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RSS STATEMENT ON PUBLICATION OF THE STUDY-PROTOCOL BIA-102474-101 FOR THE FRENCH “FIRST-IN-MAN” TRIAL IN HEALTHY VOLUNTEERS

The Royal Statistical Society welcomes the publication (in Le Figaro, 21 January 2016) of the study-protocol BIA-102474-101 for the French “first-in-man” trial. Six of eight healthy volunteers in the trial’s multiple-administration phase received daily-dosing (at an unspecified dose-level, on and after 7 January 2016) of active drug. Tragically, one of the six has died and others required hospitalization.

As there are clear statistical reservations about the study-design, the Royal Statistical Society urges that the French investigatory teams include independent statistician-members. In addition, three further disclosures are essential:

- i) The investigator brochure (minimally-redacted), which usually describes pre-clinical studies in detail, needs to be put into the public domain.
- ii) The escalated dose-levels that were actually tested in the trial’s single-administered-dose (SAD) phase need to be disclosed, together with the number of volunteer cohorts on whom each dose-level was tested. We note that back-tracking to re-test a dose-level was allowed as well as escalation.
- iii) The regimen actually selected for 10 days’ administration to first cohort of healthy volunteers in the trial’s multiple-administered-dose (MAD) phase needs to be published.

It appears that the approved study-design did not follow recommendations made in 2007 by the Royal Statistical Society’s Working Party on “Statistical Issues in First-in-Man Studies” (chair: Professor Stephen Senn) in the aftermath of a study of TGN1412 when six previously healthy volunteers were admitted to intensive care at Northwick Park Hospital.

Commenting on the inquiry Professor Stephen Senn said:

“Our thoughts are with the families of all the men in the affected cohort. Key recommendations in the RSS report cover proper risk assessment, sharing that assessment with all parties and the sharing of information across studies to improve

the assessment of risk. We hope that, as the inquiry proceeds, these matters will be properly and expertly addressed not only by physicians but also by statisticians.”

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Notes

1. The Royal Statistical Society (RSS) founded in 1834 is one of the world's most distinguished and renowned statistical societies. It is a learned society for statistics, a professional body for statisticians and a charity which promotes statistics, data and evidence for the public good. Today the Society has almost 8000 members around the world. www.rss.org.uk
2. The report of the Royal Statistical Society's Working Party on Statistical Issues in First-in-Man Studies Royal Statistical Society Working Party (chair: Prof Stephen Senn) was published in *Journal of the Royal Statistical Society, Statistics in Society* 2007; 170: 517 – 579.
<http://onlinelibrary.wiley.com/doi/10.1111/j.1467-985X.2007.00481.x/epdf>
3. As reported in today's British Medical Journal, Professor Sheila M. Bird, member of the RSS working party on Statistical Issues in First-in-Man Studies and former vice-president for external affairs, had petitioned the French authorities to release the study-protocol BIA-102474-101. The protocol was published yesterday evening by Le Figaro together with expert commentary - including by French statistician Dr Catherine Hill.
4. Professor Andy Grieve, past-president of the Royal Statistical Society and member of the RSS working party on Statistical Issues in First-in-Man Studies, notes that the published protocol appears to diverge not only from the RSS Working Party's recommendations but also from European Guidance on mitigating risk in First-in-Human studies.