Characterization of pharmacokinetics, pharmacodynamics, tolerability and clinical activity in Phase I studies of the novel allosteric tyrosine kinase 2 (TYK2) inhibitor NDI-034858


INTRODUCTION

TYK2 (Tyrosine Kinase 2) – A clinically validated target in psoriasis and psoriatic arthritis

Obligate signal transducer of receptors for interleukins IL-12 and IL-23 as well as Type I interferon

Heterodimerizes with JAK1 or JAK2; inhibition of either dimer moiety impedes signal transduction

NDI-034858 – A highly specific allosteric inhibitor of TYK2

- Novel, investigational, oral, allosteric inhibitor of TYK2.
- High specificity for TYK2 over JAK1, JAK2, JAK3 kinases.
- Single amino acid difference at allosteric binding pocket may account for high specificity for TYK2 over JAK1, JAK2, JAK3 kinases.

Fold Selectivity (vs.

<table>
<thead>
<tr>
<th>Dose</th>
<th>TYK2 – JH2 binding KD</th>
<th>JAK1 – JH2 binding KD</th>
<th>JAK2 – JH2 binding KD</th>
<th>JAK3– JH2 binding KD</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg</td>
<td>0.0004 nM</td>
<td>5000 nM</td>
<td>6000 nM</td>
<td>10000 nM</td>
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<tr>
<td>10 mg</td>
<td>0.0004 nM</td>
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<tr>
<td>20 mg</td>
<td>0.0004 nM</td>
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<tr>
<td>30 mg</td>
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<tr>
<td>50 mg</td>
<td>0.0004 nM</td>
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</table>

Biochemical Selectivity (Fold) 1.3 x 10^4

Predicted steady state plasma concentrations of NDI-034858 relative to inhibitory concentration in the human whole blood assay

- Absorption of NDI-034858 demonstrated mean peak drug concentrations observed at a median Tmax of 4-6 hours post-dose on Day 1 (single dose) as well as Day 14 (steady state).
- The Cmax and AUC changed in an approximately dose-proportional manner from 5 mg up to 75 mg and in a less than dose proportional manner at doses above 75 mg.
- The half-life was consistent across dose levels tested and ranged from 16.5 to 30.7 hours.
- Upon multiple dose administration, the accumulation ratio for Cmax and AUC was 2.2- to 2.9 and 2.5-to-3.2, respectively.

PHARMACODYNAMIC ACTIVITY IN HV

- At 5 mg and 50 mg daily, NDI-034858 is expected to cover the TYK2 IC50 and IC90, respectively, for 24 hours.

EXPLORATORY EFFICACY IN PSORIASIS

- Treatment with NDI-034858 showed a dose-dependent trend in reduction of disease severity as assessed by % reduction in PASI score.
- PASI 50 was achieved in 13%, 57% and 40% of patients in the 5, 10, and 30 mg groups, respectively, compared to 0% in the placebo group.
- PASI 75 was achieved in one subject (1/5; 20%) in the 30-mg cohort.
- PASI 90 was achieved in one subject (1/5; 20%) in the 30-mg group; the same subject also achieved PASI 90.
- Treatment with NDI-034858 also improved the sPGA score compared to placebo (data not shown), with one subject in the 30-mg cohort achieving an sPGA of 1 (minimal disease) at Day 28.

CONCLUSIONS

- The novel, investigational, allosteric, oral TYK2 inhibitor NDI-034858 exhibited pharmacodynamic and clinical activity in phase I studies.
- Early safety profile was as expected for TYK2 inhibition.
- Pharmacokinetic profile supports once daily dosing. At 50 mg daily, NDI-034858 is expected to cover IC90 for 24 hours.
- These results support further development of NDI-034858 in autoimmune disease.
- Phase 2 studies in psoriasis and psoriatic arthritis are currently ongoing.

REFERENCES

**Papp K et al., N Engl J Med 2018; 379:1313-1321
**McElwee J et al, AAD 2022
**Thaçi et al, EADV 2021

DISCLOSURES: All the authors are/were employees or consultants of Nimbus Therapeutics, LLC.