculation, Q test.
e. The AE of special interest recorded by the company in the study is considered (including arterial systemic embolism, deep vein thrombosis, myocardial infarction, pulmonary embolism, stroke and transient ischaemic attack).
f. Only subgroup analyses of any thrombotic events that occurred are available.
g. The data are assumed to relate to the period up to 30 days. Discrepancies in the overall rate between the clinical study report and the FDA analysis. Data according to the FDA analysis.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk

Table 3: Results (effective haemostasis) – RCT, direct comparison: andexanet alfa vs. standard treatment

Study Outcome	andexanet alfa		Standard treatment		andexanet alfa vs. standard treatment
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
ANNEXA-I					
Effective haemostasis at Hour 12[b]	241	151 (62.7)	233	122 (52.4)	1.19 [1.02; 1.39]; 0.024
Effective haemostasis at Hour 24[b]	241	161 (66.8)	233	126 (54.1)	1.23 (1.06; 1.42); 0.005
Effective haemostasis at Hour 72[b]	241	159 (66.0)	233	127 (54.5)	1.21 (1.04; 1.39), 0.011

a. Mantel-Haenszel method.
b. Effective haemostasis at 12, 24 and 72 hours using the NIHSS at 12, 24 and 72 hours and rescue medication between 3 and 12 hours, up to 24 or up to 72 hours; criterion for change in haematoma volume in accordance with the definition of the primary outcome (> 35% after 12 hours)

CI: confidence interval; n: number of patients with event; N: number of analysed patients; NIHSS: National Institutes of Health Stroke Scale; RCT: randomized controlled trial; RR: relative risk

Table 4: Thrombotic events in patients with/without prophylactic re-anticoagulation - RCT, direct comparison: andexanet alfa vs. standard treatment

Study	andexanet alfa N = 239	Standard treatment N = 232
ANNEXA-I		
Overall rate of thrombotic events[a]	26 (10.9)	13 (5.6)
Number of patients who were not re-anticoagulated or were only re-anticoagulated after a thrombotic event, n (%)	72 (30.1)	68 (29.3)
Patients with event, n (%)	17 (23.6[b])	5 (7.4[b])
Number of patients who were re-anticoagulated before a thrombotic event, n (%)	167 (69.9)	164 (70.7)
Patients with event, n (%)	9 (5.4[c])	8 (4.9[c])

a. The AE of special interest recorded by the company in the study is considered (including arterial systemic embolism, deep vein thrombosis, myocardial infarction, pulmonary embolism, stroke and transient ischaemic attack).
b. Proportion refers to patients without anticoagulation or with anticoagulation only after a thrombotic event.
c. Proportion refers to patients with anticoagulation before a thrombotic event.

n: number of patients with at least one event; N: number of analysed patients; RCT: randomized controlled trial