NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

NEWSLETTER

JUNE 2024 | VOLUME 3 | ISSUE 6

FASTEST

FVIIa for Acute hemorrhagic Stroke

Administered at Earliest Time

Issue Contents:

Message from Dr. Grotta

Now that the drug supply issue has been solved, we look forward to all sites getting back up and enrolling. Systems often decay when not used, so please re-inservice your ER and stroke teams to remember "every ICH patient is a potential FASTEST patient"!

James Grotta MD
Director of Stroke Research,
Clinical Institute for Research and Innovation,
Memorial Hermann - Texas Medical Center
Director, Mobile Stroke Unit Consortium.

Please join us for the *FASTEST* Monthly Webinar

Wednesday June 12th, 2:00-3:00 pm EST

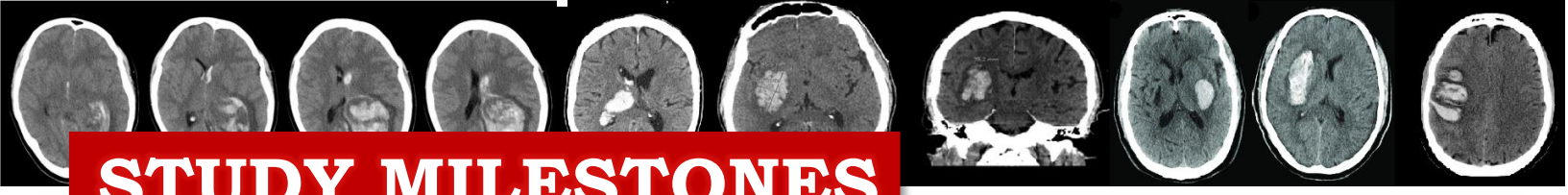
- Brief trial update.
- Dr. Broderick will discuss highlights of clinical trials of ICH from ESOC meeting in Basel.
- Pharmacy update on new IP shipment in US.

Join Zoom Meeting

https://ucincinnati.zoom.us/j/99236910048

Meeting ID: 992 3691 0048

Prior presentations and slides are available at, https://www.nihstrokenet.org/fastest/webinars



STUDY MILESTONES

Total Sites Released to Enroll: **91** (**52** USA, **39** OUS: **6** Germany, **14** Japan, **6** Spain, **9** Canadian, **4** UK)

Total MSUs Released to Enroll: **12** (**10** US and **2** OUS)

Total Randomization = **468**

- US Randomizations: **125**
- International randomizations: **342**
  - Japan = **217**
  - Canada = **57**
  - Spain =**31**
  - Germany = **27**
  - UK = **11**

Randomization last month = **26**

Total Screen Failures = **1773**

Subjects Randomized by MSU = **16**

Subjects Terminated Early = **3**

eConsent Used = **22**

Remote Consent Used = **18**

CALENDAR OF EVENTS

Upcoming *FASTEST* Monthly Webinars: **Wednesday, June 12th, @ 2:00-3:00 pm EST**

FASTEST study team office hours: **Monday, June 17th, @ 1:00-2:00 pm.**

Important Notes

Study Drug Update - USA Sites Only:

On behalf of NIH StrokeNet Pharmacy, we are pleased to inform you that our study drug has been received from Novo. Our central pharmacy is diligently working to expedite the shipment of study kits, **starting Monday, June 10th**. **Once you receive the new kits, please notify your study team to resume enrollment.** Thank you for your patience; we anticipate a highly productive month of enrollments!

Additionally, NDMC has sent an IP email update to all sites on Monday.

Please note: To help reduce drug wastage due to temperature excursions and to manage kit allocation effectively in the event of a shortage, we will only be shipping one kit to sites that have not enrolled a subject in the past three months.

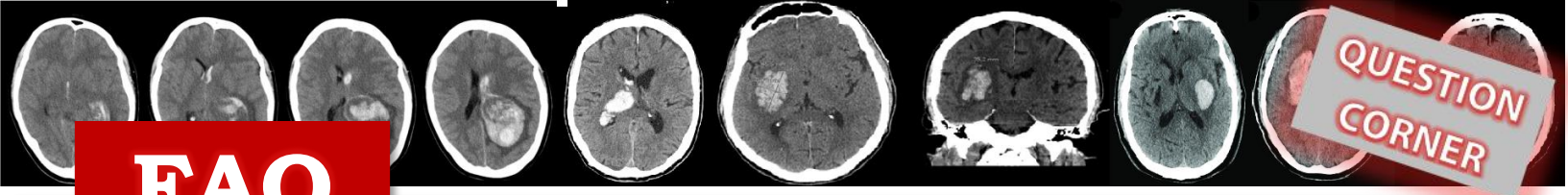
Thank you for your understanding and cooperation.

Sites Without Enrollment or Screening for Few Months:

During our recent review of study progress and site enrollment, it was brought to our attention sites that have been screening but not enrolled a subject in the past 9 months. We are reaching out to all these sites which have not enrolled or screened in **over 150 days.** Once your site receives the investigational product (IP) and enrollment resumes, we ask all U.S. sites to focus on actively enrolling eligible subjects into the trial.

Expired or missing documents in WebDCU:

There are many expired or missing documents in WebDCU. This is a reminder to always be updating missing or expired documents. Investigators are required to remain current on all study related trainings and required documents.



FAQ

Q: We had submitted the attached memo to our IRB given that there is a temporary halt to enrollment at our site and our IRB wished to know if this was provided to the external IRB and if so, what was the outcome of that reporting?
A: To clarify, the study itself did not pause; only the enrollment was temporarily halted due to the study medication being in transit. There were no safety issues, and all the sites continued screening potential subjects as usual. This was a technical/workflow issue on our end, so no CIRB notification was required. To clarify, the study itself did not pause; only the enrollment was temporarily halted due to the study medication being in transit. There were no safety issues, and all sites continued screening potential subjects as usual. This was a technical/workflow issue on our end, so no CIRB notification was required. The good news is that the IP for the US sites is now available, and the central pharmacy anticipate restocking all US sites by next week.

Q: We noted the subject had Acute Respiratory Failure and NSTEMI and think these should be entered as additional AEs. Can you please confirm?
A: Yes, these events should be reported as separate AEs. Please ensure they are entered individually.

Q: We had a potential patient, but due to the drug not being available, we were unable to enroll them. Should I classify this as a screen failure?
A: Yes, this should be recorded as a screen failure.

Q: The MSU is out of service and the log will not be in range. Do you need me to do anything about this? I was not sure since the MSU does not carry the drug at the moment.
A: Since the MSU is out of service and you are not storing the study drug there, no log is required. Please note this in the issues table.

Q: I saw that the most recent StrokeNet update mentioned new FASTEST guidelines for randomization outside of the 120-minute window. I haven't received any new guidelines and am wondering where to find them?
A: You should be able to find new FASTEST guidelines for randomization outside of the 120-minute window in the study MOP.

Please send in your questions and we will address them accordingly and share with others in the next Newsletter.

New Sites... Welcome Aboard!

The following new site was **released to enroll** in the *FASTEST* study during the last month.

Arnau de Vilanova University Hospital, Lleida, L, Spain

Site PI: Francisco PURROY

SHOUT OUTS!!

Congratulations to US sites that have completed EFIC and have been submitted to the CIRB for approval for emergency consent.

1. **St. Joseph's Hospital and Medical Center, Phoenix, AZ**
2. **Mayo Clinic, Jacksonville, FL**

Thank you to the sites recently released to enroll for their hard work:

1. **Arnau de Vilanova University Hospital, Lleida, L, Spain**

The Top Enrolling Site

Congratulations to **National Cerebral and Cardiovascular Center, Osaka, Japan** for being the highest enrolling site in the study.

Subjects enrolled = 55!!

Congratulations to Enrolling Sites last Month!

Iwate Prefectural Central Hospital, Morioka, Japan	3 Subject
National Cerebral and Cardiovascular Center, Osaka, Japan	3 Subject
Toranomon Hospital, Tokyo, Japan	1 Subject
Nakamura Memorial Hospital, Sapporo, Japan	1 Subject
Niigata City General Hospital, Niigata, Japan	1 Subject
Japanese Red Cross Kyoto Daini Hospital, Kyoto, Japan	2 Subject
Jichi Medical University Hospital, Shimotsuke, Japan	1 Subject
Gifu University Hospital, Gifu, Japan	1 Subject
University of Calgary - Foothills Medical Centre, Calgary, AB, Canada	1 Subject
University of Montreal Hospital, Montreal, QC, Canada	1 Subject
St. Michaels Hospital, Toronto, ON, Canada	1 Subject
University Hospital Heidelberg, Heidelberg, Germany	1 Subject
Tubingen University Hospital, Tubingen, Germany	1 Subject
University Hospital Erlangen, Erlangen, Germany	1 Subject
University Hospital Augsburg, Augsburg, Germany	1 Subject
Memorial Hermann Memorial City Medical Center, Houston, TX	1 Subject
Hospital Universitari Germans Trias i Pujol, Barcelona, B, Spain	1 Subject
Santa Creu and Sant Pau Hospital, Barcelona, B, Spain	1 Subject
Girona University Hospital, Girona, GI, Spain	1 Subject
Royal Victoria Infirmary, Newcastle upon Tyne, United Kingdom	1 Subject

Andexanet for Factor Xa Inhibitor–Associated Acute Intracerebral Hemorrhage

Stuart J. Connolly, M.D. https://orcid.org/0000-0002-7377-335X, Mukul Sharma, M.D., Alexander T. Cohen, M.D., Andrew M. Demchuk, M.D., Anna Członkowska, M.D., Arne G. Lindgren, M.D., Carlos A. Molina, M.D., +34, for the ANNEXA-I Investigators*

Published May 15, 2024 / N Engl J Med 2024;390:1745-1755 / DOI: 10.1056/NEJMoa2313040

Background

Patients with acute intracerebral hemorrhage who are receiving factor Xa inhibitors have a risk of hematoma expansion. The effect of andexanet alfa, an agent that reverses the effects of factor Xa inhibitors, on hematoma volume expansion has not been well studied.

Methods

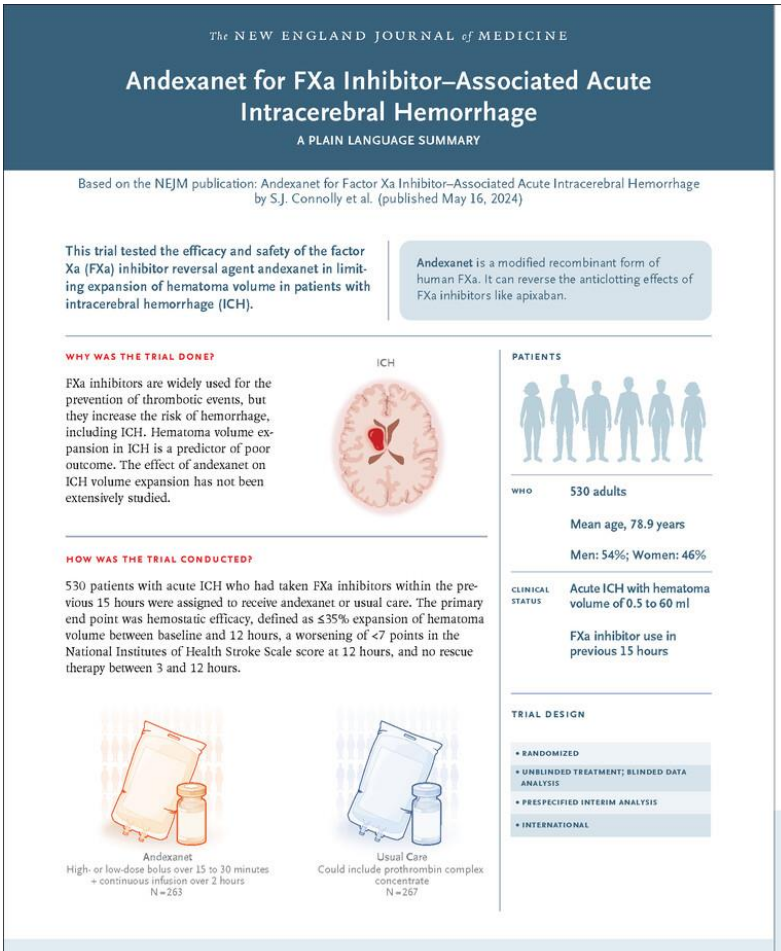
We randomly assigned, in a 1:1 ratio, patients who had taken factor Xa inhibitors within 15 hours before having an acute intracerebral hemorrhage to receive andexanet or usual care. The primary end point was hemostatic efficacy, defined by expansion of the hematoma volume by 35% or less at 12 hours after baseline, an increase in the score on the National Institutes of Health Stroke Scale of less than 7 points (scores range from 0 to 42, with higher scores indicating worse neurologic deficit) at 12 hours, and no receipt of rescue therapy between 3 hours and 12 hours. Safety end points were thrombotic events and death.

Results

A total of 263 patients were assigned to receive andexanet, and 267 to receive usual care. Efficacy was assessed in an interim analysis that included 452 patients, and safety was analyzed in all 530 enrolled patients. Atrial fibrillation was the most common indication for factor Xa inhibitors. Of the patients receiving usual care, 85.5% received prothrombin complex concentrate. Hemostatic efficacy was achieved in 150 of 224 patients (67.0%) receiving andexanet and in 121 of 228 (53.1%) receiving usual care (adjusted difference, 13.4 percentage points; 95% confidence interval [CI], 4.6 to 22.2; P=0.003). The median reduction from baseline to the 1-to-2-hour nadir in anti–factor Xa activity was 94.5% with andexanet and 26.9% with usual care (P<0.001). Thrombotic events occurred in 27 of 263 patients (10.3%) receiving andexanet and in 15 of 267 (5.6%) receiving usual care (difference, 4.6 percentage points; 95% CI, 0.1 to 9.2; P=0.048); ischemic stroke occurred in 17 patients (6.5%) and 4 patients (1.5%), respectively. There were no appreciable differences between the groups in the score on the modified Rankin scale or in death within 30 days.

Conclusions

Among patients with intracerebral hemorrhage who were receiving factor Xa inhibitors, andexanet resulted in better control of hematoma expansion than usual care but was associated with thrombotic events, including ischemic stroke. (Funded by Alexion AstraZeneca Rare Disease and others; ANNEXA-I ClinicalTrials.gov number, NCT03661528.)


The NEW ENGLAND JOURNAL of MEDICINE

Andexanet for FXa Inhibitor–Associated Acute Intracerebral Hemorrhage

A PLAIN LANGUAGE SUMMARY

Based on the NEJM publication: Andexanet for Factor Xa Inhibitor–Associated Acute Intracerebral Hemorrhage by S.J. Connolly et al. (published May 16, 2024)

This trial tested the efficacy and safety of the factor Xa (FXa) inhibitor reversal agent andexanet in limiting expansion of hematoma volume in patients with intracerebral hemorrhage (ICH).

Andexanet is a modified recombinant form of human FXa. It can reverse the anticlotting effects of FXa inhibitors like apixaban.

WHY WAS THE TRIAL DONE?

FXa inhibitors are widely used for the prevention of thrombotic events, but they increase the risk of hemorrhage, including ICH. Hematoma volume expansion in ICH is a predictor of poor outcome. The effect of andexanet on ICH volume expansion has not been extensively studied.

ICH

HOW WAS THE TRIAL CONDUCTED?

530 patients with acute ICH who had taken FXa inhibitors within the previous 15 hours were assigned to receive andexanet or usual care. The primary end point was hemostatic efficacy, defined as ≤35% expansion of hematoma volume between baseline and 12 hours, a worsening of <7 points in the National Institutes of Health Stroke Scale score at 12 hours, and no rescue therapy between 3 and 12 hours.

Andexanet
High- or low-dose bolus over 15 to 30 minutes + continuous infusion over 2 hours
N=263

Usual Care
Could include prothrombin complex concentrate
N=267

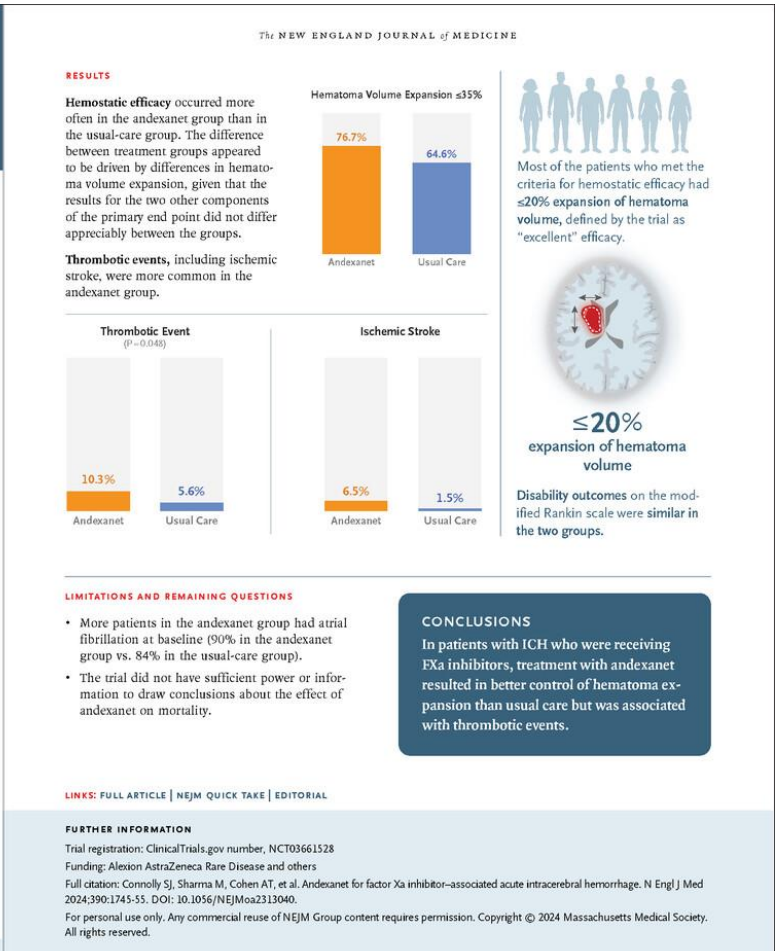
PATIENTS

WHO: 530 adults; Mean age, 78.9 years; Men: 54%; Women: 46%

CLINICAL STATUS: Acute ICH with hematoma volume of 0.5 to 60 ml; FXa inhibitor use in previous 15 hours

TRIAL DESIGN

- RANDOMIZED
- UNBLINDED TREATMENT; BLINDED DATA ANALYSIS
- PRESPECIFIED INTERIM ANALYSIS
- INTERNATIONAL


The NEW ENGLAND JOURNAL of MEDICINE

RESULTS

Hemostatic efficacy occurred more often in the andexanet group than in the usual-care group. The difference between treatment groups appeared to be driven by differences in hematoma volume expansion, given that the results for the two other components of the primary end point did not differ appreciably between the groups.

Thrombotic events, including ischemic stroke, were more common in the andexanet group.

Hematoma Volume Expansion ≤35%: 76.7% Andexanet; 64.6% Usual Care

Thrombotic Event (P=0.048): 10.3% Andexanet; 5.6% Usual Care

Ischemic Stroke: 6.5% Andexanet; 1.5% Usual Care

Most of the patients who met the criteria for hemostatic efficacy had **≤20% expansion of hematoma volume,** defined by the trial as "excellent" efficacy.

≤20% expansion of hematoma volume

Disability outcomes on the modified Rankin scale were **similar in the two groups.**

LIMITATIONS AND REMAINING QUESTIONS

- More patients in the andexanet group had atrial fibrillation at baseline (90% in the andexanet group vs. 84% in the usual-care group).
- The trial did not have sufficient power or information to draw conclusions about the effect of andexanet on mortality.

CONCLUSIONS

In patients with ICH who were receiving FXa inhibitors, treatment with andexanet resulted in better control of hematoma expansion than usual care but was associated with thrombotic events.

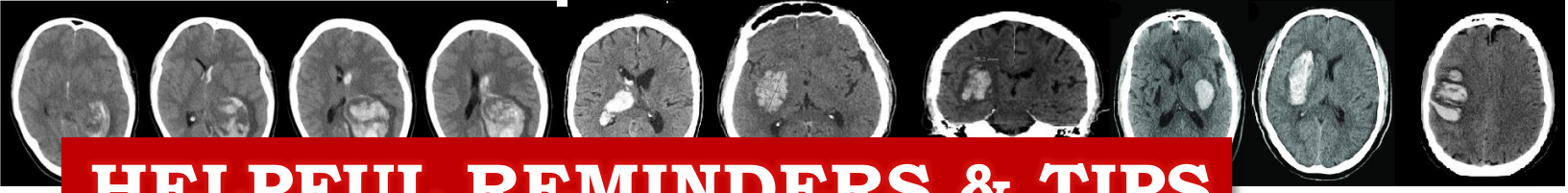
LINKS: FULL ARTICLE | NEJM QUICK TAKE | EDITORIAL

FURTHER INFORMATION

Trial registration: ClinicalTrials.gov number, NCT03661528

Funding: Alexion AstraZeneca Rare Disease and others

Full citation: Connolly SJ, Sharma M, Cohen AT, et al. Andexanet for factor Xa inhibitor–associated acute intracerebral hemorrhage. N Engl J Med 2024;390:1745-55. DOI: 10.1056/NEJMoa2313040.



HELPFUL REMINDERS & TIPS

For Project Managers, Study Coordinators & Study Teams

- **REDCap Alerts:** There will be following alerts for FASTEST sites in REDCap:
  - •Incomplete Records
  - •Remote Attestation
  - •WebDCU Subject ID

  These alerts were sent out 05-15-2024 at about 10 AM and will continue every day until the site addresses the matter.

- **New data base change:**

  F246 – Informed Consent – Regained Capacity

  - If the subject does regain capacity at some point during the trial or at end of study, but signed informed consent was not obtained, please enter the reasoning for why consent was not obtained into (Q09) 'Reason signed informed consent not obtained'.
  - If the subject does not regain capacity during the trial or at end of study, please enter the reason why into the General Comments section.
  - We will query for further information if needed.

  F104 Adverse Events

  We have had a recent database change impacting **F104 Adverse Events**. This update includes the additional question (Q31) shown below. If (Q12) *Type of event = 'Acute cerebral infarction'*, you will be prompted to answer (Q31).

  The attached PDF is Version 7 of the form and can be used as the printable form. This can also be found in the CRF Collection Schedule in WebDCU.

  Any already submitted Adverse Event forms will have warning violations triggered on forms where (Q12) = Acute Cerebral Infarction. Please update your CRFs to answer (Q31) if needed.

Q12		Type of event	○ Acute myocardial infarction ○ Acute cerebral infarction ○ Acute pulmonary embolism ○ Other adverse event	R
Q31	*If Q12 is 'Acute cerebral infarction'*	Type of acute cerebral infarction *Clinically silent new DWI positive small region on MRI is less than 1cm diameter* *Clinically silent new moderate- or large-sized ischemic lesion on CT or MRI is greater than or equal to 1 cm*	○ Clinically silent new DWI positive small region on MRI ○ Clinically silent new moderate- or large-sized ischemic lesion on CT or MRI ○ Any new cerebral infarction on MRI or CT that is accompanied by clinical worsening	W

STUDY CONTACTS & USEFUL INFO

For any study related queries or help please reach out to ***FASTEST*** Project managers

International Sites: **Syed Quadri** (quadrisd@ucmail.uc.edu)

United States Sites: **Emily Stinson** (stinsoey@ucmail.uc.edu)

FASTEST Clinical Hotline: 1-855-429-7050

For more information regarding the ***FASTEST*** study please visit : https://www.nihstrokenet.org/fastest/home

For prior ***FASTEST*** Presentations and Webinars slides and recordings visit: https://www.nihstrokenet.org/fastest/webinars

For more information regarding the StrokeNet Trials please visit: https://www.nihstrokenet.org/