BACKGROUND

HD, Huntington’s disease (HD) is characterized by an accumulation of mutant huntingtin (mHTT) protein in the brain, leading to:

- Progressive, selective neuron loss in the striatum
- Rapid striatal atrophy (Figure 1)
- Reduced total functional capacity (TFC)

AMT-130 is an experimental gene therapy for HD

- Investigational New Drug (IND) status approved by the FDA
- Comprises an adeno-associated virus (AAV) serotype 5 vector containing a transgene encoding anti-HTT miniRNA (AAV5-miRNA)
- Significantly reduces mHTT RNA by up to 80% in HD minipig brain, with dose-dependent reductions in mHTT protein of more than 50%
- Significantly improves motor symptoms and increases median survival from 120 to 149 days in R6/2 HD mice
- Well tolerated in HD animal models, with no adverse events

AMT-130 administration

- Precise volumes of AMT-130 will be administered to the striatum via magnetic resonance imaging (MRI)–guided convection-enhanced delivery (CED)
- We anticipate that striatal administration results in transport via the cortico-striatal pathway to the sensorimotor cortex, following the spread of the disease

- In non-human primates (NHPs), MRI-guided CED of AMT-130
- Provides maximum coverage of striatum
- Excellent safety profile; minimal/no cellular injury
- Mitigates the degree of non-targeted vector delivery
- Sufficient structural volume is required for successful administration
- Enables reversal of neuron dysfunction prior to neuron death
- Reduces bleeding risk by ensuring adequate tissue density

Volumetric MRI was performed on 20 patients with early manifest (Stage 1) HD from the TRACK-HD study

RESULTS

- The striatum was analyzed in 19 of the 20 MRI images; 1 image was corrupted and could not be analyzed

Striatal volumes in manifest HD patients

- Mean putamen and caudate volumes were 3.11 cm³ and 2.24 cm³, respectively;
- Volumes in Stage 1 HD were approximately 13% and 16% less than those typically observed in healthy adults (Table 1)

- Mean perivascular space in each putamen represented 11.5% (range 5% to 20%) of the putamen

Objective: To determine striatal volumes in early manifest HD patients in order to establish volumetric parameters and neurosurgical trajectories for safe, MRI-guided CED of AMT-130

METHODOLOGY

- Volumetric MRI was performed on 20 patients with early manifest HD (Stage 1) HD from the TRACK-HD study
- T2 and T1 with contrast MRI volumes acquired in the brain, leading to:
  - T2 volumes were used to estimate the volume of perivascular spaces in each putamen
  - Real-time volumes of distribution (Vd) and infusion (V) data in healthy NHPs were used to estimate volumetric parameters for AMT-130 CED in humans
  - Infusions were administered to the caudate nucleus and putamen on each side of the NHP brain using MRI-guided CED

- Simulated surgical planning indicates that the anterior catheter trajectories shown in Figure 2 can potentially achieve adequate coverage to efficiently transduce striatal neurons in patients with early manifest HD

Figure 1: Sagittal 3T volumetric MRI scans showing progressive brain atrophy in HD patients

Figure 2: Potential anterior catheter trajectories for the delivery of AMT-130 in early manifest HD patients

Table 1: Striatal volumes in healthy adults, adults with early manifest HD, and NHPs

<table>
<thead>
<tr>
<th>Brain structure/hemisphere</th>
<th>Healthy adults</th>
<th>Early manifest 1 HD (n = 19)</th>
<th>Healthy NHPs (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Putamen</td>
<td>3.57 ± 0.17</td>
<td>3.11 ± 0.54</td>
<td>0.55 ± 0.01</td>
</tr>
<tr>
<td>Caudate</td>
<td>2.73 ± 0.06</td>
<td>2.24 ± 0.36</td>
<td>0.41 ± 0.02</td>
</tr>
<tr>
<td>Striatium</td>
<td>6.33 ± 0.44</td>
<td>5.17 ± 0.88</td>
<td>0.97 ± 0.04</td>
</tr>
</tbody>
</table>

HD, Huntington’s disease; NHP, non-human primates

REFERENCES

4. Evers MM, Minianikova J, Juhas S et al. Mol Ther 2016;24:2163-77

CONCLUSIONS

- Volumetric loss in the putamen and caudate is evident in people with early manifest HD compared to healthy adults
- Results suggest that sufficient striatal volume remains in the majority of patients with early HD for appropriate surgical targeting
- Simulated surgical planning suggests that safe catheter trajectories can achieve adequate coverage to efficiently transduce striatal neurons in patients with early HD, despite striatal atrophy

DISCLOSURES

M Evers, P Konstantinova and J Higgins are uniQure B.V. employees; all other authors are members of the study steering committee and either they or their institution received consulting fees from uniQure B.V. In addition, S Gill is Medical Director of Rentshaw PLC, and RAC Roos’s institute has received a grant for a clinical trial (Teva). Writing support, funded by uniQure B.V., was provided by Jackie Read of GK Pharmacomm Ltd.

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Figure 2. Potential anterior catheter trajectories for the delivery of AMT-130 in early manifest HD patients