hormone (GH) hypersecretion and reducing circulating insulin-like growth factor-1 (IGF-1) levels in acromegaly patients.

**Methods:** Cimdelirsen was evaluated in a 4-month double-blind, placebo-controlled phase 2 study (DBL) in uncontrolled acromegaly patients (IGF-1>1.3<5xULN) treated with stable long-acting somatostatin receptor ligand (SRL) injections (NCT03548415). Due to COVID-19 pandemic, the study closed early resulting in smaller cohorts than planned. While no longer powered to assess Day 141 primary endpoint (PE), the study permitted placebo-controlled evaluation of safety and efficacy. The final analysis included 41 patients in the cimdelirsen low dose (60 and 80 mg; n=22), high dose (120 and 160 mg; n=7) or placebo (n=12) cohorts. 39 of these patients subsequently entered an open label extension (OLE) safety study where all patients were treated with cimdelirsen and at the time of interim analysis, 23 patients were treated for ≥ 1 year (NCT03967249). Patient reported outcomes were assessed using the validated ACROQoL and an acromegaly symptoms questionnaire.

**Results:** Cimdelirsen treatment resulted in a significant, dose dependent reduction in GH-binding protein (GHBP), a biomarker of hepatic GHR reduction: -2% placebo, -43% low dose, -64% high dose; p<0.001. Importantly, GHBP reductions were not associated with fasting GH increases. The GH mean change from baseline to PE was 1 ng/mL placebo, 0 ng/mL low dose and 1 ng/mL high dose (p>0.5). GHBP reductions without GH increases were maintained for up to 1 year of treatment in all patients.

Integrated AUC for IGF-1 calculated after GHBP had reached near-maximal reductions (Day 57 to PE) demonstrated dose-dependent reductions that were significant at the high dose (+692%/day placebo, -460 low dose, and -1378 high dose; p=0.21 and 0.05 for the low dose and high dose groups, respectively). A greater reduction in IGF-1 AUC was observed in patients who had higher IGF-1 levels at baseline. Patients with higher IGF-1 levels showed significant improvements in ACROQoL at the PE; all patients demonstrated improvements after 1 year. Importantly, high-dose cimdelirsen improved sweating and headaches at PE.

In both studies, there were no drug-related SAEs. The most frequently reported TEAE were UTI (16.1%) and COVID-19 (12.8%) in DBL and OLE, respectively. No safety signals were observed including no ALT elevation >3xULN and no thrombocytopenia (<100 10^3/uL). Glycemic control remained stable and showed no worsening of HbA1c. **Conclusion:** Once monthly SC cimdelirsen injections demonstrated long-term safety, were well-tolerated, and resulted in significant reductions in GHBP and IGF-1 AUC without increased GH levels. Cimdelirsen also improved PRO, collectively supporting further development of this novel, liver-directed potential therapy for uncontrolled acromegaly.

**Presentaiton:** Tuesday, June 14, 2022 10:30 a.m. - 10:45 a.m.