First-in-Human \textit{in vivo} CRISPR/Cas9 Editing of the \textit{TTR} Gene by NTLA-2001 in Patients with Transthyretin (ATTR) Amyloidosis with Cardiomyopathy

Julian D. Gillmore, Jörg Täubel, Ed Gane, Björn Pilebro, Michael L. Maitland, Mark Stroh, Yuanxin Xu, Adam Boyd, Jeffrey Cehelsky, David E. Gutstein, Tina Ho, Alison Sonderfan, Liron Walsh, David Lebwohl, and Mariana Fontana

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Clinical Trial Registration # NCT04601051
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Disclosures

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• Dr. Gillmore has received grant support from Alnylam Pharmaceuticals
Transthyretin (ATTR) amyloidosis is a progressive and fatal disease

• Accumulation of amyloid deposits composed of misfolded transthyretin (TTR) protein
  – ~50,000 hereditary ATTR amyloidosis (ATTRv) patients worldwide
  – ~200,000 – 500,000 wild-type ATTR amyloidosis (ATTRwt) patients worldwide

• Transthyretin amyloid cardiomyopathy (ATTR-CM)
  – Amyloid deposits cause impaired systolic/diastolic function and conduction disorders
  – Fatal within 3 to 10 years in the absence of treatment
  – Remains under-diagnosed

• Unmet medical need in ATTR-CM
  – Progressive heart failure leads to poor QoL, high morbidity and mortality
  – Current treatment only slows disease progression and requires lifelong administration
  – Limited access to approved therapies

QoL, Quality of life;
Lane T et al. Circulation 2019; 140:16–26
Pinney JH et al. J Am Heart Assoc 2013; 2:e000098
Rowczenio D et al. Orphanet J Rare Dis 2017; 12(Suppl 1):165; Abstract P1
Magnitude of precursor protein knockdown is associated with survival in AL amyloidosis

Incremental improvements in precursor protein reduction led to improved clinical outcomes

aCR, amyloid complete response; AL, amyloid light chain
NR, no response; PR, partial response
VGPR, very good partial response

Palladini G et al, JCO 2012;30:4541-4549
Greater TTR knockdown associated with clinical improvements in ATTR amyloidosis

- Greater TTR knockdown is associated with improved neuropathy scores for ATTRv-PN
- Emerging evidence indicates that deep TTR reductions may be clinically beneficial for patients with ATTR-CM
NTLA-2001 is a novel, investigational CRISPR/Cas9-based *in vivo* gene editing therapy.

**NTLA-2001 Uptake in Hepatocytes**

NTLA-2001

This presentation includes data for an investigational product not yet approved by regulatory authorities.
Rigorous process to select sgRNA for NTLA-2001 to achieve both potent on-target and no detectable off-target editing

1. IDENTIFICATION
   Conduct computational analysis to identify potential CRISPR-candidate sites for knockout and then eliminate sites containing TTR pathogenic variants, common SNPs and sequences with high off-target potential.

2. CANDIDATE ASSESSMENT
   Synthesize pool of initial sgRNAs and test rigorously for knockout efficiency, off-target editing and genotoxicity (including SVs), using human cells and animal models.
   - Multiple methods: in silico, biochemical/cell-based assays and image-based methods.

3. VALIDATION AND FINAL SELECTION
   Select sgRNA with the highest on-target knockout efficiency and no detectable off-target potential at multiples of human therapeutic dose.

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sgRNA, single guide RNA; SNPs, single nucleotide polymorphisms; SV, structural variants; TTR, transthyretin
In Vitro: No detectable off-target editing with pharmacologic concentration of sgRNA
NTLA-2001 expanded Phase 1 study

Two-part, open-label, multi-center study in adults with hereditary ATTR with polyneuropathy (ATTRv-PN) or ATTR amyloidosis with cardiomyopathy (ATTR-CM)

**Clinicaltrials.gov ID:** NCT0460105

**PK**, Pharmacokinetics; **PD**, Pharmacodynamics

### PRIMARY OBJECTIVES
Evaluate safety, tolerability, PK and PD
- Measure serum TTR levels

### SECONDARY OBJECTIVES
Evaluate efficacy on clinical measures of:
- Neurologic function in subjects with ATTRv-PN
- Cardiac disease in subjects with ATTR-CM

**Intervention:**
Single dose administered via an intravenous (IV) infusion

**PART I**
- Single-Ascending Dose Escalation
  - ATTRv-PN patients
  - ATTR-CM patients

**PART II**
- Dose Expansion
  - Administer selected dose from Part I

Potential to advance toward a pivotal trial for NTLA-2001 based on Phase 1 safety and efficacy data
NTLA-2001 Phase 1 study: Cardiomyopathy arm

Hereditary transthyretin amyloidosis with cardiomyopathy (ATTRv-CM) or wild-type cardiomyopathy (ATTRwt-CM), NYHA Class I - III

**PART I – DOSING COMPLETE**

**Single-Ascending Dose**
- 1.0 mg/kg NYHA Class I/II (n=3)
- 0.7 mg/kg NYHA Class III (n=6)
- 0.7 mg/kg NYHA Class I/II (n=3)

**PART II**

**Dose Expansion**
- 55 mg

**INTERVENTION:**
Single dose administered via an intravenous (IV) infusion

**PRIMARY OBJECTIVES**
Evaluate safety, tolerability, PK and PD
- Measure serum TTR levels

**SECONDARY OBJECTIVES**
Evaluate efficacy on clinical measures of cardiac disease
- Cardiac imaging, biomarkers, cardiopulmonary exercise test, 6MWT

Clinicaltrials.gov ID: NCT04601051

NYHA, New York Heart Association; PK, Pharmacokinetics; PD, Pharmacodynamics; 6MWT, 6 Minute Walk Test
# Patient demographics & characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NYHA Class I/II 0.7 mg/kg n = 3</th>
<th>NYHA Class III 0.7 mg/kg n = 6</th>
<th>NYHA Class I/II 1.0 mg/kg n = 3</th>
<th>All patients N = 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (min, max)</td>
<td>74 (71, 75)</td>
<td>78 (75, 86)</td>
<td>71 (68, 72)</td>
<td>75 (68, 86)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3 (100%)</td>
<td>6 (100%)</td>
<td>3 (100%)</td>
<td>12 (100%)</td>
</tr>
<tr>
<td>Median weight, kg (min, max)</td>
<td>85 (63, 88)</td>
<td>86 (71, 106)</td>
<td>85 (75, 88)</td>
<td>85 (63, 106)</td>
</tr>
<tr>
<td>TTR genotype, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p.V142I</td>
<td>–</td>
<td>–</td>
<td>1 (33%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>p.T80A</td>
<td>–</td>
<td>1 (17%)</td>
<td>–</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>WT</td>
<td>3 (100%)</td>
<td>5 (83%)</td>
<td>2 (67%)</td>
<td>10 (83%)</td>
</tr>
<tr>
<td>NYHA classification, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1 (33%)</td>
<td>–</td>
<td>–</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>II</td>
<td>2 (67%)</td>
<td>–</td>
<td>3 (100%)</td>
<td>5 (42%)</td>
</tr>
<tr>
<td>III</td>
<td>–</td>
<td>6 (100%)</td>
<td>–</td>
<td>6 (50%)</td>
</tr>
<tr>
<td>Median NT-proBNP, ng/L (min, max)</td>
<td>2480 (2103, 3637)</td>
<td>2463 (2112, 16690)</td>
<td>2408 (1607, 3474)</td>
<td>2461 (1607, 16690)</td>
</tr>
</tbody>
</table>

This presentation includes data for an investigational product not yet approved by regulatory authorities.

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NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; TTR, Transthyretin.
NTLA-2001 was generally well-tolerated across all cohorts through the follow-up period

- Across all cohorts, majority of adverse events were mild in severity
  - 25% (n=3) of patients reported no AEs and 67% (n=8) reported mild or moderate AEs as their highest severity
  - Infusion-related reactions were reported in 2 patients
  - All patients received a complete study dose of NTLA-2001

- A single Grade 3 infusion-related reaction was reported at the 0.7 mg/kg dose in a NYHA Class III patient and resolved without any clinical sequelae
  - NYHA Class III 0.7 mg/kg dose level cohort expanded per protocol to 6 patients to further characterize safety and PD
  - No additional patients reported a treatment-related AE higher than Grade 1

- No clinically significant laboratory findings
  - Transient Grade 1 liver enzyme elevations observed

Data Cut Off: August 25, 2022
Median follow-up for all subjects is 5.5 months
AE, adverse event; PD, pharmacodynamics

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Majority of adverse events were mild in severity

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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gr. 1  Gr. 2  Gr. 3</td>
<td>Gr. 1  Gr. 2  Gr. 3</td>
<td>Gr. 1  Gr. 2  Gr. 3</td>
<td>Gr. 1  Gr. 2  Gr. 3</td>
</tr>
<tr>
<td>Patients with at least one TEAE</td>
<td>2  –  –</td>
<td>3  1*  1</td>
<td>1  1†  –</td>
<td>6  2  1</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>–  –  –</td>
<td>–  –  1</td>
<td>1  –  –</td>
<td>1  –  1</td>
</tr>
<tr>
<td>COVID-19</td>
<td>–  –  –</td>
<td>1  –  –</td>
<td>1  –  –</td>
<td>2  –  –</td>
</tr>
</tbody>
</table>

Gr., Grade; TEAE, treatment emergent adverse event

*Gr. 2 urinary retention and Gr. 2 epistaxis in same patient
†Gr. 2 herpes zoster and Gr. 2 inguinal hernia in same patient

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Rapid and deep serum TTR reduction sustained through 4-6 months across all patients

Mean (SE) % TTR reduction by dose level

All patients achieved ≥ 90% TTR reduction by day 28

Baseline 1 2 4 6

Months

-100 -90 -80 -70 -60 -50 -40 -30 -20 -10 0

TTR reduction (%)

NYHA Class I/II 0.7 mg/kg (n=3)
NYHA Class III 0.7 mg/kg (n=6)
NYHA Class I/II 1.0 mg/kg (n=3*)

Data Cut Off: August 25, 2022

SE, standard error; TTR, transthyretin

*n=2 at Month 2 (missed patient visit)

This presentation includes data for an investigational product not yet approved by regulatory authorities.
Deep, consistent and durable TTR reductions achieved at both 0.7 and 1.0 mg/kg doses

- Mean TTR reduction >90% across both doses by day 28 and sustained 4-6 months (through data cut-off)
- NTLA-2001 was generally well-tolerated at both doses
  - Majority of adverse events were mild
  - No clinically significant laboratory findings observed
- Similar results in patients with either NYHA Class I/II or III heart failure
- Data are consistent with previously reported data from polyneuropathy arm of trial

These data further support and extend early findings from this pioneering trial, demonstrating the promise of CRISPR-based in vivo genome editing in humans
Acknowledgements

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- We thank the Charles River Laboratory, Alta sciences, Precision for Medicine, PPD and QPS for serum TTR, PK and biomarker tests, as well as XP Pharma Consulting, LLC and QuanTx Consulting for their analysis support.

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