1. SYNOPSIS

Name of Sponsor/Company: Infinity Pharmaceuticals, Inc. **Name of Finished Product:** Duvelisib **Name of Active Ingredient:** IPI-145	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

Title of Study:
A phase 2a, randomized, double-blind, placebo-controlled, multi-dose, cross over, efficacy and safety study of IPI-145 in mild asthmatic subjects undergoing allergen challenge

Principal Investigator: Dr. Rainard Fuhr, PAREXEL International GmbH Early Phase, 14050 Berlin, Germany

Investigators: Muna Albayaty, United Kingdom; Anne-Marie Kirsten, Germany; Jutta Beier, Germany

Study center(s):
Four sites in the United Kingdom and Germany

Publications (reference):
None

Studied period (years):	**Phase of development:**
Date first subject enrolled: 20 July 2012 Date last subject completed: 30 July 2014	2

Objectives:

Primary:

- The primary objective of this study was to examine the effects of multi-dose regimens of different dose strengths of duvelisib on lung function in mild asthmatic subjects following allergen challenge.

Secondary:

- Examine the effects of multi-dose regimens of different dose strengths of duvelisib on airway hyperresponsiveness (AHR) in mild asthmatic subjects following allergen challenge
- Investigate the safety profile of duvelisib in mild asthmatic subjects
- Characterize the PK profile of duvelisib in mild asthmatic subjects

Exploratory:

- Examine PI3K pathway and inflammation biomarkers in plasma and serum (plasma and serum for Cohorts 1 and 2, and serum only for Cohort 3) PD and predictive diagnostic relationships to duvelisib clinical activity
- Examine the effects of multi-dose regimens of different dose strengths of duvelisib on indices of inflammation and PI3K pathway activity in mild asthmatic subjects following allergen challenge using induced sputum (Cohorts 1 and 2 only)

Name of Sponsor/Company: Infinity Pharmaceuticals, Inc.	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Duvelisib		
Name of Active Ingredient: IPI-145		

Methodology:

A total of 50 adult subjects who met all eligibility criteria at Screening were enrolled in a step-wise manner to 1 of 3 dose cohorts:

Cohort 1: duvelisib 1 mg or placebo every 12 hours [Q12±2 hours] for 14 days (n = 14)

Cohort 2: duvelisib 5 mg Q12±2 hours or placebo for 14 days (n = 18)

Cohort 3: duvelisib 25 mg or placebo every 12 hours [Q12±2 hours] for 5 days (n = 18)

Subjects were randomized at Baseline to receive either duvelisib or placebo during Treatment Period 1 (TP1). In Cohorts 1 and 2, subjects self-administered either duvelisib or placebo (both given orally) at home for 13 days. On TP1 Day 14 subjects were admitted to the clinic and underwent an allergen challenge, with subsequent spirometry testing and other clinical evaluations, remained overnight, and underwent additional assessments on TP1 Day 15. After completing TP1 subjects entered a 7-12-day Wash-out Period prior to initiating Treatment Period 2 (TP2). In TP2, subjects were dosed with either duvelisib or placebo (whichever was not given in TP1) for 13 days, after which they were again admitted to the clinic and underwent a second allergen challenge with accompanying efficacy assessments on TP2 Day 14 and Day 15. For Cohort 3, in TP1, subjects self-administered either duvelisib 25 mg BID or placebo at home for 4 days. On TP1 Day 5, subjects were admitted to the clinic and underwent the same assessments as Cohorts 1 and 2 but on TP1 Day 5 and Day 6. After completing TP1 subjects entered a 16-21-day Wash-out Period prior to initiating TP2. In TP2, subjects were dosed with either duvelisib or placebo (whichever was not given in TP1) for 4 days, after which they were admitted to the clinic and underwent a second allergen challenge with accompanying efficacy assessments on TP2 Day 5 and Day 6. Subjects returned to the clinic for a Follow-up Safety Visit 7-10 days after the last dose of study drug (duvelisib or placebo) during TP2. A final Safety Phone Screen occurred 21±2 days after the last dose of study drug.

An adaptive approach was used to determine the dose and regimen in Cohort 2. When all subjects in Cohort 1 had completed both treatment periods of the study, selected unblinded efficacy data were analyzed to determine whether duvelisib affected lung function and inflammation following allergen challenge, and if so what was the magnitude of effect. In addition, selected unblinded safety laboratory, and blinded adverse event data from Cohort 1 were examined prior to selection of the next dose regimen in Cohort 2. Dose selection for Cohort 3 was informed based on the unblinded efficacy and safety results from Cohorts 1 and 2 in conjunction with safety data obtained from other ongoing clinical studies with duvelisib. Enrollment in Cohort 3 was staggered to allow an initial assessment of safety in the first 5 subjects (through TP1) prior to enrolling the full complement of subjects. Following completion of TP1 dosing of these 5 subjects, blinded adverse events and safety laboratory results from these 5 subjects were reviewed by the Sponsor. As no new significant safety findings were observed, the remaining subjects were enrolled to complete the cohort.

Lung function, inflammatory indices, and other endpoints were assessed before and after each allergen challenge. AEs were collected throughout the study, and safety laboratory samples were collected at each study visit through the 7-10 day Safety Follow-up Visit.

Name of Sponsor/Company: Infinity Pharmaceuticals, Inc. **Name of Finished Product:** Duvelisib **Name of Active Ingredient:** IPI-145	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

Number of subjects (planned and analyzed):

A total of 30 to 45 subjects were planned with approximately 15 (±3) subjects per dose cohort. A total of 50 subjects were enrolled (14 subjects in Cohort 1, and 18 subjects in each of Cohorts 2 and 3). Forty-seven subjects completed the study with 3 subjects withdrawing during TP1.

Diagnosis and main criteria for inclusion:

Subjects were required to have:

- A previously documented diagnosis of asthma for at least 6 months prior to Screening or a history of at least 6 months of episodic symptoms of airflow obstruction such as wheezing and/or chest tightness with other significant lung diseases ruled out (e.g., chronic obstructive pulmonary disease [COPD])
- A forced expiratory volume in 1 second (FEV_1) ≥70% of predicted value at Screening (based on American Thoracic Society [ATS]/ European Respiratory Society [ERS] standards)
- A positive skin prick test to test allergen (defined as the induration of skin test wheal ≥2 mm larger in diameter than the diameter of the control wheal)
- An early-phase asthmatic response (EAR) of at least 20% and a late-phase asthmatic response (LAR) of at least 15% to inhaled allergen challenge [response defined as a decrease from pre-challenge in FEV_1 on 2 consecutive occasions within 0 to <3 hours of last allergen challenge administered for EAR and within 3 to 10 hours for LAR]

Test product, dose and mode of administration:

Duvelisib, 1.0 mg, 5.0 mg, and 25.0 mg in capsule administered orally.

Duration of treatment:

Up to 40 days plus a 7-10 day follow-up period with a final Safety Phone Screen 21±2 days after the last dose of study drug.

Reference therapy, dose and mode of administration:

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

Name of Sponsor/Company: Infinity Pharmaceuticals, Inc. **Name of Finished Product:** Duvelisib **Name of Active Ingredient:** IPI-145	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

Criteria for evaluation:

Efficacy:

Primary Efficacy Endpoints:

The maximal decrease from pre-allergen challenge in FEV_1 following allergen challenge for the EAR and the maximal decrease from pre-allergen challenge in FEV_1 following allergen challenge for the LAR.

Secondary Efficacy Endpoints:

- Area under the curve (AUC) of FEV_1 following allergen challenge
- Provocative concentration of methacholine inducing a 20% fall in FEV_1 (PC20) following allergen challenge
- Concentration of exhaled nitric oxide (NO) after allergen challenge
- Change in C-reactive Protein (CRP) levels from Screening and/or Day 1 of each treatment period over the course of the study

Biomarker Endpoints:

- Change in serum and plasma protein biomarkers associated with inflammation and/or PI3K pathway activity in relation to allergen challenge and/or study drug activity from Day 1 to Day 14, and Day 15 of both treatment periods (Cohorts 1 and 2); and serum protein biomarkers associated with inflammation and/or PI3K pathway activity in relation to allergen challenge and/or study drug activity from Day 1 to Day 5, and Day 6 of both treatment periods (Cohort 3)
- Changes in differential count and markers of PI3K pathway activity in induced sputum from Screening to Day 15 of TP1 (Cohorts 1 and 2) and Day 15 of TP2 (Cohorts 1 and 2)

Pharmacokinetics:

- Pharmacokinetic parameters, including maximum concentration (C_{max}), AUC, terminal elimination half-life ($t_{1/2}$), derived from plasma duvelisib and IPI-656 concentrations

Safety:

Safety Endpoints:

- Treatment Emergent Adverse events (TEAEs)
- Safety laboratory findings

Name of Sponsor/Company: Infinity Pharmaceuticals, Inc. **Name of Finished Product:** Duvelisib **Name of Active Ingredient:** IPI-145	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

Statistical methods:

A sample size of 10 subjects per cohort provided an 80% probability of detecting a 12% difference in maximal percent decrease in FEV_1 during the LAR between placebo and duvelisib, assuming 2-sided alpha = 0.05 and a standard deviation of 10.5% for within-subject differences. With 10 subjects there was also 80% power to detect a 12% difference in maximal percent decrease in FEV_1 during the EAR between placebo and duvelisib assuming an 2-sided alpha = 0.05 and a standard deviation of 10.9% for within-subject differences.

To test the treatment effect on the primary endpoints of a change in either EAR or LAR, a mixed effects model was fitted. The model included fixed effects for treatment, period, sequence and FEV_1 at Day 1 of the corresponding period, and a random effect for subjects within sequence. This model was used for every cohort.

Secondary endpoints were analyzed using the same mixed effects model described above.

Subjects who did not complete the allergen challenge for both TP 1 and TP 2 were considered un-evaluable for purposes of the primary efficacy analysis; these subjects could be replaced. Data from un-evaluable subjects was collected and presented descriptively and included in analyses where appropriate. To maintain subject balance for the analysis of the primary endpoint, replacement subjects were assigned the same treatment sequence as was assigned to the un-evaluable subject they were replacing.

No adjustment for multiple comparisons was made.

Selected biomarkers of inflammation and/or PI3K pathway activity in serum (all cohorts) and/or plasma (Cohorts 1 and 2) were summarized by treatment and time, as applicable, using descriptive statistics.

Individual duvelisib and IPI-656 plasma concentrations were tabulated with descriptive statistics and PK variables were calculated from duvelisib and IPI-656 plasma concentration data using standard non-compartmental methods.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 16.1. All treated subjects were included in the assessment of safety.

SUMMARY – CONCLUSIONS

Study IPI-145-03 was the first study to evaluate duvelisib, a dual oral inhibitor of PI3K-δ,γ in an inflammatory disease (mild, allergic asthma).

EFFICACY RESULTS:

The primary efficacy endpoints were the maximum reductions from post-saline, pre-challenge in FEV_1 measured over the EAR and the LAR following the TP Day 14 (Cohorts 1 and 2) allergen challenge and the TP Day 5 (Cohort 3) allergen challenge.

For the primary endpoints, the difference between the change in mean post-challenge FEV_1 for duvelisib treatment vs the change for placebo nearly achieved statistical significance ($p = 0.0517$) for the LAR at the dose of 25 mg Q12hours × 5 days; however, there was no statistically significant difference in treatment effect on the change in post-challenge FEV_1 in the EAR for any cohort

Name of Sponsor/Company: Infinity Pharmaceuticals, Inc.	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Duvelisib		
Name of Active Ingredient: IPI-145		

($p \geq 0.4571$). In a pre-specified sensitivity analysis, the difference in mean percent change in FEV_1 for the LAR at this dose was statistically significant ($p = 0.0364$). Similarly, for the secondary endpoints, the difference between duvelisib treatment and placebo in the FEV_1 AUC, and the $\log_e$ PC_{20} of the methacholine challenge ($p = 0.0132$ and $p = 0.0362$, respectively). Also at this dose, for the secondary endpoint of a change in NO after allergen challenge there was a statistically significant decrease with placebo dosing at 6 hours after the allergen challenge ($p = 0.0235$) as compared to duvelisib dosing. At 24 hours after the challenge, there was no statistically significant treatment effect in the change from Day 5, pre-challenge ($p = 0.3962$). No statistically significant changes were observed for plasma CRP levels following treatment with duvelisib compared to placebo treatment.

Seventy-two biomarkers in plasma and serum were analyzed for Cohort 2 (5 mg Q12hour × 14 days) and for Cohort 3 (25 mg Q12hour × 5 days). In Cohort 2, after 14 days of duvelisib treatment CXCL13 CXCL10, and CCL22 showed a statistically significant reduction with duvelisib treatment compared to placebo following the allergen challenge. In Cohort 3, 8 analytes: CXCL10, CXCL13, CCL17, CCL22, MMP-2, MMP-9, TGFα, and TNFα showed a statistically significant decreases with duvelisib treatment compared to placebo. IL-5 increased upon allergen challenge in the placebo group in Cohort 2 and Cohort 3, while following duvelisib treatment a similar increase was not exhibited in Cohort 3 indicating an allergen challenge dependent change that was ameliorated by duvelisib treatment. CCL17 and MMP-10 showed an allergen-dependent change in plasma levels following the allergen challenge on Day 5 that were mitigated by duvelisib treatment ($p = 0.0218$ and $p = 0.0007$, respectively). Many of the analytes that displayed a significant change are known to be involved in the T_H2 asthmatic inflammatory response.

PHARMACOKINETIC RESULTS:

The PK parameters were generally comparable to those previously observed in healthy subjects (1 mg and 5 mg) and subjects with hematological malignancies (25 mg). The 25 mg Q12 hour dose exceeded the IC_{50} for the γ isoform for approximately 6 hours and exceeded the IC_{50} for the δ isoform throughout the 12-hour dosing interval. The 5 mg Q12hours dose exceeded IC_{50} for the δ isoform for approximately 6 hours.

SAFETY RESULTS:

Overall, duvelisib was well tolerated in the dose regimens tested. The majority of adverse events were mild, with no severe adverse events reported. There were no deaths or SAEs reported. Only 1 TEAE that occurred during treatment with placebo resulted in study drug discontinuation. The rate of TEAEs was highly variable across cohorts, both during treatment with duvelisib and during treatment with placebo, with TEAE rates for duvelisib rates ranging from 39% to 75%, and for placebo from 44% to 83%. There was no dose response in the number or frequency of TEAEs experienced during duvelisib treatment and the incidence of TEAEs was generally comparable to that observed during placebo treatment.

The most frequent TEAEs were headache, nausea, and vomiting; although vomiting was only reported during treatment with placebo. There was little difference in the incidence of headache between treatment with duvelisib and treatment with placebo. Nausea was slightly more common during treatment with duvelisib than during treatment with placebo but there was no dose-dependent

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increase in incidence, and the incidence, by cohort, during treatment with placebo paralleled that observed with duvelisib. Five subjects in Cohort 3 had clinically nonsignificant decreases in neutrophil counts on Day 5. Isolated LFT changes were observed but with no apparent dose or time pattern.

Although the number of subjects was small, the expected AEs, particularly at the 25 mg Q12h dose, based on the data from oncology studies were not observed; in particular, the rate of infections was low and similar for duvelisib and placebo treatments; the rates of TEAEs in the SOC of Gastrointestinal Disorders was similar during treatment with duvelisib and with placebo; also, there was only 1 change in LFTs that was reported as a TEAE, a subject in in Cohort 3 had a laboratory finding of hepatic enzymes increased which was reported as a TEAE of moderate severity and occurred during treatment with placebo.

CONCLUSION:

Duvelisib demonstrated biologic activity at 25 mg Q12hours × 5 days (the highest dose tested) in the allergen challenge model with an acceptable safety profile. Although the primary endpoints in this study were not met, treatment with duvelisib demonstrated proof of principle that inhibition of PI3K-δ,γ can have a positive effect on many of the clinical parameters used to monitor allergic asthma, as well as an effect on several biomarkers known to be involved in asthma pathogenesis; therefore, duvelisib may have a role in the therapy of allergic asthma.

Date of the report:

20 July 2015