Results of Preclinical Animal Studies to Evaluate the Effect of Iptacopan on Pregnancy-Related Outcomes

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Introduction: Iptacopan is a first-in-class, oral, selective inhibitor of factor B, a key component of the complement system alternative pathway. Inhibition of the complement system represents a potential mechanism for treatment of several complement-driven diseases including paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome. Here, we report results from the preclinical GLP toxicology studies of iptacopan on embryo-fetal development in rats and rabbits and pre- and postnatal development in rats.

Methods: In the definitive embryo-fetal development studies, iptacopan was dosed orally via gavage to pregnant rats at 0, 100, 300, and 1000 mg/kg/day (N=24/group) and to pregnant rabbits at doses of 0, 100, 250, and 450 mg/kg/day (N=20/group) during the period of organogenesis [Gestation Day (GD) 6 to 17 and GD7 to 20, respectively]. The progress and outcome of pregnancy were evaluated and fetuses were examined for external, visceral, and skeletal abnormalities. In a pre- and postnatal developmental toxicity study in pregnant rats, iptacopan was dosed orally via gavage at 0, 100, 300, and 1000 mg/kg/day (N=22/group) from GD6 to Lactation Day (LD) 21. The untreated offspring were allowed to mature and the effects on development, behavior, and reproductive performance were assessed.

Results: In the rat embryo-fetal development study, maternal administration of iptacopan resulted in no adverse clinical observations, no effects on maternal body weights, and no adverse fetal findings. Non-adverse fetal variations of delayed ossification were observed in the skull. Two fetuses in one out of 22 litters at 1000 mg/kg/day had benign cysts on the left side of the parietal region of the head, with no impact on skeletal (skull), CNS (brain) or any other head based structure. The No Observed Adverse Effect Level (NOAEL) for maternal toxicity and embryo-fetal development was 1000 mg/kg/day. In the definitive rabbit embryo-fetal development study, administration of iptacopan caused reduced maternal body weight gain and food consumption at 450 mg/kg/day. There were no treatment-related fetal malformations or variations. The NOAEL was 250 mg/kg/day for maternal toxicity and 450 mg/kg/day for embryo-fetal development. In the pre- and postnatal development study, no adverse findings were observed in the mated female rats during gestation, parturition and lactation and there were no adverse effects on development of their offspring, including survival, physical development, behavior, and reproductive performance. The NOAEL for maternal (F0 generation) toxicity, maternal performance, and development of the F1 generation offspring was the highest dose of 1000 mg/kg/day. NOAEL and estimated AUC-based safety margins based on total plasma concentrations for all mentioned studies are shown in the **Table**.

Conclusion: In nonclinical reproductive toxicity studies conducted in pregnant rats and rabbits, iptacopan was found to be generally safe with no teratogenic effects in the rat and rabbit. Estimated AUC-based safety margins were >5-fold for all developmental findings compared to exposure at the clinical dose of 200 mg twice daily. While these preclinical data do not provide definitive conclusions or guidance on the use of iptacopan in pregnant women, they do provide reassurance that there is no overt preclinical signal of embryo-fetal toxicity.

Table. Safety Margins at the NOAEL Dose of Iptacopan in Nonclinical Reproductive Studies in Pregnant Animals

Study	**Animal**	**Subject**	**NOAEL (mg/kg/day)**	**AUC-based safety margin[a]**
Embryo-fetal development	Rat	Maternal toxicity	1000	5.4
	Rat	Embryo-fetal toxicity	1000	5.4
	Rabbit	Maternal toxicity	250	3
	Rabbit	Embryo fetal toxicity	450	7.8
Pre- and post-natal development	Rat	Females and offspring	1000	5.4[b]

AUC, area under the curve; NOAEL, no observed adverse effect level.
[a] AUC-based safety margin compared to the dose of 200 mg twice daily used in the Phase 3 trials.
[b] Based on total $AUC_{0\text{-}24h}$ from the rat embryo-fetal development study.