Matching-Adjusted Indirect Comparison (MAIC) of Pelabresib (CPI-0610) in Combination With Ruxolitinib vs Ruxolitinib or Fedratinib Monotherapy in Patients With Intermediate- or High-risk Myelofibrosis

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Background

- JAKis ruxolitinib and fedratinib are the current standard of care in higher-risk MF patients with platelets ≥50 × 10^9/L and ineligible for allogeneic stem cell transplant.[1] Ruxolitinib, fedratinib and momelotinib have demonstrated splenic responses and symptom improvement in pivotal Phase 3 trials[2–5]
- Despite clinical success with JAKi therapy, unmet medical need still exists due to:
  - <50% of patients achieving a spleen response (SVR35 response rates of 29–42% at Week 24 in previous pivotal studies of ruxolitinib or fedratinib)[2–4,6]
  - <50% of patients achieving total symptom score reduction (TSS50 rates of 34–46% in previous pivotal studies of ruxolitinib or fedratinib)[2,4,6]
  - Progressive disease and toxicity, which frequently lead to JAKi discontinuation[7]
- Pelabresib (CPI-0610) is an investigational, oral, small-molecule BET inhibitor, and preclinical data have indicated that combined JAK/BET inhibition can lead to synergistic effects in MF[8]
- The combination of pelabresib with ruxolitinib showed encouraging responses in SVR35 (68% at Week 24) and TSS50 (56% at Week 24), and was generally well tolerated in JAKi treatment-naïve patients with intermediate- or high-risk MF in Arm 3 of the open-label Phase 2 MANIFEST study (NCT02158858)[9]
- In the absence of head-to-head data comparing this combination with JAKis, MAIC analysis was used to compare data from MANIFEST with the following randomized, double-blind Phase 3 JAKi studies
  - COMFORT-I (NCT00952289) compared oral ruxolitinib BID (n=155) with placebo (n=154),[2] and COMFORT-II (NCT00934544) compared ruxolitinib (n=146) or best available therapy (n=73),[3] both in patients with primary MF, post-PV MF or post-ET MF[2,3]
  - JAKARTA (NCT01437787), comparing oral fedratinib 400 mg QD (n=96) or 500 mg (n=97) with placebo (n=96) in patients with intermediate-2 or high-risk primary MF, post-PV MF or post-ET MF[4]
  - SIMPLIFY-1, a noninferiority trial comparing momelotinib 200 mg QD (n=104) with ruxolitinib BID in JAKi-naïve patients with high-risk, intermediate-2 risk or symptomatic intermediate-1 risk MF[6]

Objective

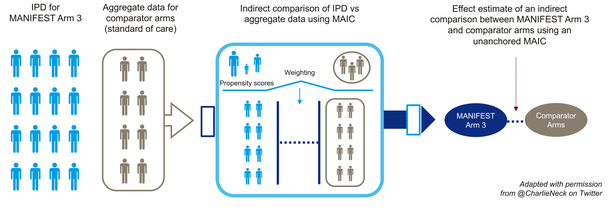
- To compare SVR35 and TSS50 response rates of pelabresib in combination with ruxolitinib vs JAKi monotherapy in the MF setting via unanchored MAIC analysis

Rationale

- No direct comparative data exist between pelabresib with ruxolitinib and JAKi monotherapy
- Indirect data comparisons are subject to bias due to cross-trial differences
- MAIC analysis adjusts for differences in baseline characteristics and is an attractive method for indirect treatment comparison using individual patient-level data (IPD) from one study vs aggregate study-level data (ASD) from comparator studies

Methods

Overview of MAIC Methodology



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Methods

Data Sources

- MANIFEST Arm 3: open-label, Phase 2 study in JAKi-naïve adult patients treated with pelabresib and ruxolitinib
- Four comparator studies: randomized, double-blind Phase 3 studies in JAKi-naïve adult patients (≥18 years) with primary or secondary MF
  - COMFORT-I: ruxolitinib monotherapy
  - COMFORT-II: ruxolitinib monotherapy
  - JAKARTA: fedratinib (400 mg and 500 mg) monotherapy
  - SIMPLIFY-I: ruxolitinib monotherapy, momelotinib monotherapy
- IPD were available for MANIFEST Arm 3, while published ASD were available for COMFORT-I and II, SIMPLIFY-1 and JAKARTA

MAIC Analysis

- Matching 8 prognostic factors/effect modifiers
  - Gender, MF subtype, IPSS risk status, previous hydroxyurea use, platelet count, hemoglobin levels, spleen volume and *JAK2V617F* status
- Handling of missing values
  - IPSS Int-1:
    - MANIFEST and SIMPLIFY-1 included patients with IPSS Int-1; COMFORT I and II and JAKARTA did not
    - **IPT:** IPSS Int-1 were excluded from MANIFEST prior to matching
    - **mITT:** IPSS Int-1 were included and combined with IPSS Int-2
  - Patients with missing values (3 pts with missing MF subtype and 1 pt with missing platelet) for the matching prognostic factors at baseline were excluded both from ITT and mITT
  - Two patients in MANIFEST Arm 3 with missing baseline TSS and TSS=0 at baseline were included as nonresponders
- Development of weighted study populations
  - Given the absence of a connected network of treatment arms, an unanchored MAIC analysis was performed
  - Weights were estimated to match IPD with the summary statistics (eg mean or median, proportions) for the 8 prognostic factors
  - The effective sample size (ESS) derived from the weights represents the number of independent nonweighted individuals who would be required to provide an estimate with the same precision as the weighted sample estimate

Outcomes of Interest

- Response rate ratios (RRR) for SVR35 and TSS50 at Wk 24
  - RRR = RR in MANIFEST Arm 3/RR in comparator arm
- RRRs before and after weighting were estimated
  - 95% confidence intervals were estimated using robust sandwich estimators for variance
- RRR >1 indicates that MANIFEST Arm 3 has a higher RR than comparator arms

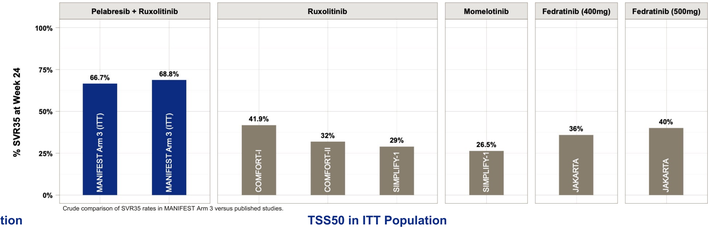
Results

Baseline Characteristics

- MAIC resulted in complete balance for all categorical baseline characteristics and a high degree of balance for continuous baseline characteristics for both ITT and mITT
- The maximum difference in medians for continuous baseline characteristics observed in any comparison was 29 cells/µl for platelet count, 0.2 g/L for hemoglobin and 191 cm^3 for spleen volume in ITT, and 20 cells/µl for platelet count, 0.2 g/L for hemoglobin and 191 cm^3 for spleen volume in mITT

Effective Sample Size

- mITT: When IPSS Int-1 patients were included, sufficiently high ESS values were obtained (Figure 2)
- ITT: Excluding IPSS Int-1 patients resulted in smaller ESS and in some cases loss of statistical significance (Figures 3 and 4)



Crude comparison of SVR35 rates in MANIFEST Arm 3 versus published studies.

SVR35 in mITT Population

- Adjusting for differences, statistically significant and clinically meaningful adjusted RRRs were observed for comparisons of pelabresib combined with ruxolitinib versus all comparators for mITT (Figure 2)

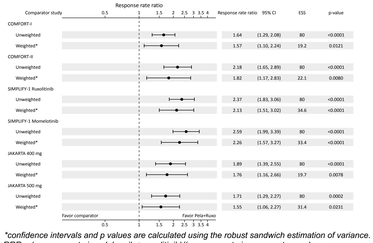
SVR35 in ITT Population

- RRRs >1 were observed for comparisons of MANIFEST Arm 3 versus all comparators for ITT (Figure 3)

TSS50 in ITT Population

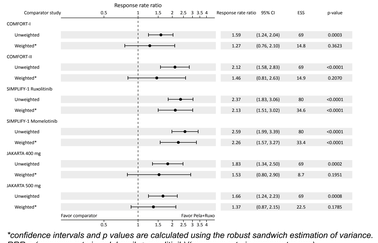
- Adjusting for differences, RRRs >1 were observed for comparisons of MANIFEST Arm 3 versus all comparators (Figure 4)

Figure 2: Forest Plot of SVR35 Response Rate Ratios in mITT (including pts with IPSS Int-1)



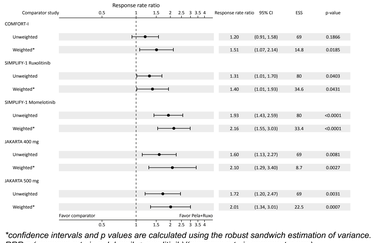
**confidence intervals and p values are calculated using the robust sandwich estimation of variance.*
RRR = (response rate in pelabresib + ruxolitinib)/(response rate in comparator arm)

Figure 3: Forest Plot of SVR35 Response Rate Ratios in ITT (excluding pts with IPSS Int-1)



**confidence intervals and p values are calculated using the robust sandwich estimation of variance.*
RRR = (response rate in pelabresib + ruxolitinib)/(response rate in comparator arm)

Figure 4: Forest Plot of TSS50 Response Rate Ratios in ITT (excluding pts with IPSS Int-1)



**confidence intervals and p values are calculated using the robust sandwich estimation of variance.*
RRR = (response rate in pelabresib + ruxolitinib)/(response rate in comparator arm)

Conclusions

- The combination of pelabresib and ruxolitinib in Arm 3 of the the Phase 2 MANIFEST trial showed encouraging results; the MAIC analysis was performed to contextualize these results by accounting for differences in baseline characteristics in an indirect comparison with results from four Phase 3 studies
- In this MAIC analysis, a high degree of balance was obtained in 8 clinically important prognostic factors in order to minimize the potential for unknown confounding, a limitation of MAIC methodology
- Results of the analysis indicate potentially improved efficacy of the combination of pelabresib and ruxolitinib versus ruxolitinib, fedratinib (currently approved) and momelotinib (investigated in 1L) monotherapy for both spleen and symptom responses, as seen in crude cross-trial comparisons
- Similar results were obtained in ITT and mITT (ie including or excluding patients with IPSS Int-1)
  - Excluding IPSS Int-1 pts resulted in lower ESS and thus loss of statistical significance in some comparisons, though similar RRRs were estimated including or excluding IPSS Int-1 pts
- This MAIC analysis provides further evidence to support a potentially higher efficacy rate of pelabresib and ruxolitinib in combination versus JAKi monotherapy
  - There is a need to improve on the current standard of care, and this combination may indicate a potential opportunity for improved outcomes
- The randomized, Phase 3 MANIFEST-2 study of pelabresib with ruxolitinib versus ruxolitinib monotherapy in JAKi treatment-naïve patients is currently ongoing (NCT04603495)

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ABBREVIATIONS: 1L, first line; ASD, aggregate study-level data; BET, bromodomain and extraterminal domain; BID, twice-daily; CI, confidence interval; CT, computed tomography; DIPSS, Dynamic International Prognostic Scoring System; ESS, effective sample size; ET, essential thrombocythemia; Int, Intermediate; IPSS, International Prognostic Scoring System; IPD, individual patient-level data; ITT, intent-to-treat; JAK, Janus kinase; JAKi, Janus kinase inhibitor; MAIC, matching-adjusted indirect comparison; MF, myelofibrosis; MFSAF, Myelofibrosis Symptom Assessment Form; mITT, modified intent-to-treat; pela, pelabresib; pt, patient; PV, polycythemia vera; QD, once-daily; RR, response rate; RRR, response rate ratio; ruxo, ruxolitinib; SVR35, ≥35% spleen volume reduction from baseline; TSS, total symptom score; TSS50, ≥50% total symptom score reduction from baseline; wk, week.