Letter to the Editor

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Issues Pertaining to the Critiques of the SAINT-I Trial
See Editor-in-Chief’s Note, page 3116.

To the Editor:

In the recent article by Ginsberg, the author advances several statements that are clearly incorrect. Additionally, the author impugns the critique written by one of us, the editorial by another one of us and aspects of the SAINT clinical trial program. We feel it appropriate to respond to these allegations and mis-statements. The author states that the critique by Hess and editorial by Fisher appeared in a section of Stroke coedited by Dr Lees, the first author of the SAINT-I article that was the subject of these 2 articles, implying impropriety. In fact, on the page preceding the article submitted by Hess in April 2006, the Editor-in-Chief of Stroke, Dr Hachinski, clearly states that Dr Lees’ appointment as section coeditor for Emerging Therapies began on July 1, 2006 and that “Dr Lees had nothing to do with the choice or editing of these articles.” No impropriety occurred.

Another mis-statement by Dr Ginsberg is “Given the marginal findings and questionable methods of SAINT I, it is natural to question the wisdom of the rationale for proceeding to invest the tens of millions of dollars and thousands of medical-personnel hours needed to conduct SAINT II.” The 2 SAINT trials were designed as concurrent trials and initiated within a short time of each other. The sample size and National Institutes of Health Stroke Scale (NIHSS) outcome assessment of SAINT II were adjusted using appropriate trial methodology after the results of SAINT I became available to enhance the ability of SAINT II to evaluate the therapeutic efficacy of NXY-059. Recruitment to SAINT II was complete before publication of the articles cited by Dr Ginsberg. The suggested “unnatural exuberance” of the stroke community had no role in the performance of the 2 SAINT trials.

Dr Ginsberg suggested that one of us “waxed enthusiastic” (Dr Hess) and the other one of us (Dr Fisher) was “insufficiently critical” in our critique and editorial. We strongly dispute these allegations and the convenient out-context quotations used to support them. For the past 7 years, the Emerging Therapies section of Stroke has solicited critiques of therapy-related articles that have appeared in other journals, and on special occasions more than 1 critique and an accompanying editorial were deemed to be warranted; balance is also achieved through invitations to authors representing a range of views. The purpose of these critiques and editorials is to provide the readership of Stroke a critical interpretation of the article in question. We firmly believe that the critique by Hess and the editorial by Fisher meet these criteria. Both of us pointed out the positive aspects of the SAINT-I trial and article reporting them, but we also acknowledged problems as well. For example, Dr Hess stated “One would have been more comfortable had the coprimary outcome and the secondary outcomes also been positive in SAINT-I.” Dr Fisher discussed that the shift in Rankin outcomes used as the primary outcome for SAINT-I may not be clinically meaningful for some components of the scale. Both authors clearly indicated that the results of SAINT II were needed to corroborate SAINT I before the value of NXY-059 could be accepted. These reviews were also balanced by an accompanying article by Drs Papadakis and Buchan that should have appeared at the same time but unfortunately was published separately in the August 2006 issue of Stroke. The critiques and editorial quality as mutedly optimistic overviews of the SAINT-I article and reflected the hope of many in the stroke community that a modest treatment effect with a safe neuroprotective drug might finally be available, pending the results of SAINT II.

Dr Ginsberg is also critical of the SAINT-I trial in regards to 2 statistical issues: the probability value chosen for the primary outcome (0.05) and the analysis approach which adjusted for stratification variables.

First, the role of the primary and coprimary variables followed a prespecified analysis plan agreed on by regulatory authorities, and was made clear in both the primary and secondary articles on SAINT-I: as a hierarchical sequence was used, adjustment for multiplicity should not be used. Second, randomization was stratified according to specified variables that included stroke severity, age and intended use of thrombolysis—published factors known to affect stroke outcome. Established statistical lore requires that after stratified randomization, correct probabilities may be calculated only if the analysis is adjusted for the final distribution of these stratification variables; the SAINT-I protocol followed that rule. Although an unadjusted analysis may indeed reach a different conclusion, that is irrelevant. The SAINT-I analysis was testing how often out of such trials with stratified randomization, the results that had been observed would be found by chance alone: the answer was fewer than 4 in 100.

The SAINT-I investigators remained cautious: “Our results were statistically significant for the primary outcome measure, but not for other outcome measures. A confirmatory study is needed to determine whether NXY-059 has a benefit in stroke” and “the probability of a false-positive result remains 0.038 . . . only a larger confirmatory trial such as SAINT II will provide conclusive evidence of whether NXY-059 is effective in limiting disability after acute ischemic stroke.”

Clinical science requires sound hypotheses, properly tested and interpreted. The SAINT program fulfilled these criteria. Good science also encourages debate: we welcome the debate but require that it should center on accurate facts.

Disclosures

M.F. and D.C.H. are consultants for AstraZeneca; K.L. is Chairman of the steering committee for SAINT-I and CHAMPS, and has received fees and expenses from AstraZeneca related to these activities.

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