Corino THERAPEUTICS

Next Generation Treatment of ATTR

Update on the Clinical Development of CRX-1008

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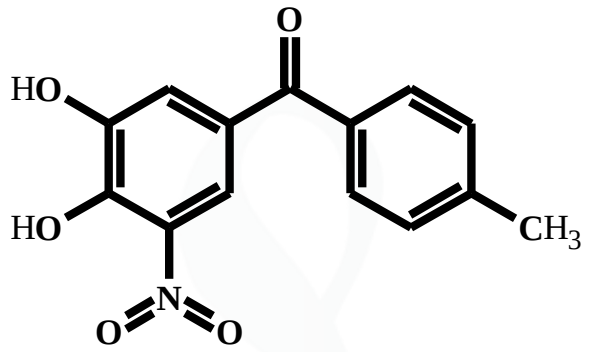
Topics

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

What is CRX-1008?

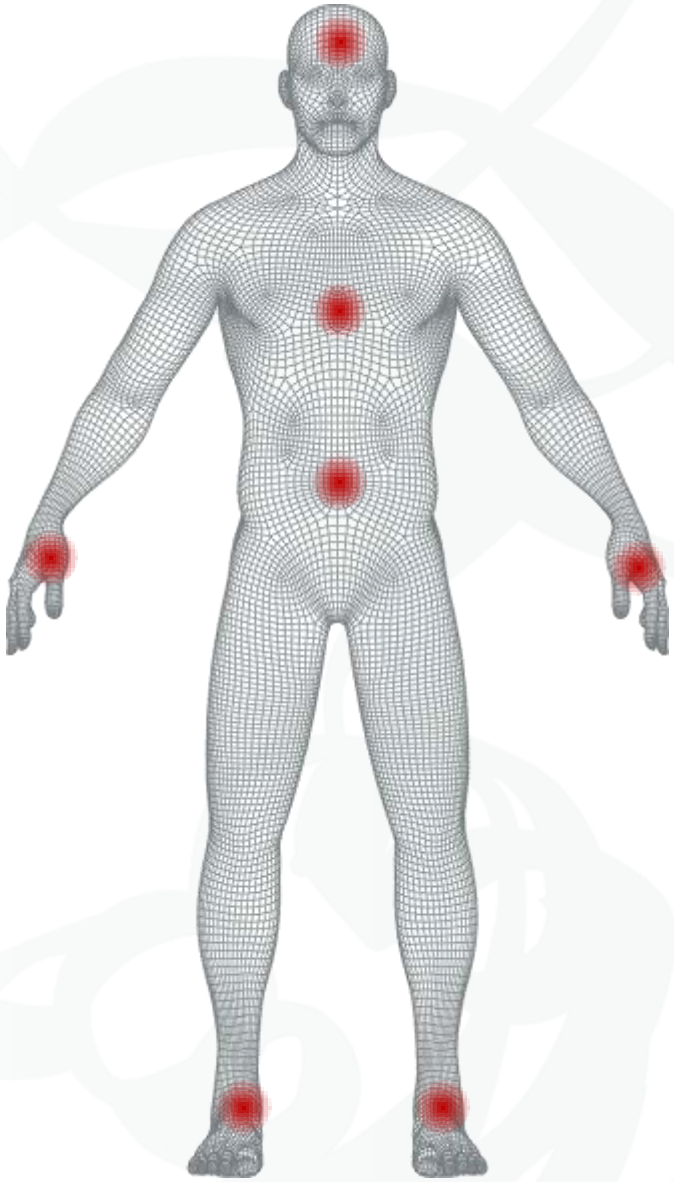
- A novel modified release formulation of tolcapone specifically engineered for ATTR
  - Twice daily oral dosing



- 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

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



CRX-1008

There is Growing Recognition of Ocular and CNS Involvement in ATTR

Sekijima Y, Wiseman RL, Matteson J, Hammarström P, Miller SR, Sawkar AR, Balch WE, Kelly JW., The biological and chemical basis for tissue selective amyloid disease, Cell. 2005 Apr 8;121(1):73-85.
Martins da Silva A, Cavaco S, Fernandes J, Samões R, Alves C, Cardoso M, Kelly JW, Monteiro C, Coelho T., Age-dependent cognitive dysfunction in untreated hereditary transthyretin amyloidosis, J Neurol. 2018 Feb;265(2):299-307

Proof of Concept Clinical Studies in ATTR

	# Subjects	Duration	Drug Arms	Objective	Status
STUDY 1					
P2 in hATTR-PN	**17** V30M/HV Subjects	**1** day	API	Stabilization: plasma	COMPLETED[1]
STUDY 2					
P2 in hATTR-PN	**8** V30M | **1** G47R Patients	**1** week	API	Stabilization: CSF/plasma	Completed (data analysis ongoing)
STUDY 3					
P2 in hATTR-Lepto	**9** Lepto Patients	**1** month	API	Stabilization: CSF/plasma	Completed (data analysis ongoing)

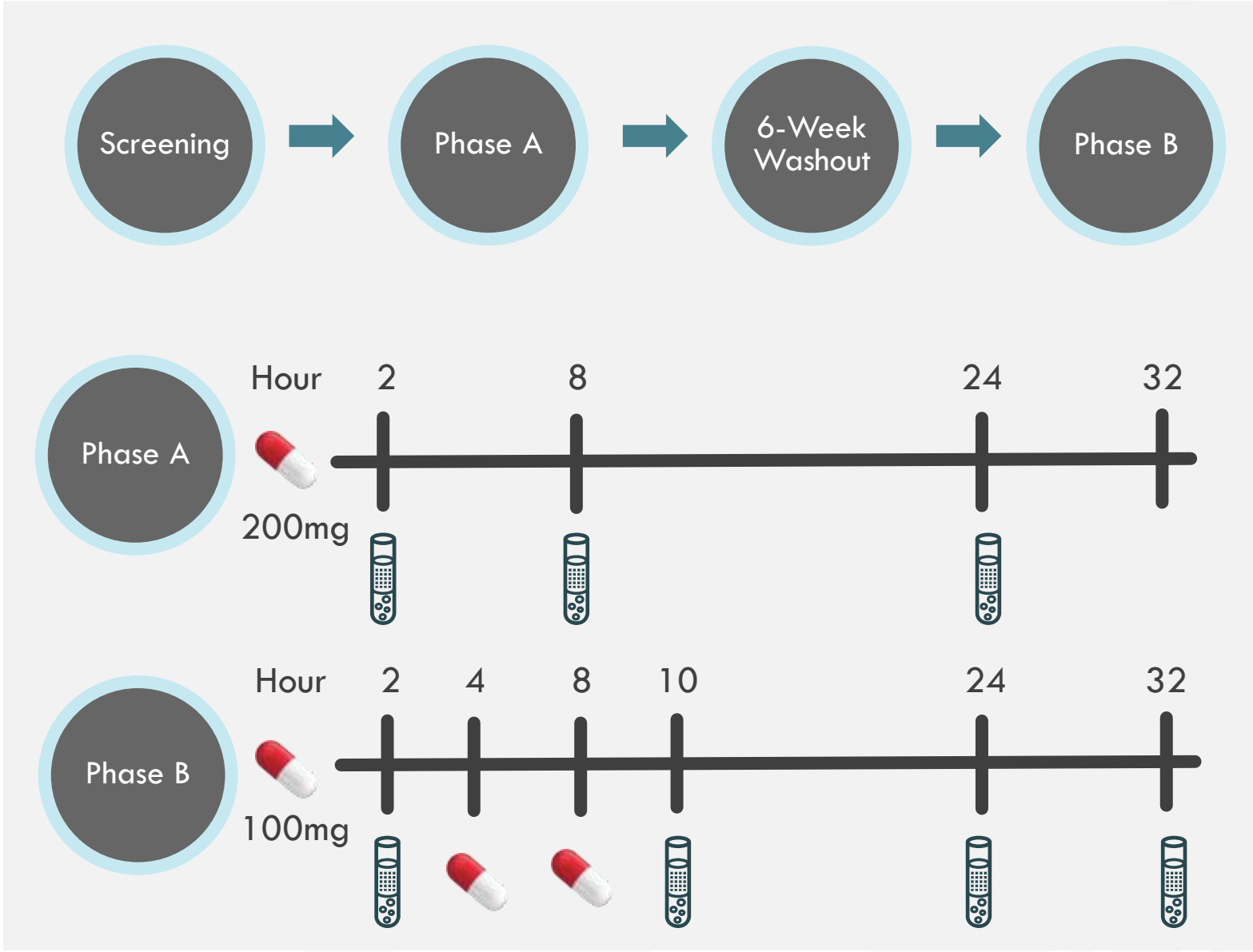
STUDY 1

P2 Study in hATTR-PN Patients

V30M TTR and wt-TTR (N=17)

Endpoints:

- **Plasma Stabilization**
- **Safety**

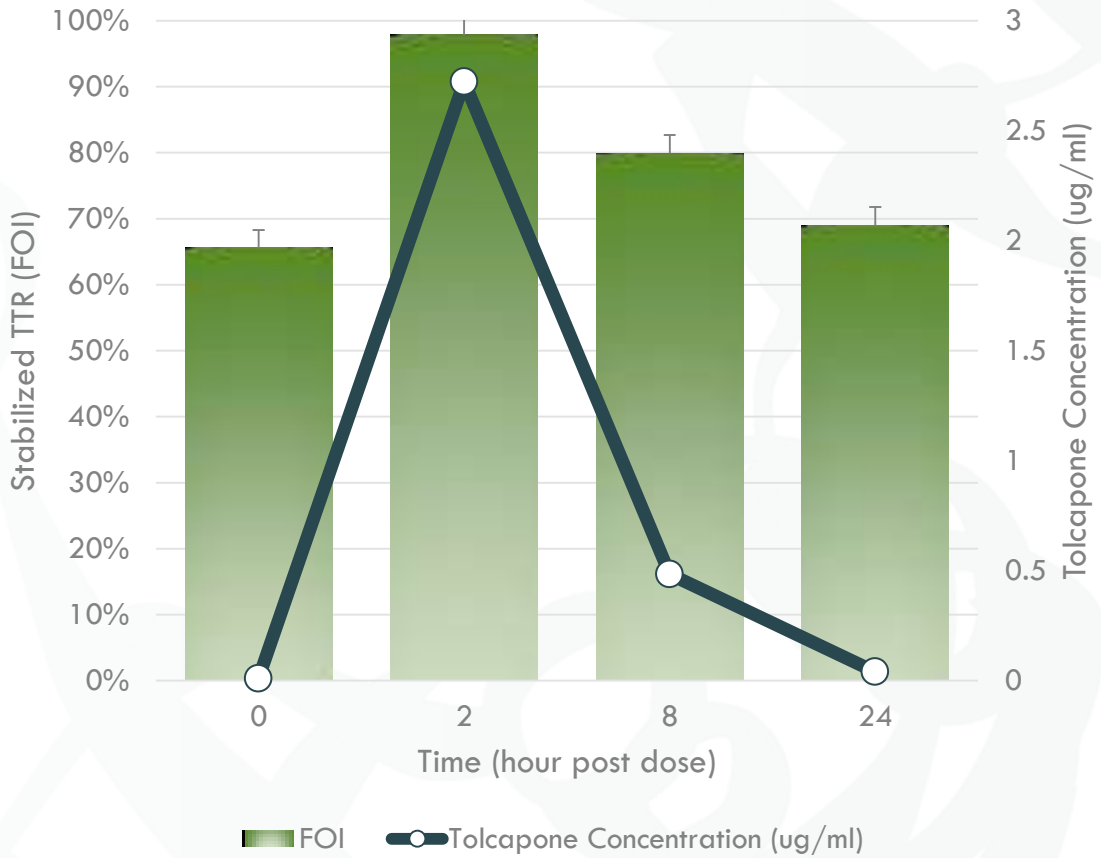


Vall d'Hebron University Hospital, Barcelona (Spain)

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))

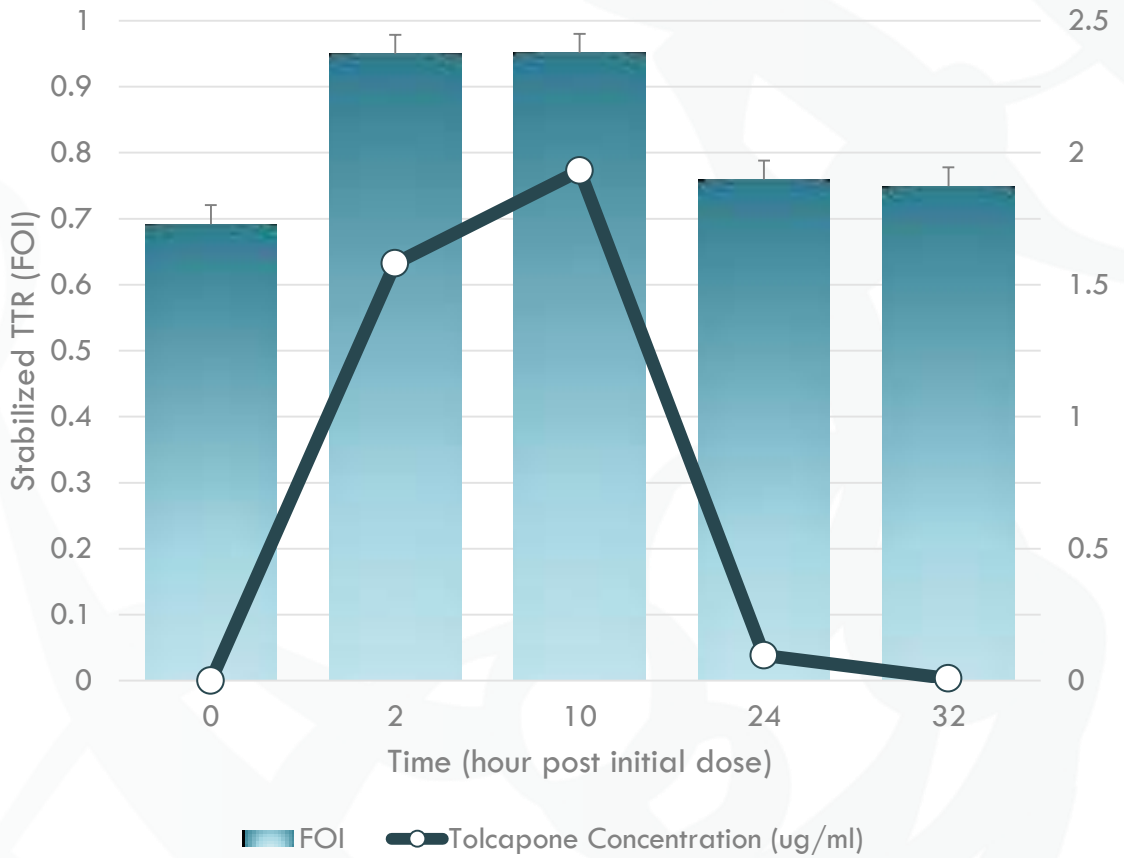


Gamez J, Salvadó M, Reig N, Suñé P, Casasnovas C, Rojas-Garcia R, Insa R., Transthyretin stabilization activity of the catechol-O-methyltransferase inhibitor tolcapone (SOM0226) in hereditary ATTR amyloidosis patients and asymptomatic carriers: proof-of-concept study., Amyloid. 2019 Jun;26(2):74-84.

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



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STUDY 2

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

Treatment for 1 week

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

(Shinshu University Hospital, Matsumoto, Japan)

STUDY 3

28-Day POC Study in hATTR-Leptomeningeal Patients

hATTR-PN Patients (Leptomeningeal) N=9

Key Inclusion Criteria

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

Endpoints

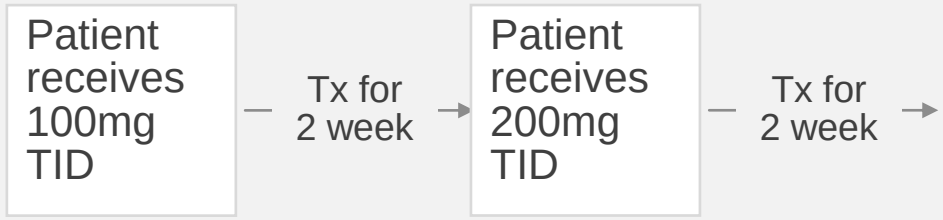
Primary

Effect of CRX-1008 on plasma and CSF TTR tetramer stability

Preliminary efficacy variable

Secondary

Safety and tolerability



(Boston University, Boston, MA, USA)

Upcoming Clinical Trials

CRX-1008

	Number of Subjects	Duration	Drug Arms	Objective	Start Date
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

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