Sir,

This letter is in context to the article published in your journal titled, "Comparative evaluation of 2 g single dose versus conventional dose azithromycin in uncomplicated skin and skin structure infections." I have certain queries regarding the methodology and conclusion of this article.

In this article, the researchers compared the efficacy of 2 g single dose azithromycin with that of conventional 5 days dose of azithromycin. The primary outcome measure in this study was clinical response characterized by cessation of spread of redness, edema, and induration around the lesion or reduction of the size of the lesion at 72 h. The investigators have reported that "this study was conducted to show the efficacy of single dose regimen…" However, the researchers also concluded on the basis of this study that "…single 2 g dose of azithromycin, given under supervision, is generally well-tolerated and can achieve clinical cure rates comparable to conventional azithromycin dosing within 7 days." This conclusion drawn on the basis of this particular study is inappropriate as the design of this study was intended to test superiority of single dose regimen, and in such a designed trial, nonsignificant P values cannot be considered as a proof of equality.

In this article, the single dose and conventional dose group are not significantly different from each other for primary end-point. However, as nonsignificant P value cannot prove the null hypothesis, on the basis of this study, it cannot be said that both drugs are equally effective. In addition, the conclusion drawn by the authors that "the difference in treatment adherence was highly significant (P < 0.001) in favor of the single dose arm" is highly influenced by observer bias as the 2 g single dose of azithromycin was taken in direct supervision of the observers which is bound to result in 100% adherence in this group. Furthermore, the feasibility of such observed treatment remains doubtful in actual clinical scenario.

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Conflicts of Interest
There are no conflicts of interest.

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Author Reply

We thank the reader for having gone through our paper meticulously and raising pertinent queries. We would like to reply as follows. The reader states that "design of this study was intended to test superiority of single dose regimen." However, this was not the intention. Since both regimens use the same drug and formulation, it is not reasonable to expect superiority of one regimen over another. Our aim was to see whether the clinical outcome was comparable.

Trials, nowadays, are being designed as superiority, inferiority, or equivalence studies on the basis of the confidence interval approach. Going by this strategy, the 2 g single dose azithromycin regimen was tested for "no worse than" contention compared to the conventional regimen (500 g daily for 5 days). However, we did not conduct it as a noninferiority trial for two reasons – this would have required defining a noninferiority margin for which there are no clear guidelines in this case and second it would have required a larger sample size which would have made things logistically difficult. We have stated in the methods section that “the sample size for the study was determined conventionally and not considering a noninferiority design.” We agree with the reader’s contention that going by the noninferiority approach, we cannot claim the results as comparable. However, let us look at the results (97.97% clinical cure rate with single dose versus 98.63% with test dose, respectively) from the clinician’s point of view. The results clearly indicate that the 2 g single dose regimen is not better than conventional region. Neither is it performing worse. Then what should be the clinical conclusion? Only statistically speaking, we can conclude nothing, but would be wrong to consider 97.97% and 98.63% cure rates as clinically comparable? If it were
wrong, then so many studies which have been done without declaring noninferiority, superiority, or equivalence margins upfront should all be discarded!

We also cannot say that the observation regarding medication adherence is subjected to bias as the 2 g regimen was deliberately intended to be a supervised regimen. We agree that supervised administration on the spot, such as in a busy OPD setting may not always be feasible. However, even in nontrial setting, it is reasonable to expect that the possibility of a patient defaulting on a single dose would be less than on a 5-day regimen. We have concluded in our abstract that “single 2 g azithromycin dose achieved same result as conventional azithromycin dosing in uncomplicated skin and skin structure infections with comparable tolerability but with the advantage of assured adherence. This dose can, therefore, be recommended as an alternative and administration supervised if feasible.” The word “feasible” reflects the readers concern.

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