2.0 Synopsis

<table>
<tr><td>AbbVie Inc.</td><td rowspan="3">Individual Study Table Referring to Part of Dossier:
Volume:

Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Study Drug: ABT-199</td></tr>
<tr><td>Name of Active Ingredient:
ABT-199</td></tr>
<tr><td colspan="3">Title of Study: A Phase 1 Study to Assess the Effect of Ketoconazole on the Pharmacokinetics of ABT-199</td></tr>
<tr><td colspan="3">Investigator:</td></tr>
<tr><td colspan="3">Study Sites: 3 sites in the United States of America</td></tr>
<tr><td colspan="3">Publications: None</td></tr>
<tr><td colspan="2">Studied Period (Years):
First Subject First Visit: 02 December 2013
Last Subject Last Visit: 26 September 2014</td><td>Phase of Development: 1</td></tr>
<tr><td colspan="3">Objectives:
The primary objective of this study was to investigate the effect of ketoconazole, a potent CYP3A inhibitor, on the pharmacokinetics of ABT-199. The secondary objective was to determine the safety of ABT-199 when administered alone and in combination with ketoconazole.</td></tr>
<tr><td colspan="3">Methodology:
This was a Phase 1, open-label study that planned to enroll up to 15 adult subjects with relapsed or refractory Non-Hodgkin lymphoma (NHL) excluding chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), and mantle cell lymphoma (MCL). The pharmacokinetic (PK) profile of the first 3 subjects to complete all 12 days of the study was to be used to adjust, if necessary, the ABT-199 dose to be evaluated. Enrollment was considered to be complete when up to 12 subjects completed all 12 days of the study, at the selected ABT-199 dose level, to allow for a minimum of 8 subjects to be evaluable for PK analysis.
Each subject received a single 50 mg dose of ABT-199 on Day 1 and Day 8, and 400 mg QD dose of ketoconazole on Days 5 through 11. On Day 8, ketoconazole was administered at the same time or within 5 minutes after the ABT-199 dose in the clinic. ABT-199 was administered orally with approximately 240 mL of water, after completion of a standard low-fat breakfast. Venous blood samples from which plasma was obtained for PK assay of ABT-199 and M27 metabolite were collected on Day 1 and Day 8.</td></tr>
<tr><td colspan="3">Number of Subjects (Planned and Analyzed): Planned: 12; Evaluated for Safety: 12; Evaluated for Pharmacokinetics: 11</td></tr>
</table>

Diagnosis and Main Criteria for Inclusion:

- Adult male and female subjects with documented diagnosis of NHL Subject had histologically documented diagnosis of NHL as defined by a B-cell neoplasm
- Subject had an Eastern Cooperative Oncology Group (ECOG) performance score of 0 to 2
- Subject had adequate bone marrow (independent of growth factor support per local laboratory reference range), coagulation, renal and hepatic function

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

Study Drug	Trademark	Formulation	Bulk Lot Numbers	Finished Lot Numbers	Manufacturer
ABT-199	N/A	50 mg Tablet	13-000001	13-002741	Abbott/AbbVie
Ketoconazole	N/A	200 mg Tablet	13-001566	13-002743	Mylan Pharmaceuticals

Duration of Treatment: Each subject received a single 50 mg dose of ABT-199 on Day 1 and Day 8, and 400 mg QD dose of ketoconazole on Days 5 through 11.

Criteria for Evaluation

Efficacy:

This was a pharmacokinetic and safety study. Efficacy was not assessed.

Pharmacokinetic:

C_{max}, T_{max}, β, $t_{1/2}$, AUC and CL/F were estimated using noncompartmental methods.

Safety:

All adverse events discussed were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 17.0 dictionary. Adverse events were summarized for 3 treatment periods: Period 1, onset Study Days 1 through 4 following ABT-199 treatment alone on Day 1; Period 2, onset Days 5 through 7 following ketoconazole treatment alone; and Period 3, onset Days 8 through 30 (end-of-study) following ketoconazole co-administration with ABT-199 on Day 8. For each MedDRA preferred term, the number of subjects with adverse events was also tabulated by rating (mild, moderate, or severe) and by degree of relationship to study drug. Laboratory test values, vital signs measurements, electrocardiograms (ECGs) and imaging results were also reported and analyzed.

Statistical Methods

Pharmacokinetic:

To compare ABT-199 and M27 PK with and without ketoconazole, an analysis of variance (ANOVA) was performed for each of the following PK parameters: T_{max}; the apparent terminal phase elimination rate constant (β, if available); and the natural logarithms of C_{max}, AUC_t and AUC_∞ (if available). The model included a fixed effect for regimen (ABT-199 alone – Day 1 and ABT-199 in combination with steady-state dose ketoconazole – Day 8). Subjects were viewed as a random effect. Within the ANOVA modeling framework, the null hypothesis of no difference between ABT-199 with ketoconazole (Day 8) relative to ABT-199 alone (Day 1) were tested with a significance level of 0.05.

Statistical Methods (Continued)

Pharmacokinetic (Continued):

Additionally for ABT-199 and M27, the oral bioavailability of ABT-199 with ketoconazole relative to ABT-199 alone have been estimated. Point estimates and corresponding 90% confidence intervals for the ratio of ABT-199 with ketoconazole relative to ABT-199 alone, for C_{max} and AUC, are provided. The point estimate was obtained by exponentiation of the estimate of the difference of the logarithmic means. The 90% confidence intervals were similarly obtained by exponentiation of the endpoints of the corresponding confidence intervals for the difference of mean logarithms obtained within the framework of the ANOVA model.

Safety:

The data for all 12 subjects who received at least one dose of study drug (N = 12) are included in the safety analyses.

Summary/Conclusions

Efficacy Results:

This was a pharmacokinetic and safety study. Efficacy was not assessed.

Pharmacokinetic Results:

Regimens[a] Test vs. Reference	Pharmacokinetic Parameter (units)	Central Value		Relative Bioavailability	
		Test	Reference	Point Estimate	90% Confidence Interval
ABT-199					
ABT-199 w/ Ketoconazole (Day 8) vs. ABT-199 Alone (Day 1)	C_{max} (µg/mL)	0.461	0.198	2.323	1.996 – 2.702
	AUC_t (µg•h/mL)	17.887	3.803	4.703	3.549 – 6.233
	AUC_∞ (µg•h/mL)	25.366	3.961	6.403[b]	4.472 – 9.168
M27 Metabolite					
ABT-199 w/ Ketoconazole (Day 8) vs. ABT-199 Alone (Day 1)	C_{max} (µg/mL)	0.009	0.018	0.499	0.419 – 0.595
	AUC_t (µg•h/mL)	0.694	0.968	0.717	0.634 – 0.812
	AUC_∞ (µg•h/mL)	2.356	1.308	1.801[c]	0.961 – 3.376

a. Reference Regimen (ABT-199 Alone) ABT-199 50 mg administered under non-fasting conditions as a single dose on Day 1.

Test Regimen (ABT-199 with Ketoconazole) Ketoconazole 400 mg QD administered under non-fasting conditions on Days 5 through 11; on Day 8, ABT-199 50 mg administered as a single dose under non-fasting conditions.

b. N = 10.

c. N = 4.

Summary/Conclusions (Continued)

Safety Results:

ABT-199 50 mg was well tolerated alone and in the presence of ketoconazole. There were no clinically meaningful or significant trends noted in the potentially clinically significant vital signs values reported. There were no interruptions, reductions or discontinuations of study drug due to adverse events. Adverse events reported in this study were consistent with previous ABT-199 clinical studies. The majority of adverse events were mild or moderate in severity (Grade 1 or Grade 2).

Conclusions:

Ketoconazole co-administration increased ABT-199 C_{max} (2.3-fold), AUC_{∞} (6.4-fold) and half-life (approximately two times longer). ABT-199 50 mg was well tolerated alone and in the presence of ketoconazole.