First data from the Phase 3 HOPE-B Gene Therapy Trial: Efficacy and Safety of Etranacogene Dezaparvovec (AAV5-Padua hFIX variant; AMT-061) in Adults with Severe or Moderate-Severe Hemophilia B Treated Irrespective of Pre-existing Anti-Capsid Neutralizing Antibodies

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Background: Etranacogene dezaparvovec is an investigational gene therapy for hemophilia B (HB) comprising an adeno-associated virus serotype 5 (AAV5) vector containing a codon-optimized Padua variant human factor IX (FIX) gene with a liver specific promoter. In a Phase 2b study, a single dose of etranacogene dezaparvovec provided mean FIX activity of 41.0% sustained at 1yr post-dose in 3 participants (pts). Although most gene therapy clinical studies exclude pts with pre-existing neutralizing antibodies (NAbs) to the capsid serotype, early clinical studies and nonhuman primate data suggest that generally prevalent titers of anti-AAV5 NAbs may not preclude successful transduction with etranacogene dezaparvovec.

Aims: A Phase 3, **H**ealth **O**utcomes with **P**adua gene; **E**valuation in Hemophilia **B** (HOPE-B; NCT03569891) was established to further assess efficacy and safety of etranacogene dezaparvovec in adults with HB with a wide range of pre-existing NAbs to AAV5. Here we report outcomes at 26 weeks (wks).

Methods: HOPE-B is a Phase 3, open-label, single-dose, single-arm, multi-national trial in adult males with severe or moderate-severe HB (FIX≤2%). All pts received routine FIX prophylaxis prior to study. Pts were not excluded based on pre-existing NAbs to AAV5. Pts entered a prospective lead-in period of at least 6 months during which bleeding/factor use was monitored, then received a single intravenous dose of etranacogene dezaparvovec ($2x10^{13}$ gc/kg). Pts will be followed for 5yrs. Primary endpoints comprised FIX activity (one stage) at 26 and 52wks after dosing and 52wk annualized bleeding rate. For pts with no clean post-treatment FIX samples (≥10d post exogenous FIX), factor activity was imputed as baseline value based on historic disease severity. Secondary endpoints include factor replacement use, adverse events (AEs), and reactive use of corticosteroids.

Results: 75 pts were screened, of whom 67 entered lead-in. 54 pts were dosed (44 severe, 10 moderately severe HB) and completed 26wks of follow-up. Mean age (±SD) was 41.5 (15.8) yrs. 38/54 pts (70.4%) had bleeds (n=123) during the lead-in despite prophylaxis, and 23/54 (42.6%) had NAbs to AAV5 at baseline (max titer: 3212.3). Following treatment, FIX activity increased rapidly to a mean (SD; min,max) of 37.2% (±19.6; 1.0, 97.1) at wk26, representing a mean (SD; min,max) change from baseline of 36.0% (±19.7; 0, 96.1 $p<0.0001$, confirmed by per-protocol sensitivity analysis). No correlation of pre-existing NAbs with FIX activity was identified up to a titer of 678.2; n=52, $R^2 = 0.078$); a single pt had a NAb titer of 3212.3 and did not respond. In addition to this pt, one other pt received a partial dose and remained on prophylaxis; all other pts (96.3%) successfully discontinued routine prophylaxis. 39/54 (72.2%) pts reported 0 bleeds in the first 26wks post-treatment; 15 pts reported a total of 21 bleeds. Mean (SD) annualized FIX consumption (IU/yr/pt) was 292,304 (±171,079) during lead-in, decreasing to 12,622 (±36,466) at wk26 (96.0% reduction, N=54). Overall, 37/54 (68.5%) pts had any treatment-related AE post-treatment, the majority of which were mild (81.5%). No deaths occurred and no treatment-related SAEs were reported. 7 pts had infusion-related reactions; the infusion was discontinued in 1 pt. Treatment-related elevations in liver enzymes were reported in 9 pts and received steroids per protocol. All discontinued steroid use prior to wk26 and FIX activity was preserved in the mild range. In addition to these, the most frequent treatment-related AEs were headache (13.0%) and influenza-like illness (13.0%). No inhibitors to FIX were reported. No relationship between safety and NAbs was observed.

Conclusions: The first co-primary endpoint of this study was met. This is the first report of a Phase 3 study in HB and the largest gene therapy trial cohort to date. Following a single dose of etranacogene dezaparvovec, FIX activity increased, without the need for prophylactic immunosuppression, into the mild-to-normal range at 26wks in pts with severe/moderately severe HB. Importantly, this included pts with titers of pre-existing anti-AAV5 NAbs. Pts were able to discontinue prophylaxis and bleeding was abolished in the majority. The safety profile was consistent with early phase AAV5 studies and together these data support a favorable safety and efficacy profile for etranacogene dezaparvovec.