Department of Pediatrics
McMaster University
Hamilton, Ontario, Canada

Kanekal Suresh Gautham, MD, FAAP
Division of Neonatology
Department of Pediatrics
Texas Children's Hospital
Baylor College of Medicine
Houston, TX

https://doi.org/10.1016/j.jpeds.2020.08.029

The authors declare no conflicts of interest.

References

1. Ramanathan R, Biniwale M, Sekar K, Hanna N, Golombek S, Bhatia J, et al. Synthetic surfactant CHF5633 compared with poractant alfa in the treatment of neonatal respiratory distress syndrome: a multicenter, double blind, randomized, controlled clinical trial. J Pediatr 2020. in press.
2. Mauri L, D'Agostino RB. Challenges in the dsign and interpretation of noninferiority trials. N Engl J Med 2017;377:1357-67.
3. Trelle S. Exploratory trials in mental health: anything to learn from other disciplines? Evidence Based Mental Health 2017;20:21.
4. Dehbi H-M, Hackshaw A. Sample size calculation in randomised phase II selection trials using a margin of practical equivalence. Trials 2020;21:301.

Reply

To the Editor:

We would like to clarify that no claims for equivalence or noninferiority were made in our article according to the exploratory design of our study. It is not an equivalence trial. Following a first-in-human clinical study,[1] the exploratory design of this phase II study was agreed and approved by Food and Drug Administration to gain additional information for designing further studies on the grounds of preliminary comparative data of the overall surfactant products' profiles. We referred to similarity between the results observed with the 2 surfactants with specific reference to the overall efficacy and safety profiles in line with the exploratory design of this study; accordingly, "Sixty-three randomized patients per treatment group (126 in total), in this vulnerable preterm population, were deemed reasonable to describe the efficacy and safety profile of CHF5633 compared with poractant alfa."

For this reason, we would like to point out that we did not decide to stop recruitment after enrolling 126 neonates and, as reported, a total of 297 infants were screened and 123 infants were randomized in this challenging study from December 2015 through February 2018 in 22 neonatal intensive care units in the US. "Similarity" is indeed mentioned with reference to the overall study endpoints.

Sample size calculations would have required a primary endpoint and a hypothesis, which is not in line with the aim of the present study. Therefore, our study could not be powered for any measured endpoint. In particular, an equivalence/noninferiority study on mortality would not have been feasible without enrolling a large number of neonates from this vulnerable very preterm population. Because of this, we think that these results on the relative risk of death at 28 days of life with CHF5633 or poractant alfa are absolutely by chance and were only reported, but not claimed as a standard outcome in preterm neonates with respiratory distress syndrome. However, and as reported in the discussion section, we acknowledge the need for further confirmatory and possibly statistically powered clinical trials to draw eventual conclusions on superiority, noninferiority, or equivalence between the 2 surfactants. We do not believe that there were any flaws in our conclusions or discussion.

Rangasamy Ramanathan, MD
Manoj Biniwale, MD
Department of Pediatrics
Division of Neonatology
LAC+USC Medical Center and Good Samaritan Hospital
Keck school of Medicine of USC
Los Angeles, CA

Krishnamurthy Sekar, MD
Department of Pediatrics
Division of Neonatology
Oklahoma University Medical Center
Children's Hospital
University of Oklahoma Health Sciences Center
Oklahoma City, OK

Nazeeh Hanna, MD
Department of Pediatrics
Division of Neonatology
NYU Winthrop Hospital
NYU Long Island School of Medicine
Mineola, NY

Sergio Golombek, MD
Department of Pediatrics
Division of Neonatology
Maria Fareri Children's Hospital at Westchester Medical Center
New York Medical College
Valhalla, New York

Current affiliation: Joseph M. Sanzari Children's Hospital, Hackensack University Medical Center, NJ.

Jatinder Bhatia, MD
Department of Pediatrics
Division of Neonatology
The Medical College of Georgia at Augusta University
Augusta, GA

Martha Naylor, MD
Department of Pediatrics
Division of Neonatology
Brody School of Medicine at East Carolina University
Greenville, NC

Laura Fabbri, PhD
Guido Varoli, Pharm D
Debora Santoro, MSc
Dorothea Del Buono, MD
Annalisa Piccinno, MSc
Global Clinical Development
Chiesi Farmaceutici SpA
Parma, Italy

Christiane E. Dammann, MD
Floating Hospital for Children at Tufts Medical Center
Boston, MA

https://doi.org/10.1016/j.jpeds.2020.08.030

Reference

1. Sweet DG, Turner MA, Straňák Z, Plavka R, Clarke P, Stenson BJ, et al. A first-in-human clinical study of a new SP-B and SP-C enriched synthetic surfactant (CHF5633) in preterm babies with respiratory distress syndrome. Arch Dis Child Fetal Neonatal Ed 2017;102:F497-503.