Author's reply: Baloxavir for influenza

de Haas, Esther C; Luijendijk, Hendrika J

Published in:
European Journal of Internal Medicine

DOI:
10.1016/j.ejim.2019.12.021

Publication date:
2020

European Journal of Internal Medicine 72 (2020) 102

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Letter to the Editor

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

ARTICLE INFO

Keywords:
Clinical trial
Enrichment
Generalisability
Baloxavir
Influenza

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 proof 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

[1] de Haas, Esther C. et al. Baloxavir for influenza: Enrichment obscured lack of effect in North-American adults. European Journal of Internal Medicine, Volume 62, e8–e9.
[2] Hayden FG, Sugaya N, Hirotsu N, et al. Baloxavir marboxil for uncomplicated influenza in adults and adolescents. N Engl J Med 2018;379:913–23.
[3] Japanese Pharmaceuticals and Medical Devices Agency. Review Report Xofluza 10 mg and 20 mg 2018 8 FebruaryAvailable via: www.pmda.go.jp/files/000225380.pdf.
[4] Genentech USA, Inc. XOFLUZA™ (baloxavir marboxil) [label]. 2018. Available via: www.accessdata.fda.gov/drugsatfda_docs/label/2018/210854s000lbl.pdf.
[5] Portsmouth S, Kawaguchi K, Uehara T, Hayden F. Re Baloxavir for influenza: enrichment obscured lack of effect in North-American adults. Eur J Int Med. 2019. this issue.
[6] Ison MG, Portsmouth S, Yoshida Y, Shishido T, Hayden F, Uehara T. LB16: phase 3 trial of Baloxavir marboxil in high-risk influenza patients (CAPSTONE-2 study). Open Forum Infect Dis 2018;5(Suppl1):S764−5.

Esther C. de Haas*, Hendrika J. Luijendijk
University Medical Centre Groningen, University of Groningen, Department of General Practice and Elderly Care Medicine, PO Box 196, 9700 AD Groningen, the Netherlands
E-mail address: e.de.haas@umcg.nl (E.C. de Haas).

DOI of original article: https://doi.org/10.1016/j.ejim.2018.12.002
* Corresponding author.

https://doi.org/10.1016/j.ejim.2019.12.021
Received 19 December 2019; Accepted 23 December 2019
Available online 03 January 2020