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## Author's reply: Baloxavir for influenza

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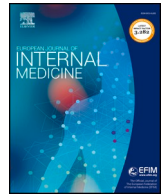
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## Letter to the Editor

## Baloxavir for influenza: Enrichment obscured lack of effect in North-American adults. Author's reply.



## ARTICLE INFO

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In response to our comment [1], Dr Portsmouth and colleagues provide additional information about the results of the CAPSTONE-1 trial [2], which we appreciate. In our comment, we underlined that the composition of the study population should have been taken into account when the study results were analysed, interpreted and presented.

The authors confirm that enrichment of the study population may have occurred. They explain that the combination of competitive enrolment and an earlier start of the influenza season in Japan has led to relatively few North-American adult participants. Since a previous population pharmacokinetic analysis has shown a difference in plasma baloxavir exposure between Asians and non-Asians [3,4], the question is why the research team did not choose a design with stratified enrolment per country.

The authors also confirm that CAPSTONE-1 did not show a reduction in time to alleviation of flu symptoms in North-American adults treated with baloxavir compared to placebo. They postulate that a baseline imbalance in eight potential prognostic factors has likely contributed to the lack of effect. Yet, the adjusted analysis, which they now present, leaves the lack of effect largely unexplained: the point estimate changed from  $-2.1$  h to  $-5.2$  h [5].

Furthermore, the authors hypothesise that the lack of effect of baloxavir in North-American adults may be due to a lack of power. We agree that the precision of the estimated effect size is lower with a smaller sample size. However, given the 95% confidence intervals around the time to alleviation of flu symptoms in both study groups and the overlap between them (baloxavir 66.2–94.0; placebo 62.7–125.8), it seems unlikely that a trial with a larger number of North-American adults will yield a difference between baloxavir and placebo that would approximate the observed effect of  $-27.2$  h in the Japanese adults.

Finally, the authors claim that baloxavir was effective in North-American adults in the CAPSTONE-2 trial, of which the full results have

not been published [6]. However, this trial was performed in patients at an increased risk of influenza complications. To prove that baloxavir has a clinically relevant effect on the time to alleviation of flu symptoms in *otherwise healthy North-American adults with uncomplicated influenza*, the target indication in CAPSTONE-1, one or more additional trials will need to be performed.

## Declaration of Competing Interest

None.

## References

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