A PHASE 1 AND 1B STUDY IN HEALTHY SUBJECTS AND OTC HETEROZYGOTES WITH CMP-CPS-001-AN INVESTIGATIONAL ANTISENSE OLIGONUCLEOTIDE FOR THE TREATMENT OF UREA CYCLE DISORDERS (UCDS)

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UCDs are a group of 8 rare genetic diseases, each caused by a distinct autosomal recessive or X-linked defect in one of the 6 enzymes or 2 transporters in the urea cycle. The urea cycle is responsible for elimination of the noxious metabolite ammonia. The most common clinical characteristic of UCDs is episodes of hyperammonemia, triggered by increased protein intake or protein catabolism. Seizures, encephalopathy, coma, and death can occur in cases with ammonia levels >200 µmol/L (adult levels). Symptomatic treatment is comprised of reducing nitrogen production (via a strict low-protein diet) and augmentation of nitrogen elimination (nitrogen scavengers) on a chronic basis. CMP-CPS-001 is an antisense oligonucleotide that targets a regulatory RNA of the gene encoding carbamoyl phosphate synthetase 1 *(CPS1*), the initial and rate-limiting enzyme responsible for catalyzing ammonia to carbamoyl phosphate and coordination of the cycle's regulatory function across downstream enzymes. Thus, CMP-CPS-001 is a new and differentiated therapeutic strategy to restore urea cycle function for OTC deficiency and potentially other UCDs.

Phase 1 and 1b study CPS-101 evaluates the effects of CMP-CPS-001 administered subcutaneously in healthy participants in 2 parts (NCT06247670) and OTC heterozygotes in Part C. Part A is a single-ascending dose (SAD) arm with 4 sequential cohorts of 12 participants (3:1 randomization ratio). After dosing, each participant was followed for 6 weeks. Part B is a multiple-ascending dose (MAD) arm with sequential cohorts (same 3:1 ratio). Participants in Parts B and C will receive 3 monthly doses of study drug with a 56-day follow-up post last dose. Parts A-C include measures of ureagenesis via isotope-labeling as a pharmacodynamic marker to be reported in the future. Part A has been completed with blinded interim results presented here.

Part A (SAD) enrolled 48 individuals (36 active:12 placebo) across 4 dose cohorts of 0.2, 0.6, 1.8, or 4.0 mg/kg. A total of 40 treatment emergent adverse events (TEAEs) were observed, with 22 participants (46%) reporting at least one TEAE. Safety results were favorable and consistent with the safety profile of approved liver-targeted ASOs, with all treatment emergent adverse events (TEAEs) being Grade 1 (mild) or Grade 2 (moderate). The two most common TEAEs across all cohorts were headache (six participants) and nausea (four participants). No safety trends of concern were observed, and CMP-CPS-001 appeared to be well-tolerated.

Completion of MAD cohorts and initiation of expansion into Phase 1b clinical study (Part C) in OTC heterozygotes is expected.