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Cardiovascular Safety of Nilotinib in Parkinson's Disease

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Running Title:

Cardiac Safety of Nilotinib in PD

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We read with interest the article by Pagan et al on the safety and clinical effects of Nilotinib in patients with Parkinson's disease (PD)(1). This open-label extension of an earlier phase 2 trial demonstrated that 90.5% patients successfully tolerated either 150mg or 300mg Nilotinib daily without significant adverse events at 15-month follow up. Of the 63 patients enrolled, there were seven dropouts – one from oesophageal carcinoma, one from cervical cord compression, one from renal failure, one from acute coronary syndrome, and three voluntary withdrawals. Exploratory analyses from this study also suggested potential symptomatic benefit of 300mg Nilotinib in the treatment of PD, however these results require further adequately powered studies for validation.

Albeit promising results, caution should be exercised when evaluating the safety of Nilotinib in future larger phase 3 trials for PD, especially with regards to risk of cardiovascular events (CVE), defined as ischaemic heart disease, ischaemic stroke and peripheral vascular disease. The landmark ENESTnd trial which evaluated the use of Nilotinib for chronic myeloid leukaemia reported a dose- and duration-dependent relationship between Nilotinib and CVE(2,3). There were no CVE reported in the trial at 12-month follow up(2), however incidence of CVE was 7.5% in the Nilotinib 300mg twice daily group and 13.4% in the 400mg twice daily group at 5-year follow up(3).

Pagan et. al reported one acute coronary syndrome (non ST elevation myocardial infarction) in the study and postulated that this event may be likely incidental and unrelated to Nilotinib therapy as it occurred four days after commencement and the patient had received placebo in the earlier phase 2 trial. It should be noted that the trial population may have moderate-high cardiovascular risk at baseline, as suggested by the reported mean age of 70 years and pre-dominant male sex in the cohort. Therefore the commencement of Nilotinib in elderly patients

with PD may be associated with increased in long-term risk of CVE. While the dose and duration of Nilotinib in this trial (150mg or 300mg daily for 12 months) were both lower than that in the ENESTnd trial, the cumulative effects of long-term Nilotinib use in PD patients with moderate or high cardiovascular risk could be of concern.

In conclusion, there is evidence to suggest that Nilotinib may be a promising treatment for PD, with 15-month data supporting the safety of its use. Nilotinib has been observed to be associated with increased long-term CVE in chronic myeloid leukemia populations and assessment of cardiovascular risk and detailed description of cardiovascular safety should be considered in the future phase 3 trials.

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None.

Authors' Roles

S.T., D.B., J.S., and B.K. contributed to the conception, drafting and writing of the text.

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References

1. Pagan FL, Wilmarth B, Torres-Yaghi Y et al. Long-Term Safety and Clinical Effects of Nilotinib in Parkinson's Disease. Mov Disord 2021;36:740-749.
2. Saglio G, Kim DW, Issaragrisil S et al. Nilotinib versus Imatinib for Newly Diagnosed Chronic Myeloid Leukemia. N Engl J Med 2010;362:2251-2259.
3. Hochhaus A, Saglio G, Hughes TP et al. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. Leukemia 2016;30:1044-54.

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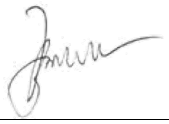

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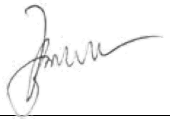

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