Introduction to DIPG

- Diffuse intrinsic pontine glioma (DIPG), the most frequent pediatric brainstem tumor, is one of the deadliest childhood cancers.
- Estimated incidence at ~1000 subjects annually worldwide with ~300-400 in the USA so it is considered an ultra-rare orphan disease.
- Current standard of care treatment for DIPG is focal radiotherapy (RT), using a 1 cm margin to cover microscopic disease, to a total dose of 54–60 Gy administered over 6 weeks, usually in weekdays in 180–200 cGy fractions.
  - Hyperfractionated RT provided no survival benefit over conventional RT
  - Radiation sensitizing agents have shown no benefit to date.
- Recent important advances in its molecular characterization have not yet translated into improved treatments so new therapies are urgently needed.
  - Mutation in histone H3 (H3.1K27M or H3.3K27M) (~90%) leading to epigenetic changes useful as biomarker, also alterations in PDGFRα (~36%) or ACRV1 (~20%) genes.
  - Other therapies being tried include HADAC and AK2 inhibitors, bevacizumab, CAR-T, etc.

Veledimex crosses the blood–brain barrier (~20% Ad genes
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Required before dosing of DIPG could begin.

Background on Controlled IL-12

Ad-RT5-IL-12 + veledimex (Ad+V) results in increased survival in orthotopic pontine glioma mouse model.

Day 14: MRI showed some relative increase in pre-existing midline cyst, status post 1 line of therapy (photon radiotherapy), and assessed as unifocal disease at study entry.

Day 42: Subject received 14/14 doses (93% compliance) of veledimex.

Day 56: Further increase in size of cystic component with peripheral mass effect with PD.

Study Design

Clinical Study AT1001-103 Amendment 2 – DIPG (NCT03330197)

Multicenter, open-label study, of Ad (2 x 10⁹ viral particles IT) + V doses (10 mg and 20 mg PO, BSA adjusted), focusing on DIPG (arm 2)

- Key eligibility criteria (arm 2):
  - M/F, ≤ 22 years-of-age
  - Clinical presentation of DIPG involving ~2/3 of pons on MRI
  - ≥ 2 and ≤ 10 weeks post standard focal radiotherapy (5400-5960 cGy)
  - Maximum dexamethasone of 1 mg/m²/day, on a stable or decreasing dose of steroids for the last 7 days.
  - Lansky score ≥ 50, Karnofsky performance status ≥ 50 or ECOG score ≤ 2
  - Adequate bone marrow, liver and kidney function

- Standard 3+3 dose escalation design
- Primary Objective: Safety and tolerability
- Secondary objectives: RP2D, PK of V, cellular/humoral immune responses, assess response (ORR, PFS), OS
- Toxicity: Neutrophil decreased, Hyponatraemia, Headache, Aphasia, Any related AE

TEAEs Related to Ad+V

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The cumulative TEAs for Study 103 are summarized in the table below:

Safety Results

First DIPG Subject Dosed

Subject 004: 5-year-old male diagnosed November 2019 – biopsy showed a H3K27M-mutant diffuse midline glioma, WHO Grade IV consistent with DIPG with pre-existing midline cyst, status post 1 line of therapy (photon radiotherapy), and assessed as unifocal disease at study entry.

Day 14: Stereotactic injection was performed administering 0.1 ml Ad-RT5-IL-12 (2 x 10⁶ viral particles) with a modified technique to enable a contralateral approach to avoid the cyst.

Day 0-4:
- Alert, responsive to questions, reports of mild right sided facial muscle weakness (esotropia), subject had a constellation of findings (mild-moderate fever; nausea, leukopenia, lymphopenia; borderline hypotension and neutropenia) consistent with low-grade CRS

Day 14:
- No SAEs and no dexamethasone during active dosing (Days 0-14)

Day 2:
- Prior cranial nerve 12 neuropathy improved, partial right lid closure was unchanged, left partial paresis, and notably partial eyebrow loss. Speculatively, the latter finding is suggestive of mild alopecia areata, an immune related effect (mild cross reactivity).

Day 56:
- Clinical progression noted
- Neurosurgery consult for management of increasing cyst size.

Week 17:
- Subject died from Progression of Disease (PD)

Representative Serial MRI Scans

- Baseline: Expansile infiltrative T2 hyperintense lesion of pons, predominantly right-sided, extending caudally into upper medulla as well as through the right cerebellar peduncle, with compression of fourth ventricle and postoperative changes.
- Target 1 and 1 non-target lesion identified
- Day 14: MRI showed some relative increase in pre-existing cyst size with no appreciable change in the solid component of the tumor (SD)
- Day 28: Minimal increase in TD (SD) and no change in NTL
- Day 56: Further increase in size of cystic component with peripheral mass effect with lesser increase in the solid, nodular component of the tumor on MRI (PD).
- High signal in cyst seen in T2 FLAIR sequence in conjunction with T1 findings (not shown) is presumably due to increased proteinaceous content (e.g., hemorrhage and/or sloughing).
- Day 80: Increase in TL (PD) with decrease in size of cyst status post shunt insertion
- Week 16: Mild increase in TL (PD)

Biomarker Results

Viral shedding
- Evaluated using a qPCR assay for RT5° viral DNA

Flow Cytometry
- Determined by IHC

Introduction to Controlled IL-12

Therapeutic System® (RT5°)
- Localized production of recombinant IL-12
- Proportional to oral dosing of veledimex
- Veledimex crosses the blood-brain barrier
- Real-time adjustment of IL-12
- Adapt to patient's needs
- Pause/stop in the event of cytokine release syndrome

Studied in subjects with supratentorial brain tumors (arm 1)
- Most of the related AEs were expected; all were mild to moderate in severity and most were promptly reversible upon withholding of veledimex doses
- Overall, monotherapy was well-tolerated at current dose levels.

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- Viral shedding
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Discussion and Conclusions

Initial safety findings for the first subject dosed in arm 2 (DIPG) were generally similar to the 3 pediatric subjects with supratentorial tumors (arm 1)
- No DLTs were observed
- No SAEs or SUSARs were reported

- Safety results for the subject with DIPG (arm 2) were generally similar to the 3 pediatric subjects with supratentorial tumors (arm 1)
  - No DLTs were observed
  - No SAEs or SUSARs were reported
  - Most of the related AEs were expected; all were mild to moderate in severity and most were promptly reversible upon withholding of veledimex doses
  - Overall, monotherapy was well-tolerated at current dose levels.