Phase 1/2, dose-escalation study of oral NS-018 in patients with primary myelofibrosis (PMF), post-polycthemia vera MF (post-PV MF), or post-essential thrombocythemia MF (post-ET MF)

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INTRODUCTION

Myelofibrosis (MF) is a BCR-ABL1-negative myeloproliferative neoplasm, the clinical characteristics of which include cytoplasmic, splenomegaly, and debilitating constitutional symptoms.1

Ablation JAK-STAT signaling in MF, most commonly as a result of the hypereactivating JAK2V617F mutation, underlies disease pathogenesis.2 Inhibition of JAK-STAT signaling is a key target for the treatment of MF.3

METHODS

This is a multi-center, Phase 1/2, 3+3 dose-escalation study of once-daily (QD) or twice-daily (BID) NS-018, given in 28-day cycles, in patients with primary MF, post-polythemia vera MF or post-essential thrombocythemia MF. The primary endpoint is the maximum tolerated dose (MTD) and recommended dose (RDS). Secondary endpoints include safety, pharmacokinetics, pharmacodynamics, and clinical response.4

RESULTS

Baseline demographics

In the Phase 1 part of this study, all patients were enrolled across the 10 dose cohorts.

- Three patients included in all QD dose cohorts, except the 300 mg QD cohort which included six patients.

- Three patients each included in the 130 and 300 mg BID cohorts, and eight patients enrolled in the other BID dose cohorts.

The most common drug-related hematologic events were thrombocytopenia and anemia, and the most frequent drug-related non-hematologic events were diarrhea and nausea (Table 4).

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>Reaction severity (%)</th>
<th>Diarrhea</th>
<th>Nausea</th>
<th>Fatigue</th>
<th>Pruritus</th>
<th>Spleen size reduction</th>
<th>Symptom</th>
<th>Symptom reduction (&gt;20%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QD 200 mg</td>
<td>88 (17/10)</td>
<td>40 (17/10)</td>
<td>30 (15/4)</td>
<td>23 (15/4)</td>
<td>1 (2%)</td>
<td>41% (13/33)</td>
<td>3 (30)</td>
<td>6 (6/0)</td>
</tr>
<tr>
<td>QD 300 mg</td>
<td>80 (17/10)</td>
<td>48 (17/10)</td>
<td>41 (15/4)</td>
<td>33 (15/4)</td>
<td>0 (0)</td>
<td>41% (13/33)</td>
<td>3 (30)</td>
<td>6 (6/0)</td>
</tr>
<tr>
<td>QD 400 mg</td>
<td>63 (12/4)</td>
<td>46 (12/4)</td>
<td>45 (12/4)</td>
<td>45 (12/4)</td>
<td>2 (5%)</td>
<td>42% (10/24)</td>
<td>3 (30)</td>
<td>6 (6/0)</td>
</tr>
<tr>
<td>BID 100 mg</td>
<td>77 (15/2)</td>
<td>47 (15/2)</td>
<td>45 (15/2)</td>
<td>45 (15/2)</td>
<td>0 (0)</td>
<td>41% (10/24)</td>
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</tbody>
</table>

- Across the total evaluable population, reductions in MF-SAF score were observed for all symptoms by Week 4 (Figure 2).

- The proportion of patients with ≥50% reduction in symptom score was similar or increased from Week 4 to Week 12 for each symptom, according to the criteria of patients enrolled at each dose cohort.

- A ≥50% reduction in symptom score was observed in 78% of evaluable patients at Week 12 (p<0.05).

- A reduction in scores for all symptoms was also observed in those patients who had received previous JAK2 inhibitor treatment (Figure 3).

- Pharmacokinetics

On Day 1, peak plasma concentration was achieved 2-4 hours postsing for all dose cohorts (Figure 4).

- Systemic exposure of NS-018 based on maximum serum concentration of NS-018 was approximately dose proportional across the 75-400 mg dose range tested (Figure 5).

- The Phase 2 portion of the study is ongoing and only includes patients who have received prior JAK2 inhibitor treatment.

REFERENCES


CONCLUSIONS

- Based on tolerability and preliminary efficacy data, the NS-018 300 mg QD dose was recommended for use in the Phase 2 part of the study.

- NS-018 400 mg QD and 400 mg BID were considered intolerable.

- Improved tolerability was observed with 300 mg QD on 30 mg BID or 300 mg QD.

- 50% of patients achieved ≥50% reduction in palpable spleen size at 300 mg QD.

- NS-018 300 mg QD is a tolerable dosage schedule, with up to 45 cycles administered at this dose level.

- An overall improvement in all assessed symptoms was observed at Week 4, with this improvement maintained or increased at Week 12 for most symptoms.

- NS-018 was effective in patients who had previously received JAK2 inhibitor treatment, with reductions in splenomegaly (47%) and symptoms burden observed.

The Phase 2 portion of the study is ongoing and only includes patients who have received prior JAK2 inhibitor treatment.

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DISCLOSURES

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