MO042

LNP023: A NOVEL ORAL COMPLEMENT ALTERNATIVE PATHWAY FACTOR B INHIBITOR FOR THE TREATMENT OF GLOMERULAR DISEASE

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Background and Aims: The alternative complement pathway (AP) provides the central amplification loop of complement activation and is critically involved in a number of diseases including C3 glomerulopathy (C3G), paroxysmal nocturnal haemoglobinuria (PNH) and atypical haemolytic uremic syndrome. There is also evidence for AP dysregulation in IgA and membranous nephropathies (IgAN, MN). Novartis has developed a highly selective oral low molecular weight inhibitor of complement Factor B, a key AP protease. LNP023 potently blocks AP activation *in vitro* and *in vivo* and is efficacious in passive Heymann nephritis in rats, suggesting an important role of the AP in classical-pathway mediated nephropathies.

Method: LNP023 was tested at increasing single or multiple ascending doses in a Phase I safety, tolerability, pharmacokinetic (PK) and pharmacodynamic study in healthy volunteers. Complement inhibition was measured by the *ex vivo* Wieslab assay and by quantifying fragment Bb level.

Results: LNP023 was well tolerated at all doses from 5 mg to 400 mg (single dose) and from 25 mg to 200 mg bid for 14 days (multiple dose). There were no deaths, SAEs or AEs leading to study drug discontinuation in LNP023-treated subjects. LNP023 dose-dependently inhibited the AP complement system. Based on the Wieslab assay, maximal inhibition of AP activity (80% or more) was observed 2 hours after a single dose of 10 mg or higher. The level of Bb decreased until 12 hours post-dose. Approximately 30% to 50% decrease in Bb, relative to baseline, was achieved for subjects receiving a single dose of LNP023 of 5mg or higher. For both assays, the duration of this inhibition was dependent upon the dose administered. Persistent inhibition was obtained in the multiple dose cohorts, the magnitude of inhibition being dose-dependent for the Wieslab assay but not for Bb. PK studies showed rapid drug absorption and no evidence of food effect. The plasma clearance was moderate and the terminal half-life was around 20h. There was an under-proportional dose-exposure relationship. Among other mechanisms, binding to highly expressed target (Factor B) is believed to affect clearance and thus exposure.

Following a successful proof of concept Phase 2 study in PNH (data not shown), LNP023 is currently being investigated in three ongoing Phase 2 studies in IgAN (NCT03373461), C3G (NCT03832114) and MN (NCT04154787). The IgAN study has an adaptive seamless design; the first part has recently completed, 46 patients having received 3 months of one of three LNP023 doses or placebo. The study remains blinded; however, similar to the FIH study safety appears excellent, with only one treatment-emergent SAE (inhalation of chlorine gas) and two SAEs in the post-treatment follow-up period. No patient discontinued randomised treatment for any reason. There were no episodes of proven infection with encapsulated bacteria. The independent data safety monitoring committee have endorsed the study proceeding to the second part with the addition of a fourth LNP023 dose and recruitment is ongoing, completion being anticipated in mid-2020.