

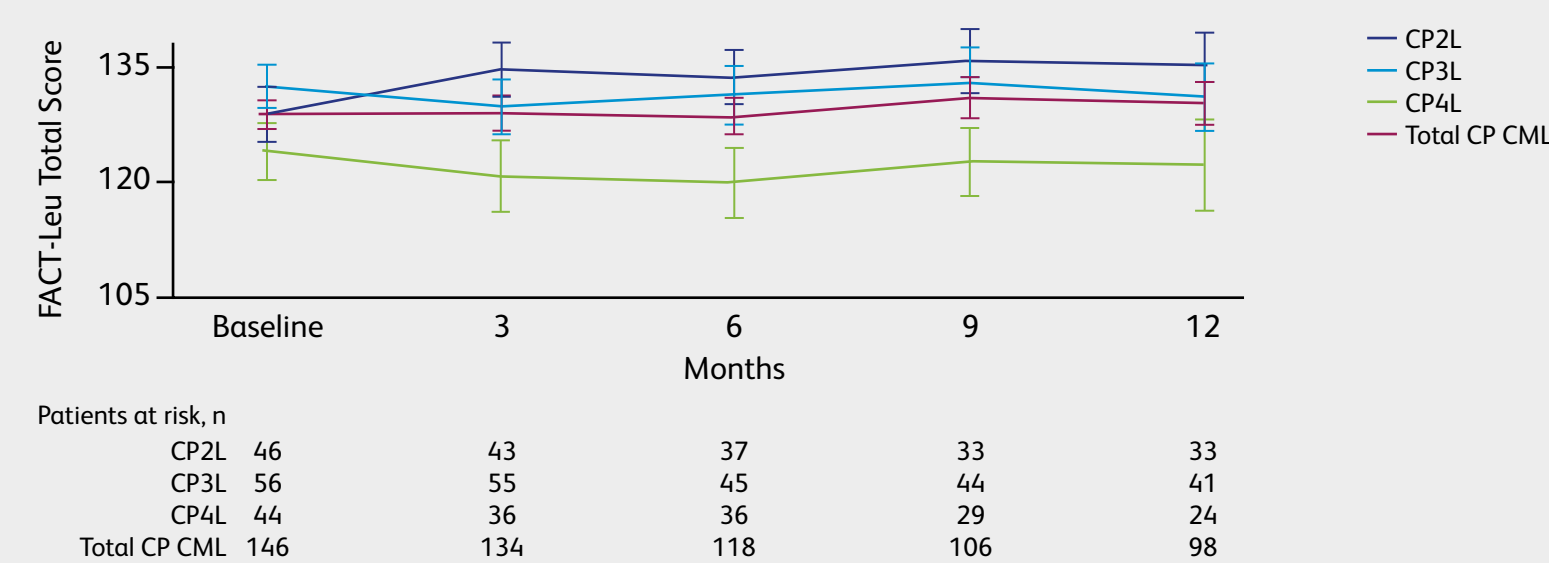
# Maintenance of Health-Related Quality of Life in the Phase 4 BYOND Study of Bosutinib for Pretreated Chronic Phase Chronic Myeloid Leukemia

## Objective

- To evaluate patient-reported HRQoL in the phase 4 BYOND study of bosutinib in patients with CML after failure of prior TKI treatment and to examine the relationship between molecular response and HRQoL.

## Conclusions

- HRQoL was maintained from baseline in patients with CP CML following 12 months of bosutinib treatment in the BYOND study.



- HRQoL changes at Month 12 were comparable to those observed in previously treated patients in the initial phase 1/2 study of bosutinib, wherein long-term efficacy and HRQoL stability were subsequently reported.<sup>1-3</sup>
- FACT-G scores in the BYOND study were consistent with those previously reported for general populations as well as patients with various cancers.<sup>4-6</sup>
- The impact of clinical improvement on different dimensions of HRQoL was variable; for the majority of domains, a deeper molecular response was associated with better HRQoL.
  - Results were largely similar to this analysis in the BFORE trial.<sup>7</sup>
- HRQoL results from BYOND suggest bosutinib is a well-tolerated treatment option, thus providing further support for its use in this patient population.



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## Background

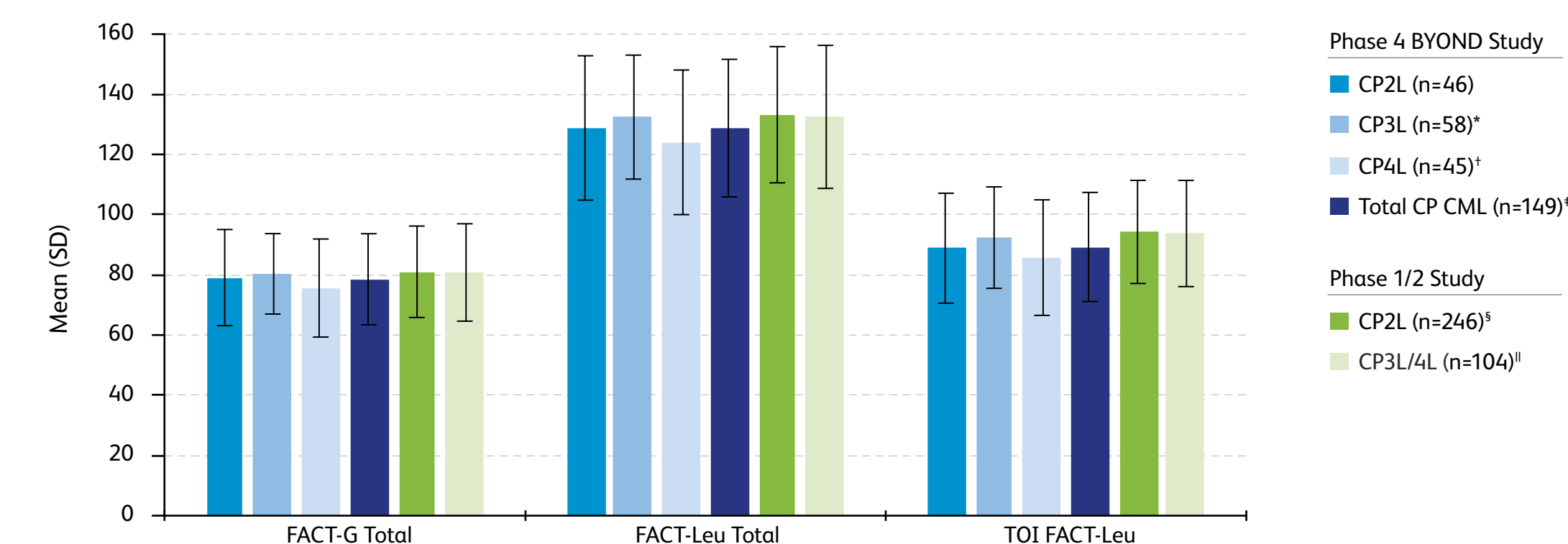
- Bosutinib is a tyrosine kinase inhibitor (TKI) approved for the treatment of Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) resistant/intolerant to prior therapy and newly diagnosed chronic phase (CP) Ph+ CML.
  - After ≥4 years' follow-up of a phase 1/2 study, durable responses and maintenance of health-related quality of life (HRQoL) were seen in patients with CP CML after prior imatinib (CP CML second-line [CP2L] cohort [n=284]) or prior imatinib + dasatinib and/or nilotinib (CP CML third/fourth-line [CP3L/4L] cohort [n=115/4]).<sup>1,3</sup>
- The BYOND study is providing additional safety and efficacy data for bosutinib in patients with CML after failure of prior TKI treatment.
  - In the primary BYOND analysis, patients had high rates of cytogenetic and molecular responses across all lines of treatment.<sup>8</sup>

## Results

### HRQoL AT BASELINE AND MONTH 12 OF BOSUTINIB TREATMENT

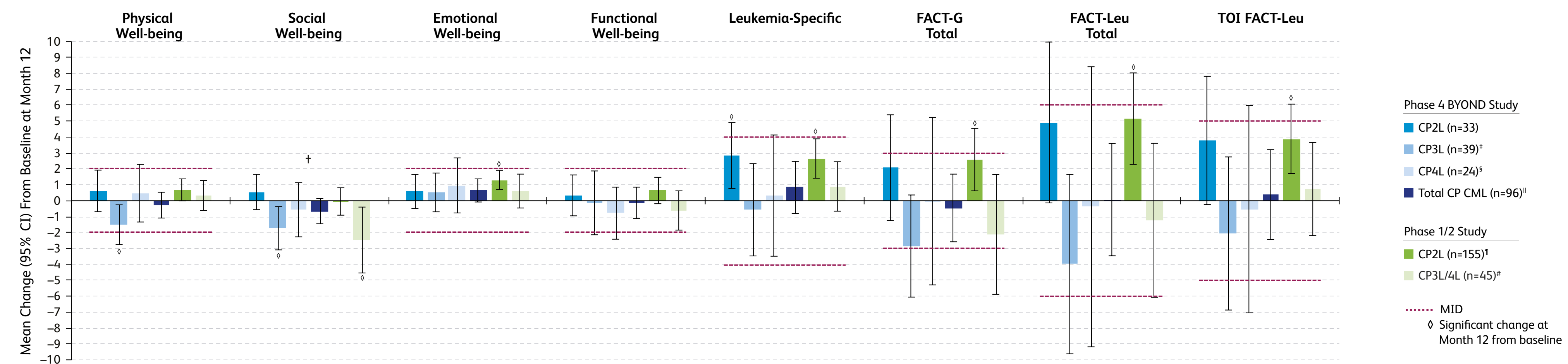
- At baseline, most FACT-Leu domain and summary scores were similar (<5% difference) in the CP2L and CP3L cohorts of the BYOND study (Figure 1 and Figure S1).
  - Baseline FACT-Leu scores were lower in the CP4L cohort, with >5% differences seen for all summary scores vs the CP3L cohort (Figure 1 and Figure S1).
- At Month 12, no mean change in a FACT-Leu domain or summary score met the minimal important difference (MID; Figure 2), indicating preservation of baseline HRQoL across all cohorts.
  - Mean changes in FACT-Leu scores from baseline to Month 12 were similar in the CP2L cohorts of the BYOND study and the phase 1/2 study.
  - HRQoL trends were also generally similar in the CP3L cohort of BYOND and the CP3L/4L cohort of the phase 1/2 study, in which 97% of patients received third-line bosutinib.
  - Noting small sample sizes and no adjustment for multiplicity of testing, significant changes at Month 12 from baseline for some domain and summary scores were indicated by 95% CIs that do not include 0 (Figure 2).

Figure 1: Baseline FACT-Leu Summary Scores



\* n=56 for FACT-Leu total and TOI FACT-Leu scores. † n=44 for FACT-Leu total and TOI FACT-Leu scores. ‡ n=146 for FACT-Leu total and TOI FACT-Leu scores. § n=245 for FACT-Leu total and TOI FACT-Leu scores. ¶ n=103 for FACT-G total and FACT-Leu total scores.  
CML=chronic myeloid leukemia; CP2L/3L/4L=chronic phase second/third/fourth-line cohort; FACT-G=Functional Assessment of Cancer Therapy-General; FACT-Leu=Functional Assessment of Cancer Therapy-Leukemia; TOI=trial outcome index

Figure 2: Changes in FACT-Leu Scores From Baseline After 12 Months\* of Bosutinib Treatment



\* Week 52 for phase 4 BYOND study and Week 48 for phase 1/2 study. † MID, ie, the change identified as being clinically meaningful to a patient, has not been defined for social well-being. ‡ n=38 for leukemia-specific and n=37 for FACT-Leu total and TOI FACT-Leu scores. § n=23 for social well-being, FACT-G total, and TOI FACT-Leu and n=22 for FACT-Leu total scores. ¶ n=95 for social well-being, leukemia-specific, and FACT-G total, n=93 for TOI FACT-Leu, and n=92 for FACT-Leu total scores. # n=152 for leukemia-specific, FACT-Leu total, and TOI FACT-Leu scores. †† n=44 for leukemia-specific and TOI FACT-Leu and n=43 for social well-being, FACT-G total, and FACT-Leu total scores.  
CP2L/3L/4L=chronic phase second/third/fourth-line cohort; FACT-G=Functional Assessment of Cancer Therapy-General; FACT-Leu=Functional Assessment of Cancer Therapy-Leukemia; MID=minimal important difference; SD=standard deviation; TOI=trial outcome index

## Methods

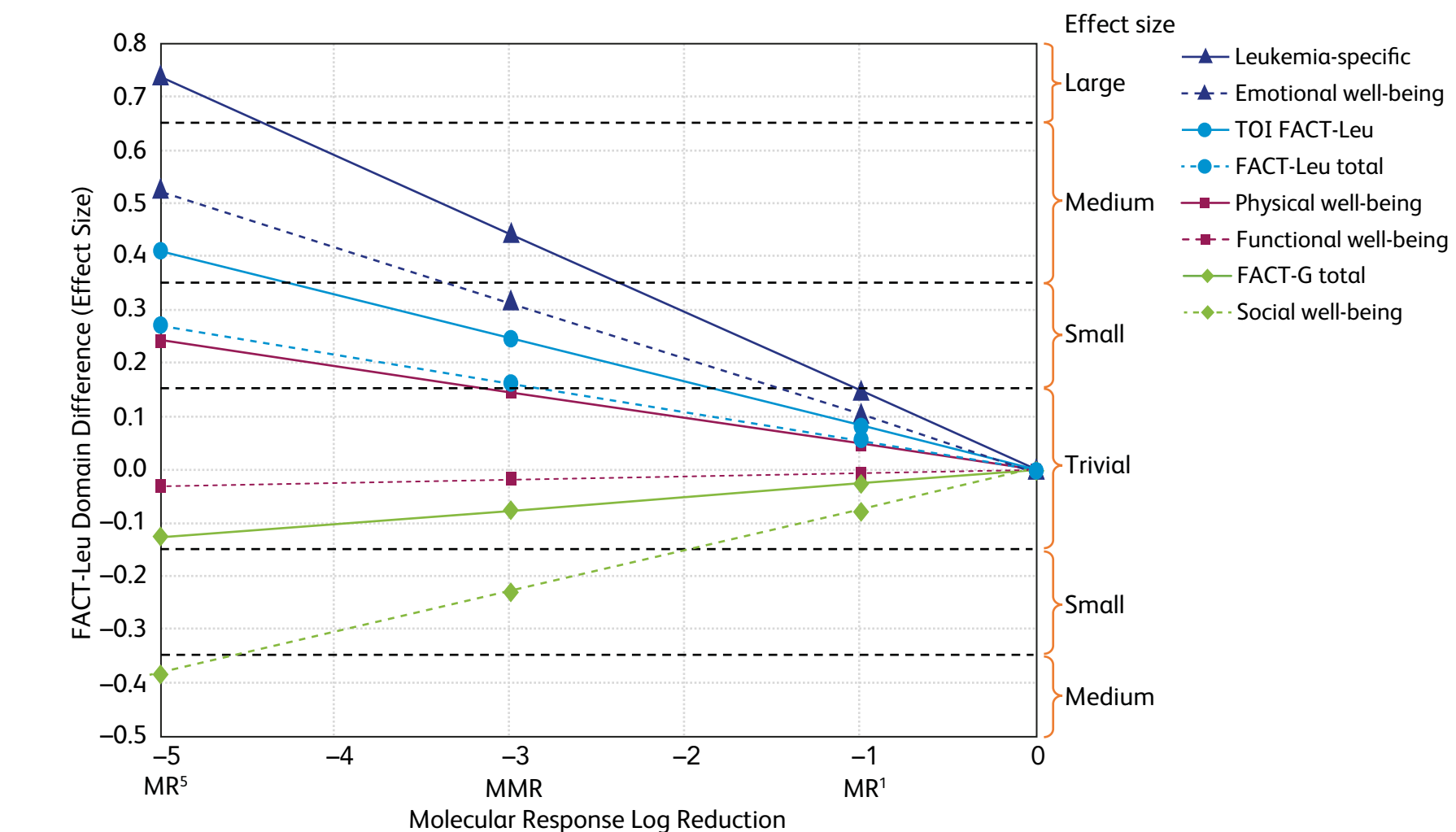
- BYOND (NCT02228382) is an ongoing, phase 4, single-arm, open-label study of bosutinib at a starting dose of 500 mg once daily in patients with CML and resistance/intolerance to prior treatment.
  - Evaluation of HRQoL through patient-reported outcome measures is an exploratory objective.
- HRQoL was assessed with the Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu, v4) questionnaire,<sup>4,9</sup> which consists of a set of general HRQoL questions (FACT-General [FACT-G]) and a set of leukemia-specific questions (Table S1).
  - Each item is scored on a scale from 0 to 4, with higher scores indicating better HRQoL.

- We report HRQoL results at baseline and Month 12 of bosutinib treatment in the CP CML cohorts of BYOND (data cutoff date: September 18, 2018, ≥12 months after last enrolled patient).
  - For comparison, we present HRQoL data at baseline and Month 12 from the CP CML cohorts of the phase 1/2 study of bosutinib in previously treated patients.
- For methods analyzing relationship between molecular response and HRQoL, please refer to the supplementary material that is downloadable using the QR code.

## LONGITUDINAL ANALYSES OF MOLECULAR RESPONSE AND HRQoL

- The effect of molecular response on HRQoL was variable (Figure 3).
- For patients who achieved MR<sup>5</sup>, the leukemia-specific domain showed the greatest improvement, with a large effect size, followed by the emotional well-being domain and total outcome index (TOI) FACT-Leu, with medium effect sizes (Figure 3).

Figure 3: Comparison of the Relationships Between Molecular Response and HRQoL (Effect Size\*)



\* A (standardized) effect size of 0.2 is considered small (ie, the difference in means being 0.2 SD unit), 0.5 medium, and 0.8 large; a value of -0.1 is trivial; midpoints between values of 0.1, 0.2, 0.5, and 0.8 were used to create categorization intervals for effect size.  
FACT-G=Functional Assessment of Cancer Therapy-General; FACT-Leu=Functional Assessment of Cancer Therapy-Leukemia; MMR=major molecular response; MR=molecular response; TOI=trial outcome index

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## Methods

**Table S1: FACT-Leu Questionnaire<sup>4,9</sup>**

FACT-Leu domain	Items, n	Score, range	MID,* range <sup>10</sup>
FACT-Leu total <sup>†</sup>	44	0–176	6–12
FACT-G total	27	0–108	3–7
Physical well-being	7	0–28	2–3
Social well-being	7	0–28	ND
Emotional well-being	6	0–24	2
Functional well-being	7	0–28	2–3
Leukemia-specific	17	0–68	4–7
TOI FACT-Leu <sup>‡</sup>	241	0–124	5–6

\* Changes in health-related quality of life scores that are clinically meaningful to a patient.

† Sum of the FACT-G total score and the leukemia-specific score.

‡ Sum of physical and functional well-being domain scores and the leukemia-specific score.

FACT-G=Functional Assessment of Cancer Therapy–General; FACT-Leu=Functional Assessment of Cancer Therapy–Leukemia; MID=minimal important difference; ND=not defined; TOI=trial outcome index

## RELATIONSHIP BETWEEN MOLECULAR RESPONSE AND HRQoL

- A repeated measures longitudinal model was used to estimate the relationships between molecular response (represented by a log-reduction scale) as a predictor and the FACT-Leu total score and each domain as an outcome.
- As a signal-to-noise ratio, standardized effect sizes were calculated to determine strength of effects and allow comparisons across FACT-Leu domains:

$$\text{Standardized effect size} = \frac{\text{Differences in predicted mean FACT-Leu scores corresponding to MRLR values of } -1 \text{ } [-3, -5] \text{ vs MRLR value of } 0}{\text{SD of the corresponding FACT-Leu scores at screening}}$$

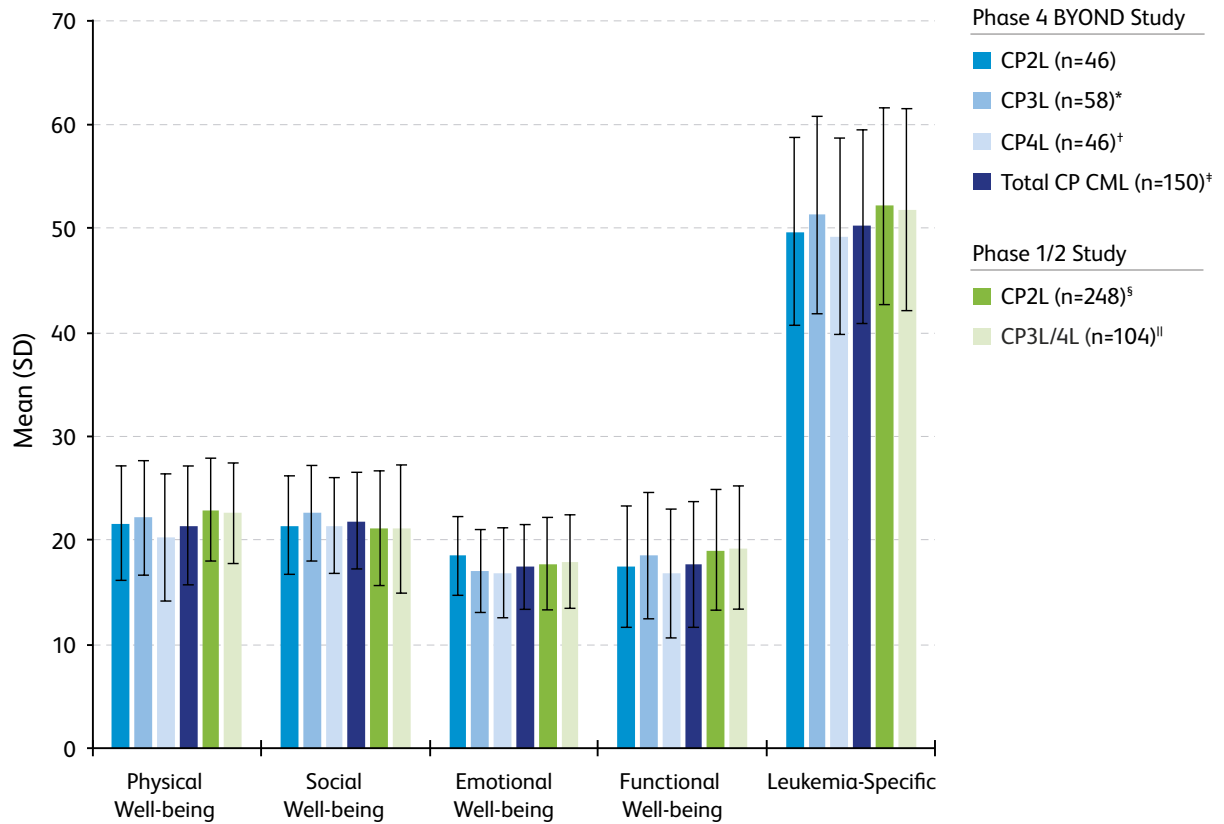
FACT-Leu=Functional Assessment of Cancer Therapy–Leukemia; MRLR=molecular response log reduction; SD=standard deviation

## Results

### HRQoL AT BASELINE

- Social and functional well-being scores were >5 % lower and the emotional well-being score was >5 % higher in the CP2L cohort compared with the CP3L cohort of BYOND (Figure S1).
- In the CP4L cohort of BYOND, scores were >5 % lower for physical and emotional well-being vs scores in the CP2L cohort, and for physical, social, and functional well-being scores vs the CP3L cohort (Figure S1).

**Figure S1: Baseline FACT-Leu Domain Scores**



\* n=57 for leukemia-specific score.

† n=45 for physical well-being score.

‡ n=149 for physical well-being and leukemia-specific scores.

§ n=247 for leukemia-specific and n=246 for physical well-being scores.

¶ n=103 for social well-being score.

CML=chronic myeloid leukemia; CP2L/3L/4L=chronic phase second/third/fourth-line cohort; FACT-Leu=Functional Assessment of Cancer Therapy–Leukemia