Notice

• Some information contained in this presentation may not be included in the approved Prescribing Information for JAKAFI® (ruxolitinib). This presentation is not intended to offer recommendations for any administration, indication, dosage, or other use for JAKAFI in a manner inconsistent with the approved Prescribing Information

• The data and conclusions of the following presentation are those of the authors and are provided as they were presented

• The data and conclusions included in the following presentation are not intended to comment on the diagnosis, treatment, or circumstances applicable to any specific patient

INDICATIONS AND USAGE

• JAKAFI® (ruxolitinib) is indicated for treatment of:
  – Intermediate or high-risk MF, including primary MF, post-PV MF, and post-essential thrombocythemia MF in adults
  – PV in adults who have had an inadequate response to or are intolerant of hydroxyurea
  – SR-aGVHD in adult and pediatric patients 12 years and older
  – cGVHD after failure of one or two lines of systemic therapy in adult and pediatric patients 12 years and older
Ruxolitinib In Pediatric Patients with Treatment-NAïve or Steroid-Refractory Acute Graft-versus-Host Disease: Primary Findings from the Phase I/II REACH4 Study

Introduction

- aGvHD is a major complication of allogenic stem cell transplantation (alloSCT)
- Among pediatric patients in the US who received alloSCT from an unrelated donor, 40–85% of patients developed grade II–IV aGvHD
- Only 30–50% of patients with aGvHD respond to first-line corticosteroid treatment
- In the phase 3 REACH2 study (NCT0291261), ruxolitinib, an oral JAK1/2 inhibitor, was superior to best available therapy (BAT) in patients ≥12 years of age with steroid-refractory aGvHD (N=309)
  - In REACH2 ruxolitinib demonstrated:
    - A significantly superior overall response rate (ORR) than BAT at day 28 (62.3% [96/154] vs 39.4% [61/155]; P<0.001)
    - A significantly higher durable ORR than BAT at day 56 (39.6% [61/154] vs 21.9% [34/155]; P<0.001)
- We present the first data from REACH4 (NCT03491215), a phase 1/2 open-label, single-arm, multicenter study of ruxolitinib added to corticosteroids in pediatric patients with grade II-IV treatment-naïve or steroid-refractory aGvHD

aGvHD, acute graft-vs-host disease; JAK, Janus kinase.
Study Design

- **Primary endpoints:**
  - **Phase 1:** derivation of ruxolitinib PK parameters, and determination of an age-appropriate RP2D
  - **Phase 2:** ORR at day 28

- **Key secondary endpoint:** the rate of durable ORR at day 56

- **Efficacy data** were analyzed once all patients had completed 24 weeks of treatment or discontinued earlier
  - **Data cut-off for current analysis:** February 22, 2022

**Screening Period (up to 28 days)**

- **Enrollment**
  - Treatment-naïve and steroid-refractory grade II-IV aGvHD
  - Patients were enrolled into treatment groups based on age to allow appropriate dosing
  - Before treatment initiation, aGvHD organ staging is graded using the Mount Sinai criteria

**Treatment Period (24 weeks)**

- All patients received ruxolitinib plus CS ± CNI for 24 weeks or until discontinuation

  **Phase 1**
  - Day 1
  - 28 days
  - 12 months
  - 24 months

  **Phase 2**
  - 24 weeks
  - 18 months
  - 24 months

  - Taper (D56 to Wk 24)
  - Taper/aGvHD flare (24 wks)

**Follow-up Period (18 months)**

- EOT/Safety follow-up

- Long-term follow-up

**ORR** is defined as the proportion of patients achieving CR or PR. EOT occurs when a patient discontinues treatment at any time. Safety follow-up will occur 30 days after the last dose. A patient will continue the visit schedule even if treatment is discontinued early. Responding patients may be tapered off ruxolitinib as needed, starting no earlier than day 56, and should be completed by week 24. Patients may continue to taper ruxolitinib beyond 24 weeks up to a maximum of 48 weeks if an aGvHD flare requires treatment re-initiation or if ruxolitinib is not fully discontinued by the end of 24 weeks due to extended tapering.

- aGvHD, acute graft-vs-host disease; CNI, calcineurin inhibitor; CR, complete response; CS, corticosteroids; D, day; EOT, end of treatment; PK, pharmacokinetic; PR, partial response; ORR, overall response rate; RP2D, recommended phase 2 dose; Wk, week.
## Ruxolitinib Dose and Treatment Schedule

<table>
<thead>
<tr>
<th>Age</th>
<th>Ruxolitinib Starting Dose</th>
<th>Confirmed Phase 2 Ruxolitinib Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>≥12 to &lt;18 years</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Group 1 adolescent patients are enrolled directly at ruxolitinib 10 mg BID; the dose used in REACH2³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>≥6 to &lt;12 years</td>
<td>Preliminary dose 5 mg BID</td>
</tr>
<tr>
<td>Recommended phase 2 dose confirmed at 5 mg BID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 3</td>
<td>≥2 to &lt;6 years</td>
<td>Preliminary dose 4 mg/m² BID</td>
</tr>
<tr>
<td>Recommended phase 2 dose confirmed at 4 mg/m² BID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 4</td>
<td>≥28 days to &lt;2 years</td>
<td>—</td>
</tr>
<tr>
<td>Recommended phase 2 dose has not been established yet and will be determined via modeling using PK data from the older age groups (No patients enrolled)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- All patients received **ruxolitinib** as either tablet(s) or liquid pediatric formulation twice daily

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* Physiologically based pharmacokinetic-derived equivalent predicted to yield similar exposure to 10 mg BID adult dose.

BID, twice daily; PK, pharmacokinetic.

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Oral presentation at: 64th ASH Annual Meeting & Exposition; December 10-13, 2022; New Orleans, LA, and virtual
## Patient Disposition

<table>
<thead>
<tr>
<th>Patients enrolled, n (%)</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥12yrs to &lt;18yrs (N=18)</td>
<td>≥6yrs to &lt;12yrs (N=12)</td>
<td>≥2yrs to &lt;6yrs (N=15)</td>
<td>N=45</td>
</tr>
<tr>
<td>Treated</td>
<td>18 (100)</td>
<td>12 (100)</td>
<td>15 (100)</td>
<td>45 (100)</td>
</tr>
<tr>
<td>Completed 24 weeks of treatment</td>
<td>7 (38.9)</td>
<td>5 (41.7)</td>
<td>10 (66.7)</td>
<td>22 (48.9)</td>
</tr>
<tr>
<td>Discontinued ruxolitinib</td>
<td>11 (61.1)</td>
<td>7 (58.3)</td>
<td>5 (33.3)</td>
<td>23 (51.1)</td>
</tr>
</tbody>
</table>

### Reason for ruxolitinib discontinuation

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of efficacy</td>
<td>6 (33.3)</td>
<td>3 (25.0)</td>
<td>3 (20.0)</td>
<td>12 (26.7)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>5 (27.8)</td>
<td>3 (25.0)</td>
<td>2 (13.3)</td>
<td>10 (22.2)</td>
</tr>
<tr>
<td>Disease relapse</td>
<td>0</td>
<td>1 (8.3)</td>
<td>0</td>
<td>1 (2.2)</td>
</tr>
</tbody>
</table>

### Study status, n (%)

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entered long-term follow-up&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8 (44.4)</td>
<td>8 (66.7)</td>
<td>14 (93.3)</td>
<td>30 (66.7)</td>
</tr>
<tr>
<td>Discontinued the study</td>
<td>10 (55.6)</td>
<td>3 (25.0)</td>
<td>1 (6.7)</td>
<td>14 (31.1)</td>
</tr>
</tbody>
</table>

### Reason for study discontinuation

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed</td>
<td>4 (22.2)</td>
<td>2 (16.7)</td>
<td>0</td>
<td>6 (13.3)</td>
</tr>
<tr>
<td>Death</td>
<td>5 (27.8)</td>
<td>1 (8.3)</td>
<td>1 (6.7)</td>
<td>7 (15.6)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Physician decision</td>
<td>1 (5.6)</td>
<td>0</td>
<td>0</td>
<td>1 (2.2)</td>
</tr>
</tbody>
</table>

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<sup>a</sup> Up to month 24; ongoing at the time of data cutoff. Includes patients who had completed the 24-week treatment period and patients who discontinued ruxolitinib treatment before 24 weeks.

<sup>b</sup> Causes of death were adverse event (1 patient; not deemed related to ruxolitinib), study indication (2 patients), underlying disease relapse (2 patients), underlying disease complication (1 patient), and chronic GvHD (1 patient). GvHD, graft vs host disease; n, number of patients with the characteristic; N, number of patients in the treatment group; yrs, years.

### Observations

- **Overall, 45 patients** were treated with ruxolitinib.
- **48.9% of patients** had completed the 24-week treatment period.
- **66.7% of patients** entered long-term follow-up (up to month 24)<sup>a</sup>
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group 1 ≥12yrs to &lt;18yrs N=18</th>
<th>Group 2 ≥6yrs to &lt;12yrs N=12</th>
<th>Group 3 ≥2yrs to &lt;6yrs N=15</th>
<th>All Patients N=45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>13 (72.2)</td>
<td>5 (41.7)</td>
<td>10 (66.7)</td>
<td>28 (62.2)</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>49.2 (12.83)</td>
<td>22.8 (3.06)</td>
<td>15.5 (3.61)</td>
<td>30.9 (17.50)</td>
</tr>
<tr>
<td>Height, mean (SD), cm</td>
<td>157.2 (12.15)</td>
<td>120.0 (4.42)</td>
<td>97.6 (10.05)</td>
<td>127.9 (27.83)</td>
</tr>
<tr>
<td>BSA, mean (SD), m²</td>
<td>1.5 (0.22)</td>
<td>0.9 (0.07)</td>
<td>0.6 (0.10)</td>
<td>1.0 (0.39)</td>
</tr>
<tr>
<td>Steroid-refractory, n (%)</td>
<td>15 (83.3)</td>
<td>6 (50.0)</td>
<td>11 (73.3)</td>
<td>32 (71.1)</td>
</tr>
<tr>
<td>Treatment-naïve, n (%)</td>
<td>3 (16.7)</td>
<td>6 (50.0)</td>
<td>4 (26.7)</td>
<td>13 (28.9)</td>
</tr>
<tr>
<td>aGvHD grade at start of study treatment, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade II</td>
<td>12 (66.7)</td>
<td>8 (66.7)</td>
<td>9 (60.0)</td>
<td>29 (64.4)</td>
</tr>
<tr>
<td>Grade III</td>
<td>5 (27.8)</td>
<td>4 (33.3)</td>
<td>3 (20.0)</td>
<td>12 (26.7)</td>
</tr>
<tr>
<td>Grade IV</td>
<td>1 (5.6)</td>
<td>0</td>
<td>3 (20.0)</td>
<td>4 (8.9)</td>
</tr>
<tr>
<td>aGvHD organ involvement at baseline, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>13 (72.2)</td>
<td>9 (75.0)</td>
<td>12 (80.0)</td>
<td>34 (75.6)</td>
</tr>
<tr>
<td>Liver</td>
<td>2 (11.1)</td>
<td>0</td>
<td>1 (6.7)</td>
<td>3 (6.7)</td>
</tr>
<tr>
<td>Upper GI</td>
<td>3 (16.7)</td>
<td>5 (41.7)</td>
<td>2 (13.3)</td>
<td>10 (22.2)</td>
</tr>
<tr>
<td>Lower GI</td>
<td>6 (33.3)</td>
<td>5 (41.7)</td>
<td>7 (46.7)</td>
<td>18 (40.0)</td>
</tr>
<tr>
<td>CS dose at start of study treatment, mean (SD) (mg/kg/day)</td>
<td>2.1 (1.10)</td>
<td>2.0 (0.69)</td>
<td>1.7 (0.84)</td>
<td>1.9 (0.91)</td>
</tr>
</tbody>
</table>

• The median age was **7.6 years** (range, 2.3–17.4)

• 71.1% (32/45) were steroid-refractory

• 28.9% (13/45) were treatment-naïve

• At study start, the mean CS dose in all patients\(^a\) was 1.9 (SD 0.91) mg/kg/day

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\(^a\) Only patients with non-zero steroid dose are included. aGvHD, acute graft-vs-host disease; BSA, body surface area; CS, corticosteroids; GI, gastrointestinal; n, number of patients with the characteristic; N, number of patients in the treatment group; SD, standard deviation; yrs, years.

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# Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th></th>
<th>Group 1 ≥12yrs to &lt;18yrs</th>
<th>Group 2 ≥6yrs to &lt;12yrs</th>
<th>Group 3 ≥2yrs to &lt;6yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ruxolitinib dose, BID</strong></td>
<td>10 mg</td>
<td>5 mg</td>
<td>4 mg/m²</td>
</tr>
<tr>
<td><strong>AUC$_{\text{last}}$ (h.ng/mL)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>5</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>412 (403)</td>
<td>365 (195)</td>
<td>286 (166)</td>
</tr>
<tr>
<td>G$_{\text{mean}}$ (GCV)</td>
<td>252 (187)</td>
<td>311 (70.2)</td>
<td>249 (56.9)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>358 (45.1–1070)</td>
<td>337 (105–676)</td>
<td>231 (94.8–702)</td>
</tr>
<tr>
<td><strong>C$_{\text{max}}$ (ng/mL)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>5</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>96.3 (68.5)</td>
<td>110 (72.7)</td>
<td>78.1 (58.8)</td>
</tr>
<tr>
<td>G$_{\text{mean}}$ (GCV)</td>
<td>66.1 (170)</td>
<td>90.3 (74.6)</td>
<td>64.0 (67.5)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>102 (9.89–184)</td>
<td>72.5 (36.3–257)</td>
<td>58.4 (31.1–229)</td>
</tr>
<tr>
<td><strong>C$_{\text{trough}}$ (ng/mL)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>6</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>23.8 (42.1)</td>
<td>15.3 (16.8)</td>
<td>8.70 (12.7)</td>
</tr>
<tr>
<td>G$_{\text{mean}}$ (GCV)</td>
<td>8.85 (539)</td>
<td>7.37 (237)</td>
<td>4.79 (225)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>5.18 (0–108)</td>
<td>7.13 (1.26–48.8)</td>
<td>3.44 (0–44.3)</td>
</tr>
</tbody>
</table>

- **Ruxolitinib** exposure ($\text{AUC}_{\text{last}}$ and $\text{C}_{\text{max}}$) was **similar across age groups**
- The **ruxolitinib** starting doses were confirmed as the recommended phase 2 doses for Groups 2 and 3
Overall Response Rate to Ruxolitinib at Day 28
All Patients

In preliminary efficacy analysis, the **ORR at day 28** in all patients was **84.4%**

Efficacy was analyzed once all patients had completed 24 weeks of treatment or discontinued earlier; data cut-off 22 Feb 2022. ORR is defined as the proportion of patients achieving CR or PR. The two-sided 90% CI for the response rate was calculated using Clopper Pearson exact method.

- **Patients, %**
  - **ORR (90%CI)**
  - **PR**
  - **CR**

- **Group 1**
  - ≥12yrs to <18yrs
  - N=18
  - 83.3 (62.3, 95.3)
  - 38.9
  - 44.4

- **Group 2**
  - ≥6yrs to <12yrs
  - N=12
  - 83.3 (56.2, 97.0)
  - 50.0
  - 33.3

- **Group 3**
  - ≥2yrs to <6yrs
  - N=15
  - 86.7 (63.7, 97.6)
  - 66.7
  - 20.0

- **All Patients**
  - N=45
  - 84.4 (72.8, 92.5)
  - 48.9
  - 35.6
Overall Response Rate to Ruxolitinib at Day 28 Treatment-naïve and Steroid-Refractory

<table>
<thead>
<tr>
<th>Treatment-naïve</th>
<th>Steroid-refractory</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=13</td>
<td>N=32</td>
<td>N=45</td>
</tr>
<tr>
<td>ORR (90%CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>69.2 (42.7, 88.7)</td>
<td>90.6 (77.5, 97.4)</td>
<td>84.4 (72.8, 92.5)</td>
</tr>
<tr>
<td>CR (%)</td>
<td>PR (%)</td>
<td>ORR (%)</td>
</tr>
<tr>
<td>15.4</td>
<td>43.8</td>
<td>35.6</td>
</tr>
<tr>
<td>53.8</td>
<td>46.9</td>
<td>48.9</td>
</tr>
</tbody>
</table>

• ORR at day 28 was:
  - 69.2% among treatment-naïve patients
  - 90.6% among steroid-refractory patients
  - Pediatric patients who are resistant to steroids will still benefit from ruxolitinib treatment

Efficacy was analyzed once all patients had completed 24 weeks of treatment or discontinued earlier; data cut-off 22 Feb 2022. ORR is defined as the proportion of patients achieving CR or PR. The two-sided 90% CI for the response rate was calculated using Clopper Pearson exact method.
Efficacy was analyzed once all patients had completed 24 weeks of treatment or discontinued earlier; data cut-off 22 Feb 2022. ORR is defined as the proportion of patients achieving CR or PR. Durable ORR at day 56 is defined as the proportion of patients who achieved a CR or PR at day 28 and maintained a CR or PR at day 56. The two-sided 90% CI for the response rate was calculated using Clopper Pearson exact method.

CI, confidence interval; CR, complete response; n, number of patients with the specified response; N, number of patients in the treatment group; ORR, overall response rate; PR, partial response; yrs, years.

• In preliminary efficacy analysis, the **durable ORR at day 56** in all patients was **66.7%**
Durable Overall Response Rate to Ruxolitinib at Day 56
Treatment-naïve and Steroid-Refractory

Efficacy was analyzed once all patients had completed 24 weeks of treatment or discontinued earlier; data cut-off 22 Feb 2022. ORR is defined as the proportion of patients achieving CR or PR. The two-sided 90% CI for the response rate was calculated using Clopper Pearson exact method.

CI, confidence interval; CR, complete response; n, number of patients with the specified response; N, number of patients in the treatment group; ORR, overall response rate; PR, partial response.

- Durable ORR at day 56 was:
  - 61.5% among **treatment-naïve** patients
  - 68.8% among **steroid-refractory** patients
## Ruxolitinib Dose Change or Interruption

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥12yrs to &lt;18yrs</td>
<td>≥6yrs to &lt;12yrs</td>
<td>≥2yrs to &lt;6yrs</td>
<td>N=45</td>
</tr>
<tr>
<td>N=18</td>
<td>N=12</td>
<td>N=15</td>
<td></td>
</tr>
<tr>
<td>At least one dose change or interruption, n (%)</td>
<td>15 (83.3)</td>
<td>11 (91.7)</td>
<td>12 (80.0)</td>
</tr>
<tr>
<td>At least one dose change</td>
<td>15 (83.3)</td>
<td>9 (75.0)</td>
<td>12 (80.0)</td>
</tr>
<tr>
<td>At least one dose interruption</td>
<td>9 (50.0)</td>
<td>4 (33.3)</td>
<td>5 (33.3)</td>
</tr>
</tbody>
</table>

**Common reasons for at least one dose change or interruption, n (%)**

<table>
<thead>
<tr>
<th>Reason</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event</td>
<td>11 (61.1)</td>
<td>5 (41.7)</td>
<td>7 (46.7)</td>
<td>23 (51.1)</td>
</tr>
<tr>
<td>Dose tapering (permitted per protocol)</td>
<td>6 (33.3)</td>
<td>5 (41.7)</td>
<td>9 (60.0)</td>
<td>20 (44.4)</td>
</tr>
<tr>
<td>Per protocol dose change or interruption</td>
<td>5 (27.8)</td>
<td>3 (25.0)</td>
<td>6 (40.0)</td>
<td>14 (31.1)</td>
</tr>
</tbody>
</table>

- In total, **38 (84.4%)** patients had at least one ruxolitinib dose change or interruption.
- The most common reasons for ruxolitinib dose change or interruption were **adverse events** and **per protocol dose tapering or dose change/interruption**.

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*Patients may have had multiple dose changes or interruptions for different reasons and are counted as separate events; b Ruxolitinib dose taper could start at day 56 for patients with a day 28 response.*
Safety

- **No new safety signals were observed**, and the most frequently reported adverse events were in line with those previously observed in ruxolitinib clinical trials
  - Per protocol, detailed safety data will be reported following study completion in February 2023
- **There were no confirmed cases of graft failure**
Ruxolitinib exposure was similar across age groups and the PK parameters were in the range of those previously reported in REACH23

In phase 1, the RP2D of ruxolitinib of 5 mg and 4 mg/m² BID, as predicted by PBPK, were confirmed in Groups 2 and 3, respectively

Among all patients, ruxolitinib treatment led to:

- High ORR at day 28 of 84.4% (90% CI: 72.8, 92.5)
- Durable ORR at day 56 of 66.7% (90% CI: 65.2, 89.1)

The ORR observed in REACH4 are comparable to those previously reported in REACH23 and from retrospective studies of ruxolitinib-treated pediatric patients5,6

The safety profile was also consistent with that expected for ruxolitinib in this population

CI, confidence interval; ORR, overall response rate; PBPK, physiologically based pharmacokinetic; RP2D, recommended phase 2 dose.
Acknowledgments

- The authors would like to thank the patients enrolled in this study and their families, as well as all the participating investigators and their site teams.

- Medical writing support was provided by Helen Findlow, PhD, of Novartis Pharmaceuticals UK, which was funded by Novartis Pharmaceuticals in accordance with Good Publication Practice (GPP) 2022 guidelines (www.ismpp.org/gpp-2022).

- This study is sponsored by Novartis Pharma AG.

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References

Thank you
Supplementary Slides
Study Design

**Screening Period (up to 28 days)**

- **Enrollment**
  - Treatment-naïve and steroid-refractory grade II-IV aGvHD
  - Patients were enrolled into treatment groups based on age to allow appropriate dosing
  - Before treatment initiation, aGvHD organ staging is graded using the Mount Sinai criteria

**Treatment Period (24 weeks)**

- **All patients received ruxolitinib plus CS ± CNI for 24 weeks or until discontinuation**
- **Phase 1**
  - Ruxolitinib taper could start at day 56 for patients with a day 28 response
  - CS taper could start from week 1 visit date in patients demonstrating a PR or CR
  - CNI taper was permitted in patients who had completed CS taper and had a PR or CR
- **Phase 2**
  - Taper\(^b\) (DS6 to Wk 24)
  - Taper/aGvHD flare\(^c\) (24 wks)

**Follow-up Period (18 months)**

- EOT/Safety follow-up\(^a\)
- Long-term follow-up

**Day 1 - 28 days**

- 28 days
- 24 weeks
- 12 months
- 18 months
- 24 months

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**Study Design**

- **Ruxolitinib** taper could start at day 56 for patients with a day 28 response
  - **CS taper** could start from week 1 visit date in patients demonstrating a PR or CR
  - **CNI taper** was permitted in patients who had completed CS taper and had a PR or CR
- **PK data** were analyzed at the time of confirming the RP2D of ruxolitinib
- **Efficacy data** were analyzed once all patients had completed 24 weeks of treatment or discontinued earlier (data cut-off 22 February 2022)
- **Safety data** were analyzed to support regular safety monitoring and are from the latest review
- At data cut-off (22 February 2022), the observed median duration of ruxolitinib exposure was 117 days (range 8.0–342.0)
# Objectives and Endpoints

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>Objective</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Primary objective</strong></td>
<td><strong>Primary endpoint</strong></td>
</tr>
</tbody>
</table>
|         | • To assess PK parameters of ruxolitinib, and define an age-appropriate recommended phase 2 dose | • PK parameters (AUC, $C_{\text{max}}$, $C_{\text{trough}}$)  
• Determination of an age-appropriate recommended phase 2 dose based on observed PK parameters |

<table>
<thead>
<tr>
<th>Phase 2</th>
<th>Objective</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Primary objective</strong></td>
<td><strong>Primary endpoint</strong></td>
</tr>
<tr>
<td></td>
<td>• To measure the activity of ruxolitinib</td>
<td>• ORR to ruxolitinib at day 28</td>
</tr>
<tr>
<td></td>
<td><strong>Key secondary objective</strong></td>
<td><strong>Key secondary endpoint</strong></td>
</tr>
<tr>
<td></td>
<td>• To assess the rate of durable ORR at day 56</td>
<td>• Proportion of patients who achieved a response (CR or PR) at day 28 and maintained a response at day 56</td>
</tr>
</tbody>
</table>

*ORR is defined as the proportion of patients achieving CR or PR.*

*AUC, area under curve; $C_{\text{max}}$, maximum concentration; $C_{\text{trough}}$, minimum concentration; CR, complete response; PK, pharmacokinetic; PR, partial response; ORR, overall response rate.*
## Ruxolitinib Dose

<table>
<thead>
<tr>
<th>Age</th>
<th>Ruxolitinib Starting Dose</th>
<th>Confirmed Phase 2 Ruxolitinib Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 ≥12 to &lt;18 years</td>
<td>Not applicable</td>
<td>Group 1 adolescent patients are enrolled directly at <strong>ruxolitinib</strong> 10 mg BID; the dose used in REACH2³</td>
</tr>
<tr>
<td>Group 2 ≥6 to &lt;12 years</td>
<td>Preliminary dose 5 mg BIDᵃ</td>
<td>Recommended phase 2 dose confirmed at <strong>5 mg BID</strong></td>
</tr>
<tr>
<td>Group 3 ≥2 to &lt;6 years</td>
<td>Preliminary dose 4 mg/m² BIDᵃ</td>
<td>Recommended phase 2 dose confirmed at <strong>4 mg/m² BID</strong></td>
</tr>
<tr>
<td>Group 4 ≥28 days to &lt;2 years</td>
<td>—</td>
<td><strong>Recommended phase 2 dose</strong> has not been established yet and will be determined via modeling using PK data from the older age groups (No patients enrolled)</td>
</tr>
</tbody>
</table>

- Pharmacokinetic predictions in pediatric patients with aGvHD were based on the observed **ruxolitinib** pharmacokinetic profile in adults.
- Preliminary doses for pediatric patients were selected to match the observed **ruxolitinib** exposure in adults treated with a dose of 10 mg BID.
- All patients received **ruxolitinib** as either tablet(s) or liquid pediatric formulation twice daily.

ᵃ Physiologically based pharmacokinetic-derived equivalent predicted to yield similar exposure to 10 mg BID adult dose.

aGvHD, acute graft-vs-host disease; BID, twice daily; PK, pharmacokinetic.
Efficacy was analyzed once all patients had completed 24 weeks of treatment or discontinued earlier; data cut-off 22 Feb 2022. ORR is defined as the proportion of patients achieving CR or PR. The two-sided 90% CI for the response rate was calculated using Clopper Pearson exact method.

CI, confidence interval; CR, complete response; n, number of patients with the specified response; N, number of patients in the treatment group; ORR, overall response rate; PR, partial response; y, year.
Durable Overall Response Rate at Day 56 to Ruxolitinib Treatment-Naïve and Steroid-Refractory

Efficacy was analyzed once all patients had completed 24 weeks of treatment or discontinued earlier; data cut-off 22 Feb 2022. ORR is defined as the proportion of patients achieving CR or PR. Durable ORR at day 56 is defined as the proportion of patients who achieved a CR or PR at day 28 and maintained a CR or PR at day 56. The two-sided 90% CI for the response rate was calculated using Clopper Pearson exact method.

CR, complete response; n, number of patients with the specified response; N, number of patients in the treatment group; ORR, overall response rate; PR, partial response; yrs, years.

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