

ASCEMBL Phase 3 Health-Related Quality of Life Comparison of Asciminib and Bosutinib for Patients with Chronic Myelogenous Leukemia in Chronic Phase, Previously Treated with 2 or More Tyrosine Kinase Inhibitors

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KEY FINDINGS & CONCLUSIONS

- Mean baseline MDASI-CML scores indicated in general a low impact of CML in HRQL; mean scores around 2 in a scale ranging from 0 to 10 with higher scores indicating more severity/interference
- Fatigue and feeling upset were the most common baseline symptoms. Mean baseline scores were higher for distress items, with impact on work, mood, and general activity contributing to overall symptom distress
- Symptoms improved after treatment with asciminib (up to 24 weeks of treatment), particularly fatigue, feeling upset, and mood. In contrast some symptoms worsened after treatment with bosutinib, with the greatest deterioration seen in nausea and diarrhea
- The low baseline scores prevented identification of clinically meaningful changes; however, the difference between treatment arms for all but two items was in favor of asciminib compared to bosutinib, particularly for nausea and diarrhea
- Further work is needed to better characterize HRQL for patients in later lines of therapy
- **In conclusion, asciminib patients showed improvement in treatment-related symptoms and HRQL compared with baseline and relative to bosutinib, within the first 24 weeks of treatment**

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INTRODUCTION

- Despite availability of current adenosine triphosphate (ATP)-competitive tyrosine kinase inhibitor (TKI) therapy, most patients with chronic myelogenous leukemia in chronic phase (CML-CP) on 3+ line treatment do not achieve an adequate response, and many experience poor tolerability and deteriorated health-related quality of life (HRQL)
- Asciminib is a first-in-class potent and specific BCR-ABL1 inhibitor that specifically targets the ABL1 myristoyl pocket (STAMP), as opposed to the ATP-binding site
- ASCEMBL, the first randomized controlled study comparing treatments for resistant/intolerant CML-CP, demonstrated that asciminib has a superior efficacy and an improved safety profile compared with bosutinib, with the major molecular response rate at 24 weeks meeting the primary endpoint (treatment difference after adjustment for MCyR^{*} = 12.2%, p=0.029)¹
- The goal of this study was to evaluate the HRQL impact of asciminib compared with bosutinib at 24 weeks of treatment, to understand treatment benefit from the patient perspective

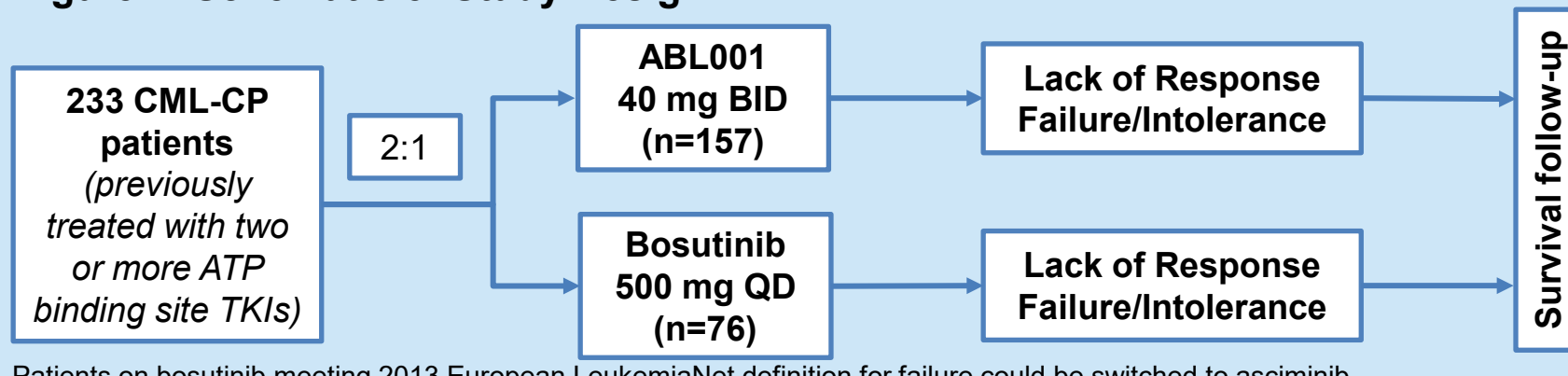
*MCyR = major cytogenetic response

METHODS

Study Design

- ASCEMBL is a phase 3, multi-center, open-label, randomized clinical trial (**Figure 1**)
- A total of 157 patients were randomized to asciminib 40mg twice-daily and 76 patients were randomized to bosutinib 500mg once-daily

Figure 1. Schematic of Study Design



Patients on bosutinib meeting 2013 European LeukemiaNet definition for failure could be switched to asciminib. During the switch phase, ePROs are not administered

RESULTS

PRO Completion Rate

- The completion rate for the MDASI-CML at baseline was 96% for asciminib and 92% for bosutinib
- MDASI-CML completion rates for both treatment arms were high, remaining >80% out of the expected population throughout the first 24 weeks of treatment (**Table 1**)

Table 1. MDASI-CML Completion Rate

Timepoint	Completion rate (out of expected population)	
	Asciminib	Bosutinib
Baseline	151/157 (96.2%)	70/76 (92.1%)
4	140/152 (92.1%)	65/72 (90.3%)
8	132/149 (88.6%)	61/68 (89.7%)
12	126/143 (88.1%)	55/65 (84.6%)
16	118/140 (84.3%)	50/60 (83.3%)
24	108/130 (83.1%)	41/50 (82.0%)

Baseline PRO Scores

- Mean MDASI-CML total symptom score (mean of 20 symptom items) was 2.0 at baseline
- Fatigue (4.0) was the most severe symptom at baseline (**Figure 2**)
- Mean MDASI-CML symptom distress score (mean of 6 interference items) was 2.3 at baseline
- Work (2.7) was the daily life activity most impacted by symptoms at baseline (**Figure 3**)

Figure 2. MDASI-CML Mean Baseline Symptom Scores (both treatment arms, N=207)

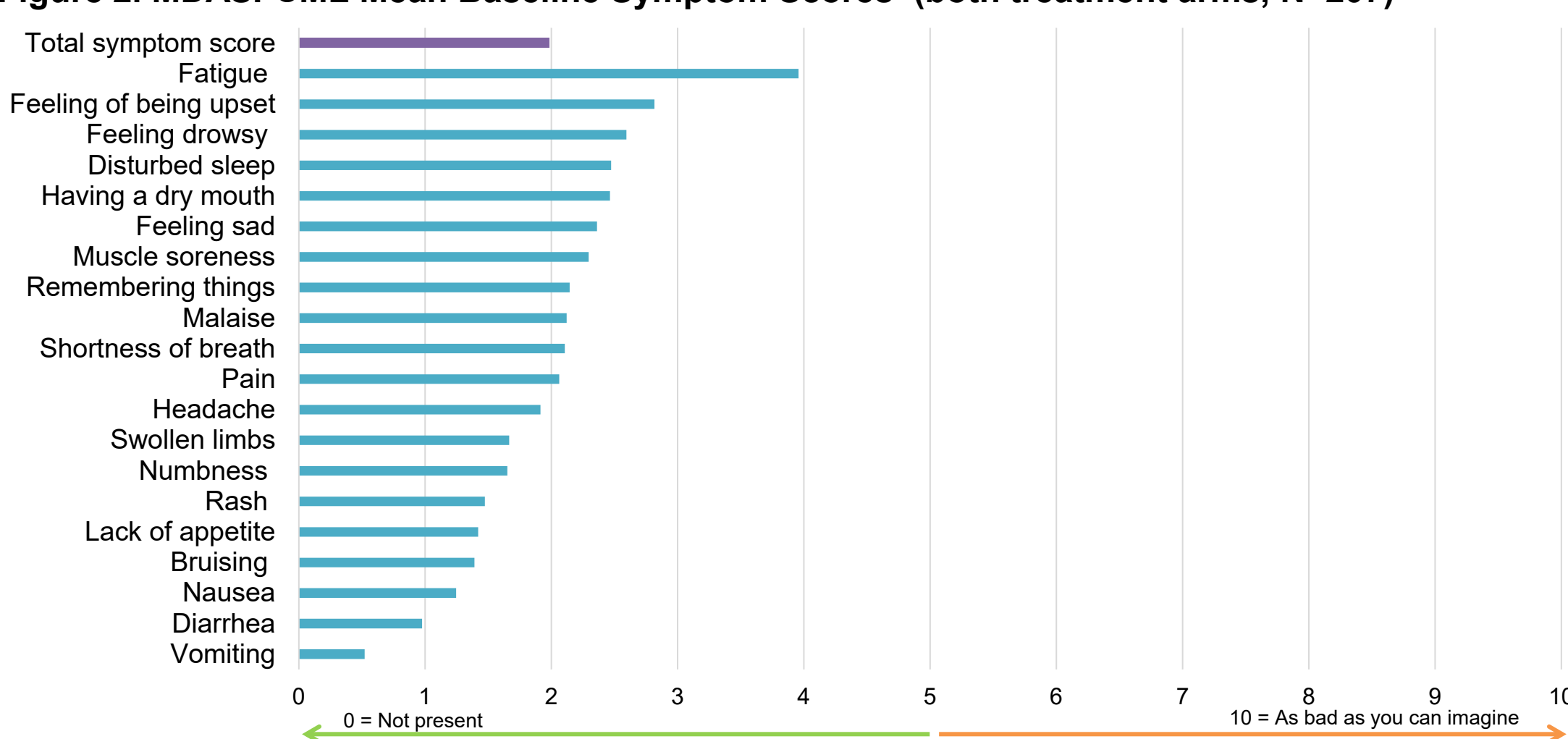
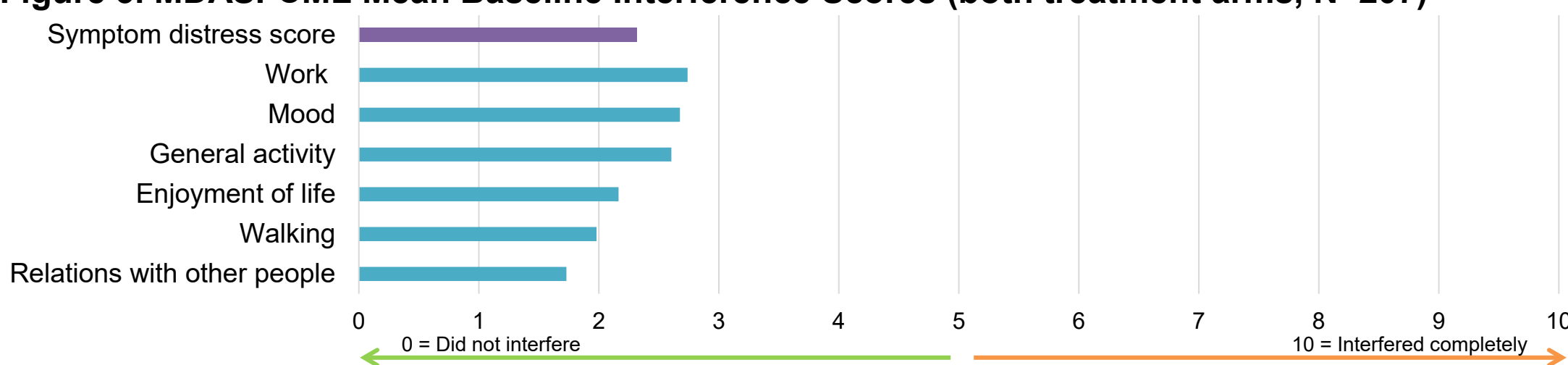


Figure 3. MDASI-CML Mean Baseline Interference Scores (both treatment arms, N=207)



MMRM: Least Squares (LS) Mean Changes from Baseline

- LS mean overall changes from baseline for MDASI-CML symptom items and interference items are presented in **Figures 4 and 5**, respectively
- LS mean changes from baseline showed that MDASI-CML symptoms improved after treatment with asciminib (up to 24 weeks of treatment)
 - Asciminib patients maintained or improved from baseline on all items (demonstrating improvement on 21 out of 26 items), total symptom score, and symptom distress score
 - Most notable improvements in fatigue, feeling upset, and mood
- In contrast, bosutinib patients remained stable or deteriorated in all but four items
 - Deteriorations in diarrhea, nausea, vomiting, and lack of appetite
- LS mean changes from baseline were small and improvements did not meet the clinically meaningful threshold, but there is a clear pattern of improvement in all symptom and interference items after treatment with asciminib relative to bosutinib (with the exception of bruising and walking)
- When LS mean changes from baseline were plotted over time, the scores remained relatively stable from Week 4 to Week 24, with no clinically meaningful changes from baseline in either treatment arm at any timepoint

Figure 4. MDASI-CML MMRM Overall LS Mean Change from Baseline (95% CIs): Symptom Items

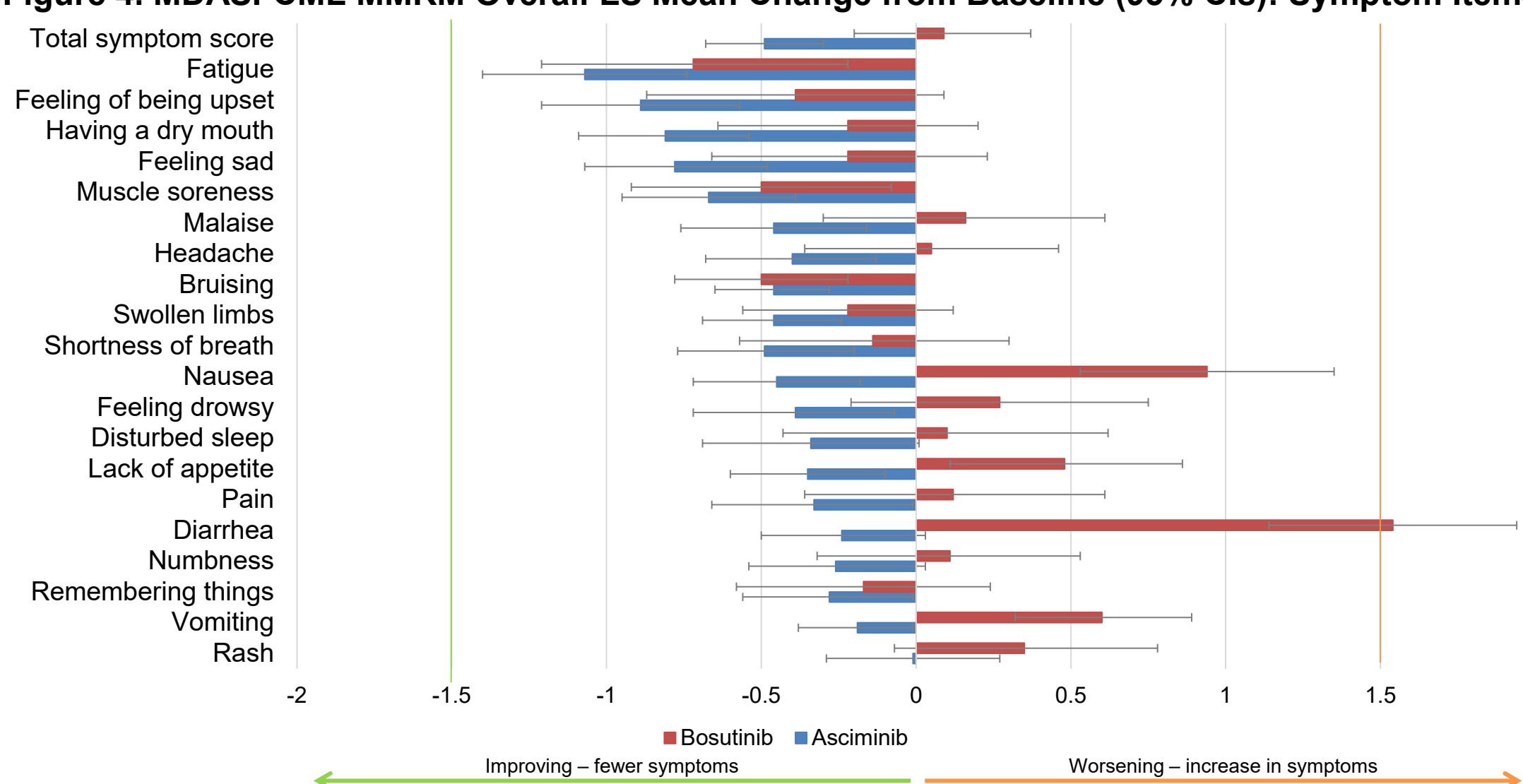
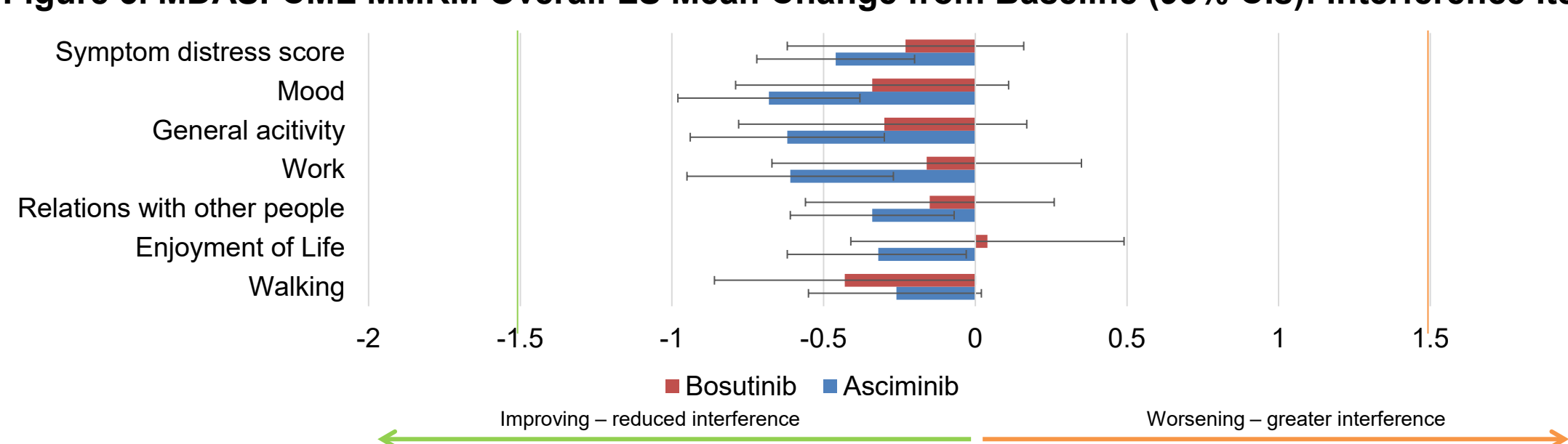


Figure 5. MDASI-CML MMRM Overall LS Mean Change from Baseline (95% CIs): Interference Items

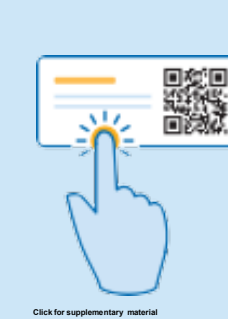


Patient-reported Outcomes (PROs)

- Patient-reported HRQL was assessed as an exploratory endpoint using the M.D. Anderson Symptom Inventory – Chronic Myeloid Leukemia (MDASI-CML) at screening/baseline and weeks 4, 8, 12, 16, 24, 36, 48, and 96 whilst patients remained in the study
 - Data up to week 24 were included in the current analysis
- The MDASI-CML is a 26-item self-administered questionnaire for adult CML patients capturing 20 items relating to severity of disease-related symptoms and 6 items relating to symptom interference with daily life^{2,3}
 - Items are scored from 0 to 10 with higher scores indicating more severity/interference
 - A symptom severity score is the mean of the 20 symptom items, and a symptom distress score is mean of the 6 interference items
 - A clinically meaningful difference in change in score of 1.5 points was used for interpretation for changes in score
- Other PRO instruments collected in the trial as exploratory endpoints included the five-level EQ-5D (EQ-5D-5L), Work Productivity and Activity Impairment (WPAI) questionnaire, and Patient Global Impression of Change (PGIC)

Analyses

- The completion rate of PRO instruments was summarized out of the expected population at each visit and used to assess missing data
- For each of the PRO scales, analysis of change from baseline and difference between treatments was conducted using a mixed-effects model for repeated measures (MMRM), using PRO data up to week 24
 - Baseline PRO score, stratification factor (cytogenetic response), treatment arm, study visit, and interaction of treatment arm and study visit were included in the models as fixed effects
 - Subject was included as a repeated effect
 - An unstructured covariance matrix was used
- MMRM analysis population included patients with change from baseline scores (i.e., patients with baseline and at least one post-baseline assessment)
- Analyses reported herein are focused on the MDASI-CML



MMRM: LS Mean Differences between Treatments

- There was a difference in overall LS means between treatments in favor of asciminib compared to bosutinib for the following MDASI-CML scores:
 - Total symptom score
 - Symptoms of nausea, feeling drowsy, feeling sad, dry mouth, vomiting, diarrhea, lack of appetite, and malaise
- The difference between treatments was clinically meaningful for diarrhea, and almost reached the clinically meaningful threshold for nausea (**Figure 6**)
- Although there was a trend for improvements in symptom distress items for asciminib compared to bosutinib, the LS mean between-treatment differences were not clinically meaningful (**Figure 7**)

Figure 6. MDASI-CML MMRM Difference between Treatments in Overall LS Means (95% CIs): Symptom Items

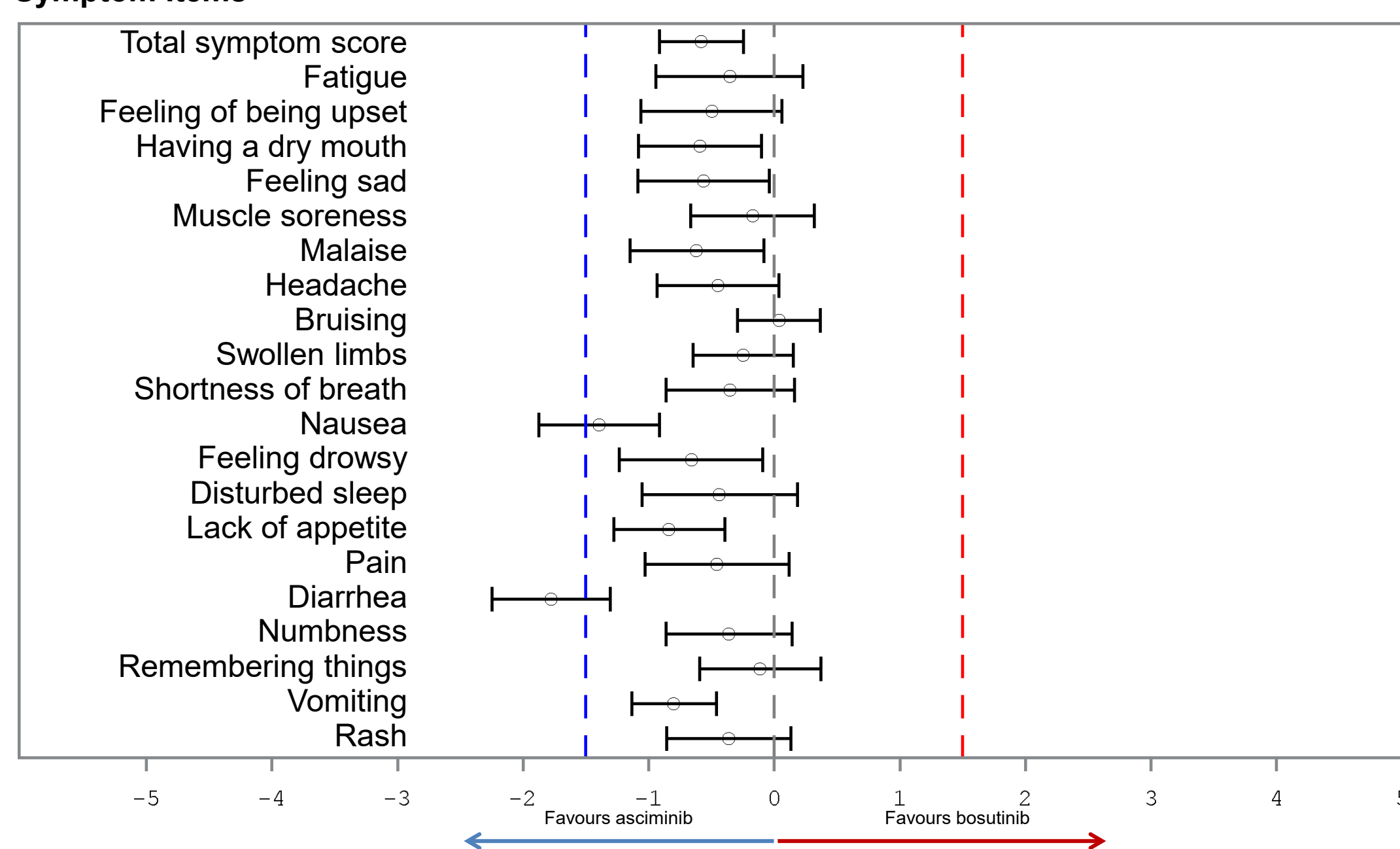
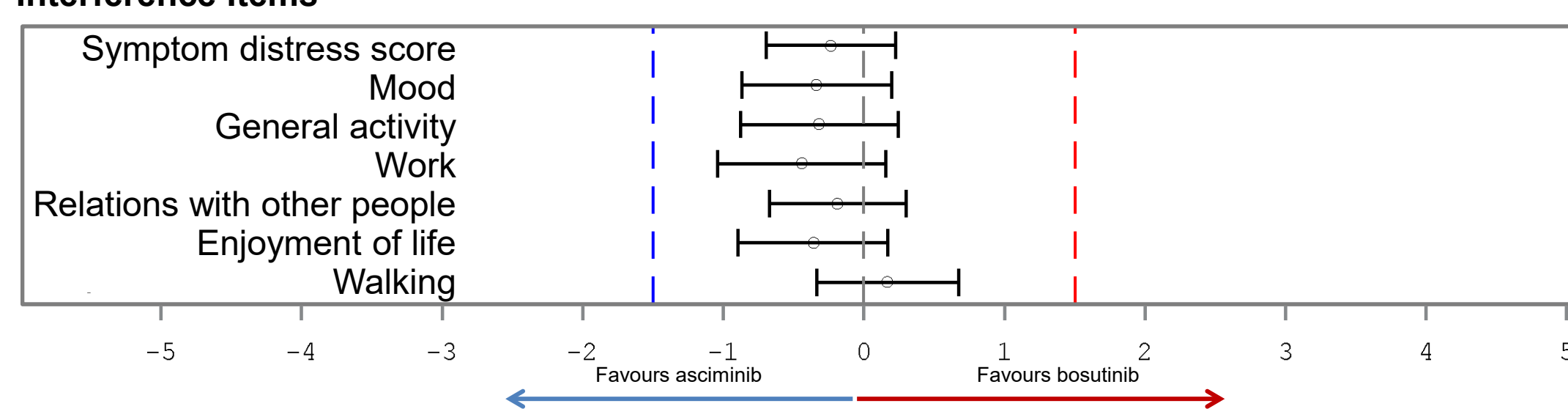


Figure 7. MDASI-CML MMRM Difference between Treatments in Overall LS Means (95% CIs): Interference Items



Disclosures

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