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LETTER

Methodological Considerations in the Bioequivalence Assessment of Recombinant Human Serum Albumin [Letter]

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Dear editor

We recently read with great interest the Phase I study by Panuganti et al, which evaluated the pharmacokinetics (PK), pharmacodynamics (PD), safety, and immunogenicity of recombinant human serum albumin (rHSA) compared with plasma-derived human serum albumin (pdHSA) in healthy adults.[1] The authors conclude that rHSA demonstrated comparable PK, safety and immunogenicity profiles to pdHSA, supporting its potential as a viable alternative. While we acknowledge the clinical importance of developing a pathogen-free albumin product, we wish to highlight several methodological and statistical concerns that, in our view, substantially weaken the bioequivalence (BE) conclusion.

The most critical issue concerns the discordant results between baseline-corrected and uncorrected PK analyses. Baseline correction was prespecified "to account for endogenous albumin concentrations and to better isolate exogenous drug exposure". However, the corrected data failed to meet BE criteria: the T/R ratio for C_{max} was 131.15% (90% CI: 80.03–214.93%), and for AUC_t it was 189.73% (90% CI: 92.68–388.40%), both exceeding the 80–125% limits. The authors dismiss these findings as artifacts of amplified inter-individual variability and instead rely on uncorrected data to claim equivalence. This analytical selection is problematic. Endogenous substances are under tight homeostatic control, with saturable synthesis, reversible metabolism, renal thresholds and circadian fluctuations, and their PK rarely follows linear processes.[2] The baseline subtraction may introduce bias up to 14% in AUC and elimination half-life estimates.[3] Several scholars emphasised that baseline handling is "a non-solvable problem" for endogenous compounds, and that subtracting baseline values can artificially inflate variability and distort true treatment-attributable exposure.[3–6]

Second, the primary PK endpoint was changed from the protocol-defined AUC_∞ to AUC_t without adequate justification. The authors note that "only one participant met criteria for reliable terminal slope estimation", precluding robust AUC_∞ estimation in most participants. While this difficulty is well recognised for endogenous proteins, it does not justify an unplanned endpoint substitution. When AUC_∞ cannot be reliably estimated—particularly for long-half-life drugs or endogenous substances—AUC_t or truncated AUC may serve only as an ancillary procedure, not as a primary replacement endpoint.[7] Using AUC_t as the sole basis for BE conclusion, without prior protocol amendment and regulatory concurrence, introduces bias and compromises the interpretability of total systemic exposure, especially for albumin with a long pharmacokinetic half-life in healthy adults (~19–21 days).

Third, the effective sample size severely undermines statistical power. The initial calculation required 42 participants, and 50 were enrolled (25 per arm) to account for ~20% dropout. However, in the baseline-corrected analysis—the method intended to isolate exogenous albumin—only 11 participants were evaluable for C_{max} and AUC_t. This represents an effective sample size reduction of more than half relative to the planned 25 per arm, directly causing the excessively wide confidence intervals observed. The study therefore lacks adequate power to confirm equivalence under the rigorous corrected approach, making the negative BE result in the corrected dataset entirely expected rather than dismissible.

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Fourth, the analysis lacks adjustment for multiplicity. The study evaluates three dose levels, multiple PK parameters (C_{max}, AUC_t, Kel, t½, CL, V_d), two PD markers (COP, HCT), and two analytical approaches (corrected/uncorrected). No correction (eg, closed testing procedures or alpha-adaptive sequential methods) is mentioned. As Hua et al have shown, BE assessment typically requires simultaneous equivalence in both AUC and C_{max}, involving four one-sided hypotheses; without multiplicity adjustment, the family wise error rate (FWER) may substantially exceed the nominal 5% level.[8] This inflation increases the risk of false-positive findings when multiple comparisons are interpreted cumulatively.

Finally, we would like to suggest that future bioequivalence studies of recombinant therapeutic proteins, including rHSA, consider more diverse study populations. The current investigation was conducted exclusively in Asian males, which, while acceptable for an initial Phase I evaluation, may limit the generalisability of findings to the intended target populations—such as patients with cirrhosis, septic shock, or hepatorenal syndrome—who exhibit substantially different fluid distribution, volume of distribution, and albumin catabolic rates. We therefore propose that subsequent trials incorporate population pharmacokinetic (PopPK) modelling with covariate effects, including sex, body weight, and disease status, to better characterise the sources of inter-individual variability and to enhance the interpretability of bioequivalence results across relevant patient subgroups, as previously recommended for endogenous substances.

In conclusion, while Panuganti et al have conducted a carefully designed initial exploration, the current evidence for PK bioequivalence is less robust than concluded. The discordance between corrected and uncorrected analyses, the unplanned endpoint switch, the inadequate effective sample size in the primary analysis, and the lack of multiplicity adjustments collectively weaken the statistical foundation for claiming equivalence. Explicitly acknowledging these limitations would strengthen the translational value of this important work and provide a more accurate roadmap for future clinical development of rHSA.

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Disclosure

The authors report no conflicts of interest in this communication.

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