Next Generation Treatment of ATTR

Update on the Clinical Development of CRX-1008

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CEO
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Topics

1. CRX-1008 background
2. Ongoing and completed clinical evaluation
3. Future clinical trials
What is CRX-1008?

- A novel modified release formulation of tolcapone specifically engineered for ATTR
  - Twice daily oral dosing

- Tolcapone, the active drug in CRX-1008, was approved in 1998 as an adjunctive treatment for Parkinson’s Disease
  - Inhibitor of catechol-O-methyltransferase (COMT)
  - Current use in Parkinson’s Disease is in combination with levodopa to slow its metabolism
  - Fast half-life in circulation after oral dosing
  - Crosses the blood brain barrier

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Potential Treatment of All Forms of ATTR

- Potent Kinetic Stabilizer
  - Binds with high affinity to TTR (4X lower IC50 than tafamidis)
  - Lowest negative binding cooperativity of kinetic stabilizers
- Other mechanisms that reduce the instability of TTR tetramer
- Fibril disruptor
- Crosses the blood brain barrier
- Enhance neurotransmitter levels in the CNS

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There is Growing Recognition of Ocular and CNS Involvement in ATTR


<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Duration</th>
<th>Drug Arms</th>
<th>Objective</th>
<th>Status</th>
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<td>1 day</td>
<td>API</td>
<td>Stabilization: plasma</td>
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<td>1 G47R Patients</td>
<td>1 week</td>
<td>API</td>
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<td>1 month</td>
<td>API</td>
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</tbody>
</table>
P2 Study in hATTR-PN Patients

V30M TTR and wt-TTR (N=17)

Endpoints:
- Plasma Stabilization
- Safety

Vall d’Hebron University Hospital, Barcelona (Spain)
CRX-1008 Demonstrates Near Complete TTR Stabilization

Phase A

- 17 participants
- Near complete stabilization at 2 hours after single dose
- <50% of maximal effect at 8 hours
- No effect detectable after 24 hours
- Maximum stabilization occurs at a CRX-1008 plasma concentration of 2.7 μg/ml (9.9 μM) after a single dose (50% at 0.5 μg/ml (1.8 μM))

CRX-1008 Demonstrates Near Complete TTR Stabilization

Phase B

- 15 participants
- Near complete stabilization at 2 hours and 10 hours (2 hours after last dose administered)
- No effect between 24 and 32 hours
- Maximal stabilization occurs at a CRX-1008 plasma concentration of 1.5-2.0 μg/ml (5.5-7.3 μM) after multiple doses of CRX-1008

No AEs

7-Day P2 Study in hATTR-PN Patients

hATTR-PN Patients (8 V30M, 1 G47R) N=9

Patient randomized to either 100mg TID or 200mg TID

Key Inclusion Criteria
- Biopsy proven amyloid deposition
- Genotyping of variant TTR

Endpoints
Primary
Effect of CRX-1008 on plasma and CSF TTR tetramer stability
Secondary
Safety & tolerability

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(Shinshu University Hospital, Matsumoto, Japan)
28-Day POC Study in hATTR-Leptomeningeal Patients

STUDY 3

hATTR-PN Patients (Leptomeningeal) N=9

Key Inclusion Criteria
- Biopsy proven amyloid deposition
- Genotyping of variant TTR
- Documented CNS disease or leptomeningeal variant

Endpoints
Primary
Effect of CRX-1008 on plasma and CSF TTR tetramer stability
Preliminary efficacy variable
Secondary
Safety and tolerability

Patient receives 100mg TID → Tx for 2 week → Patient receives 200mg TID → Tx for 2 week

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(Boston University, Boston, MA, USA)
## Upcoming Clinical Trials
### CRX-1008

<table>
<thead>
<tr>
<th>PHASE</th>
<th>Condition</th>
<th>Number of Subjects</th>
<th>Duration</th>
<th>Drug Arms</th>
<th>Objective</th>
<th>Start Date</th>
</tr>
</thead>
</table>
| PHASE 3 | hATTR-PN | Est. 110-150 | 12+ mo. | • Placebo/other  
• CRX-1008 | • Biomarker  
• Clinical benefit | 2020 |
| PHASE 3 | hATTR-Leptomeningeal/CNS | Est. 25-50 | 24+ mo. | • Placebo  
• CRX-1008 | • Biomarker  
• Imaging  
• Clinical Benefit | 2020 |
| PHASE 3 | ATTR-CM | Unknown | 24+ mo. | • Active  
• CRX-1008 | • Biomarker  
• Imaging  
• Clinical Benefit | Planning Stages |