CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205552Orig2s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 205552
Supplement #:	
Drug Name:	Ibrutinib
Indication(s):	Relapsed or refractory Chronic Lymphocytic Leukemia
Applicant:	Pharmacyclics
Date(s):	Submission Date: May 31, 2013 PDUFA due Date: February 28, 2014 Review Completion Date: 31 January, 2014
Review Priority:	Priority
Biometrics Division:	Division of Biometrics V
Statistical Reviewer:	Yun Wang, PhD
Concurring Reviewers:	Lei Nie, PhD, Acting Team Leader Thomas Gwise, PhD, Deputy Division Director
Medical Division:	Office of Hematology and Oncology Product
Clinical Team:	Nicole Verdun, MD Angelo De Claro, MD
Project Manager:	Diane Hanner, MPH

Keywords: Chronic Lymphocytic Leukemia, Overall Response Rate, Duration of Response; Single arm trial.

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1 EXECUTIVE SUMMARY

New drug application (NDA) 205552 submission was split into two separate submissions based on two different indications: original-1 submission for mantle cell lymphoma (MCL), and original-2 submission for chronic lymphocytic leukemia (CLL). FDA granted accelerated approval in November 2013 for MCL indication based on original-1 submission. This statistical review is for original-2 submission. In original-2 submission, the applicant seeks the approval of ibrutinib for treatment of relapsed or refractory CLL patients who received at least one prior regimen.

This NDA original-2 submission is based on two clinical studies (Study PCYC-1102-CA and Study PCYC-04753) in 149 subjects in which ibrutinib was evaluated as a single agent at different doses for the treatment of CLL patients. PCYC-1102-CA is a Phase 1b/2 study of ibrutinib at two dose levels (420 mg or 840 mg) in 133 subjects with treatment-naïve or relapsed/refractory CLL/Small Lymphocytic Lymphoma (SLL). This statistical review only considers 48 subjects with relapsed/refractory CLL treated at dose of 420 mg, the targeted dose and indication the applicant seeks the approval for, in the Study PCYC-1102-CA. Study PCYC-04753 enrolled 16 CLL patients into different doses and only provided preliminary efficacy results of ibrutinib. Therefore, Study PCYC-04753 was not included in this statistical review.

Study PCYC-1102-CA was designed as a nonrandomized study. Therefore, all statistical analyses were descriptive and no formal statistical comparisons were performed.

In Study PCYC-1102-CA, the overall response rate (ORR) per independent review committee (IRC) assessments was 56.3% (95% CI [41.2%, 70.5%]) with median duration of response (DOR) not achieved yet (95% CI not evaluable).

The response data from Study PCYC-1102-CA demonstrated some clinically meaningful treatment effect of ibrutinib for relapsed and refractory CLL patients. Top line results from Study PCYC-1112-CA, an ongoing randomized, multicenter, and open-label Phase 3 study of the ibrutinib versus ofatumumab in patients with relapsed or refractory CLL/SLL, showed significant improvement in PFS for ibrutinib compared to ofatumumb, which provided more evidence of clinical benefit of ibrutinib for refractor/relapsed CLL patients.

2 INTRODUCTION

2.1 Overview

Ibrutinib is a selective, irreversible small molecule inhibitor of Bruton's tyrosine kinase (BTK) for the treatment of B-cell malignancies. By combining fast covalent binding to BTK with rapid in vivo elimination, ibrutinib provides a unique approach to improve selectivity for BTK in vivo relative to reversibly inhibited off-target kinases.

The proposed indication submitted in this NDA original-2 application is for the treatment of patients with relapsed/refractory CLL who have received at least one prior regimen.

Ofatumumab (Arzerra) is currently approved for treatment of patients with CLL based on an open-label, single-arm, multicenter study of 154 patients with relapsed or refractory CLL.

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