Title

Response of authors to Ganju and Dias' comments on 'Inclusion of Placebos and Blinding for Ascending Dose First-in-Human Studies and Other Underpowered Phase 1 Studies Has Not Been Justified and on Balance is Not Useful' by D. A. Parasrampuria and L....

Journal

Basic and Clinical Pharmacology and Toxicology, 117(6)

ISSN

1742-7835

Authors

Parasrampuria, DA
Benet, LZ

Publication Date

2015-12-01

DOI

10.1111/bcpt.12483

Peer reviewed

Response of Authors to Ganju and Dias Comments on “Inclusion of Placebos and Blinding for Ascending Dose First-in-Human Studies and Other Underpowered Phase 1 Studies Has Not Been Justified and on Balance is Not Useful” by D. A. Parasrampuria and L. Z. Benet

We thank Ganju and Dias for engaging in a discussion regarding blinding and inclusion of placebos in Phase I trials with respect to our published manuscript. The Ganju and Dias article that we referenced, and to which they refer in their response, proposed that in many cases it was advantageous for sponsors to be unblinded in randomized, double-blind, Phase I clinical trials. We had argued that the increased complexity and the additional documentation required to maintain the blind and the “additional documentation required to maintain a blind, procedures and monitoring necessary to ensure the blind in the study, monitoring pharmacy procedures and safety procedures and safety activities related to bioanalytical analysis and safety adjudication” in Phase I studies was not justified. If Ganju and Dias are now proposing that they do not support study design and procedures for blinding in drug interaction and bioequivalence Phase I studies, but are only proposing that sponsors “not access the relevant data until a final SAP is prepared and the database locked” we are not opposed to such a recommendation. That recommendation would not entail any increased time or cost in running the Phase I study and would only involve voluntary restraint by the sponsor. We would gladly modify our statement to “We cannot imagine how and why bioequivalence or drug interaction studies should be blinded for any of the investigators or study subjects except sample bioanalysts and possibly the study sponsor”.

Ganju and Dias also comment on our assertion that inclusion of placebo patients in underpowered Phase I dose ascending studies is not justified and on balance not useful. They propose that particularly when patients are enrolled in Phase I trials, data from placebo patients with respect to biomarkers, surrogate end points and clinical measure serve a useful purpose, but, they provide no supporting data. In our paper we state “If a sound rationale and plan for assessment of data from the placebo group is justified, a placebo group should be included”. We believe that we could have just as easily prepared a Table 2 entitled “Decision paradigm for pharmacodynamic effects in small Phase I studies”, as we did for adverse events within our paper, and demonstrate little support for gaining useful knowledge by inclusion of placebo dosed patients in such underpowered Phase I studies. We repeat our conclusion: “We see no scientific evidence for the utility of placebos and blinding for FIH dose-escalation studies. The practice seems to be more based on faith and an ill-considered precedent”.

Dolly A. Parasrampuria
Leslie Z. Benet
leslie.benet@ucsf.edu
Department of Bioengineering and Therapeutic Sciences
Schools of Pharmacy and Medicine
University of California San Francisco