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APPLICATION NUMBER:

205552Orig2s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC MEMO

Application Number	NDA 205552
Submission Number (Date)	Original-2 (06/28/2013)
Compound	Ibrutinib
Dosing regimen	420 mg QD (Chronic Lymphocytic Leukemia)
Clinical Division	DHP
Primary PM Reviewer	Bahru A Habtemariam, Pharm.D.
Clinical Pharmacology Team Leader	Julie M. Bullock, Pharm. D.
Secondary PM Reviewer	Anshu Marathe, Ph.D.

Background

The original NDA for Ibrutinib (submitted on 6/28/13) proposed the treatment of patients with: mantle cell lymphoma (MCL; Original-1) and chronic lymphocytic leukemia (CLL; Original-2). The applicant submitted two pivotal clinical trials: a phase 2 trial (study 1104) in patients with MCL and a phase 1b/2 trial (study 1102) in patients with CLL.

The Original-1 NDA was approved on 11/13/2013 for patients with MCL. Exposure-efficacy analysis for patients with MCL and exposure-safety analysis for all patients which included both patients with MCL and CLL was conducted as part of the Pharmacometric review (for details see review in DARRTS dated 11/01/2013). At the time of the Original-1 NDA review, several issues with regards to interpretation of the efficacy data were identified by the Clinical Reviewers for patients enrolled in the CLL study 1102. Thus the approval for the CLL indication was deferred until data interpretation issues were resolved. Consequently the exposure-efficacy analysis for CLL patients was also deferred until updated data/analysis was submitted.

The initial treatment-response analysis in study 1102 was based on investigator assessment. On 12/17/2013, the sponsor submitted updated data, reports and analysis for CLL patients enrolled in study 1102 based on response assessment conducted by an independent review committee (IRC). The sponsor's IRC efficacy analysis found that the overall response rate (ORR) was 67.4% for all treated subjects (N=132). Details of the IRC efficacy analysis results are provided in **appendix 1**. Study design and treatment and dosing details are provided in **Table 1**.

Table 1. Study design details for trial 1102

Study Number	Study Description	Treatment Arms	Primary Study Endpoint
PCYC-1102-CA	Phase 1b/2 open-label trial in treatment naïve (N=47) or relapsed/ refractory (N=85) CLL/SLL	High-Risk RR 420 mg (N=23) RR 420 mg (=27) RR 840 mg (N=31) RR Food Effect 420 mg (16) TN 420 mg (N=26) TN 840 mg (N=3)	Overall Response Rate (ORR)

RR= Relapsed/Refractory, TN=Treatment-Naive

Summary of Findings: The purpose of this memo is to address the following key questions.

Is there exposure-response relationship for effectiveness endpoint in CLL patients?

There is no evidence of an exposure-response for overall response rate (ORR) in the range of exposures observed following ibrutinib doses of 420 mg or 840 mg in patients with CLL. Steady state trough plasma concentrations were available from a total of 132 patients who were enrolled in study 1102. Trough concentrations were obtained on days 1, 8, and 15. Trough concentrations collected on days 8 or later were used to calculate mean steady state trough concentrations.

Figure 1 below shows that there is no increase in proportion of patients with ORR with increasing trough concentrations of ibrutinib. Because the proposed dose is 420 mg for patients with at least one prior treatment, a separate exposure-efficacy analysis was conducted for those with refractory disease treated at 420 mg once daily. **Figure 2** below shows that the proportion of patients with ORR is not influenced by trough concentration in refractory CLL patients treated with ibrutinib dose of 420 mg once daily. However, the data was limited with only 45 subjects included in this analysis.

Figure 1. The proportion of patients with ORR versus steady trough concentrations in CLL patients treated with 420 or 840 mg once daily.

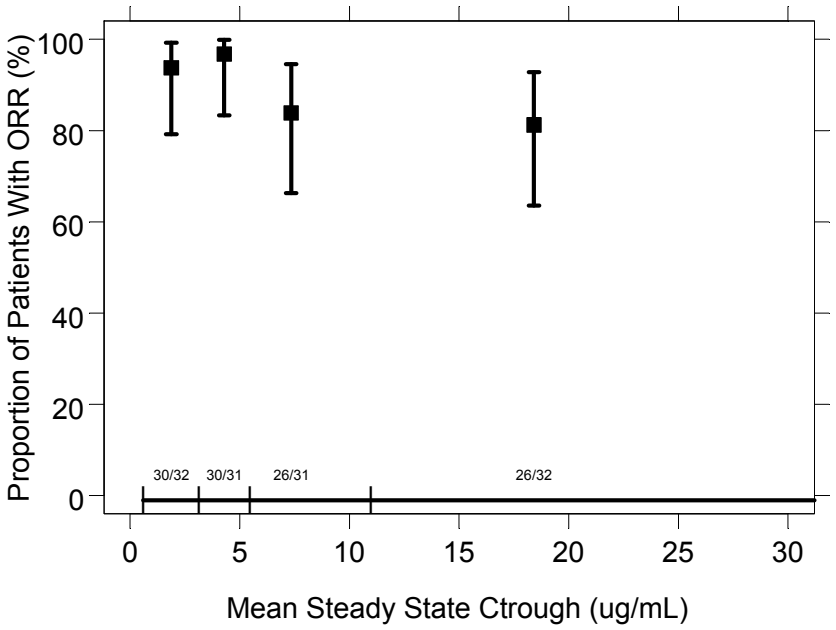
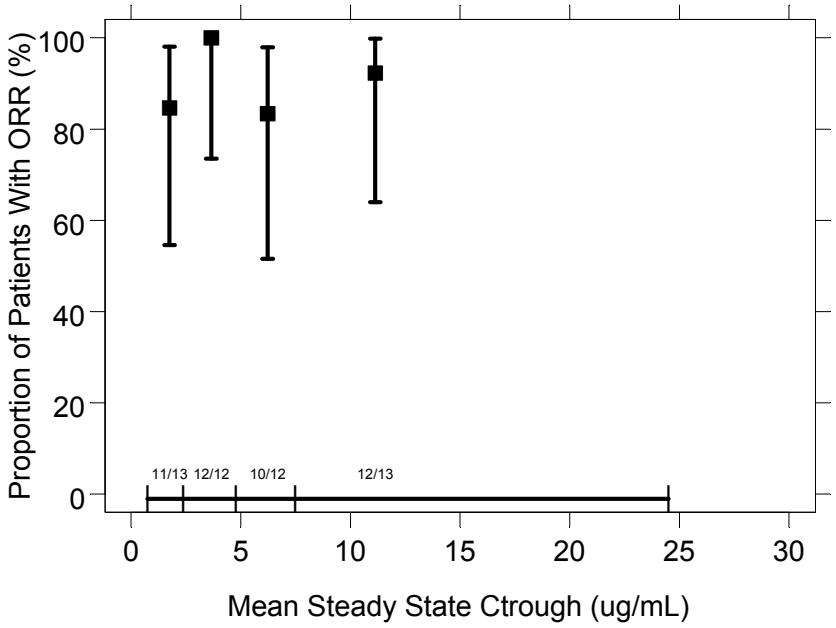


Figure 2. The proportion of patients ORR is not influenced by increasing steady trough concentrations in refractory CLL patients treated with 420 mg once daily.



Is the proposed dose of 420 mg QD in CLL patients appropriate?

The proposed dose of 420 mg QD in CLL patients appears acceptable based on reasonable safety profile and a response rate of 67.4% that was achieved in the phase 1b/2 trial. Additionally, no meaningful exposure-response relationship is identified for Grade 3 or 4 neutropenia and Grade 3 or 4 infections and infestations (see Pharmacometrics review in DARRTS dated 11/01/2013). Thus based on available effectiveness and safety data, the proposed dose appears acceptable.

However, the proposed dose is 2.4-fold higher than the lowest dose that resulted in maximum BTK occupancy and maximum clinical response. Dose-response relationship for ORR and BTK occupancy from Phase 1 study suggested that maximum ORR and maximum occupancy was achieved at doses of ≥ 2.5 mg/kg (≥ 175 mg for average weight of 70 kg) [see Pharmacometrics review in DARRTS dated 11/01/2013. The sponsor should thus consider exploring lower doses in future development programs.

Recommendation: Division of Pharmacometrics finds NDA 205552 acceptable from a clinical pharmacology perspective.

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