Improved Respiratory Outcomes for X-Linked Myotubular Myopathy (XLMTM) with Gene Replacement Therapy, Resamirigene Bilparvovec (ASPIRO): Preliminary Results from ASPIRO, a Phase 1/2/3 Study

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Introduction: XLMTM is a rare, life-threatening congenital myopathy caused by mutations in the MTM1 gene. Approximately 80% of XLMTM patients experience profound muscle weakness leading to respiratory distress/failure at birth and chronic ventilator dependency. Most children with XLMTM cannot sit without support >10 seconds and 70-85% are non-ambulant. There is no approved treatment for XLMTM. Method: ASPIRO (NCT03199469), a Phase 1/2/3 randomized, open-label study is investigating the safety and efficacy of AT132 (resamirigene bilparvovec), a single-dose gene replacement therapy for XLMTM. Participants were boys (aged <5 years at day 1 and/or enrolled in INCEPTUS, NCT02704273, a prospective run-in study) with genetically confirmed XLMTM. The primary efficacy outcome was the change in hours of daily ventilator support from baseline through Week 48. Here we report the key respiratory outcomes from 23 AT132 dosed participants (n=6, lower-dose of 1.3 x 1014 vg/kg; n=17, higher-dose of 3.5 x 1014 vg/kg) and compared with 15 untreated controls (including 12 participants from INCEPTUS), as of 01/29/2021. Results: The age at dosing (mean, range) was 20·4 (9·5-49·7) and 39·4 (6·8-72·7) in the lower- and higher-dose groups, respectively, and 19·6 (5·939·3) months at enrolment in the control group. Across all groups, 32 (84%) used transtracheal ventilation ranging from 16-24 hours/day and 6 (16%) used non-invasive ventilation ranging from 12-24 hours/day at baseline. Maximal American Thoracic Society 2022, May 13-18, 2022San Francisco inspiratory pressure (MIP) values (mean, range) were 30.0 (14.1-44.1), 24.3 (10.4-44.6) and 35.4 (20.150.9) cmH2O for the lower-dose, higher-dose, and control groups, respectively, at baseline. After AT132 dosing, ventilator independence was achieved by 6 (100%) lower-dose; 9 (53%) higher-dose; 0 control participants between 16 and 72 weeks post-dosing (however, one lower-dose participant subsequently required intermittent ventilator

support). Change from baseline in MIP was significantly higher in both dose groups compared with controls (P<0.0001, Figure). As of January 2021, three deaths in the higher-dose cohort (attributed to severe liver dysfunction) and three deaths in the control cohort (2/3 attributed to respiratory events) occurred. As of September 2021, a newly dosed participant in the lower-dose cohort has died; the cause of death is sti l pending. Conclusion: In XLMTM patients, a rapid increase in muscle strength and significant reduction in ventilator support requirements was observed among AT132 dosed vs controls. The ASPIRO program is on clinical hold while relevant clinical information is being gathered and reviewed alongside the ongoing investigation regarding other previously observed fatalities in 2020.

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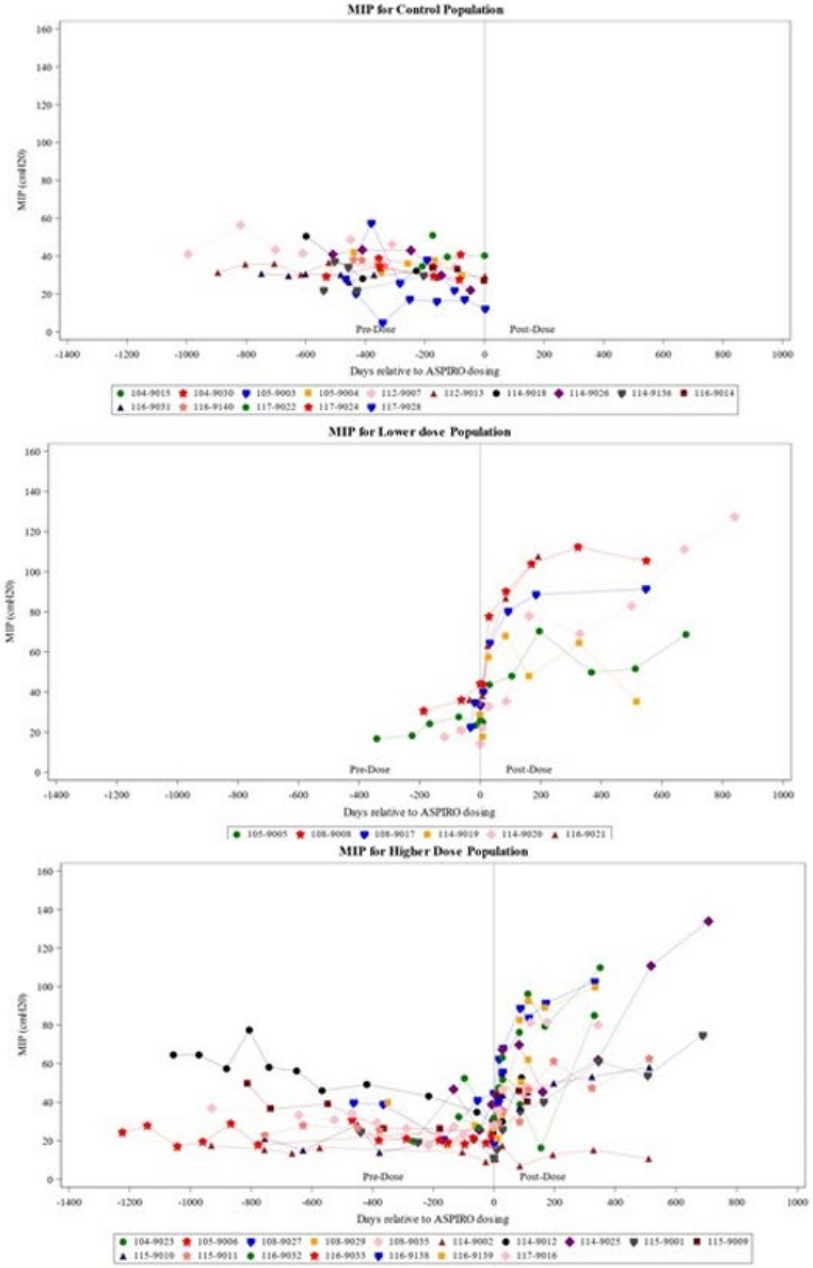
Figure: Respiratory Outcomes after Gene Therapy. Absolute MIP values vs relative time to AT132 dosing shown for individual participants in control (Panel A), lower-dose (Panel B) and higher-dose (Panel C) cohorts separately*



*Several values for MIP were missed due to COVID-19 pandemic