NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

NEWSLETTER

MAY 2024 | VOLUME 3 | ISSUE 5

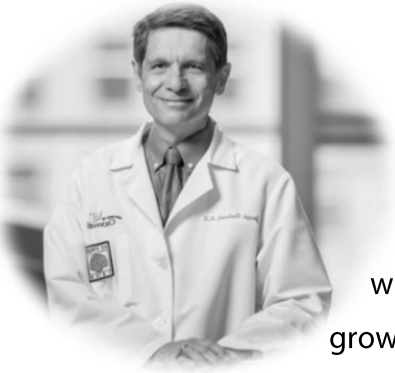
FASTEST

FVIIa for Acute hemorrhagic Stroke

Administered at Earliest Time

Issue Contents:

Message from Dr. Broderick



Let's be clear – FASTEST is all about answering the question whether a reduction in hematoma growth results in improvement in clinical outcome, and I think that FASTEST is the best opportunity to positively answer this question. At the just completed ESOC conference, we heard tremendously good news from the INTERACT 4 study very relevant to the FASTEST trial that controlling blood pressure with a target of 140 mm Hg systolic within the first 2 hours of onset improves outcome. This means that patients in both arms of our trial are receiving treatment that improves outcome. We are hopeful that the addition of rFVIIa can improve outcome further but know that your work is already changing lives. Keep on recruiting well so we can answer this important question.

Joseph Broderick, MD
Director NIH StrokeNet
FASTEST Principal Investigator

Please join us for the *FASTEST* Monthly Webinar

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

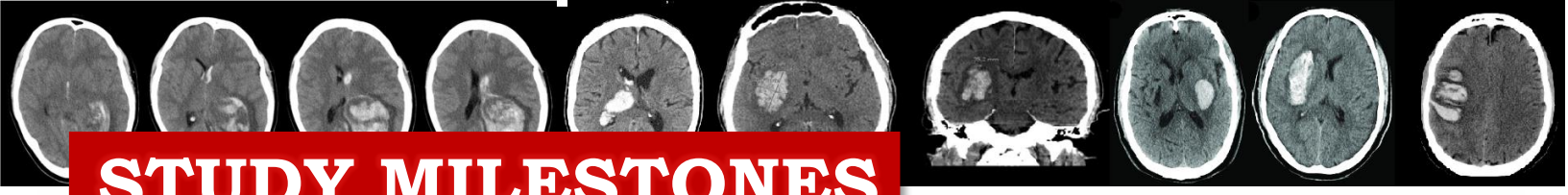
- Case discussion form *FASTEST* European sites.
- Dr. Broderick will discuss highlights of clinical trials of ICH from ESOC meeting in Basel.
- Pharmacy update on new IP shipment in US
- NDMC will be discussing database updates.

Join Zoom Meeting

https://ucincinnati.zoom.us/j/94084789726

Meeting ID: 940 8478 9726

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



STUDY MILESTONES

Total Sites Released to Enroll: **79** (**44** USA, **35** OUS: **6** Germany, **14** Japan, **4** Spain, **7** Canadian, **4** UK)

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

Total Randomization = **450**

- US Randomizations: **125**
- International randomizations: **325**
  - Japan = **211**
  - Canada = **53**
  - Spain =**28**
  - Germany = **23**
  - UK = **10**

Randomization last month = **21**

Total Screen Failures = **1423**

Subjects Randomized by MSU = **16**

Subjects Terminated Early = **2**

eConsent Used = **16**

Remote Consent Used = **12**

CALENDAR OF EVENTS

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

FASTEST study team office hours: **Monday, May 20th, @ 1:00-2:00 pm.**

Important Notes

Study Drug Expiration - USA Sites Only:

Due to delays in receiving the study drug from Novo and the limited availability of kits with extended expiration date at StrokeNet Pharmacy, **two communication memos** were distributed last week.

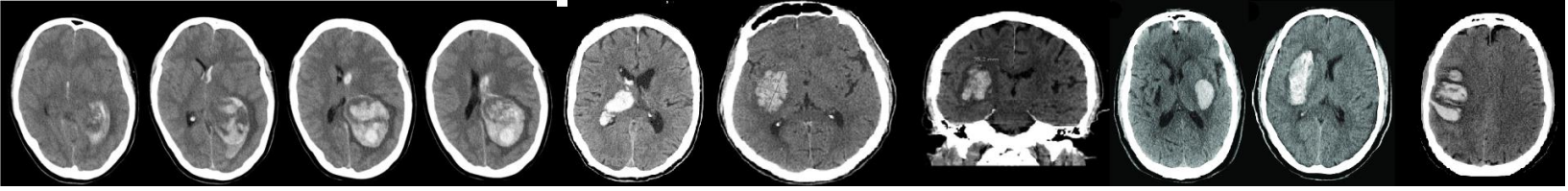
- For sites **not** identified as high-enrolling, an email has been sent to your Site PI, coordinators, and site pharmacist, instructing them to **pause enrollment** until the study drug is received from Novo and all sites are restocked by StrokeNet Pharmacy.

- For sites identified as **high-enrolling**, an email has been sent to your Site PI, coordinators, and site pharmacist, informing them that the extended expiration date IP has been shipped to your site to cover this interim period.

All kits that expired on May 17th must be destroyed, **and** this action should be documented in WebDCU

How to remove **expiring study drug kits** from inventory from WebDCU™:

1. From the main menu page, click on [**Drug Tracking**], then on [**Site Drug Kit Removing**].
2. Filter the "Expiration Date" column to = 17-May-2024.
3. Click the **blue number** in the first column of the 'List Record' table adjacent to the kit code you are reporting as expired.
4. Click [**Edit Record**] at the top of the screen.
5. Click the **radio button** to indicate that you are removing the kit, then select the calendar icon to enter the date the kit was removed. Removing type should be **expired**.
6. To finish, click [**Save Record**].



Repeat for all kits **expiring 17-May-2024** in your current inventory by clicking [**List Record**] to return to the list.

Expired/unused study drug should be destroyed at your site per your local procedures OR may be returned to Central Pharmacy if required by your institutional policy.

How to return **expired study drug kits:**

If your clinical site is returning study drug to Central Pharmacy, the following steps need to be followed:

1. The Study Drug Return Form must be completed and returned with the drug. Study Drug Return Form can be found on WebDCU>FASTEST>Toolbox>Project Documents>FASTEST Study Drug Return Form.
2. The drug will be addressed and shipped to the Central Pharmacy via the institution's preferred postal carrier.
3. Package **tracking information must** be provided to Central Pharmacy via email.
4. Returned drug does not require temperature monitoring during transit, therefore a temperature recorder does not need to be included with the shipment.
5. Returned drug to the Central Pharmacy may not contain any patient identifiers.
6. ***Return Shipment will be at the cost of the clinical site.***

PSCs, kindly disseminate this information among your pharmacy personnel and ensure they are informed by sharing the memo with them. It's essential to keep everyone updated.

Database Change: F104 Adverse Event

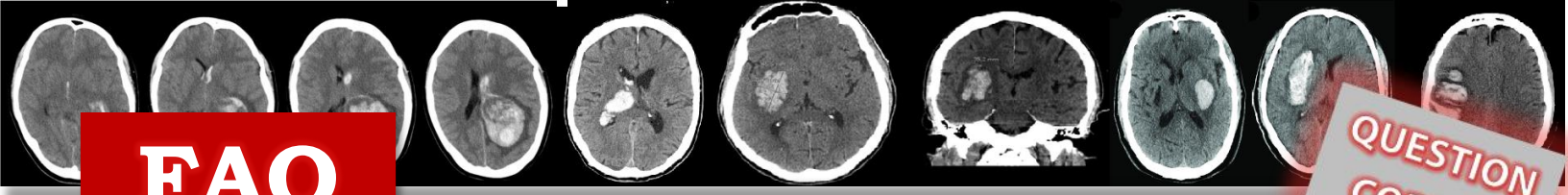
(Q31) *Type of acute cerebral infarction* has been added to the AE form. If ***(Q12)*** *Type of event = Acute cerebral infarction*, you will be prompted to answer (Q31). Any already submitted Adverse Event forms will have warning violations triggered on forms where (Q12) = Acute Cerebral Infarction. Please update your CRFs to answer (Q31) if needed.

New Sites... Welcome Aboard!

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

University of Montreal Hospital, Montreal, QC, Canada

Site PI: Laura GIOIA



FAQ

QUESTION CORNER

Q: We ended up opening a drug kit. The drug was not compounded but the tamper seal was broken. Per our ED pharmacist, we cannot put the drug back into the OmniCell (where we normally store meds as it is temperature monitored) with the tamper seal broken. The drug has not been compounded – only the main box with the tamper seal was opened. However, with the kit being out of the OmniCell, it is no longer being temperature monitored.
A: If the study drug has not been compounded, and only the main box with the tamper seal has been opened, it may be used for the next patient as long as it is being temperature monitored. However, if your institutional policy prohibits returning the study drug to the OmniCell, please discard the study kit and update WebDCU accordingly.

Q: In July, we'll be welcoming a new group of fellows. I believe it would greatly enhance their training to provide them with practical experience in compounding the FASTEST study drug. Would it be possible to utilize the expiring drug kits for this purpose, with our pharmacy handling the appropriate destruction of the kits afterward?
A: Yes, you can use them for training the new fellows. Please remove it from WEBDU and for removal type choose "**others**". In the comment section, mention: "**Received approval from StrokeNet pharmacy to use the expiring kits for demonstration purposes during site training.**"

Also, make sure it is clearly labeled as "**FOR DEMO USE ONLY, not suitable for human administration**" and keep it.

Q: Is protocol training required to be completed by the sub-I's before they are added to the 1572?
A: It is fine to add your sub-I's that plan to participate in the trial to the 1572. Please also add them to the DoA and have them do the protocol training as soon as possible. However, they should not perform study procedures until they complete all required study training.

Q: Should a patient have persistent chronic neurological impairments resulting from a stroke that occurred over 90 days ago, would they still be considered for study participation? What should should be the acceptable modified Rankin Scale (mRS) score if we enroll such patients?
A: According to the ***exclusion criteria #6*** -Symptomatic thrombo-embolic or vaso-occlusive disease in past 90 days (e.g., cerebral infarction, myocardial infarction, pulmonary embolus, deep vein thrombosis, or unstable angina). Therefore, such patients can be enrolled in the trial if they had a stroke more than 90 days ago. If they have a neurological impairment due to the previous stroke leading to a mRS score **2 or less**, they should qualify for the trial. However, if the neurological impairment from the previous stroke is severe enough to yield an mRS score of greater than 2, then the patient does not meet the criteria for enrollment in the FASTEST trial.

Q: How do living arrangements, such as nursing homes or group homes, impact the evaluation of a participant's modified Rankin Scale (mRS). If a participant resides in such a setting, would their mRS score be automatically assessed as more than 2, leading to their exclusion from the study?
A: Nursing home residents may have a range of mRS scores, from 0 (no symptoms) and above. It is essential to remember that nursing home residents have diverse medical histories and conditions and reasons for being in assisted living or nursing facilities (sometimes even temporary as they may be recovering from recent surgery). Rather than automatically assessing/assuming the mRS for such patients as more than 2 it should be based on the mRS score you get from a patient or family member at the time of enrollment.

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

SHOUT OUTS!!

Congratulations to US sites that have completed EFIC and have been approved for emergency consent.

1. **Massachusetts General Hospital, Boston, MA**

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

1. **University of Montreal Hospital, Montreal, QC, Canada**

The Top Enrolling Site

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

Subjects enrolled = 52!!

Congratulations to Enrolling Sites last Month!

Kobe City Medical Center General Hospital, Kobe, Japan	3 Subject
National Cerebral and Cardiovascular Center, Osaka, Japan	2 Subject
Toranomon Hospital, Tokyo, Japan	1 Subject
Nakamura Memorial Hospital, Sapporo, Japan	1 Subject
University of Alberta Hospital, Edmonton, AB, Canada	1 Subject
Vancouver General Hospital, Vancouver, BC, 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
Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA	1 Subject
The Queen's Medical Center, Honolulu, HI	1 Subject
Memorial Hermann Memorial City Medical Center, Houston, TX	1 Subject
The Mount Sinai Hospital, New York, NY	1 Subject
Mills Peninsula Medical Center, Burlingame, CA	1 Subject
Hospital Universitari Germans Trias i Pujol, Barcelona, B, Spain	2 Subject
Vall d'Hebron Hospital, Barcelona, B, Spain	1 Subject

Tranexamic acid versus placebo in individuals with intracerebral haemorrhage treated within 2 h of symptom onset (STOP-MSU): an international, double-blind, randomised, phase 2 trial

Nawaf Yassi*, Henry Zhao*, Leonid Churilov, Teddy Y Wu, Henry Ma, Huy-Thang Nguyen, Andrew Cheung, Atte Meretoja, Duy Ton Mai, Timothy Kleinig, Jiann-Shing Jeng, Philip M C Choi, Phuc Dang Duc, Helen Brown, Annemarei Ranta, Neil Spratt, Geoffrey C Cloud, Hao-Kuang Wang, Rohan Grimley, Karim Mahawish, Der-Yang Cho, Darshan Shah, Thai My Phuong Nguyen, Gagan Sharma, Vignan Yogendrakumar, Bernard Yan, Emma L Harrison, Michael Devlin, Dennis Cordato, Nicolas Martinez-Majander, Daniel Strbian, Vincent Thijs, Lauren M Sanders, David Anderson, Mark W Parsons, Bruce C V Campbell, Geoffrey A Donnan†, Stephen M Davis†, and the STOP-MSU Trial Investigators‡

Originally published in Lancet Neurology April 19, 2024. DOI: https://doi.org/10.1016/S1474-4422(24)00128-5

Background

Tranexamic acid, an antifibrinolytic agent, might attenuate haematoma growth after an intracerebral haemorrhage. We aimed to determine whether treatment with intravenous tranexamic acid within 2 h of an intracerebral haemorrhage would reduce haematoma growth compared with placebo.

Methods

STOP-MSU was an investigator-led, double-blind, randomised, phase 2 trial conducted at 24 hospitals and one mobile stroke unit in Australia, Finland, New Zealand, Taiwan, and Viet Nam. Eligible participants had acute spontaneous intracerebral haemorrhage confirmed on non-contrast CT, were aged 18 years or older, and could be treated with the investigational product within 2 h of stroke onset. Using randomly permuted blocks (block size of 4) and a concealed pre-randomised assignment procedure, participants were randomly assigned (1:1) to receive intravenous tranexamic acid (1 g over 10 min followed by 1 g over 8 h) or placebo (saline; matched dosing regimen) commencing within 2 h of symptom onset. Participants, investigators, and treating teams were masked to group assignment. The primary outcome was haematoma growth, defined as either at least 33% relative growth or at least 6 mL absolute growth on CT at 24 h (target range 18–30 h) from the baseline CT. The analysis was conducted within the estimand framework with primary analyses adhering to the intention-to-treat principle. The primary endpoint and secondary safety endpoints (mortality at days 7 and 90 and major thromboembolic events at day 90) were assessed in all participants randomly assigned to treatment groups who did not withdraw consent to use any data. This study was registered with ClinicalTrials.gov, NCT03385928, and the trial is now complete.

Findings

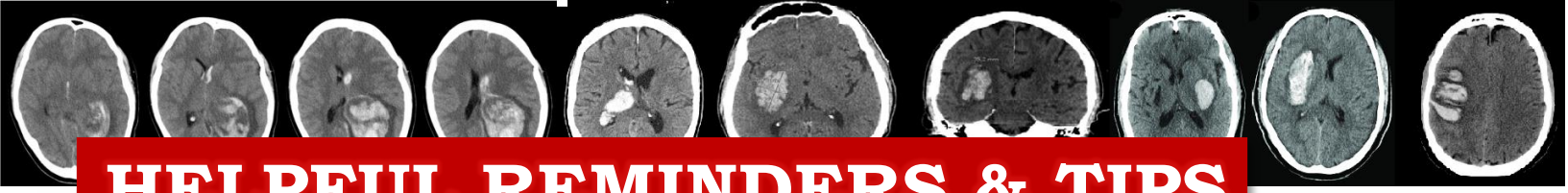
Between March 19, 2018, and Feb 27, 2023, 202 participants were recruited, of whom one withdrew consent for any data use. The remaining 201 participants were randomly assigned to either placebo (n=98) or tranexamic acid (n=103; intention-to-treat population). Median age was 66 years (IQR 55–77), and 82 (41%) were female and 119 (59%) were male; no data on race or ethnicity were collected. CT scans at baseline or follow-up were missing or of inadequate quality in three participants (one in the placebo group and two in the tranexamic acid group), and were considered missing at random. Haematoma growth occurred in 37 (38%) of 97 assessable participants in the placebo group and 43 (43%) of 101 assessable participants in the tranexamic acid group (adjusted odds ratio [aOR] 1·31 [95% CI 0·72 to 2·40], p=0·37). Major thromboembolic events occurred in one (1%) of 98 participants in the placebo group and three (3%) of 103 in the tranexamic acid group (risk difference 0·02 [95% CI –0·02 to 0·06]). By 7 days, eight (8%) participants in the placebo group and eight (8%) in the tranexamic acid group had died (aOR 1·08 [95% CI 0·35 to 3·35]) and by 90 days, 15 (15%) participants in the placebo group and 19 (18%) in the tranexamic acid group had died (aOR 1·61 [95% CI 0·65 to 3·98]).

Interpretation

Intravenous tranexamic acid did not reduce haematoma growth when administered within 2 h of intracerebral haemorrhage symptom onset. There were no observed effects on other imaging endpoints, functional outcome, or safety. Based on our results, tranexamic acid should not be used routinely in primary intracerebral haemorrhage, although results of ongoing phase 3 trials will add further context to these findings.

Funding

Australian Government Medical Research Future Fund.



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:** 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

From the Pharmacy

- Please ensure that any expiring study drug kits are promptly destroyed and that this action is documented in WebDCU.
- Kindly adhere to the instructions provided for removing expiring study drug kits from inventory in WebDCU™.
- In case your clinical site is returning study drug to Central Pharmacy kindly adhere to the instructions provided for returning expired study drug kits.

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/