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# Deferoxamine Mesylate in patients with intracerebral haemorrhage: a Multi-Center, Randomised, Double-Blind, Placebo-Controlled, Phase II Trial

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Contributions

Magdy Selim -- organized the trial hypotheses, designed the trial, provided guidance about the data analysis and interpretation and presentation of the data, and drafted most of the sections of the manuscript.

Lydia Foster -- involved in the statistical analysis and data interpretation, and Contributed to the development and revisions to the manuscript.

Claudia Moy -- involved in the oversight of the trial conduct and progress

Guohua Xi -- organized the trial hypotheses, and provided critical revisions to the manuscript.

MH, MJ, VS, and WC contributed to recruitment and randomization of trial participants, and provided critical revisions to the manuscript.

LM and SG were involved in the design of the trial and provided critical revisions to the manuscript.

Casey Norton -- provided volumetric measurements of imaging data.

Yuko Palesch -- involved in the design of the study, statistical analysis and data interpretation, and provided critical revisions to the manuscript.

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The idef investigators (see appendix) -- contributed to the identification and, when eligible, randomization of trial participants.

DECLARATION OF INTERESTS

This was an investigator-initiated study, funded by the NINDS (U01 NS074425). Deferoxamine Mesylate is a generic drug, and there was no commercial or industrial support for the trial. None of the authors has any competing interests related to the submitted work. MS reports grants from the NIH/NINDS (i-DEF) and the American Heart Association (outside the submitted work), and personal fees for serving on the advisory board of CSL Behring (outside the submitted work) during the conduct of the trial. SDY reports grant support from the NINDS, personal fees from Genentech and other fees from CR Bard Inc. (outside the submitted work) during the conduct of the study. SG, LDF, YP, and GX report grants from the NIH/NINDS. MDH reports personal fees from Merck, non-financial support from Hoffmann-La Roche Canada Ltd, grants from Covidien (Medtronic), grants from Boehringer-Ingleheim, grants from Stryker Inc., grants from Medtronic LLC, grants from NoNO Inc., (outside the submitted work); In addition, MDH has a patent Systems and Methods for Assisting in Decision-Making and Triaging for Acute Stroke Patients pending to US Patent office Number: 62/086,077 and owns stock in Calgary Scientific Incorporated, a company that focuses on medical imaging software, is a director of the Canadian Federation of Neurological Sciences, a not-for-profit group and has received grant support from Alberta Innovates Health Solutions, CIHR, Heart & Stroke Foundation of Canada, and NINDS. LM, VS, WC, MJ, CM, and CN have nothing to disclose.

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## SUMMARY

**Background:** Iron, from hemolyzed blood, is implicated in secondary injury after intracerebral haemorrhage (ICH). We aimed to evaluate the safety of the iron chelator, Deferoxamine Mesylate (DFO), and whether it merits investigation in a Phase-III study to definitively assess its effectiveness in improving outcomes in ICH patients.

**Methods:** We conducted a multi-center, randomised, double-blind, placebo-controlled, Phase-II trial at 40 hospitals in USA and Canada. Adults (aged 18–80 years) with primary, spontaneous, supratentorial ICH were randomly assigned (1:1) to DFO (32 mg/kg/day) or saline (placebo) infusions for 3 consecutive days, within 24-hours of ICH-onset. Randomisation was done centrally in real-time and treatment allocation was concealed from participants and investigators. Primary outcome was good clinical outcome, defined as modified Rankin Scale (mRS) score 0–2 at day-90. We performed a futility analysis; if the 90% upper confidence bound (90%UCB) on the absolute risk difference in good outcome proportions is <12% in favour of DFO, then it would be futile to move to Phase-III. Outcome and safety data were analysed based on modified intention-to-treat. (ClinicalTrials.gov Identifier:NCT02175225).

**Findings:** We recruited 294 participants between November 23, 2014 and November 10, 2017. Three were post-randomisation failure; 291 were included in the analyses (144 randomised to DFO; 147 to placebo). Primary outcome was assessed for 283 (97.3%) participants. At day-90, 48/140 (34.3%) of DFO- and 47/143 (32.9%) of placebo-treated subjects had mRS 0–2 (adjusted absolute risk difference 0.6%; 90%UCB 6.8%). By day-90, 70 serious adverse events were

reported in 39/144 (27.1%) DFO group and 78 in 49/174 (33.3%) placebo-treated subjects. Death occurred in 10 (6.9%) DFO- and 11 (7.5%) placebo-subjects; none was treatment-related.

**Interpretation:** DFO was safe. The primary result showed it would be futile to further study the effectiveness of DFO with anticipation that it would significantly improve the chance of good outcome (mRS 0–2) at day-90.

## INTRODUCTION

Intracerebral haemorrhage (ICH) is a devastating disease. Worldwide, the overall incidence of ICH is approximately 25 per 100,000 person-years, with estimates as high as 2.3 million cases a year [1]. It is a frequent cause of permanent disability and mortality which confers substantial burden on global healthcare systems and societies. Supportive medical care remains the mainstay treatment, and ongoing efforts targeting haematoma expansion or reduction have had limited impact. Release of iron from hemoglobin degradation products following hemolysis of red blood cells within the haematoma has been implicated in various processes including apoptosis, oxidative stress, inflammation, and autophagy, which contribute to secondary neuronal injury after ICH [2–4]. Accumulating pre-clinical data indicate that the iron chelator, Deferoxamine Mesylate (DFO), exerts neuroprotective effects following ICH [5–7] and is a promising treatment option. We previously conducted phase-I, dose-finding, safety, and feasibility study of DFO in patients with acute ICH [8] to translate pre-clinical findings into the clinical setting. Based on the results of this study, we designed a pilot, phase-II trial using a futility-design to evaluate the safety of DFO in a larger cohort of patients and to assess whether DFO may be a viable therapy for ICH before embarking on a large phase-III efficacy trial.

## METHODS

### Study Design And Participants

The Intracerebral Haemorrhage Deferoxamine (i-DEF) trial was a prospective, multi-center, double-blind, randomised, placebo-controlled, futility-design, phase-II clinical trial. Participants were recruited from emergency rooms and stroke units at 40 hospitals in USA and Canada. Subjects aged 18 to ≤80 years with spontaneous, primary, supratentorial ICH in whom study drug could be initiated within 24-hours of ICH-onset were considered for recruitment. Key exclusion criteria were: suspected secondary cause for ICH; infratentorial ICH; severe iron deficiency; pregnancy or breastfeeding; serum creatinine ≥2 mg/dL; coagulopathy (defined as activated prothrombin time >40 seconds, International Normalized Ratio >1.3, or concurrent use of direct oral anticoagulants or low-molecular-weight heparin upon presentation); pre-ICH mRS ≥2; deep coma (GCS score ≤6 or score of 3 on item 1a of NIHSS); irreversibly impaired brainstem function; NIHSS <6 upon presentation; plans for haematoma evacuation prior to administering study drug; indication that withdrawal-of-care was going to be implemented within 72-hours; and subjects at high-risk for developing adult respiratory distress syndrome (ARDS). Please refer to the Supplementary Appendix for details of ARDS-related and other exclusion criteria, and rationale for study futility-design, dose-selection, treatment time-window, and duration of treatment. Ethics approval was

obtained at each participating site. Signed written informed consent was obtained from each participant or legally-authorized representative according to local regulations.

## Randomisation and Masking

After local investigators determined eligibility and obtained written informed consent, investigators enrolled the subjects and entered randomisation covariates into the web-based trial management system (WebDCU™). Subjects were randomly allocated to DFO or placebo infusion (1:1) through WebDCU™, which allowed randomisation to occur dynamically in real-time and ensured complete concealment of treatment allocation. Balance on important known covariates was controlled using a combination of minimization and biased coin methodologies: minimization, to minimize the sum of imbalances in baseline covariates, and biased-coin, to avoid deterministic assignments. WebDCU™ confirmed eligibility, evaluated treatment-arm distribution within each baseline covariate, calculated the sum of the marginal imbalances, and dynamically generated the random allocation. When imbalance measure was zero, simple randomisation was applied; otherwise, a biased-coin probability of 0.75 was applied in favour of the treatment which would reduce the imbalance. The key variables were clinical site, baseline ICH score (<3 vs. ≥3), ICH-onset-to-treatment time (≤12-hours vs. >12-hours), warfarin use at ICH-onset, NIHSS score (≤10 vs. >10), and ICH volume (≤10 vs. >10 mL) at presentation. Haematoma volume on admission CT scan, estimated by the local investigators using the ABC/2 method [9], was used for randomisation purposes.

Study drug was reconstituted by the sites' pharmacists in the pharmacy in all cases. Reconstituted solution was colourless (indistinguishable from saline) and was provided to the investigators on the ward for blinded administration. All participants and site trial personnel, except for the pharmacists, were masked to treatment assignments throughout the course of the trial and until completions of data analyses. Pharmacists were not involved in any other study-related assessments.

## Study Assessments and Procedures

Brain CT scan was performed at presentation to confirm the diagnosis of ICH. Demographic and baseline clinical characteristics of eligible subjects were recorded at the time of enrollment. Severity of ICH was assessed with the use of the GCS, NIHSS and ICH score [10]. The study drug DFO (at 32 mg/kg/day up to a maximum dose of 6000 mg/day) or saline (placebo) was given by intravenous infusions at a rate of 7.5 mg/kg/hour repeated daily for 3 consecutive days. First infusion was started within 24-hours of ICH-onset.

Participants were evaluated in-person daily until the day following last study infusion, on day-7 or discharge (whichever was earlier), and at day-30 and day-90. Assessments included NIHSS, GCS, Montreal Cognitive Assessment (MoCA), and a study-specific visual and auditory assessment battery in capable participants to assess for newly emerging visual or auditory changes, which have been reported with long-term use of DFO. Participants were contacted by telephone at day-60 to assess for any emerging serious adverse events (SAEs), and at day-180 to assess mRS [11]. All assessments were conducted by qualified investigators certified in mRS and NIHSS administration, and masked to treatment

assignment. A study-related CT scan was performed within 24-hours following completion of the last study infusion.

## Outcomes

The primary outcome measure was good clinical outcome (defined as a dichotomized mRS score of 0–2) at day-90. Pre-specified secondary outcomes were mRS dichotomized to 0–3 to define good outcome at day-90; mRS 0–2 and 0–3 at day-180 because of emerging data suggesting that recovery following ICH may be delayed past 3-month [12]; ordinal distribution of mRS scores at day-90 and day-180; the difference between early vs. late treatment (≤12-hours vs. >12-hours from ICH-symptom-onset) on functional outcome; and the change in NIHSS between presentation and day-90, and MoCA score at day-90.

Safety outcomes were: 1) Adverse events of special interest (AESI - anaphylaxis at any time during the study infusion, hypotension requiring medical intervention at any time point during the study infusion that could not be explained by other causes, development of new and unexplained visual or auditory changes after initiating the study infusion, and respiratory compromise of any cause including ARDS during the in-hospital phase until day-7 or discharge whichever was earlier; 2) All SAEs through day-90; 3) Deaths (all-cause and ICH-related) through day-180; and 4) Any adverse event until day-7 or discharge (whichever was earlier).

## Statistical Analysis

The primary hypothesis specified that if the difference in good outcome proportions (mRS 0–2 at day-90) is less than 12% in favour of DFO, then it would be futile to move DFO forward to Phase-III evaluation. We estimated that 254 subjects (127 in each arm) were required to test the futility hypothesis with 80% power, assuming that approximately 28% of placebo-treated subjects would have mRS 0–2 at 90 days based on the weighted average of good outcome proportions reported in the literature. Final sample size was then inflated to 294 to account for possible dilution of treatment effect associated with lost-to-follow-up (LTFU), withdrawal-of-consent, and randomised subjects in whom the study infusion was never initiated. Additionally, the trial was adequately powered to assess the futility hypothesis using mRS 0–3 as the secondary outcome based on an absolute risk difference in treatment effect less than 13% in favour of DFO.

We followed a pre-specified statistical analysis plan (SAP), which was finalized before locking the database and conducting final data analysis. In accordance with the futility design, the primary hypothesis and analysis plan specified that if the one-sided $90^{th}$ percentile upper confidence bound on the treatment effect (absolute adjusted risk difference; AARD) was <12% in favour of DFO, then it would be futile to move to Phase-III. The hypothesis was tested via generalized linear model relating the probability of good outcome to treatment after adjusting for the randomisation covariates as specified in the SAP. The choice of 12% as the futility threshold was to some extent arbitrary. Previous Phase-III trials in ICH were powered to detect a minimum clinically important difference (MCID) of 10%. Taking into consideration this MCID, the fact that no treatments exist to prevent disability after ICH, and the observation that effect size tends to be overestimated in pre Phase-III

trials, the futility threshold for the primary outcome in i-DEF was set at 12% [13]. The pre-specified futility threshold for mRS 0–3 was set at 13% (not 12%) in order to maintain statistical power for this mRS dichotomization.

The generalized linear model described above was also used for secondary analyses of mRS outcomes (0–3 at days 90 and 180, and 0–2 at day-180), and expanded to include an interaction between treatment and ICH-onset-to-treatment time (≤12 vs >12-hours). A shift analysis of the full distribution of the mRS at day-90 and day-180 was analysed via proportional odds model. Wilcoxon Rank-Sum test was performed to evaluate NIHSS and MoCA on day-90. The primary outcome was also assessed for treatment differences in pre-specified subgroups (ICH-onset-to-treatment time ≤12 vs >12-hours, ICH score: 0–2 vs 3–5, sex, race, age <60 vs ≥60, and IVH present vs absent), where each covariate was evaluated individually with a model that includes treatment, subgroup, and an interaction effect between the treatment (DFO or placebo) to derive subgroup specific treatment effect estimates and assess heterogeneity across the subgroups.

Adverse events were classified with the use of terminology from the Medical Dictionary for Regulatory Activities combined with Principal Investigator (PI) preferred adjustments. Treatment differences in the cumulative incidences of mortality, as well as AESI, were evaluated via relative risk and corresponding 95% confidence interval. The log-rank test was used to compare the survival curves for each treatment group.

The protocol specified that participants who exhibit significant deterioration (development of fixed and dilated pupils or a decrease in GCS to ≤6) after randomisation and before initiation of the study infusion would be deemed post-randomisation failures and would be excluded from subsequent study-related procedures. As such, the futility analysis and safety outcomes were evaluated under a modified intention-to-treat (mITT) principle, wherein the evaluable sample includes only subjects in whom the study infusion was initiated.

Pre-specified sensitivity analyses of dichotomized mRS outcomes at day-90 and day-180 were also performed in intention-to-treat, as-treated, and per-protocol cohorts (refer to footnotes of Figure 2 for definitions). Complete case analysis was planned as the primary analytic approach, with pre-specified sensitivity analyses using last-observation-carried-forward, best/worst scenario (where favourable outcome [best case] is imputed for the placebo arm, and unfavourable outcome [worst case] is imputed for the DFO arm), and multiple imputation approaches (refer to Figure S3 in Supplementary Appendix and SAP for details). Briefly, an imputation for each missing outcome was generated, based on observed relationship between the outcome and covariates. This process was repeated to create 100 sample data sets with complete outcomes; each data set was analyzed as described and results compiled to yield a single statistical inference about treatment effect.. Dichotomized mRS outcomes were additionally analysed (*post-hoc*) using multivariable models adjusting for additional prognostic baseline variables including volume of IVH and thalamic vs. non-thalamic location of ICH, and severity index quartiles [14] (refer to Figure S3 and SAP). SDY and LDF performed all statistical analyses using SAS software version 9.4.

All CT scans were sent to the iDEF core imaging laboratory for further review by experienced raters, blinded to clinical data and treatment assignment, to confirm ICH location and presence vs. absence of intraventricular haemorrhage (IVH), and to perform volumetric measurements of ICH and perihaematomal oedema (PHE). Areas of the haematoma and PHE were automatically delineated by imaging analysis software (Analyze 11.0 Visualization and Analysis Software for Medical Imaging. AnalyzeDirect, Overland Park, KS, USA) with the use of density thresholds on each slice followed by manual correction. The software provided total volume measurements for ICH, IVH, and PHE by summing up the volumes from all respective slices. We previously validated inter- and intra-rater reliability of this methodology [15].

The trial was approved by the US Food and Drug Administration (IND #77306), Health Canada (CTA #160713), and Institutional Review Boards or Ethics Committees at all participating sites. The trial was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use - Good Clinical Practice Consolidated Guidelines. The trial is registered on Clinicaltrials.gov (NCT02175225). The trial was overseen by an Executive Committee and monitored by an independent DSMB appointed by the NINDS. Study data were centrally monitored and analyzed by the Data Coordination Unit, Department of Public Health Sciences at Medical University of South Carolina.

### Role of The Funding Source

The PI (MS) and personnel at the Data Management Center at MUSC conceived, organized, and executed this trial. The PI and study statisticians (SDY and LDF) had full access to all study data and had final responsibility for the decision to submit for publication. The sponsor (NIH/NINDS) provided input regarding the study design during the grant review process and the NIH/NINDS-appointed DSMB provided the same during active recruitment.

## RESULTS

Recruitment started on November 23, 2014 and ended on November 10, 2017. Figure 1 summarizes the study profile; 9070 subjects were assessed for eligibility, 8776 were ineligible. We recruited 294 participants. Three subjects were deemed post-randomisation failures, with one being removed from the database due to missing informed consent documentation. The remaining 291 subjects in the mITT sample were included in the analysis; 144 were assigned to DFO and 147 to placebo. Primary outcome at day-90 was determined for 140 (97.2%) of the participants in the DFO group and 143 (97.3%) in the placebo group. Four subjects in each group had missing day-90 outcomes; 3 withdrew consent and 2 were LTFU before day-90 without primary outcome collected, and 3 had their assessments more than 30 days outside day-90. Nine DFO- and 12 placebo-treated participants had missing 180-day outcomes; 11 were LTFU, 3 withdrew consent, and 7 had mRS assessments >30 days beyond day-180.

Table 1 summarizes the demographic and clinical characteristics of the two groups. Mean age was 60±12 years, 38.5% were females, 37.8% non-white, and 16.5% Hispanic. Median ICH volume was 12.9 $cm^3$ (range: 0.1–110.2). More patients in the placebo group had

thalamic ICH, IVH, and history of prior ischemic stroke. Conversely, more patients in the DFO group had non-thalamic deep ICH and history of prior ICH, and were Asians. The groups were comparable with regard to other characteristics.

At day-90, 34.3% (48/140) of DFO- and 32.9% (47/143) of placebo-treated subjects achieved the primary outcome (mRS score 0–2) (AARD 0.6%; 90%UCB 6.8%, which fell below the pre-specified 12% futility threshold) (Figure 2). In secondary analyses, 65.0% (91/140) vs. 57.3% (82/143) achieved mRS scores 0–3 (AARD 6.2%; 90%UCB 12.1%) at day-90; and 71.9% (97/135) vs. 68.1% (92/135) had mRS scores 0–3 (AARD −1.8%; 90%UCB 2.9%) at day-180. These between-group differences also fell below the corresponding futility thresholds (Figure 2). At day-180, 45.2% (61/135) of DFO-treated subjects and 35.6% (48/135) in the placebo group had mRS scores of 0–2 (AARD 8.6%; 90% UCB 15.6%, which exceeded the futility threshold). Figure 3 shows ordinal distribution of mRS scores at day-90 and day-180. The odds of good outcome, defined at all order-preserving dichotomizations of mRS, in the DFO group were estimated to be 10% higher at day-90 (adjusted common odds ratio 1.10, 95% CI:0.72–1.67), and 26% higher at day-180 (adjusted common odds ratio 1.26, 95% CI:0.82–1.93), than in the placebo group. Day-90 median NIHSS score was 3 (IQR:1–7) in the DFO group vs. 4 (IQR:2–7) in the placebo group (p= 0.37). Day-90 median MoCA score was 24 (IQR:18–27) in both groups (p= 0.83).

Analysis of the primary outcome according to ICH-onset-to-treatment-time and pre-specified subgroups (Figure 4) showed no statistically significant differences. Risk differences in the primary outcome at day-90 when study infusion was initiated within ≤12-hours from ICH-onset was 2.4% (95% CI:−17.1%–22.0%) and 0% (95% CI:−11.0%–10.9%) at >12-hours (p=0.83 for interaction). At day-180, the risk difference was 15.1% (95% CI:−5.5%–35.6%) at ≤12-hours and 6.1% (95% CI:−6.6%–18.8%) at >12-hours (p=0.47 for interaction).

The rates of SAEs, including those occurring within the first 7 days and AESI, were balanced between the groups (Table 2). Unlike HI-DEF where 6/21 (28.6%) of DFO-treated patients developed ARDS, there were only 2 cases (1.4%) of ARDS among DFO-treated patients; one was adjudicated to be possibly-related and the other unlikely/unrelated to study drug by the Safety Monitors. A listing of all adverse events is provided in Tables S4–S5 (Supplementary Appendix). Mortality was similar in the DFO and placebo groups. All-cause mortality rates were 10/144 (6.9%) vs. 11/147 (7.5%) at day-90 and 12/144 (8.3%) vs. 12/147 (8.2%) at day-180. ICH-related death occurred in 7/144 (4.9%) vs. 8/147 (5.4%) of the DFO and placebo arms respectively. Four (33.3%) of all deaths in the DFO and two (16.7%) in the placebo group occurred within 7 days of randomisation. Only two (16.7%) and one (8.3%) of deaths in the DFO and placebo groups occurred between days 90 and 180 (Figure 5).

In exploratory analyses, changes in ICH, IVH, and relative PHE (rPHE) volumes from baseline-to-follow-up scans were comparable between the groups. Median time-from-randomisation-to-post-last-infusion scan was 4416 minutes (IQR:4155–4662) in DFO group and 4404 minutes (IQR:4278–4578) in placebo. Median change in ICH volume was −0.2 mL (IQR:−1.4–1.0) in the DFO group vs. −0.2 (−1.7–0.8) in the placebo group (95% CI:−.

03–0.7); IVH 0 (−0.6–0) vs. 0 (−1.9–0) (95% CI:0–0); and rPHE 0.9 (0.4–2.3) vs. 0.7 (0.3–1.2) (95% CI:−0.1–0.3). We performed a *post-hoc* exploratory analysis to examine the interaction between DFO treatment, ICH-onset-to-treatment-time (≤12 vs. >12-hours), baseline rPHE, and their effects on post-infusion rPHE, after adjusting for baseline serum glucose, concomitant use of anti-edema agents, and ICH volume. The interaction between baseline rPHE and onset-to-treatment-time varied according to the treatment arm (p= 0.0022). Within the 12-hours window, for every one unit increase in baseline rPHE, post-last infusion rPHE increased by 0.28 (95% CI:0.03–0.53) in DFO-treated subjects vs. 0.83 (95% CI:0.43–1.24) in placebo patients. Beyond the 12-hours window, the corresponding increase in post-last infusion rPHE was 0.87 (95% CI:0.64–1.11) in DFO vs. 0.52 (95% CI: 0.24–0.79) in placebo group.

## DISCUSSION

The i-DEF trial did not show that treating ICH patients with DFO was sufficiently promising to warrant further phase-III investigation to determine its effectiveness with anticipation that it would significantly improve the chance of good clinical outcome (mRS 0–2) at day-90. However, in futility analysis at day-180, the AARD in the proportion of mRS 0–2 was 8.6% in favour of DFO, and this between-group difference fell above the specified futility threshold. Furthermore, secondary analysis using ordinal assessment of mRS showed that the common odds of good-outcome were higher in the DFO group, particularly at day-180. Given the pathophysiology of ICH and known patterns of late recovery, these may be relevant results.

Treatment with DFO (IV infusion at 32 mg/kg/day for 3 consecutive days) was safe. There was no increase in the rates of SAEs, major disability, or death. The dose, regimen, and duration of treatment with DFO have important safety implications. Unlike HI-DEF where continuous IV infusion of high-dose DFO at 62 mg/kg/day for 5 consecutive days was associated with increased pulmonary toxicity and ARDS, interrupted (daily) IV infusions of DFO at 32 mg/kg/day for 3 days in i-DEF was not associated with an increase in all-cause respiratory compromise including ARDS [17].

The results of our pre-specified secondary analyses regarding mRS 0–3 at day-90, mRS 0–2 at day-180, and ordinal analysis of mRS tended to be in favour of DFO. These results raise important and challenging questions regarding the appropriate effect size, timing of outcome assessment in ICH trials, and interpretation of i-DEF results. Determining the smallest clinically-meaningful effect size that would have an impact on clinical practice is challenging, and a lower futility threshold in i-DEF would have required a much larger sample size. The Hemorrhagic Stroke Academia Industry (HEADS) roundtable recently recommended that a realistic absolute effect size for an acute intervention in ICH should be 3% to 10% (average 5%), and that acceptance of a small effect size may hinge upon the safety, nature, and cost of the intervention [18]. Deferoxamine may be such a candidate. It is generic and low-cost (~$100-$150 per infusion), and experience from i-DEF indicates that an intermediate dose-regimen of 32 mg/kg/day is safe, simple to administer, and does not require highly specialized skills or facilities. Future studies targeting a small effect size will require a large number of patients (likely 2000-to-3000), and global collaboration.

Timing of endpoints (3 months vs. 6–12 months) in stroke trials has been recently debated [19]. It has been argued that ICH patients who tend to be severely affected due to consequences of the mass effect from the haematoma, associated oedema, and IVH often require longer time for these secondary effects to resolve and to show improvement on measures of functional disability; differences in outcome between treatment groups may not be maximal at the traditional 3-month time-point. Accumulating evidence suggests that survivors of hemorrhagic stroke continually improve past 3 months and up to one year [12; 20–22]. i-DEF results are consistent with these observations. Improvement in unadjusted mRS measures of disability from 3-to-6 months was observed in both DFO- and placebo-treated subjects. Both groups experienced improvement in mRS 0–3 between day-90 and day-180 (6.9% in DFO group and 10.8% in placebo), whereas the proportion of patients with mRS 0–2 increased by 10.9% in the DFO group and 2.7% in placebo during this same period. Furthermore, the number of placebo patients with mRS 4–6 decreased during this time period indicating that observed differences between DFO and placebo groups at day-180 were not related to interim worsening or death of subjects in the latter group.

Perihaematomal oedema is thought to represent a radiological marker of secondary injury in ICH. Therefore, we explored the effect of DFO on rPHE growth as a potential surrogate marker of the drug's biological activity in the brain. In contrast to findings from other studies [23–24], DFO did not seem to have a clear effect on rPHE growth. This may be attributed to other PHE-independent effects of DFO [5; 8], short interval between baseline and post-infusion scans to capture the peak of PHE, insensitivities and crude nature of rPHE measurements [25], or true lack of effect of DFO on PHE growth. The rate of PHE growth and oedema extension distance are emerging parameters which might represent better measures than rPHE, and will require further assessments in our cohort. Animal studies reported that the optimal therapeutic window for DFO to reduce oedema was ≤12-hours (but correlation between oedema and neurological deficits weeks-to-months later was weak) [7], and that 24-hours delayed treatment failed to reduce brain oedema but yet improved neurological function [5]. Our *post-hoc* exploratory analyses examining the interaction between DFO treatment, ICH-onset-to-treatment time (≤12 vs. >12-hours), baseline rPHE, and their effects on post-infusion rPHE suggest that the effect of DFO on PHE varies according to ICH-onset-to-treatment time, and are in line with animal data. We did not power the trial to examine the effects of DFO on PHE, and this may have impacted our ability to detect a main effect of DFO on PHE. Only, 31% of our patients received treatment within 12-hours from ICH-onset, and we found no evidence of significant heterogeneity in the effect of treatment with DFO on functional outcome in any pre-specified subgroup, including ≤12h vs. >12h ICH-onset-to-treatment window.

The putative beneficial effects of DFO may not necessarily be dependent on its effects on PHE, and may be more dependent to its iron-chelating properties which decreases free iron's availability for the production of hydroxyl radicals, and protects against oxidative stress, apoptosis, ferroptosis, and the cascade of events involved in secondary injury [5; 7–8]. We posit that DFO primes this machinery, that the severity of injury after ICH may mask some of the benefits of therapy early on, and that the benefit gradually accumulates but does not become fully apparent until adverse consequences of haematomal mass effect and IVH are resolved over time. The findings that the AARD was 6.2% in favour of DFO for moderate

disability at day-90, and 8.6% for mild disability at day-180 may lend support to this hypothesis.

We caution against misinterpretation of our secondary results to conclude that DFO is more efficacious than placebo. i-DEF was a phase-II futility-design trial that was intentionally not designed to test the efficacy hypothesis [26]. In addition, several confounders may have impacted our findings. A higher percentage of patients in the placebo group had thalamic and intraventricular haemorrhages; these unfavourable baseline prognostic characteristics may have contributed to poorer outcomes in the placebo group, although sensitivity analyses adjusting for these prognostic confounders did not substantively alter the overall interpretation of results. On the other hand, observed rates of mRS 0–2 in the placebo group (32.9% at day-90 and 35.6% at day-180) were higher than the rate that we anticipated during the trial design (28%), which may be attributed to differences in eligibility criteria, milder severity of ICH in our cohort, or temporal changes in ICH management. This may have resulted in a slight decline in our power to declare futility (from 80% to 76%); however, the power of the primary endpoint is not of concern because futility was declared, and the point-estimates at day-180 are not consistent with futility. We also performed multiple secondary analyses of mRS, which yields concern over increased type-I error. However, the futility hypothesis differs from hypotheses specified in traditional Phase-III efficacy trials and the probabilities of type-I and type-II errors are interpreted differently [26]. Because the null hypothesis in futility design is that the active intervention (DFO) improves outcome relative to control by a pre-specified threshold and the rejection of this hypothesis implies futility, increased type-I error (incorrect rejection of a true null hypothesis) due to multiple testing cannot account for the non-futile mRS 0–2 results at day-180. We cannot, however, rule out that non-futility of mRS 0–2 at day-180 is a type-II error, although iDEF was designed to achieve 80% power when treatment outcomes are identical.

Our study has other limitations. We excluded patients with significant respiratory conditions at high-risk for ARDS (~ 3.4% of screened subjects) and those older than 80 years-of-age, and our patients had mild deficits, small ICH volumes, and greater proportions of deep ICH, which may limit the generalizability of results to the overall ICH population.

In conclusion, our results indicate that patients with ICH continue to improve past 90 days, and that treatment with DFO at 32 mg/kg/day for 3 consecutive days was safe. It seems futile to conduct a large Phase-III to determine the efficacy of DFO for improving good-outcome (mRS scores 0–2) at day-90 in ICH patients. Our pre-specified secondary analyses leave open the possibility that DFO might not be futile for improving outcome at day-180 and require further scrutiny. These findings have important implications for the design of future trials in ICH and future studies of DFO in ICH.

## DATA SHARING

The study will follow NIH policies on data sharing (as described at http://grants2.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm) and any updates thereto. Complete de-identified dataset will be made available via the NIH Archived Clinical Research Datasets (https://www.ninds.nih.gov/Current-Research/Research-Funded-NINDS/Clinical-

Research/Archived-Clinical-Research-Datasets) within one year of manuscript publication. The dataset will be made available for limited use to researchers whose proposed use of the data is approved by the NIH/NINDS in accordance with the terms and conditions of the NINDS data request form (https://www.ninds.nih.gov/sites/default/files/NINDS_Data_Request_Form_508C.pdf)

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Funding:

NIH/NINDS

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## RESEARCH IN CONTEXT

### Evidence Before This Study

We searched the literature on PubMed from its inception until January 5, 2019 with the terms: ICH, intracerebral haemorrhage, haemorrhage AND deferoxamine. We did not apply time or language restrictions. We identified 123 preclinical and 6 human studies. Forty-five preclinical studies and two clinical studies were excluded after review of the title, abstract, or full article. The criteria for exclusion were non-ICH related study, non-*in vivo* experimental study, duplicate publications, and non-primary or non-spontaneous ICH or lack of pre-specified outcomes in human studies. Preclinical studies suggested that iron accumulates in the brain after experimental ICH; iron-mediated toxicity contributes to delayed cellular injury and neurological deficits; and that treatment with deferoxamine mesylate (DFO) attenuates neuronal death and improves recovery after ICH in various species. We examined the studies for methodological rigor, use of blinding and randomization, and outcome assessment to determine the risk of bias. The human studies were non-randomised, open-label, and small, varying in sample size from 20 to 42 participants, and were classified as being at high risk of bias. Therefore, there was insufficient evidence before i-DEF to fully ascertain the appropriate dose regimen of DFO or its safety in this patient population, and to examine its effects on neurologic outcomes after ICH.

### Added Value of This Study

To our knowledge, i-DEF is the first multi-center, randomised, double-blind, placebo-controlled trial to prospectively collect clinical, functional, and imaging outcome data from a relatively large number of DFO-treated ICH patients. Care throughout the trial was standardized and data were collected in a pre-defined and uniform manner. Its predecessor, HI-DEF (High Dose Deferoxamine in ICH Trial; clinicaltrials.gov NCT01662895), was terminated due to increased pulmonary toxicity of continuous infusions of DFO at 62 mg/kg/day for 5 days. The i-DEF trial provides evidence that intermediate dosage of DFO at 32 mg/kg/day for 3 days is well-tolerated by ICH patients and does not increase rates of serious adverse events, major disability, or death. The trial showed treatment with DFO does not significantly improve the chances of good outcome at three months after ICH. Secondary and exploratory results suggest that DFO might improve outcomes at six months. This requires further scrutiny.

### Implications of All Available Evidence

The i-DEF trial was not designed or intended to test the efficacy of DFO, and our findings should not impact current standards of clinical practice. The primary results indicate that it would be futile to test DFO as a treatment for ICH with anticipation that it would significantly improve the chance of good outcome at 3 months in ICH survivors. An important observation from this study is that patients with ICH continue to improve past 3 months. Future studies in ICH should consider assessment of outcomes beyond this traditional time point to capture the full extent of recovery. Sharing the full safety and outcome data from i-DEF is likely to stimulate further investigations of therapeutic

interventions targeting iron-mediated toxicity and secondary injury after ICH, a devastating condition without specific treatments.

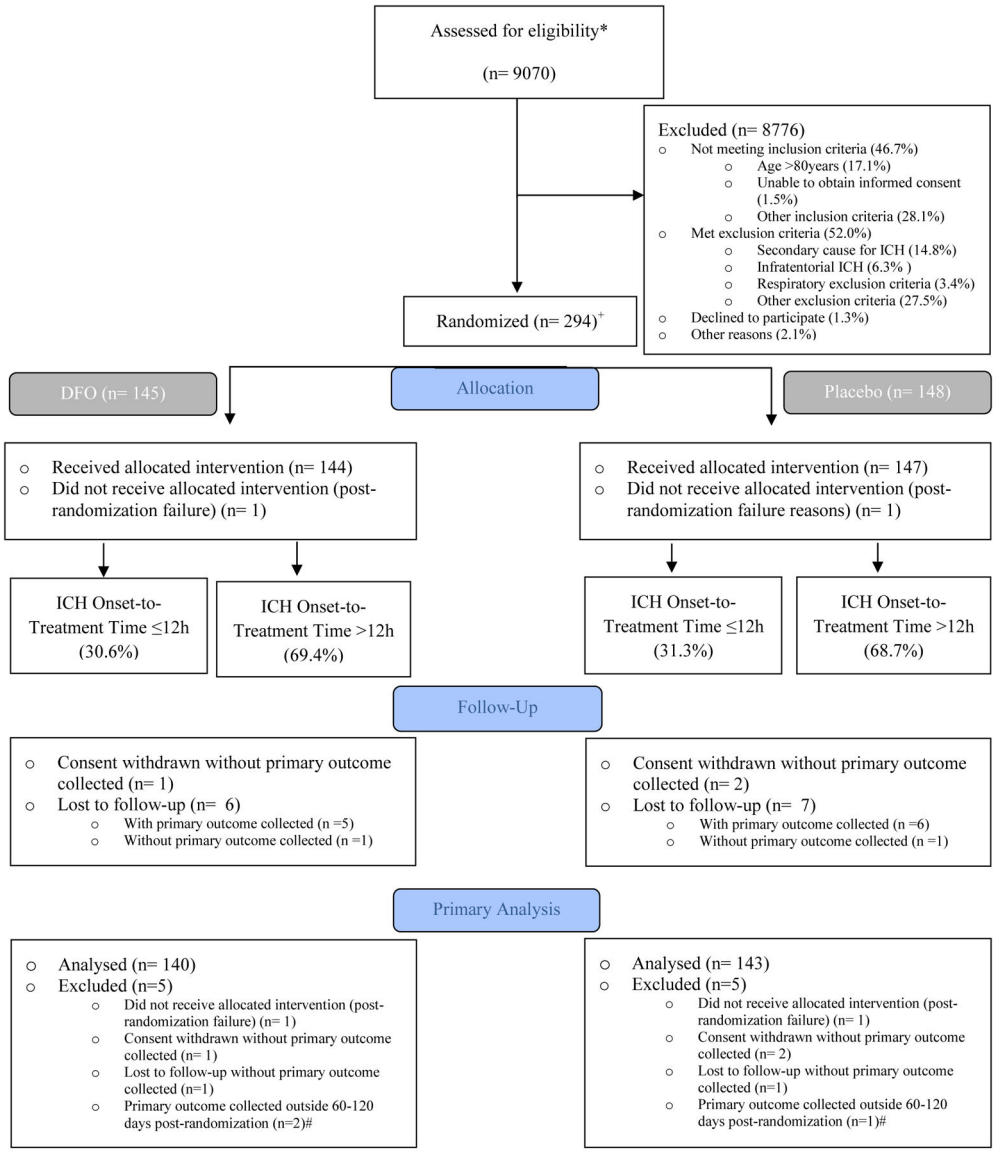


**Figure 1:**
Trial profile.

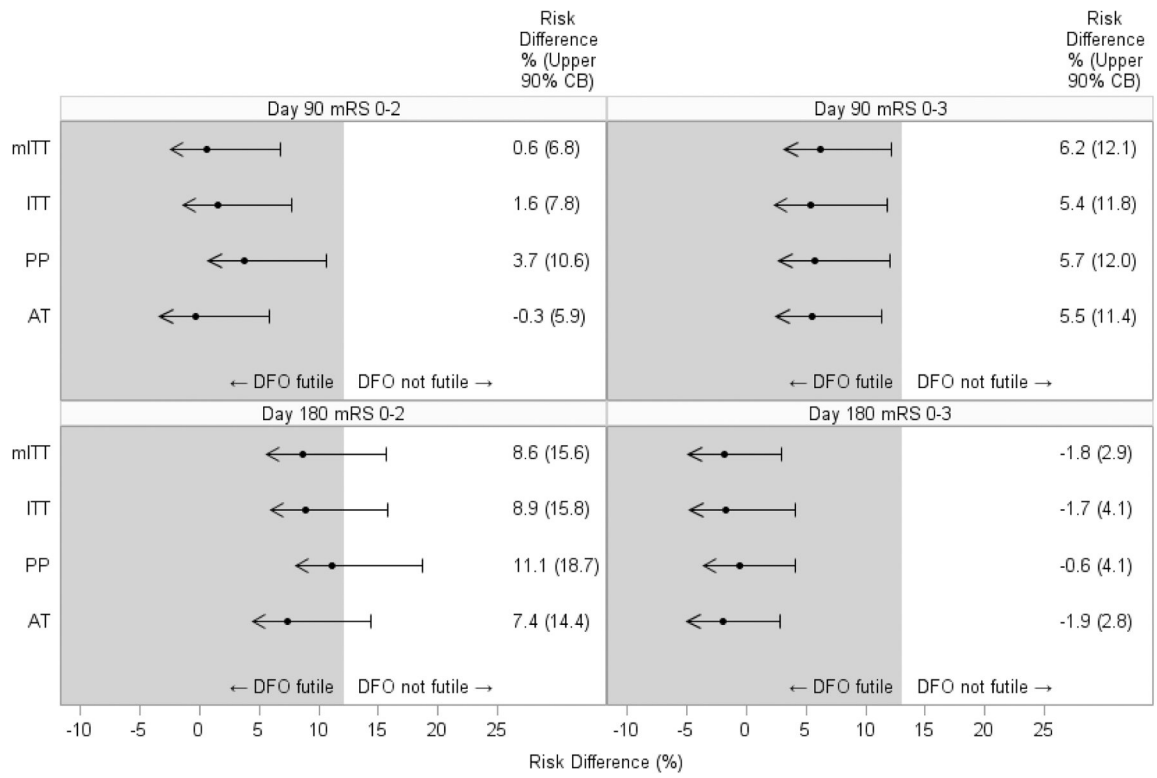


**Figure 2:**
Results of Futility Analyses at day-90 and day-180.

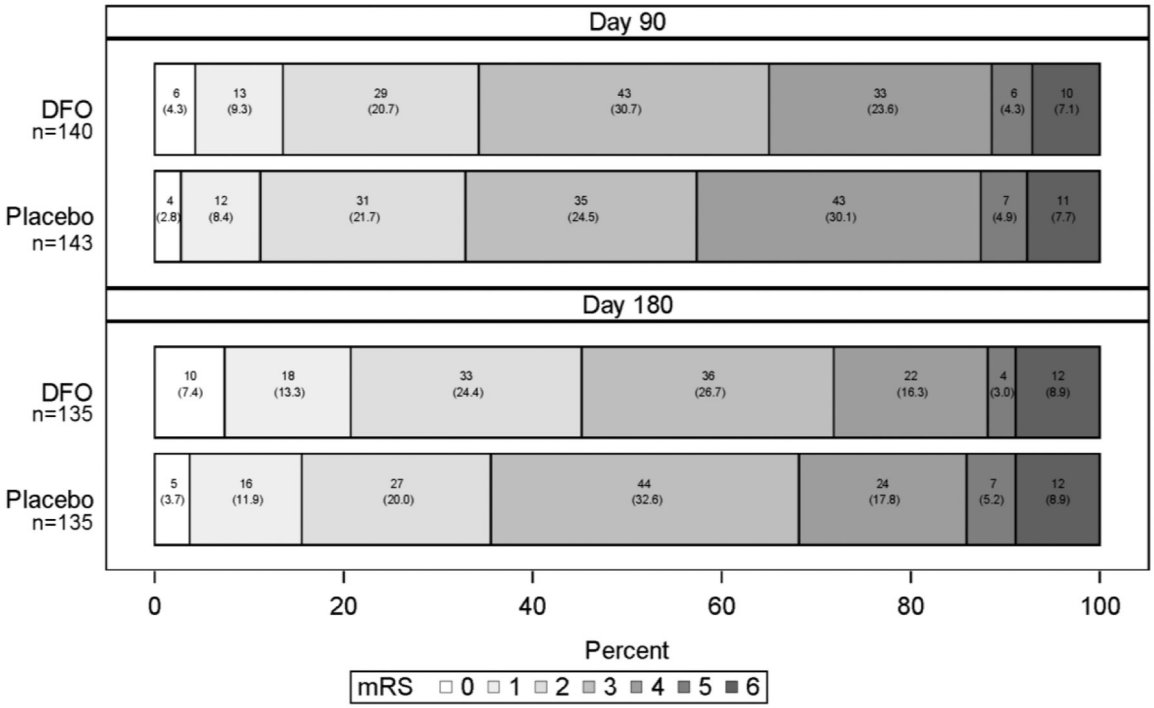


**Figure 3:**

Ordinal Distribution of raw mRS Scores at Day-90 and Day-180 According to Treatment Group.

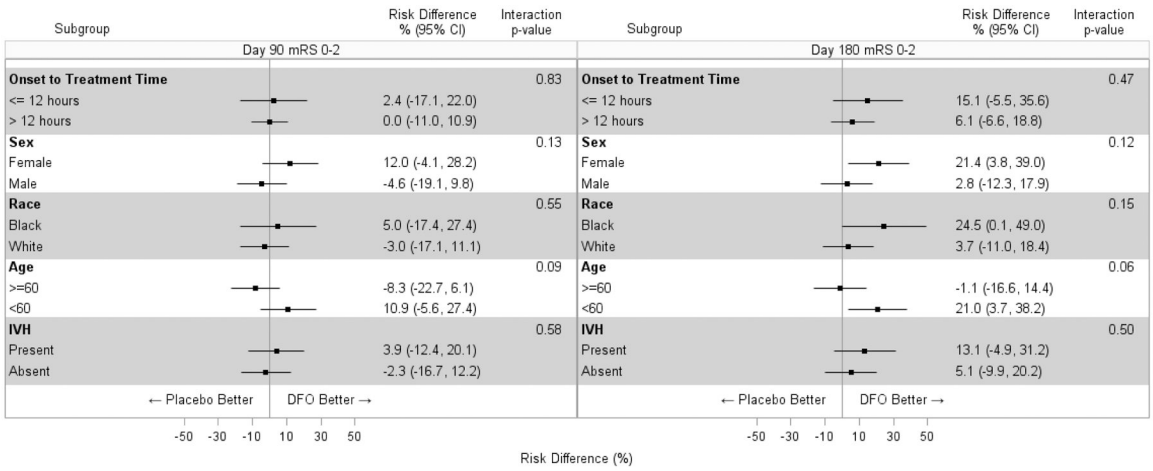


**Figure 4:**
Good Outcome (mRS 0–2) at Day-90 and Day-180 According to Prespecified Subgroups

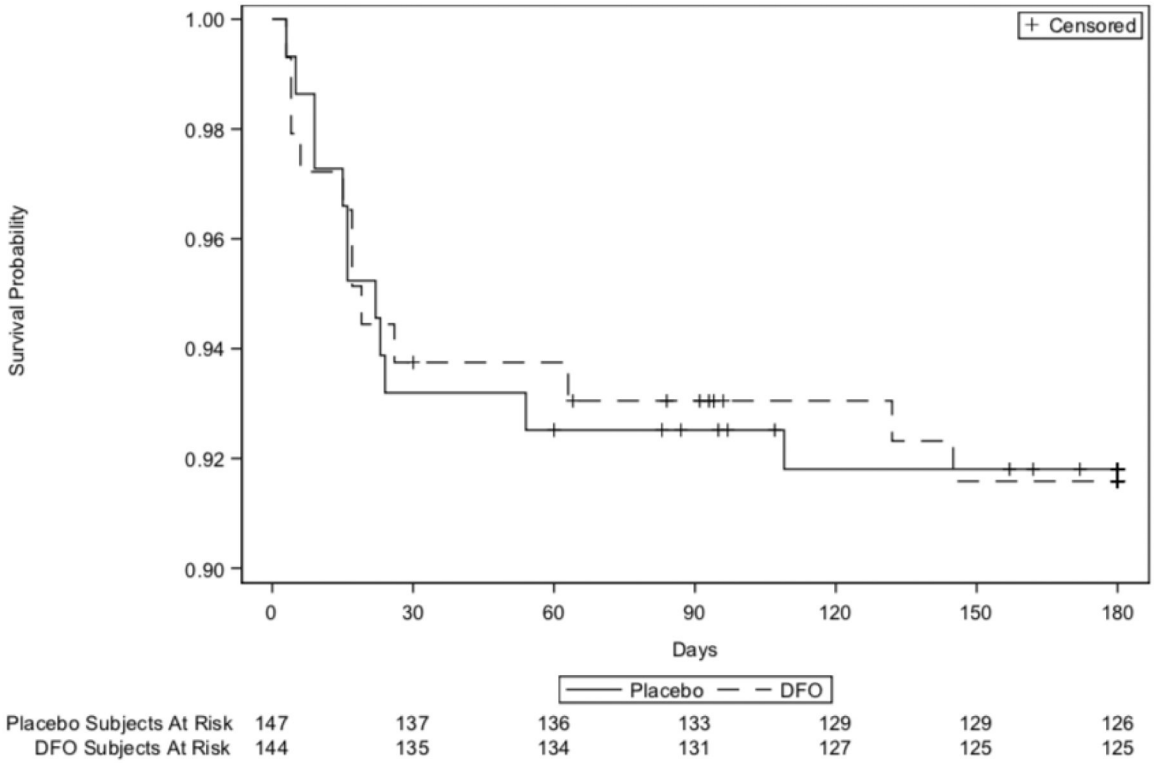


**Figure 5:**
Kaplan-Mejer Survival Curves for 180-day Mortality by Treatment Group.

## Table 1

Demographic and Clinical Characteristics of the Participants According to Treatment Group.

| CHARACTERISTIC | DFO (N=144) | Placebo (N=147) |
|---|---|---|
| **AGE** (YEARS) | | |
| MEDIAN (IQR) | 59 (51–71) | 62 (54–70) |
| **WOMEN** (No / %) | 56 (38.9) | 56 (38.1) |
| MEN (No / %) | 88 (61.1) | 91 (61.9) |
| **RACE** (No / %) | | |
| WHITE | 81 (56.3) | 100 (68.0) |
| BLACK | 31 (21.5) | 33 (22.4) |
| ASIAN | 25 (17.4) | 12(8.2) |
| AMERICAN INDIAN OR ALASKAN NATIVE | 2 (1.4) | 0 (0.0) |
| ANTIVE HAWAIIAN OR OTHER PACIFIC ISLANDER | 3 (2.1) | 1 (0.7) |
| UNKNOWN | 2 (1.4) | 1 (0.7) |
| **ETHNICITY** (No / %) | | |
| HISPANIC OR LATINO | 21 (14.6) | 27 (18.4) |
| NOT HISPANIC OR LATINO | 123 (85.4) | 120 (81.6) |
| **GCS SCORE AT SCREENING** | | |
| MEDIAN (IQR) | 14 (13–15) | 14 (11–15) |
| MINIMUM/MAXIMUM | 8/15 | 7/15 |
| **NIHSS SCORE AT SCREENING** | | |
| MEDIAN (IQR) | 13 (8–17) | 13 (9–19) |
| MINIMUM/MAXIMUM | 6/33 | 6/32 |
| **ICH SCORE** | | |
| MEDIAN (IQR) | 1 (0–1) | 1 (0–2) |
| ICH SCORE ≤2 | 139 (96.5) | 138 (93.9) |
| ICH SCORE >2 | 5 (3.5) | 9 (6.1) |
| **MEDICAL HISTORY** | | |
| HYPERTENSION | 113 (78.5) | 124 (84.4) |
| DIABETES MELLITUS | 32 (22.2) | 43 (29.3) |
| CARDIAC DISEASE | 14 (9.7) | 15 (10.2) |
| PULMONARY DISEASE | 31 (21.5) | 26 (17.7) |
| PRIOR ISCHEMIC STROKE/TTA | 10 (6.9) | 16 (10.9) |
| PRIOR ICH | 7 (4.9) | 3 (2.0) |
| **PRE-ICH MEDICATIONS** | | |
| ANTIPLATELETS | 42 (29.2) | 49 (33.3) |
| WARFARIN | 1 (0.7) | 1 (0.7) |
| ANTIHYPERTENSIVES | 119 (82.6) | 125 (85.0) |
| STATINS | 38 (26.4) | 36 (24.5) |
| **PRE-ICH MODIFIED RANKIN SCALE SCORE** | | |
| mRS = 0 | 130 (90.3) | 130 (88.4) |
| mRS = l | 14 (9.7) | 17 (11.6) |

| CHARACTERISTIC | DFO (N=144) | Placebo (N=147) |
|---|---|---|
| **BASELINE BLOOD PRESSURE** (mm/Hg) | | |
| SYSTOLIC (MEAN ± SD) | 134.9±16.0 | 136.8±15.0 |
| DIASTOLIC (MEAN ± SD) | 71.4±13.9 | 70.5±13.2 |
| **ADMISSION BLOOD GLUCOSE** (mg/dL) | | |
| MEDIAN (IQR) | 133.5 (113.2–153.5) | 138 (118.0–164.0) |
| **TIME FROM ICH ONSET TO TREATMENT (HOURS)** | | |
| MEDIAN (IQR) | 17.4 (10.8–22.4) | 19.5 (11.2–22.9) |
| **IMAGING DATA** | | |
| LOCATION OF ICH | | |
| LOBAR | 26 (18.1) | 33 (22.4) |
| DEEP (THALAMUS) | 45 (31.3) | 61 (41.5) |
| DEEP (NON-THALAMIC) | 73 (50.7) | 53 (36.1) |
| VOLUME OF ICH (mL) * | | |
| BASELINE (MEDIAN/IQR) | 12.1 (6.1–23.8) | 13.0 (6.7–27.3) |
| IVH | | |
| PRESENT | 47 (32.6) | 62 (42.2) |
| BASELINE VOLUME * (MEDIAN/IQR)) | 0 (0–2.1) | 0 (0–5.4) |
| RELATIVE PHE VOLUME * | | |
| BASELINE (MEDIAN/IQR) | 1.2 (1.0–1.6) | 1.1 (0.9–1.5) |

GCS = Glasgow Coma Scale; NIHSS = National Institute of Health Stroke Scale; mRS = modified Rankin Scale; ICH = intracerebral haemorrhage; IVH = intraventricular haemorrhage

-In accordance with the CONSORT guidelines on the reporting of randomised clinical trials, statistical tests of baseline characteristics were not conducted; instead, the clinical relevance of the observed imbalances is considered [16].

-The GCS is a measure of the level of consciousness. The GCS score ranges from 3 to 15, with 3 indicating deep unconsciousness and higher scores indicating milder impairment of consciousness.

-The NIHSS provides as measure of neurological deficits. The NIHSS score ranges from 0 to 42, with a score of 0 indicating no neurological deficits and higher scores indicating greater severity of neurological deficits.

-The ICH Score is a prognostic model for predicting disability and mortality among patients with spontaneous ICH based on age, GCS score, ICH volume, presence of IVH, and ICH location (supratentorial vs. infratentorial). The ICH score ranges from 0 to 5, with increased probability for disability and mortality with increasing scores.

-The mRS provides a measure of the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. The mRS score ranges from 0 to 6, with 0 indicating no symptoms at all, higher scores indicating greater disability and dependence, and 6 death.

* Based on volumetric measurements of ICH and IVH by a central reader.

**Table 2:**

Safety Outcomes at day-90 According to Treatment Group

| VARIABLE | DFO (N=144) | Placebo (N=147) | RR | 95% CI |
|---|---|---|---|---|
| **SERIOUS ADVERSE EVENTS** | | | | |
| AT ANY TIME | 39 (27.1) | 49 (33.3) | 0.81 | 0.6–1.2 |
| WITHIN 7 DAYS | 24 (16.7) | 26 (17.7) | 0.94 | 0.6–1.6 |
| **ADVERSE EVENTS OF SPECIAL INTEREST** | | | | |
| ALLERGIC REACTION (DURING STUDY INFUSIONS) * | 3 (2.1) | 0(0) | -- | -- |
| HYPOTENSION * | 1 (0.7) | 2 (1.4) | -- | -- |
| NEW VISUAL OR AUDITORY CHANGES ** | 3 (2.1) | 4 (2.7) | 0.77 | 0–15.0 |
| RESPIRATORY COMPROMISE (ALL CAUSE) | 20 (13.9) | 23 (15.6) | 0.89 | 0.5–1.5 |
| RESPIRATORY COMPROMISE DUE TO ARDS * | 2 (1.4) | 1 (0.7) | -- | -- |
| **SYMPTOMATIC CEREBRAL EDEMA** | 9 (6.3) | 5 (3.4) | 1.84 | 0.6–5.4 |

Symptomatic cerebral edema was defined as clinician-reported edema accompanied by an unexplained increase in NIHSS score >4 points, or a decrease in Glasgow Coma Scale score >2 points during the first week after ICH

* RR and Confidence intervals not calculated due to limited number of events.

** Exact confidence intervals provided.