Announcing MOMENTUM: Registration-Intent Phase 3 Clinical Trial in Myelofibrosis

June 2019

NASDAQ: SRRA
SAFEG HARBOR STATEMENT

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Addressing Unmet Medical Needs with a Broad Pipeline

**Lead Program**

**momelotinib**
TARGETING JAK1/2 AND ACVR1

**THERAPEUTIC FOCUS**
Myelofibrosis

**DDR Network Programs**

**SRA737**
TARGETING Chk1

**THERAPEUTIC FOCUS**
Anogenital Cancer & Other Solid Tumors

**SRA141**
TARGETING Cdc7

**THERAPEUTIC FOCUS**
Colorectal Cancer
## Our Pipeline of Targeted Therapeutics

### Momeilotinib

<table>
<thead>
<tr>
<th>Phase</th>
<th>SIMPLIFY-1</th>
<th>Phase</th>
<th>SIMPLIFY-2</th>
<th>Phase</th>
<th>Registration Study</th>
<th>Phase</th>
<th>Phase</th>
<th>Focus</th>
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<tbody>
<tr>
<td>Preclinical</td>
<td>[ ]</td>
<td>Phase 1</td>
<td>[ ]</td>
<td>Phase 2</td>
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### SRA737

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<tr>
<th>Phase</th>
<th>SRA737-01 Monotherapy</th>
<th>Phase</th>
<th>SRA737-02 LDG Combination</th>
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<th>PARP Inhibitor Combination</th>
<th>Phase</th>
<th>I/O Combination</th>
<th>Phase</th>
<th>Focus</th>
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<td>Phase 3</td>
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<td>Solid Tumors</td>
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### SRA141

<table>
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<tr>
<th>Phase</th>
<th>Monotherapy</th>
<th>Phase</th>
<th>Phase</th>
<th>Phase</th>
<th>Focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical</td>
<td>[ ]</td>
<td>Phase 1</td>
<td>[ ]</td>
<td>Phase 2</td>
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</tr>
</tbody>
</table>
MOMELOTINIB
Targeting JAK1, JAK2 and ACVR1
MOMELOTINIB
Uniquely positioned to potentially provide robust benefits in myelofibrosis: spleen, symptoms and anemia

- >20 studies (Phase 1, 2 and 3)
- >1,200 people dosed with momelotinib
- >820 patients with myelofibrosis treated
- >7 years on treatment for several patients
Momelotinib Potentially Addresses Key Needs in Myelofibrosis Treatment

Opportunity
Intermediate/High-risk MF who have previously received a JAKi*; large unmet need with no approved therapies

Benefit
Only agent to robustly impact all three myelofibrosis hallmarks: constitutional symptoms, anemia, and enlarged spleen

Robust Data
Two P3 SIMPLIFY studies support safety & efficacy profile; provides confidence for MOMENTUM

Registration
Regulatory clarity obtained; MOMENTUM P3 study launch ~Q4 2019; topline data ~Q4 2021

*As per MMB Fast Track Designation, May 2019
Myelofibrosis: More Treatment Options Needed

INITIAL TREATMENT:

• Only one agent approved: ruxolitinib (Jakafi®) for 1st-line myelofibrosis
• Ruxolitinib:
  • Addresses ~70% 1st-line patients
  • Projected global market: >$2.5B
  • Only treats spleen and symptoms

UNMET MEDICAL NEEDS:

• Optimal myelofibrosis therapeutic would address all three hallmarks:
  • Constitutional symptoms
  • Anemia and transfusion dependency
  • Splenomegaly

Anemia is not addressed by ruxolitinib

Physicians need more choices than ruxolitinib

PREVIOUSLY JAKi-TREATED MF REMAINS A SIGNIFICANT UNMET MEDICAL NEED
Myelofibrosis
The Challenge of Anemia

“Anemia is major area of unmet need. That’s one of the major problems… a quarter of the patients at the beginning may require transfusions, and after one year of therapy almost half of the patients already require transfusion. Anemia and transfusion dependency are important prognostic factors.”

Srdan Verstovsek, MD, PhD
Professor in the Department of Leukemia at
The University of Texas MD Anderson Cancer Center, Houston

Unmet Medical Needs In Myelofibrosis; company conference call October 2018

Three Hallmarks of a Progressive Disease
>1 YEAR AFTER DIAGNOSIS

ANEMIA
Progressive bone marrow fibrosis due to inflammation; decreased erythropoiesis

45% Transfusion Dependent

Splenomegaly
Extramedullary hematopoiesis in the spleen and other organs

46%

Constitutional Symptoms
Anemia, chronic inflammation, and splenomegaly lead to constitutional symptoms

34%

Momelotinib: Attractive Acquisition Terms & Patent Life

- Sierra Management has unique insight into MMB.
- Full asset acquisition.
- $3M upfront; $5M at start of Phase 3.
- $195M in additional Milestones; heavily weighted to commercial success.
- Royalties from mid-teens to high-twenties; tiered by commercial success.
- Long patent life remaining:
  U.S. exclusivity projected to 2040*
  EU exclusivity projected to 2032-2040**/***

*assumes anticipated 5 years PTE and SPC extensions
**pending issue
Myelofibrosis Biology:
JAK1, JAK2 & ACVR1 Drive MF Disease Hallmarks

- Aberrant activation of hepcidin transcription via hyperactivated ACVR1 signaling resulting in profound functional iron deficiency anemia
- Inflammation & aberrant cytokine signaling producing debilitating constitutional symptoms
- Clonal proliferation leading to extramedullary hematopoiesis and burdensome splenomegaly
Myelofibrosis Biology: MMB Uniquely Inhibits All Three Disease Drivers

Interleukins
Interferons
Cytokine Receptors

Ligand
EPOR / MPL

BMP2, BMP6
ACVR1

JAK1
JAK2/3

JAK2

JAK1

JAK2

MOMELOTINIB

STAT

P

P

P

P

• Decreased inflammation and aberrant cytokine signaling improves constitutional symptoms

• Reduced extramedullary hematopoiesis improves splenomegaly

• Decreased hepcidin transcription restores iron homeostasis and increases hemoglobin leading to array of anemia benefits
Myelofibrosis Anemia: Multiple Pathways to Anemia Positively Impacted by MMB

INFLAMMATION (JAK1)
- Alterations in bone marrow cytokine expression
- Pro-inflammatory cytokine profile
- Impaired erythroid differentiation

EXTRAMEDULLARY HEMATOPOIESIS (JAK2)
- Displacement of marrow erythropoietic tissue by fibrosis
- Extramedullary hematopoiesis and splenomegaly
- Inadequate extramedullary hematopoiesis and red blood cell sequestration

HEPCIDIN (ACVR1)
- Activated ACVR1
- Elevated hepcidin
- Impairment of iron metabolism

OTHER JAKi THERAPIES
- Other JAK inhibitors induce myelosuppression
Myelofibrosis Anemia: High Hepcidin & Severe Anemia Predict Poor Survival

Hepcidin predicts poor survival in myelofibrosis

- High hepcidin
- Low hepcidin

Cumulative Survival

Anemia predicts poor survival in myelofibrosis

- No anemia
  - Median survival 7.9 years
- Mild anemia
  - Median survival 4.9 years
- Moderate anemia
  - Median survival 3.4 years
- Severe anemia
  - Median survival 2.1 years

P<0.0001

Pardanani et al; American Journal of Hematology 2013.

Nicolosi M et al; Leukemia. 2018.
Myelofibrosis Anemia: Reducing Hepcidin Restores Red Blood Cell Production

PLASMA IRON DEFICIENCY

PLASMA IRON NORMALIZATION

Momelotinib-mediated plasma iron elevation leads to stimulation of erythropoiesis and red blood cell production
Momelotinib: SIMPLIFY Data Strongly Support Benefits in Three Hallmarks of MF

**ANEMIA**
Increased hemoglobin: lower rates of RBC transfusion, fewer transfusion dependent patients, etc. in 1L & 2L

**CONSTITUTIONAL SYMPTOMS**
Pronounced TSS benefit: clinically compelling & consistent symptom improvement across all domains in 1L & 2L

**SPLENOMEGALY**
Only JAKi to show equivalent splenic response to ruxolitinib in 1L
Momelotinib: Regulatory Clarity Announced

- MOMENTUM Phase 3 pivotal trial designed to support registration of momelotinib
- Productive interactions with US and EU regulators
- FDA supportive of delineating a regulatory path for MMB in context of SIMPLIFY study data
- FDA provided very constructive input to help delineate a P3 study intended to yield compelling and persuasive data to support MMB’s potential registration
- Focus of MOMENTUM on unmet need population of 2L MF patients previously treated with a JAKi
  - MMB is ideally positioned to potentially provide all three clinical benefits for this substantial population of patients: symptoms, anemia & spleen
Momelotinib:
Fast Track Designation

Fast Track Designation Granted (May 2019):
Patients with intermediate/high-risk myelofibrosis who have previously received a JAK inhibitor
Planned Launch Q4 2019
Momentum P3 Trial:
Phase 3 Registration Trial Schema

A Randomized, Double-Blind, Phase 3 Study to Evaluate the Activity of Momelotinib (MMB) versus Danazol (DAN) in Symptomatic, Anemic Subjects with Primary Myelofibrosis (PMF), Post-Polycythemia Vera (PV) Myelofibrosis, or Post Essential Thrombocythemia (ET) Myelofibrosis who were Previously Treated with JAK Inhibitor Therapy

Previously Treated with JAK inhibitor
Symptomatic (TSS > 10) and Anemic (Hgb < 10 g/dL)

Subjects N=180

2:1 randomization

Day 1

Week 24

Primary Endpoint

Double-Blind Treatment

Open Label/Crossover

Long Term Follow-up

Momelotinib 200 mg daily + Placebo

Momelotinib 200 mg daily

Danazol 600 mg daily + Placebo

Danazol has been selected as an appropriate treatment comparator given its use to ameliorate anemia in myelofibrosis patients, as recommended by NCCN and ESMO guidelines.
Momentum P3 Trial: Study Objectives

Primary Endpoint:
- Total symptom score (TSS) response rate of MMB vs DAN at Week 24 in symptomatic and anemic patients with PMF, post-PV myelofibrosis, or post-ET myelofibrosis who were previously treated with an approved JAK inhibitor therapy.

Secondary & Exploratory Endpoints:
- Transfusion independence (TI) rate at Week 24 for subjects treated with MMB vs DAN.
- Splenic response rate (SRR) at Week 24 for subjects treated with MMB vs DAN.
- Duration of TSS response for subjects treated with MMB.
- Other measures of anemia benefit, including TD-TI rate and measures of cumulative transfusion burden.
- Additional Patient Reported Outcomes, including assessments of fatigue and physical function.
# Momentum P3 Trial: Key Design Elements

**Chief Investigator:**
Dr. Srdan Verstovsek, MD Anderson Cancer Center, Houston, Texas, USA

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Order &amp; Powering</th>
<th>Supporting Data/Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom (TSS) response rate</td>
<td><em>Primary (W24)</em></td>
<td>FDA preferred measure of clinical benefit in Myelofibrosis</td>
</tr>
<tr>
<td></td>
<td>99% powered; p&lt;0.05</td>
<td>Consistent and meaningful TSS responses in S-1 &amp; S-2</td>
</tr>
<tr>
<td>Transfusion Independence rate</td>
<td><em>Key Secondary (W24)</em></td>
<td>Favorable &amp; statistically significant TI rates in S-1 &amp; S-2</td>
</tr>
<tr>
<td></td>
<td>&gt;90% powered; p&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Spleen (SRR) response rate</td>
<td><em>Secondary (W24)</em></td>
<td>Defined washout allows for splenic rebound &amp; SRR benefit</td>
</tr>
<tr>
<td></td>
<td>&gt;90% powered; p&lt;0.05</td>
<td>Non-inferior SRR benefit H2H vs RUX in S-1</td>
</tr>
<tr>
<td>Durability of TSS response</td>
<td><em>Secondary (W48)</em></td>
<td>Durability of symptomatic benefit to W48 established in S-1 &amp; S-2</td>
</tr>
<tr>
<td>Other anemia measures</td>
<td><em>Secondary &amp; Exploratory</em></td>
<td>Consistent suite of benefits: TD-TI rates, improved HGB, reduced transfusion frequency, etc.</td>
</tr>
</tbody>
</table>

*Stratified for baseline TSS, RBC transfusions & spleen*
### Momentum P3 Trial: Key Trial Assumptions

<table>
<thead>
<tr>
<th>Key Assumption</th>
<th>Comment*</th>
</tr>
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<tbody>
<tr>
<td># Patients</td>
<td>180 (2:1 randomization)</td>
</tr>
<tr>
<td>Territory</td>
<td>Global study: North America, EU, APAC, etc.</td>
</tr>
<tr>
<td>Study Start</td>
<td>Planned launch in Q4 2019</td>
</tr>
<tr>
<td>Estimated Time to Enroll</td>
<td>~18 months</td>
</tr>
<tr>
<td>Estimated Time to Primary Endpoint</td>
<td>~6 months to primary endpoint after enrollment</td>
</tr>
<tr>
<td>Estimated Topline Data</td>
<td>~Q4 2021</td>
</tr>
<tr>
<td>Estimated Filing Date</td>
<td>~Q2 2022</td>
</tr>
<tr>
<td>Potential Regulatory Approval</td>
<td>~Q4 2022-Q2 2023**</td>
</tr>
</tbody>
</table>

*Company estimates

**Dependent on regulatory review process (priority or standard)
Momentum P3 Trial: Chief Investigator

• Dr. Srdan (Serge) Verstovsek, Chief, Section for Myeloproliferative Neoplasms, MD Anderson Cancer Center, Houston, has been named Chief Investigator of MOMENTUM.

• World-renowned physician-scientist, and a leading global authority on the treatment of myelofibrosis.
• Dr. Verstovsek’s clinical and translational research is focused on understanding the biology of and developing new therapies for myeloproliferative neoplasms (MPNs).
• Principal investigator for more than 50 clinical trials testing novel therapies for patients with MPNs
• Published more than 400 peer-reviewed manuscripts.
• Recipient of numerous awards and accolades.

Srdan Verstovsek, MD, PhD
Chief, Section for Myeloproliferative Neoplasms, Department of Leukemia, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston.
Momelotinib: Potential To Address All Three Hallmarks of Myelofibrosis

<table>
<thead>
<tr>
<th>Status in Myelofibrosis</th>
<th>Momelotinib (MMB)</th>
<th>Ruxolitinib (RUX)</th>
<th>Fedratinib (FED)</th>
<th>Pacritinib (PAC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 3 (Two completed P3s; P2 translational biology)</td>
<td>Approved (intermediate / high-risk; platelets ≥50 × 10⁹/dL)</td>
<td>Post-Phase 3 (P3 safety and efficacy study; NDA Filed Q4 2018)</td>
<td>Phase 2 (P3 trial requested by FDA; EA MAA withdrawn)</td>
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</tr>
<tr>
<td>Targets</td>
<td>JAK1, JAK2, ACVR1</td>
<td>JAK1, JAK2</td>
<td>JAK2, FLT3</td>
<td>JAK2, FLT3</td>
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<tr>
<td>Splenic Response</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Symptom Benefit</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Anemia Benefit</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>Toxicity: Anemia and Thrombocytopenia</td>
<td>LOW</td>
<td>HIGH</td>
<td>HIGH</td>
<td>HIGH</td>
</tr>
</tbody>
</table>
Momelotinib 2\textsuperscript{nd}-Line Market Opportunity* 

**Diagnosis**
- ~50K patients living with myelofibrosis
- ~75% are intermediate/high risk

\textbf{1\textsuperscript{st}-Line}
- ~70% receive 1\textsuperscript{st}-line treatment

\textbf{2\textsuperscript{nd}-Line}
- >75% will need 2\textsuperscript{nd}-line treatment
  - >70% of INT-2/High myelofibrosis patients have anemia
  - >50% of patients are transfusion dependent

**Favorable patent exclusivity**
- potential extensions to 2040\textsuperscript{**} provide a compelling commercial opportunity

\textsuperscript{*}Company estimates
\textsuperscript{**}assumes anticipated 5 years PTE and SPC extensions

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

Dr. Srdan Verstovsek
June 2019
FAST TRACK DESIGNATION

MOMENTUM
MYELOFIBROSIS CLINICAL TRIAL

Planned Launch Q4 2019
SIMPLIFY
P3 STUDIES

Prior Clinical Data
Support MOMENTUM
SIMPLIFY P3

Studies:

Prior Clinical Data Supportive of MOMENTUM

SIMPLIFY-1

- Gilead did not file for registration on the basis of the SIMPLIFY studies and presented only top-line results to FDA/EMA.
  - Sierra has identified and analyzed design flaws in the SIMPLIFY studies.
  - Moreover, we have addressed these issues in the design of MOMENTUM.

SIMPLIFY-2

- MOMENTUM is designed to convincingly demonstrate MMB’s benefits on all three hallmarks of myelofibrosis (symptoms, anemia and spleen).
- MOMENTUM is intended to provide a persuasive and compelling path to registration in context of the SIMPLIFY P3 datasets.
Momelotinib: Completed SIMPLIFY Phase 3 Studies

**SIMPLIFY-1**

**1st-Line Population:** Previously untreated with JAKi

- **Goal:** Non-Inferiority
- **Primary Endpoint:** Splenic Response Rate
- **Secondary Endpoints:**
  - Total Symptom Score
  - Transfusion Independence Rate
  - Transfusion Dependence Rate
  - RBC Transfusion Requirements

**1:1 randomization**

<table>
<thead>
<tr>
<th>JAK Naïve Double-blind, N=432</th>
<th>Momelotinib 200 mg QD</th>
<th>Ruxolitinib 20 mg BID</th>
<th>Momelotinib 200 mg QD</th>
</tr>
</thead>
</table>

- **Day 1**
- **Week 24**
- **LTFU**

**SIMPLIFY-2**

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

- **Goal:** Superiority
- **Primary Endpoint:** Splenic Response Rate
- **Secondary Endpoints:**
  - Total Symptom Score
  - Transfusion Independence Rate
  - Transfusion Dependence Rate
  - RBC Transfusion Requirements

**2:1 randomization**

<table>
<thead>
<tr>
<th>JAK Exposed Open label, N=156</th>
<th>Momelotinib 200 mg QD</th>
<th>Best available therapy</th>
</tr>
</thead>
</table>

- **Randomized treatment**
- **Extension**
- **LTFU**

**Primary Endpoint**

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</thead>
<tbody>
<tr>
<td>BAT: Best Available Therapy</td>
<td>90% = RUX/RUX+</td>
<td>RBC transfusions on RUX = 64%</td>
</tr>
</tbody>
</table>

**RUX dose adjustment for:**
- thrombocytopenia = 21%
- anemia/hematoma = 35%
SIMPLIFY Phase 3 Study Results: Design Flaws Mask Compelling Efficacy

SIMPLIFY-1: Head-to-Head MMB vs RUX

1st-Line Population: Previously untreated with JAKi

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>Splenic Response Rate (SRR)</th>
<th>Non-Inferiority</th>
<th>Superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary Endpoints</td>
<td>• Total Symptom Score (TSS)</td>
<td>Non-Inferiority</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>• Transfusion Independence Rate</td>
<td>Superiority</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>• Transfusion Dependence Rate</td>
<td>Superiority</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>• RBC Transfusion Requirements</td>
<td>Superiority</td>
<td>✓</td>
</tr>
</tbody>
</table>

Lack of symptom stratification

SIMPLIFY-2: MMB vs BAT (~90% RUX)

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

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>Splenic Response Rate (SRR)</th>
<th>Superiority</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary Endpoints</td>
<td>• Total Symptom Score (TSS)</td>
<td>Superiority</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>• Transfusion Independence Rate</td>
<td>Superiority</td>
<td>✓</td>
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<td>Superiority</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>• RBC Transfusion Requirements</td>
<td>Superiority</td>
<td>✓</td>
</tr>
</tbody>
</table>

Lack of prior RUX washout
SIMPLIFY-1 Symptom Response: Lack of Stratification for TSS in SIMPLIFY-1

Momelotinib was not statistically non-inferior to ruxolitinib on TSS Response Rate at Week 24
(Noninferior Proportion Difference 0.00
(-0.08, 0.08))

Total Symptom Score (TSS) response defined as ≥ 50% reduction in TSS at W24 from baseline

Critical design flaws in SIMPLIFY-1

No stratification for symptoms
- Imbalance in baseline TSS at enrollment.
- Mean & median baseline TSS favored RUX
  • more MMB subjects enrolled with very low (TSS<6) and very high (TSS>40) symptoms at baseline.
  • TSS extremes: challenging to achieve TSS 50% reduction.

No exclusion of minimally-symptomatic patients
- Patients with low TSS were not excluded
- FDA: establishment of clinically meaningful symptom benefit requires demonstrable baseline symptomatic burden.
## SIMPLIFY-1 Symptom Response: MMB Has Clinically Comparable TSS Benefit in 1L

### SIMPLIFY-1 Baseline TSS

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Median</th>
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</thead>
<tbody>
<tr>
<td>MMB</td>
<td>19.4</td>
<td>18.2</td>
</tr>
<tr>
<td>Ruxolitinib</td>
<td>16.8</td>
<td>16.2</td>
</tr>
</tbody>
</table>

**MMB arm:** More symptomatic at baseline

- Baseline TSS was not a stratification factor in SIMPLIFY-1.
- Higher baseline TSS in the MMB treatment arm necessitated a larger absolute treatment effect to achieve response.
- Patients with very low TSS also imbalanced in SIMPLIFY-1.

### SIMPLIFY-1 Single Item Analysis

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Week 24 (MBB)</th>
<th>Week 24 (Ruxolitinib)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Discomfort</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Itching</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Bone Pain</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Night Sweats</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Early Satiety</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Pain Under Left Ribs</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Pain Under Left Ribs</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Early Satiety</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Tiredness</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Tiredness</td>
<td>7</td>
<td>6</td>
</tr>
</tbody>
</table>

**Data from Sierra’s post-hoc analyses of SIMPLIFY-1 & SIMPLIFY-2 studies**

- Single item analysis was explored to better understand the TSS result in SIMPLIFY-1.
- Demonstrates clinically comparable symptom benefits in all domains.
- TSS6 mirrors data from COMFORT & JAKARTA studies; TSS6 post hoc non-inferior to RUX (p = 0.0002)
SIMPLIFY-1 Symptom Response:  
Post Hoc TSS Analysis Supports MOMENTUM Design

• Post hoc analysis demonstrates an enrollment imbalance due to lack of stratification
  > more MMB pts had very low TSS (TSS <6)
  > more MMB pts had very high TSS (TSS >40)

• To model the putative impact of stratification, various post hoc analyses were conducted
  non-inferiority \( (p = 0.033) \) in patients with demonstrable symptom burden (TSS ≥ 6; 82% enrolled patients)
  non-inferiority \( (p = 0.015) \) without extreme outliers (TSS ≥6 & <40; 77% enrolled patients)

<table>
<thead>
<tr>
<th>TSS Range</th>
<th>% Subjects In Range</th>
<th>Non-inferior p value</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>100%</td>
<td>( p = 0.191 )</td>
<td>Missed non-inferior ✗</td>
</tr>
<tr>
<td>TSS ≥ 6</td>
<td>82%</td>
<td>( p = 0.033 )</td>
<td>Non-inferior ✓</td>
</tr>
<tr>
<td>TSS ≥6 &amp; &lt;40</td>
<td>77%</td>
<td>( p = 0.015 )</td>
<td>Non-inferior ✓</td>
</tr>
</tbody>
</table>

Data from Sierra’s post-hoc analyses of SIMPLIFY-1
SIMPLIFY-2 Symptom Response: Pronounced TSS Benefit in 2L: Relevance to MOMENTUM

**SIMPLIFY-2**

Statistically Significant Symptom Response

Momelotinib compared to best available therapy (~90% ruxolitinib) in 2\textsuperscript{nd}-line patients

26.2% TSS ✓

vs 5.9% best available therapy

\( p < 0.001 \)

Baseline TSS was a stratification factor in SIMPLIFY-2
Hemoglobin Improvement: Hemoglobin Benefit vs Ruxolitinib Toxicity in 1L

SIMPLIFY-1

- Momelotinib has a mechanism-driven anemia benefit via ACVR1 inhibition.
- Results in immediate and sustained increase in hemoglobin and array of anemia benefits.
- Ruxolitinib (and other JAKi) associated with pronounced decrease in hemoglobin, recovered after MMB crossover.

![Graph showing hemoglobin levels over weeks with crossover from double-blind to open-label phase.]
Maintenance of Transfusion Independence

Transfusion Independence response defined as the proportion of subjects who were transfusion independent at Week 24, where transfusion independence was defined as the absence of RBC transfusion and no hemoglobin level below 8 g/dL in the prior 12 weeks.

**SIMPLIFY-1**

66% ✓

vs 49% ruxolitinib

Statistically significant transfusion independence rate ($p < 0.001$)

**SIMPLIFY-2**

43% ✓

vs 21% BAT (~90% RUX)

Statistically significant transfusion independence rate ($p = 0.001$)

Key Secondary Endpt >90% Powered
Conversion from Transfusion Dependence to Transfusion Independence

Transfusion Dependent Subset Analysis

SIMPLIFY-1

49.1%

vs 28.8% ruxolitinib

(p = 0.0299)

≥ 12 Week Transfusion Dependence Response Rate*

SIMPLIFY-2

46.6%

vs 18.6% BAT

(p = 0.0048)

≥ 12 Week Transfusion Dependence Response Rate*

Transfusion Dependence response defined as the proportion of transfusion dependent subjects who became transfusion independent for any 12 week or greater period on study, where transfusion independence was defined as the absence of RBC transfusion and no hemoglobin level below 8 g/dL.

*Data from Sierra’s post-hoc analyses of SIMPLIFY-1 & SIMPLIFY-2 studies
**SIMPLIFY-1 Additional Anemia Benefits:**

**Pre-specified & Post Hoc Analyses in 1L**

Pre-specified and post hoc analyses demonstrate consistent, compelling and persuasive evidence of MMB’s anemia benefit in direct head-to-head comparison with RUX

<table>
<thead>
<tr>
<th>Anemia Benefit (to Week 24)</th>
<th>Statistical Value</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusion dependent rate @ W24</td>
<td>$p = 0.019$</td>
<td>Less patients transfusion dependent on MMB vs RUX</td>
</tr>
<tr>
<td>Rate of RBC transfusions</td>
<td>$p &lt; 0.001$</td>
<td>Lower rate of RBC transfusions on MMB vs RUX</td>
</tr>
<tr>
<td>Risk of being transfused*</td>
<td>$hazard ratio = 0.522$</td>
<td>Risk of being transfused halved on MMB vs RUX</td>
</tr>
<tr>
<td>Odds of being transfusion free*</td>
<td>$p &lt; 0.0001$</td>
<td>Odds of being transfusion free 9x better on MMB vs RUX</td>
</tr>
<tr>
<td>Time to first transfusion*</td>
<td>log-rank $p&lt; 0.0001$</td>
<td>Significantly longer time to first transfusion on MMB vs RUX</td>
</tr>
</tbody>
</table>

*Data from Sierra’s post-hoc analyses of SIMPLIFY-1

**SIMPLIFY-2**

Similar findings observed in SIMPLIFY-2

*Other Secondary & Exploratory Endpoints*
Non-Inferior Head-to-Head Activity on Splenomegaly in 1L

**SIMPLIFY-1**

26.5% SRR vs 29% ruxolitinib

Momelotinib statistically non-inferior to ruxolitinib on spleen \((p=0.011)\)

Only JAKi to show equivalent splenic response to ruxolitinib in 1st-line

Splenic Response Rate (SRR) defined as ≥ 50% reduction in spleen volume at W24 versus baseline
Momelotinib not statistically superior on SRR vs Best Available Therapy at Week 24

**SIMPLIFY-2**

**Critical design flaws in SIMPLIFY-2:**

**No washout**
- prior therapy (RUX) maintained at stable dose throughout screening until study start.
- all other 2L JAK inhibitor trials insist on ≥2 week washout from RUX to allow spleen rebound.

**Mismatched endpoint to population & design**
- enrolment for hematology, *not* progressive spleen.
- likely persisting spleen response after >1y on RUX.
- designed as superiority study to inactive control - inadvertently became *de facto* H2H vs RUX unanticipated preponderance of RUX (~90% of patients) in BAT; RUX not excluded.
- FDA suggested TSS as primary endpoint (vs SRR).
Myelofibrosis 2L Clinical Trials: Impact of Washout vs Stable Dosing

- **Ruxolitinib treatment for ≥ 28 days**
  - No ruxolitinib washout
  - Objective measures of ruxolitinib intolerance

- **Ruxolitinib treatment for ≥ 14 days**
  - Forced ruxolitinib washout ≥ 14 days
  - Objective measures of ruxolitinib intolerance
  - Subjective measures of ruxolitinib resistance or intolerance

- **6 month maximum prior cumulative exposure to ruxolitinib**
  - No minimum prior exposure to ruxolitinib
  - Ruxolitinib resistance/ intolerance not defined

- **Forced ruxolitinib washout ≥ 14 day**

**Treatment Options**

- **SIMPLIFY-2**
  - Momelotinib

- **JAKARTA-2**
  - Fedratinib

- **PERSIST-2**
  - Pacritinib

**Markers**

- Splenomegaly rebound

Momelotinib Safety:
Overall Similar to RUX & Less Hematologic Toxicity

### SIMPLIFY-1

<table>
<thead>
<tr>
<th>Common Adverse Event</th>
<th>MMB</th>
<th>RUX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia*</td>
<td>19%</td>
<td>29%</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>18%</td>
<td>20%</td>
</tr>
<tr>
<td>Headache</td>
<td>17%</td>
<td>20%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>16%</td>
<td>12%</td>
</tr>
<tr>
<td>Nausea</td>
<td>16%</td>
<td>4%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15%</td>
<td>12%</td>
</tr>
<tr>
<td>Anemia**</td>
<td>14%</td>
<td>38%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>10%</td>
<td>11%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade 3 or 4 Adverse Event</th>
<th>MMB</th>
<th>RUX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia*</td>
<td>7%</td>
<td>5%</td>
</tr>
<tr>
<td>Anemia**</td>
<td>6%</td>
<td>23%</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3%</td>
<td>5%</td>
</tr>
</tbody>
</table>

* dose reduction/interruption for thrombocytopenia: MMB = 5.6%  RUX = 24.5%
** dose reduction/interruption for anemia: MMB = 1.4%  RUX = 6.0%

### SIMPLIFY-1

<table>
<thead>
<tr>
<th></th>
<th>Momelotinib (n = 214)</th>
<th>Ruxolitinib (n= 216)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs</td>
<td>92%</td>
<td>95%</td>
</tr>
<tr>
<td>Grade 3 or 4 AE</td>
<td>34%</td>
<td>44%</td>
</tr>
<tr>
<td>≥Grade 3 AE Related to Study Drug</td>
<td>21%</td>
<td>29%</td>
</tr>
<tr>
<td>Serious AE</td>
<td>23%</td>
<td>18%</td>
</tr>
<tr>
<td>Serious AE Related to Study Drug</td>
<td>7%</td>
<td>6%</td>
</tr>
</tbody>
</table>

**MMB Safety:**
- No Adverse Event concerns flagged in our Regulatory interactions
- No evidence of cumulative toxicity/safety issues in long-term dosing & follow-up
Noteworthy Survival Trends for Momelotinib

**SIMPLIFY-1**

At the time of the primary (Week 24) analysis the stratified hazard ratio for overall survival favored momelotinib: 0.80 ($p = 0.52$)

**SIMPLIFY-2**

At the time of the primary (Week 24) analysis the stratified hazard ratio for overall survival favored momelotinib: 0.62 ($p = 0.24$)

28 months

Median Overall Survival

vs 7-14 months*

Historical control survival in post-ruxolitinib treated patients
