SMALL MOLECULES TARGETING TAU PROPAGATION DEMONSTRATE EFFICACY IN AN AGGRESSIVE TAUOPATHY MOUSE MODEL
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Disclosures

Sonia Poli is an AC Immune’s employee
No off-label nor investigational use of therapeutic products will be presented
SMALL MOLECULES TARGETING TAU PROPAGATION DEMONSTRATE EFFICACY IN AN AGGRESSIVE TAUOPATHY MOUSE MODEL

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Head of Translational Science

March 31st, 2019
Rationale for targeting Tau

Aggregated Tau is inversely correlated with reduced MMSE score

- Tau pathology correlates well with disease severity

AD patients brain histology:
Inverse correlation of NFT with MMSE score

AD patients brain Pet Imaging:
Excellent inverse correlation of Pet signal and MME score

Ref: Okamura et al, Brain 2014


R² = 0.7368

\[ r = -0.781 \]

\[ P = 0.022 \]
Morphomer platform: Discovery of ACI-3024
Generation of conformation–specific small molecules

- Conformation-specific, non-peptidic, small molecules with drug like properties
- Protein propagation inhibitors (Kroth et al., 2012)
- Validated for selective binding to Abeta, Tau and alpha-Synuclein through *in vitro* efficacy
- Robust library of around 4500 compounds with desirable properties including brain penetration
- Around 1000 compounds screened so far for the Tau SME program
- Combination of library and medicinal chemistry program led to the discovery of ACI-3024
Morphomer binding induced conformational changes in Tau aggregates
Most of the conformational changes in Tau are located between amino acids 231-281
# ACI-3024 - Lead characterization

## Summary of *in vitro* results

### Tau aggregation inhibition
- Potent reduction of Tau aggregation
- Effect independent of Tau and FTDP-17 isoform mutants

### Target engagement
- Selective binding to aggregated Tau (25.1 nM)
- No binding to monomeric forms of Tau
- Selective binding to AD brain-derived pathological Tau (Ki 11.7 nM)

### Cross-reactivity to Abeta and α-Synuclein
- No binding to Abeta from AD human brain
- No binding to Alpha-synuclein from human brain
- No binding to healthy control tissue
ACI-3024 – *In vitro* Pharmacology

Dose-dependent reduction of intracellular pathological Tau

**Intracellular Tau misfolding in *in vitro* differentiated neuroblastoma cells expressing Tau P301L**

- **Bright field**
  - Undifferentiated cells
  - Retinoic acid differentiated cells

- **Misfolded Tau (MC-1)**

**Dose-dependent reduction of misfolded Tau**

- *In vitro* treatment with ACI-3024 led to a dose-dependent decrease of misfolded Tau at low nM concentrations
ACI-3024 - Target engagement and functional selectivity

- ACI-3024 specifically binds Tau NFTs and is able to disaggregate Tau NFTs from human AD brain sections even in presence of amyloid plaques.
ACI-3024 - *In vivo* Evaluation in rTg4510 mice

**Treatment study in aged transgenic mice**

**Mice**
- rTg4510 tauopathy model expresses repressible (Tet promotor Tau on/off) human 4R0N Tau carrying the P301L mutation (SantaCruz, 2005)

**Treatment**
- Oral administration for 1 month starting at 5 months of age
  - ACI-3024 30mg/kg bi-daily
  - Dose and dosing regimen selected based on the assumption that efficacy is driven by 24 h CSF concentrations above target EC$_{50}$

**Read-out**
- Biochemistry: total, aggregated, and hyperphosphorylated brain Tau and CSF Tau
- Immuno-histochemistry: misfolded Tau
- Neuroinflammation: microglial analysis
Treatment study results
Assessment of compound efficacy in an aggressive Tauopathy model

Biochemistry: Analysis of pathological Tau in Tau ON/OFF rTg4510 mice

- Treatment with ACI-3024 significantly reduced aggregated and insoluble pS202/pT205 hyper-phosphorylated Tau in cortical homogenates
- The decrease was proportional to the plasma exposure to ACI-3024

Ref.: Poli S, et al., CTAD 2018
Treatment study results
Assessment of ACI-3024 treatment effects on misfolded Tau

Immunohistochemistry: Analysis of misfolded Tau (MC1) in rTg4510 brain section

- Treatment with ACI-3024 significantly reduced misfolded Tau
- The decrease was proportional to the plasma exposure to ACI-3024
ACI-3024 - Correlations between Tau in CSF and plasma exposure in rTg4510 mice

Evaluation of a potential biomarker for efficacy

- The significant inverse correlation between CSF Tau and ACI-3024 exposure in plasma might indicate an increase of Tau clearance from the brain
- CSF Tau concentrations will be explored as a biomarker for efficacy
ACI-3024 - Effect on neuro-inflammation
Assessment of compound efficacy on pathological Tau-induced neuro-inflammation

In vivo treatment study

In rTg4510 mice, treatment with ACI-3024 reduced microgliosis.
This was likely due to a detoxification of Tau aggregates that consequently decreases pathological Tau induced-microglial activation.
ACI-3024 - Effect on neuro-degeneration

Assessment of compound efficacy on pathological Tau-induced neuro-degeneration

Human AD-brain seeded Tau induction of neurodegeneration in primary neuron-microglia co-cultures

Detoxification of Tau aggregates with ACI-3024 significantly decreased Tau-induced neuro-degeneration

- Full-length Tau aggregated with 1/200 PHF seeds for 3 days; pre-incubated in presence of compounds for 1h and then incubated with cells for 3 days

Neurite length measured with Tuj1 staining

* Mean + SEM
1-way ANOVA
Fisher’s LSD

Ref.: AC Immune unpublished
ACI-3024 - Effect on neuro-inflammation
Assessment of compound efficacy on pathological Tau-induced neuro-inflammation

- This was likely due to a detoxification of Tau aggregates that consequently decreases pathological Tau induced-microglial activation
ACI-3024 – Proposed Mode of Action

1. Pathological Tau release from neurons
2. Pathological Tau uptake by microglia and following activation
3. Neurodegeneration

Direct ACI-3024 effects

Intracellular Tau pathology

Extracellular Tau toxicity

Downstream ACI-3024 effects

Microglia activation

Release

Legend

Aggregated Tau
Monomeric Tau
Soluble factors C1q
CD68+ vesicles

Neurodegeneration

AD PDJ April 2019

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AC Immune’s targets in spreading hypothesis of misfolded tau in neuro-degenerative diseases

AC Immune’s therapies intervene at key points in the disease pathway

- Targeting both intracellular seeds and extracellular spreading by combination therapy of Morphomers and immunotherapy enables to fully control Tau pathology progression
- High selective Tau imaging diagnostic enables more precise patient characterization and potentially more precise prediction of AD progression
## ACI-3024 – Summary of Preclinical evaluation

GLP-toxicology package for CTA submission for FiH studies

| **In vitro on- and off-target activity** | • ACI-3024 is active and selective in multiple *in vitro* pharmacology assays  
• Binding assessed on 138 targets (Cerep Bioprint profile) shows good selectivity |
| **In vivo studies** | • In an *in vivo* therapeutic study ACI-3024 showed compound related treatment effects by biochemistry and IHC (brain, CSF and microglia) |
| **ADME** | • ACI-3024 has good *in vitro* and *in vivo* ADME properties, including low clearance, long half-life and good CNS disposition as assessed by brain and CSF concentrations |
| **In vitro tox and DDI** | • ACI-3024 has low potential for DDI in vitro (EC$_{50}$ on CYP > 25uM)  
• It has and no PgP interaction  
• It is negative in *in vitro* genotoxicity assays (AMES and MNT), and in the *in vivo* MLY |
| **GLP tox in rodents and non rodents** | • 4-week toxicology study with 2-week recovery successfully completed  
• NOAEL established at 300 mg/kg in rodent and 450 mg/kg in non rodent |
| **GLP safety pharmacology** | • ICH S7 safety pharmacology battery successfully completed: cardiovascular telemetry study in non rodent; respiratory and Irwin study in rodents |
| **CTA submission** | • Preclinical safety evaluation completed and preparation for First in Human studies planned |

DDD drug-drug interaction; AMES bacterial mutagenesis and carcinogenesis test; MNT micronucleus test in human cell lines; MLY *in vivo* mouse mymphoma
## ACI-3024 - Selective Tau aggregation in inhibitors

### Conclusions

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<td>1</td>
<td>The Morphomer platform has enabled identification of a new class of low molecular weight compounds, which specifically target misfolded and aggregated Tau.</td>
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<td>2</td>
<td>Through a thorough medicinal chemistry program, ACI-3024 was identified as lead candidate with optimal drug like properties suitable for clinical development.</td>
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<td>3</td>
<td>ACI-3024 has shown efficacy in pathological and functional read-outs in an aggressive transgenic Tauopathy model, with a strong PKPD correlation.</td>
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<td>4</td>
<td>ACI-3024 has shown excellent preclinical safety and tolerability profile and is entering clinical development as disease-modifying agent for neurodegenerative diseases characterized by misfolded tau.</td>
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TO BE UPDATED
Lilly?
Backup slides