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SIERRA ONCOLOGY
Lead Asset Momelotinib in Phase 3 for Myelofibrosis

Global Phase 3 ‘MOMENTUM’ study reads out H1 2022

US Commercial launch projected for 2023

Program de-risked by existing clinical experience in >800 myelofibrosis patients; several treated >10 years

Differentiated activity and profile may be uniquely suited to myelofibrosis patients with cytopenias

Significant commercial opportunity enhanced by potential for long-term and combination use

Nasdaq: SRRA

- Well funded
  - $123.2M in cash and cash equivalents (6/30/20)
  - Cash runway extends beyond pivotal data read-out
- Strong investor base
  - Additional funds potentially available at topline data

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Myelofibrosis (MF) is a bone marrow cancer that progressively impairs red blood cell production.

Constitutive activation of JAK-STAT signaling pathway results in local inflammation and progressive bone marrow fibrosis, reducing the hematopoietic capacity of the marrow (anemia) and triggering extramedullary hematopoiesis in the spleen (splenomegaly).

The systemic pro-inflammatory cytokine profile (eg IL-6) induces a hyper-metabolic state and constitutional symptoms and drives production of hepcidin, the master regulator of iron homeostasis.

Elevated hepcidin restricts iron availability for erythropoiesis, further reducing red blood cell (RBC) production, through the contribution of anemia of inflammation.

These factors coalesce leading to:

Classic disease hallmarks of myelofibrosis: anemia, constitutional symptoms and splenomegaly.
Myelofibrosis is a Chronic Progressive Disease

Anemia and transfusion dependence are important prognostic factors for survival

>1 YEAR AFTER DIAGNOSIS

US prevalence: 16,000 - 18,500 patients

Median age at diagnosis: 60 - 67 years

Survival (untreated): 3 - 10 years

ANEMIA
Bone marrow cancer impairs red blood cell production

64%

SPLENOMEGALY
Spleen tries to compensate by making blood cells, leading to pain and discomfort

46%

TRANSFUSION DEPENDENCY
Transfusion dependency impacts quality of life and overall survival

45%

CONSTITUTIONAL SYMPTOMS
Patients also experience debilitating symptoms

34%

THROMBOCYTOPENIA
Platelet count <150 x 10^9 /L
Becomes more common with disease progression.

31%

Anemia and transfusion dependence impacts quality of life and overall survival.

Current Treatments and the Unmet Need

• Allogeneic stem-cell transplantation reserved for younger, fit patients

• Ruxolitinib (JAK1 & JAK2 inhibitor) has been the cornerstone of MF therapy
  • Robust improvements in splenomegaly and symptoms often observed
  • Ruxolitinib transformed MF into a manageable condition

• However, current approved JAK inhibitors are myelosuppressive
  • Dose reductions due to cytopenias are common
  • Some patients never receive a JAK inhibitor due to anemia and/or thrombocytopenia at diagnosis

Unmet Need: Effective treatment of patients with cytopenias and amelioration of anemia
Momelotinib

A JAK1, JAK2 and ACVR1 inhibitor
Myelofibrosis Biology: JAK1, JAK2 & ACVR1 Drive Myelofibrosis Disease Hallmarks

Inflammation and aberrant cytokine signaling producing debilitating constitutional symptoms

Clonal proliferation leading to extra medullary hematopoiesis and burdensome splenomegaly

Aberrant activation of hepcidin transcription via hyperactivated ACVR1 signaling resulting in profound functional iron deficiency anemia
Myelofibrosis Biology: Momelotinib Potentially Inhibits All Three Disease Drivers

**Hypothesis:** Momelotinib should improve constitutional symptoms and splenomegaly whilst maintaining or improving hemoglobin.
Does Momelotinib Lower Hepcidin Levels in Humans?

- Phase 2 Translation Biology Study in 41 transfusion dependent myelofibrosis patients
- Hepcidin measured pre-dose and 6 hours post-dose
- Momelotinib acutely and chronically lowered hepcidin levels

### Hepcidin Concentrations over 24W MMB Dosing Period

- Pre dose: Mean % change from baseline: -19%
- 6h post dose: Mean % change from baseline: -25%
Anemia Severity Predicts Poor Survival in Myelofibrosis

**Anemia of inflammation** in MF driven by the production of hepcidin via the ACVR1 pathway.

**Elevated hepcidin** inhibits iron transport and exacerbates the anemia of bone marrow fibrosis.

Both anemia and elevated hepcidin are **powerful negative prognostic indicators** in myelofibrosis.

Optimal MF therapeutic would provide **sustained benefits** for constitutional symptoms, splenomegaly and **anemia**.

---

![Anemia severity predicts poor survival in myelofibrosis](image1)

![Hepcidin predicts poor survival in myelofibrosis](image2)

Nicolosi M et al, Leukemia 2018

Pardanani et al, American Journal of Hematology 2013
# Momelotinib: Ongoing Clinical Development Program

**SIMPLIFY-1**

**PHASE 3 CLINICAL TRIAL**
Ongoing pivotal study with ~180 subjects

**Ongoing Data Expected H1 2022**

**SIMPLIFY-2**

**PHASE 3 CLINICAL TRIAL**
JAKi-naïve patients (n=432) randomized 1:1 to momelotinib or ruxolitinib

**COMPLETED**

**XAP**

**PHASE 3 CLINICAL TRIAL**
Prior ruxolitinib-treated myelofibrosis patients (n=156) randomized 2:1 to momelotinib or best available therapy

**COMPLETED**

**EXTENDED ACCESS PROGRAM**
Ongoing with some patients receiving momelotinib for more than 10 years

**Ongoing >10 years**

- **JAK1**
- **JAK2**
- **ACVR1**

A potential therapy for anemic and thrombocytopenic patient groups
Momelotinib Completed Phase 3 Studies: SIMPLIFY-1, SIMPLIFY-2

**SIMPLIFY-1**

1st-Line Population: JAK inhibitor naïve subjects

Primary Endpoint

![Diagram](image)

- JAKi Naïve Double-blind, N=432
- Randomization 1:1
- Double-blind treatment
- Open label
- LTFU
- Year 7

Day 1

Week 24

Year 7

**Goal:** Non-Inferiority

**Primary Endpoint**

- Splenic Response Rate

**Secondary Endpoints**

- Total Symptom Score
- Transfusion Independence Rate

<table>
<thead>
<tr>
<th>JAKi Naïve</th>
<th>Momelotinib 200 mg QD</th>
<th>Ruxolitinib 20 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMB:</td>
<td>N=215</td>
<td></td>
</tr>
<tr>
<td>RUX:</td>
<td>N=217</td>
<td></td>
</tr>
</tbody>
</table>

**SIMPLIFY-2**

2nd-Line Population: Anemic or thrombocytopenic subjects previously treated with ruxolitinib

Primary Endpoint

![Diagram](image)

- JAKi Exposed Open label, N=156
- Randomized treatment
- Extension
- LTFU
- Year 7

Day 1

Week 24

Year 7

**Goal:** Superiority

**Primary Endpoint**

- Splenic Response Rate

**Secondary Endpoints**

- Total Symptom Score
- Transfusion Independence Rate

<table>
<thead>
<tr>
<th>JAKi Exposed</th>
<th>Momelotinib 200 mg QD</th>
<th>Best available therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMB:</td>
<td>N=104</td>
<td></td>
</tr>
<tr>
<td>BAT:</td>
<td>N=52</td>
<td></td>
</tr>
</tbody>
</table>

Journal of Clinical Oncology, 2017 35(34):3844

The Lancet Haematology, 2018 5(2): 7
## Headline Results of the SIMPLIFY Trials

**SIMPLIFY-1** | **SIMPLIFY-2**
---|---
| MMB | RUX | Non-Inferior? | MMB | BAT | Superior?
---|---|---|---|---|---
**Primary Endpoint** | Splenic reduction ≥35% @w24 | 27% | 29% | ✓ | 7% | 6% | ☒
| | | | | | | | |
| Non-Inferior? | | | | | | | |
| **Secondary Endpoint** | Symptom score reduction >50% @w24 | 28% | 42% | ☒ | 26% | 6% | ✓
| | | | | | | | |
| Superior? | | | | | | | |
| **Secondary Endpoint** | Transfusion independence for >12weeks* | 49% | 29% | ✓ | 47% | 19% | ✓

(✓) = nominal significance  
* Measured in patients who were transfusion-dependent at baseline

- Extensive data set provides a roadmap for further late-stage development
Momelotinib Safety:
Long-Term Safety Profile

- Safety generally similar for momelotinib, ruxolitinib in the 24-week double-blind period
  - Anemia and thrombocytopenia were more common in the ruxolitinib arm
  - Nausea was more common with momelotinib and drove higher early withdrawal rate in S-1

- With 3.5 to 5.5 years of follow up, >90 patients from SIMPLIFY-1 and -2 continuing to receive momelotinib
- Tolerability persists with extended treatment; Enables long duration of dosing
- No evidence of long-term cumulative toxicity observed
  - Several patients from early trials have now received >10 years of continuous momelotinib therapy.

### SIMPLIFY-1

<table>
<thead>
<tr>
<th>Frequent TEAEs¹ by PT</th>
<th>MMB (N=214)</th>
<th>RUX (N=216)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts with any TEAE, n (%)</td>
<td>198 (92.5%)</td>
<td>206 (95.4%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>39 (18.2%)</td>
<td>43 (19.9%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>31 (14.5%)</td>
<td>81 (37.5%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>40 (18.7%)</td>
<td>63 (29.2%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>34 (15.9%)</td>
<td>8 (3.7%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>31 (14.5%)</td>
<td>26 (12.0%)</td>
</tr>
</tbody>
</table>

### S-1 Extended

<table>
<thead>
<tr>
<th>Most Frequent TEAEs¹ by PT</th>
<th>MMB Final Safety Analysis (N=411)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts with any TEAE, n (%)</td>
<td>397 (96.6%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>99 (24.1%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>93 (22.6%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>94 (22.9%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>85 (20.7%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>84 (20.4%)</td>
</tr>
</tbody>
</table>

¹ TEAEs occurring in >20% pts in the “Overall exposed to MMB” population including the 214 subjects receiving blinded momelotinib and 197 additional subjects who received momelotinib after cross-over from ruxolitinib
### Splenic Reduction Endpoint in the SIMPLIFY Trials

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>SIMPLIFY-1</th>
<th></th>
<th>SIMPLIFY-2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MMB</td>
<td>RUX</td>
<td>Non-Inferior?</td>
<td>MMB</td>
</tr>
<tr>
<td>Splenic reduction ≥35% @w24</td>
<td>27%</td>
<td>29%</td>
<td>✓</td>
<td>7%</td>
</tr>
</tbody>
</table>

- SIMPLIFY-1 achieved primary endpoint: non-inferiority on splenic response rate
- SIMPLIFY-2 patients entered study following long-term ruxolitinib
  - 88.5% of patients randomized to ‘best available therapy’ remained on ruxolitinib
  - SIMPLIFY-2 was effectively a comparison of RUX → MMB vs RUX → RUX
- SIMPLIFY-2 did not include a washout period from prior ruxolitinib
  - Splenic control was likely maintained from prior treatment, confounding the primary endpoint

Future trials in previously-treated patients should include a washout period
Symptom Score Endpoint in the SIMPLIFY Trials

- In SIMPLIFY-1 and SIMPLIFY-2, MMB showed similar impact on TSS
- In SIMPLIFY-1 there was a higher early withdrawal rate on MMB (18.6%) vs RUX (7.4%)
  - Early withdrawals were counted as TSS ‘failures’
  - MMB early withdrawals often tolerability-related, not disease control failure
- In SIMPLIFY-1, baseline imbalance in TSS scores may have contributed to the outcome

<table>
<thead>
<tr>
<th>Secondary Endpoint</th>
<th>SIMPLIFY-1</th>
<th>SIMPLIFY-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom score reduction &gt;50% @w24</td>
<td>MMB 28% RUX 42%</td>
<td>MMB 26% BAT 6%</td>
</tr>
</tbody>
</table>

Ruxolitinib had a slightly greater impact on symptoms over first 24 weeks
Important to manage early tolerability-related withdrawals on momelotinib
SIMPLIFY-1: Comparison of Hemoglobin (Hgb) Levels and Transfusion Burden

SIMPLIFY-1 data suggest a clinically meaningful difference in Hgb levels and transfusion requirements between treatment arms. Maintained and improved Hgb level suggests momelotinib could become an option for patients with pre-existing anemia.
Higher platelet counts were observed in the momelotinib arm, despite similar baseline values.
Platelet counts increased in patients who switched from ruxolitinib to momelotinib at week 24.
Efficacy by treatment arm in patients with low baseline platelet count to be presented in Q4 2020.
**SIMPLIFY-1:**
Comparative Dose Intensity over 48 Weeks of Treatment

- Dose intensity (DI) of momelotinib maintained over extended duration of treatment
- Limited hematologic toxicity

**Hypothesis:** Maintained dose-intensity may drive better long-term outcomes for patients
The Pivotal Phase 3 ‘MOMENTUM’ Trial is Underway

Global Study, currently enrolling patients
Topline Data Expected H1 2022

Subjects
N=180
Previously Treated with JAK inhibitor
Symptomatic (TSS ≥ 10) and Anemic
(Hgb < 10 g/dL)
2:1 randomization
JAKi taper/washout ≥ 21 day

Day 1

Momelotinib 200 mg daily + Placebo

Early crossover to open label in the event of confirmed symptomatic splenic progression

Long Term Follow-up

Double-Blind Treatment

Open Label/Crossover

Momelotinib 200 mg daily

Danazol* 600 mg daily + Placebo

Primary Endpoint

Primary Endpoint:
• Total symptom score (TSS) response rate at Week 24

Secondary Endpoints:
• Transfusion independence (TI) rate at Week 24
• Splenic response rate (SRR) at Week 24

*Danazol was selected as an appropriate comparator given its use to ameliorate anemia in MF patients, as recommended by NCCN, ESMO guidelines.
Momelotinib
Preparing for Commercialization
Executive Leadership:
Leadership Team Purpose-Built for the Next Phase

Stephen G. Dilly, MBBS, PhD
President & Chief Executive Officer
Former CEO and Board Member of Aimmune Therapeutics

Sukhi Jagpal, CPA, CA, CBV, MBA
Chief Financial Officer
Former CFO of QLT Inc

Barbara Klencke, MD
Chief Development Officer
Former SVP of Onyx Pharmaceuticals
Former Group Medical Director Genentech

Mark Kowalski, MD, PhD
Chief Medical Officer
Former CMO and SVP of Arbutus Biopharma, Former CMO of YM BioSciences Inc

Kevin Norrett, MS, MBA
Chief Business Officer
Former Chief Commercial Officer of Angion Biomedica

Christina Thomson, MS, JD
General Counsel and Corporate Secretary
Former General Counsel of Athira Pharma, APT Pharmaceuticals and Avigen

William Turner
Chief Regulatory & Technical Operations Officer
Former SVP of Technical Operations and Regulatory Science at Aimmune Therapeutics
Clinician Enthusiasm For Momelotinib

Supports 1L Market Opportunity:
Patients with anemia, thrombocytopenia or transfusion dependency

Supports 2L Market Opportunity:
Broad utility across all patients; particularly anemic/thrombocytopenic patients

"The dual mechanism and clinical data... point to a strong anemia benefit, so I would definitely look to prescribe this in my front-line patients who have severe anemia”

US High Volume Prescriber*
February 2020

"Transfusions can be a major problem for patients and this product shows a clear benefit for transfusion independence in all studies, so I would use it in the majority of my front-line patients with severe anemia”

EU KOL*
February 2020

"The majority of patients in second-line would potentially be candidates for momelotinib”

Dr. Srdan Verstovsek
June 2019

*Sierra market research conducted by 3rd party
Upcoming Milestones

Q4 2020: Anticipated data analyses
Further data analyses from SIMPLIFY-1 highlighting comparable symptom improvements with MMB and RUX
Further data analyses from SIMPLIFY-1 and SIMPLIFY-2 highlighting efficacy of MMB vs RUX in patients with low platelets
Long-term outcome data including updated overall survival results with MMB to be presented

H2 2021: Enrollment complete in MOMENTUM clinical trial

H1 2022: MOMENTUM data readout

2023: Expected Approval & Commercialization

H2 2022: File New Drug Application with FDA
SIERRA ONCOLOGY
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