Background

Mmotelitinib (MMB) is a potent JAK1, JAK2 and ACRV1 inhibitor, previously investigated in the two SIMPLIFY Phase 3 studies. This unique profile results in demonstrable clinical activity against each of the three hallmark features of myelofibrosis (MF), anemia, constitutional symptoms and splenomegaly, across the continuum of JAKi-naïve and previously JAKi-treated patients with intermediate/high risk MF. MMB’s favorable hematological profile and anemia benefit facilitated sustained dose intensity (DI) and prolonged clinical activity, in contrast to ruxolitinib (RUX) where progressive dose reductions due to induced or exacerbated myelosuppression are common.

A companion analysis of the long-term safety of MMB during the SIMPLIFY studies is presented on poster #EP1113.

Aims

This analysis was conducted to:
1. Characterize MMB dose intensity (DI) versus RUX in the previously conducted SIMPLIFY Phase 3 studies;
2. Investigate MMB DI in patients switching from RUX to MMB, and;
3. Quantify dose modifications for both compounds.

Results

High MMB Dose Intensity is Maintained Throughout the 24-Week Study and Beyond

- 100% of patients randomized to MMB in S1 commenced dosing at its maximum recommended dose of 200 mg QD.
- MMB was maintained during the 24W RT period, with 88.6% of MMB patients receiving a daily dose between 151 - 200 mg at the end of the RT period. The mean MMB daily dose over this period was 188.4 mg (94.2% of the maximum dose).
- High MMB DI continued during the ET period, with over 85% of patients receiving a mean daily dose between 151 - 200 mg throughout the extended treatment period.
- The overall mean daily dose of MMB for the ET period was 183.3 mg (90% of the maximum dose).

RUX Requires Progressive Dose Reductions Resulting in Reduced Dose Intensity While MMB Dose Intensity is Maintained Following Crossover

- Only 58.8% of RUX randomized patients received the maximum per label 20 mg BID dose at treatment initiation, due to RUX’s platelet-dictated dose schema.
- Despite these attenuated starting doses, progressive RUX dose-reductions as a consequence of toxicity or intolerance (commonly, induced or exacerbated myelosuppression) were still observed, with only 36.9% of patients receiving the 20/25 mg BID dose by the end of the 24W RT period (31 - 40 and 50 mg daily groups).
- The mean daily RUX dose across the 24W RT period was 28.0 mg.
- Notably, patients who switched from RUX to MMB in the ET period achieved high MMB DI in the first week (88.8% within 150 - 200 QD), despite the preponderance of RUX dose reductions during the prior 24W RT period.
- MMB’s high DI was maintained throughout the ET period with a mean daily MMB dose of 274.6 mg (87.3% of MMB maximum dose).

Conclusions

- MMB’s differentiated pharmacological and clinical profile facilitated robust and sustained DI throughout the Phase 3 SIMPLIFY studies across the continuum of JAKi-naïve and previously JAKi-treated patients, including those with significant disease-related myelosuppression and prior RUX-induced hematological toxicity.
- These findings contrast with the data for RUX where attenuated platelet-dictated starting doses and substantive rates of dose reduction due to induced or exacerbated myelosuppression lead to a loss of dose intensity in both studies. Importantly, a significant proportion of patients who switched from RUX to MMB, including those patients receiving markedly reduced RUX doses, went on to receive full-dose MMB over an extended period, confirming MMB’s ability to address the unmet need in patients with RUX-induced hematological toxicity and/or progressive underlying loss of hematopoietic capacity.
- These data are consistent with the favorable tolerability and long-term safety analysis of MMB presented on poster #EP1113 and in totality demonstrates molotiginib’s differentiated clinical profile.

Clinical Relevance

- Sustained DI is an important characteristic of extended MMB therapy in the S1 and S2 studies in JAKi naïve and prior JAKi-treated patients, consistent with the compound’s favorable safety profile and demonstrable anemia benefits.
- MMB’s sustained DI facilitates ongoing control of the cardinal features of MF, including reduction in constitutional symptoms, resolution of splenomegaly and improved hemoglobin associated with a suite of anemia benefits, which contrast markedly with the currently approved myelosuppressive JAK inhibitors.
- Patients who switch from RUX to MMB see an immediate and sustained improvement in therapeutic DI, suggesting that MMB may be the optimal MF therapy in patients experiencing hematological toxicity and disease-related myelosuppression.
- The ongoing MOMENTUM Phase 3 clinical study (NCT04173414) is designed to confirm the efficacy of molotitinib on myelofibrosis symptoms, transfusion independence and splenomegaly in symptomatic, anemic MF patients previously treated with a JAKi.