2. SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
Infinity Pharmaceuticals, Inc.</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier
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<tr><td>Name of Finished Product:
Duvelisib</td></tr>
<tr><td>Name of Active Ingredient:
IPI-145</td></tr>
<tr><td colspan="3">Title of Study:
A phase 2, double-blind, parallel, placebo controlled, randomized study to evaluate multiple dose levels of IPI-145 with background methotrexate in subjects with active rheumatoid arthritis and an inadequate response to methotrexate alone</td></tr>
<tr><td colspan="3">Principal Investigator: Sunil Kumar, MD, Center for Clinical research and Effective Practice, Auckland, New Zealand</td></tr>
<tr><td colspan="3">Study center(s):
85 sites in 11 countries enrolled at least 1 subject.</td></tr>
<tr><td colspan="3">Publications (reference):
Not applicable</td></tr>
<tr><td colspan="2">Studied period (years):
Date first patient enrolled: 16 May 2013
Date last patient completed: 23 December 2014</td><td>Phase of development:
2</td></tr>
<tr><td colspan="3">Objectives:
Primary:
The primary objective of the study was to evaluate the efficacy of multiple dose levels of duvelisib compared to placebo in subjects with moderate-to-severe active rheumatoid arthritis (RA) taking a stable dose of methotrexate (MTX).
Secondary:
• Evaluate the safety of multiple dose levels of duvelisib compared to placebo in subjects with moderate-to-severe active RA taking a stable dose of MTX
• Characterize the pharmacokinetics (PK) of duvelisib in subjects with moderate-to-severe RA taking a stable dose of MTX</td></tr>
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Methodology:

A total of 322 adult subjects who met all eligibility criteria at Screening were randomized at Baseline in a 1:1:1:1 ratio to one of 4 dose groups: duvelisib 0.5 mg, 1 mg, and 5 mg twice daily (BID), or placebo BID. All treatments were administered every 12±2 hours. After randomization, subjects entered a 12-week Treatment Period, in which study drug (duvelisib or placebo) was self-administered BID as an outpatient, with the exception of the Week 2 visit where the dose of study drug was administered in-clinic to support the examination of PK. During the Treatment Period, subjects returned to the clinic for efficacy and safety assessments at Week 2 (Day 14±2), Week 4 (Day 28±2), Week 6 (Day 42±2), Week 8 (Day 56±2), Week 10 (Day 70±2), and Week 12 (Day 84±2). Following Treatment Period completion at Week 12, subjects entered a 3-week Follow-up Period which included 1 clinic visit approximately 3 weeks after the last dose of study drug.

Number of subjects (planned and analyzed):

A total of 316 subjects were planned and 322 were enrolled and analyzed as the Full Analysis Set (FAS) and Safety Analysis Set; 259 subjects met the criteria for the Efficacy Evaluable Set and Per Protocol Set.

Diagnosis and main criteria for inclusion:

Subjects were required to:

- Meet the 1987 American College of Rheumatology (ACR) criteria for RA
- Have ACR functional class I-III
- Have ≥5 swollen AND ≥5 tender joints (based on 66 and 68 joint counts, respectively) at Screening and Baseline
- Have C-reactive protein (CRP) >7 mg/L (>1.4 × upper limit of normal [ULN] for central laboratory) at Screening
- Have a positive laboratory result at Screening for rheumatoid factor (RF) and/or anti-citrullinated protein antibodies (ACPA)
- Be diagnosed with RA disease duration of at least 6 months
- Be taking MTX for at least 3 months prior to Screening, and on a stable dose and route for at least 6 weeks prior to dosing (Day 1)
- Be taking folic or folinic acid and willing to maintain a stable dose from Screening through the final Follow-up Visit
- If taking sulfasalazine, chloroquine, or hydroxychloroquine, be on stable doses from at least 8 weeks prior to Dosing (Day 1) and be willing to maintain stable doses through final Follow-up Visit.

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- If taking systemic steroids (such as prednisone), be on a stable dose (≤equivalent of 10 mg per day prednisone) within 4 weeks of dosing (Day 1) and be willing to maintain stable dose through final Follow-up Visit

Test product, dose and mode of administration, batch number:

Duvelisib, 0.5 mg, 1.0 mg, and 5.0 mg in capsule administered orally.

Duration of treatment:

12 weeks plus a 3-week follow-up period.

Reference therapy, dose and mode of administration, batch number:

Placebo capsules containing same excipients as duvelisib capsules and of identical appearance.

Criteria for evaluation:

Efficacy:

Primary Efficacy Endpoint:

Proportion of subjects who achieved a 20% improvement in the ACR20 from Baseline to Week 12

Secondary Efficacy Endpoints:

- Proportion of subjects who achieve an ACR20 over Week 4 through Week 12, based on a repeated measures model
- Proportion of subjects who achieve an ACR20 from Baseline to each of Weeks 2, 4, 6, 8 and 10
- Proportion of subjects who achieve a 50% improvement in ACR Criteria (ACR50) from Baseline to each of Weeks 2, 4, 6, 8, 10, and 12
- Proportion of subjects who achieve a 70% improvement in ACR Criteria (ACR70) from Baseline to each of Weeks 2, 4, 6, 8, 10, and 12
- Change in the number of tender/painful joints from Baseline to each of Weeks 2, 4, 6, 8, 10, and 12 (68 joint count)
- Change in the number of swollen joints from Baseline to each of Weeks 2, 4, 6, 8, 10, and 12 (66 joint count)
- Change in the health assessment questionnaire disability index (HAQ-DI) from Baseline to each of Weeks 2, 4, 6, 8, 10, and 12
- Change in subject assessment of pain from Baseline to each of Weeks 2, 4, 6, 8, 10, and 12 (visual analog scale [VAS] 100 mm)
- Change in subject global assessment of disease activity from Baseline to each of Weeks 2, 4, 6, 8, 10, and 12 (VAS 100 mm)

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- Change in physician global assessment of disease activity from Baseline to each of Weeks 2, 4, 6, 8, 10, and 12 (VAS 100 mm)
- Change in CRP from Baseline to each of Weeks 2, 4, 6, 8, 10, and 12
- Change in the 3-variable Disease Activity Score in 28 joints (DAS28)-CRP from Baseline to each of Weeks 2, 4, 6, 8, 10, and 12
- Proportion of subjects who achieve a response on the DAS28-CRP from Baseline to each of Weeks 2, 4, 6, 8, 10, and 12

Pharmacokinetics:

- Pharmacokinetic parameters derived from plasma duvelisib concentrations

Safety:

Safety Endpoints:

- Adverse events (AEs)
- Safety laboratory findings

Statistical methods:

The primary efficacy endpoint was the ACR20 response at Week 12. Each duvelisib dose group was compared with the placebo group for ACR20 response at Week 12 using a one-sided Cochran-Mantel-Haenszel (CMH) test stratified for geographic region. Analyses were based on the FAS. In the event that subjects discontinued the study after their first dose of study drug but prior to the Week 12 efficacy assessments, the ACR20 was analyzed as a non-response (i.e., having not achieved the ACR20) at each assessment missed as a result of discontinuation, regardless of the reason for discontinuation.

Statistical comparisons were performed at a 1-sided alpha level of 0.05, and no adjustments of multiple comparisons were made. Sensitivity analyses of the imputation method were performed. The treatment effect on continuous endpoints were analyzed using analysis of covariance models that included treatment, geographic region and the baseline value of the endpoint. Non-parametric methods were applied as appropriate.

The severity of AEs was graded using National Cancer Institute Common Terminology Criteria for Adverse Events

SUMMARY – CONCLUSIONS

The goal of Study IPI-145-04 was to evaluate duvelisib, a potent PI3K-δ,γ inhibitor in subjects with active rheumatoid arthritis on a background of methotrexate.

EFFICACY RESULTS:

An improvement over placebo in the ACR20 at Week 12 was not demonstrated for any of the doses of duvelisib tested in this study. Although statistically significant improvements were noted at some time points for the 0.5 mg BID and 1.0 mg BID doses, none were noted for the 5.0 mg BID dose; thus

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there was no consistent or dose-related improvement over placebo. Subgroup analyses using a number of stratification criteria and logistic regression analyses did not reveal any consistent, dose-related improvements over placebo. Some improvements over placebo were noted in the analyses of tender and swollen joints counts (both the 66/68-joint counts and the 28-joint counts subsets) and DAS28-CRP (sometimes a more sensitive assessment of effect than the ACR20); however, these improvements were small, and not consistent or dose related. The ACR20 at Week 12 for placebo at 40% was as expected in the region for Europe/Oceania which enrolled most of the subjects but was higher than anticipated in Latin America at 64%. However, subjects were stratified by geographic region at baseline, and the lack of a difference in ACR20 among treatment cohorts including placebo in Europe/Oceania supports the primary conclusions on efficacy.

SAFETY RESULTS:

Overall, duvelisib appeared to be well tolerated over 12 weeks of treatment in this disease population. The 5.0 mg BID dose did have a higher percentage of subjects who discontinued study drug due to an AE; this was mainly due to reversible increases in AST and ALT which met study-defined stopping rules. Of note, during the study, based upon the ongoing data available at the time, the independent DMC suggested and the sponsor adjusted those stopping rules. Also, there appeared to be a dose-related increase for the AEs of AST increased, ALT increased and possibly lymphopenia, and in the 5.0 mg BID dose cohort a higher percentage of TEAEs of ≥Grade 3.

Overall, the majority of AEs were Grade 1 or Grade 2 in severity. With the exception of a Grade 4 SAE of Guillain-Barre syndrome, the AEs were self-limiting, resolving with or without medication. The percentage of female subjects experiencing a TEAE was higher than for male subjects for the duvelisib dose cohorts. The most frequent TEAEs during treatment were anemia, lymphopenia, AST increased, ALT increased, nausea, nasopharyngitis, and headache, all of which were more common in subjects receiving duvelisib than subjects receiving placebo. There were no deaths reported during the study, although 1 subject died from Guillain Barre syndrome 77 days after the last dose of duvelisib; the Guillain-Barre syndrome was not related to duvelisib treatment. The infections of acarodermatitis, herpes zoster, impetigo, orchitis, urinary tract infection, and varicella only occurred in the duvelisib cohorts.

All the SAEs occurred in the duvelisib cohorts, with 5 of the 10 SAEs assessed as related to study drug (urinary tract infection, acarodermatitis, impetigo, neurodermatitis and dermatitis exfoliative).

There was a relatively high number of subjects with AEs related to liver function tests (LFTs), most of which occurred in the duvelisib 5.0 mg BID cohort and resulted in discontinuation of study drug. Some of the LFT AEs may have been attributable to concomitant methotrexate administration, however, although the numbers are small, the higher concentration in the duvelisib 5.0 mg BID cohort is suggestive of a dose effect.

CONCLUSION:

There was no clinically meaningful beneficial effect upon the signs and symptoms of RA at any of the doses of duvelisib evaluated. The findings indicated that duvelisib administered at 0.5, 1.0 and 5.0 mg BID had no added benefit over placebo in this study.

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