Alternative complement pathway pharmacodynamics of iptacopan

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Introduction

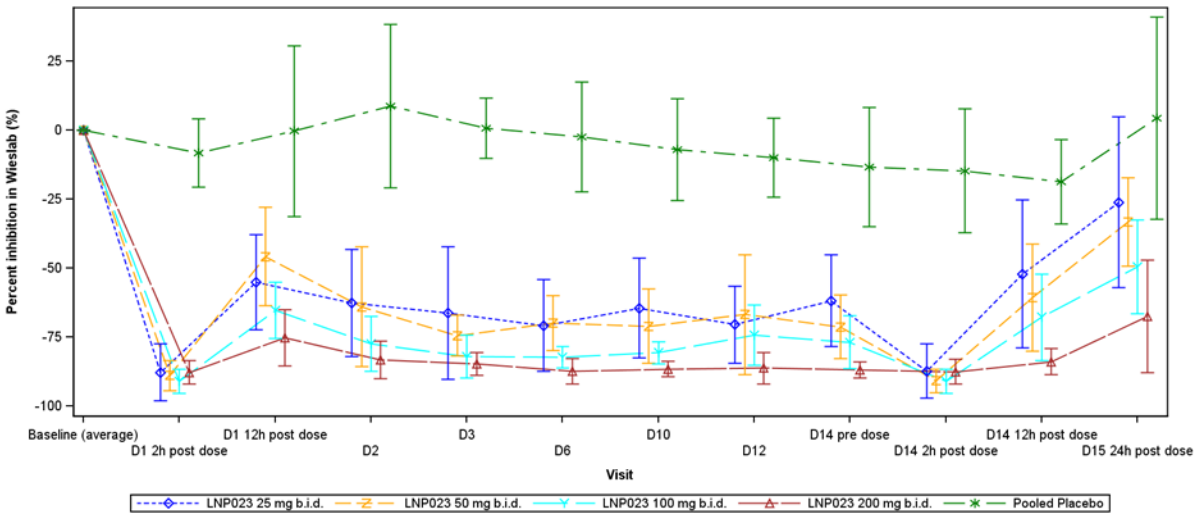
Iptacopan (LNP023) is a first-in-class, oral, low molecular weight, Factor B inhibitor being developed for the treatment of diseases associated with activation of the alternative complement pathway. Current Phase III studies of iptacopan include paroxysmal nocturnal hemoglobinuria, C3 glomerulonephritis, IgA nephropathy, and atypical hemolytic uremic syndrome. The Wieslab assay, a highly specific biomarker for alternative pathway activity, was measured in healthy subjects to determine the effect of steady-state dosing of iptacopan on alternative complement pathway inhibition.

Methods

A total of 32 healthy participants where enrolled into four iptacopan treatment groups (25, 50, 100 and 200 mg twice daily, n=6 per group) and one placebo group (n=8) The duration of treatment was 14 days. The Wieslab assay was measured at 12 timepoints over 15 days (baseline at time 0 and post-dose on day 1 at hours 2 and 12, and then pre-AM dose on days 2,3,6,10, 12, and 14 (pre-dose and hour 12) and finally day 15 (24 hours post last dose).

Results

Iptacopan treatment was safe and well tolerated. The mean (±SD) percent inhibition of the Wieslab assay from baseline (average of baseline and day 1 pre-dose values) for the five treatment groups over time is shown in the figure below. The placebo group had little change in Wieslab over the course of the study. The four iptacopan treatment groups manifested a rapid decrease in Wieslab activity at 2 hours post initial dose. Over the remaining course of treatment, a dose dependent decrease in Wieslab was observed with the 200 mg BID dose having the maximal (>80%) inhibition of this pathway biomarker. After treatment cessation, the 200 mg BID dose also had the longest persistence of inhibition of the assay.



Conclusion

As measured by the Wieslab assay, iptacopan treatment resulted in a rapid and substantial inhibition of the alternative complement pathway. The clinical dose of 200 mg BID, which has been used in the Phase III studies, resulted in greatest (>80%) inhibition of Wieslab assay. Finally, even one day after stopping iptacopan 200 mg BID treatment, >70% inhibition was still present. These results support the iptacopan clinical dose of 200 mg BID and provide the promise of durable alternative pathway inhibition in patients on iptacopan therapy.