ADORÉ: A Randomized, Open-Label, Phase 1/2, Open-Platform Study Evaluating Safety and Efficacy of Novel Ruxolitinib Combinations in Patients with Myelofibrosis

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Study rationale

- MF is a progressive, severe, and life-threatening MPN characterized by bone marrow fibrosis and splenomegaly, and is associated with debilitating constitutional symptoms as well as reduced survival\(^1,2\).

- Ruxolitinib (RUX) is a first-in-class JAK1/JAK2 inhibitor\(^3\) that has shown superiority over placebo (COMFORT-I) and best available therapy (COMFORT-II) in improving splenomegaly, MF-related symptoms, and QoL\(^4,5\), and has demonstrated an overall survival benefit\(^6–9\).

- However, RUX is not curative, cytopenias remain a challenge and some patients lose response or discontinue treatment due to adverse events\(^6,7\).

- The ADORE study (NCT04097821) is a three-part, open-label, multicenter, phase 1/2 platform study assessing the safety and efficacy of RUX in combination with five novel compounds that impact the hematopoietic environment through different mechanisms.

### Study design

**Part 1:**
- **Dose escalation**
  - Ruxolitinib + siremadlin
  - Ruxolitinib + rineterkib
  - Ruxolitinib + crizanlizumab
  - Ruxolitinib + sabatolimab
  - Ruxolitinib + NIS793

  - **Safety run-in**
    - Ruxolitinib + crizanlizumab
    - Ruxolitinib + sabatolimab
    - Ruxolitinib + NIS793

  - **Part 1 primary endpoint:** incidence and severity of dose-limiting toxicities within the first 2 cycles

**Part 2:**
- Patients randomized to one of the selected combinations or RUX monotherapy (control)

**Part 3:**
- Patients randomized to the combination treatment, RUX cessation, or RUX monotherapy

- **Parts 2/3 primary endpoint:** response rate (a composite of anemia improvement [increase in Hb of ≥1.5 g/dL], no spleen volume progression, and no symptom worsening) at the end of cycle 8 (NIS793 arms) or cycle 6 (other arms) (24 weeks)

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<tr>
<td><strong>Part 1:</strong> Dose escalation</td>
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<tr>
<td>Ruxolitinib + siremadlin</td>
<td>Ruxolitinib + siremadlin</td>
<td>Ruxolitinib + Part 2 compound</td>
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<td>Ruxolitinib + rineterkib</td>
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<tr>
<td>Ruxolitinib + NIS793</td>
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- **≥24 weeks (2-cycle minimum)**
- **≥48 weeks**
- **≥48 weeks**

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* Dose escalation required to determine Phase 2 dose for siremadlin and rineterkib arms (already known for other agents). Rineterkib and NIS793 added to study protocol in November 2020. NIS793 has a 21-day cycle; all other arms have 28-day cycles. Patients will be treated with combination therapy for 12 weeks, followed by novel agent monotherapy. RUX, ruxolitinib.
### Key inclusion and exclusion criteria

#### Inclusion
- Age ≥ 18 years
- ECOG performance status of 0-2
- Diagnosis of PMF, PET-MF or PPV-MF
- Palpable spleen of at least 5 cm from the left costal margin or enlarged spleen volume of at least 450 cm³ per MRI or CT scan
- Treated with RUX for at least 12 weeks prior to study treatment
- Stable (no dose adjustments) RUX dose (between 5 and 25 mg bid) for ≥ 4 weeks prior to first dose of study treatment
- Hb < 11 g/dL (≤ 6.8 mmol/L)
- Absolute neutrophil count ≥ 1,000/μL
- Part 1: Platelet counts ≥ 75,000/μL
- Part 2 and part 3: Platelet counts ≥ 50,000/μL

#### Exclusion
- Received any investigational agent for the treatment of MF (except RUX) within 30 days of first dose of study treatment
- Peripheral blood blasts count of > 10%
- Inadequate liver function and/or severely impaired renal function
- Active infection that requires therapy
- History of a second primary malignancy in the past 3 years in need of systemic treatment
- History or current diagnosis of uncontrolled or significant cardiac disease
- Significant immune deficiency (including use of immunosuppressive drugs)
- Subjects with known TP53 mutation or deletion of TP53

CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; Hb, hemoglobin; MF, myelofibrosis; MRI, magnetic resonance imaging; PET-MF, essential thrombocytemia MF; PMF, primary MF; PPV-MF, polycythemia vera MF; RUX, ruxolitinib; TP53, tumor protein 53.
**Study compounds**

### RUX + rineterkib
- Constitutive JAK2 signaling results in activation of MEK/ERK signaling, which may limit the efficacy of JAK2 inhibition\(^1\)
- Rineterkib is a small molecule inhibitor of ERK1/2\(^2\)

### RUX + siremadlin
- JAK2 mutations are thought to induce the expression of HDM2, which acts to degrade p53\(^3,4\)
- Siremadlin is a small molecule inhibitor of the p53/HDM2 interaction, protecting p53 from degradation\(^5\)

### RUX + crizanlizumab
- In patients with MF, impaired megakaryocytes express high levels of P-selectin, which leads to increased TGF-\(\beta\) release and disease progression\(^6\)
- Crizanlizumab is a mAb that binds to and inhibits P-selectin\(^7\)

### RUX + sabatolimab
- Sabatolimab is a mAb that blocks the binding of TIM-3 to its ligand PtdSer\(^8\)
- TIM-3 blockade restores activity of exhausted T cells, and may diminish suppressor activity of regulatory T cells\(^9\)

### RUX + NIS793
- TGF-\(\beta\) is a pro-inflammatory cytokine that promotes bone marrow fibrosis\(^10,11\)
- NIS793 is a mAb that binds to TGF-\(\beta1\) and TGF-\(\beta2\) and displays TGF-\(\beta1\)- and TGF-\(\beta2\)-neutralizing activity\(^12\)

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Combining RUX with novel therapies may deliver clinical benefits in MF.

The ADORE study is assessing the five novel compounds in combination with RUX in patients with MF.

A total of approximately 240 patients are planned to be enrolled.*

As of October 2021, the study is enrolling the Part 1 siremadlin 30 mg cohort.

*assuming all five combination treatments enter Part 2 and one combination treatment is expanded in Part 3. MF, myelofibrosis; RUX, ruxolitinib.
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