

## Phase I/II Trial of Adeno-Associated Virus-Mediated Alpha-Glucosidase Gene Therapy to the Diaphragm for Chronic Respiratory Failure in Pompe Disease: Initial Safety and Ventilatory Outcomes

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### ABSTRACT

Pompe disease is an inherited neuromuscular disease caused by deficiency of lysosomal acid alpha-glucosidase (GAA) leading to glycogen accumulation in muscle and motoneurons. Cardiopulmonary failure in infancy leads to early mortality, and GAA enzyme replacement therapy (ERT) results in improved survival, reduction of cardiac hypertrophy, and developmental gains. However, many children have progressive ventilatory insufficiency and need additional support. Preclinical work shows that gene transfer restores phrenic neural activity and corrects ventilatory deficits. Here we present 180-day safety and ventilatory outcomes for five ventilator-dependent children in a phase I/II clinical trial of AAV-mediated GAA gene therapy (rAAV1-hGAA) following intradiaphragmatic delivery. We assessed whether rAAV1-hGAA results in acceptable safety outcomes and detectable functional changes, using general safety measures, immunological studies, and pulmonary functional testing. All subjects required chronic, full-time mechanical ventilation because of respiratory failure that was unresponsive to both ERT and preoperative muscle-conditioning exercises. After receiving a dose of either  $1 \times 10^{12}$  vg ( $n=3$ ) or  $5 \times 10^{12}$  vg ( $n=2$ ) of rAAV1-hGAA, the subjects' unassisted tidal volume was significantly larger (median [interquartile range] 28.8% increase [15.2–35.2],  $p < 0.05$ ). Further, most patients tolerated appreciably longer periods of unassisted breathing (425% increase [103–851],  $p = 0.08$ ). Gene transfer did not improve maximal inspiratory pressure. Expected levels of circulating antibodies and no T-cell-mediated immune responses to the vector (capsids) were observed. One subject demonstrated a slight increase in anti-GAA antibody that was not considered clinically significant. These results indicate that rAAV1-hGAA was safe and may lead to modest improvements in volitional ventilatory performance measures. Evaluation of the next five patients will determine whether earlier intervention can further enhance the functional benefit.