NOVARTIS

Sponsor

Novartis

Generic Drug Name

LFF571

Therapeutic Area of Trial

Infectious Diseases

Approved Indication

Mild and Moderate Clostridium difficile infections

Protocol Number

CLFF571X2201

Title

Multi-center, randomized, evaluator-blind, active-controlled, parallel-group design to determine safety, tolerability, and efficacy of multiple daily administration of LFF571 for 10 days in patients with moderate *Clostridium difficile* infections

Study Phase

Phase II

Study Start/End Dates

First patient enrolled: 10-Feb-2012

Last patient completed: 17-Jul-2013 (end of study visit)

If terminated early: Give reason for early termination.

The study was terminated early after the interim analysis because the observed sustained cure rate among the patients enrolled up to that point predicted that with continued enrollment, it was unlikely that LFF571 could be differentiated from fidaxomicin in

terms of a better sustained cure rate as defined by a rate of at least 75% (probability <1%).

Study Design/Methodology

This was a multi-center, randomized, evaluator-blind, parallel-group study, designed to determine safety, tolerability, and efficacy of multiple daily administrations of LFF571 for 10 days in patients with mild to moderate *C. difficile* infections. This study part was subsequent to an original earlier proof-of-concept part, and was introduced as an adaptive dose ranging phase to evaluate the efficacy and safety profile of four different LFF571 dose regimens: 100 mg twice daily (bid), 200 mg bid, 400 mg bid, and LFF571 400 mg once daily (qd).

Centers

In total there were seven centers that enrolled patients into the study, located in Canada (2), and the United States (5)

Publication

N.A.

Objectives

Primary

- To evaluate the clinical response (clinical cure) rates of patients with mild and moderate C. difficile infections to different LFF571 dose regimens and total daily doses administered orally for 10 days.
- To characterize the dose-response relationship of different dose regimens and total daily doses of LFF571
- To assess the safety and tolerability of different LFF571 dose regimens and total daily doses administered orally for 10 days to C. difficile infected patients.

Secondary

- To evaluate the time to resolution of diarrhea during the treatment period for oral LFF571 in C. difficile infected patients.
- To evaluate the serum concentrations of oral LFF571 following different dose regimens in C. difficile infected patients.
- To evaluate the fecal concentrations of LFF571 following different oral LFF571 dose regimens in C. difficile infected patients.
- To evaluate the sustained response (sustained clinical cure) rate and clinical relapse rate at 30 days following completion of different oral LFF571 dose regimens.
- To evaluate the microbiological response to different oral LFF571 dose regimens in patients with mild and moderate C. difficile infections.

- To evaluate the relationship of C. difficile susceptibility to LFF571 and clinical response (clinical cure).
- To evaluate the relationship of C. difficile susceptibility to LFF571 and tufA or tufB genotype.

Outcome Measures

Efficacy: The primary efficacy variable was the rate of Clinical Cure at end-of treatment in the mITT population. This parameter was derived from a summary of the clinical outcomes (clinical cure, clinical improvement, failure, or indeterminate) by treatment at EOT and at EOS visits of patients in the LFF571 treatment groups based on investigator assignment.

Secondary efficacy variables were sustained clinical cure, clinical relapse, microbiological response, time to diarrhea resolution and number of bowel movements. These variables were based on clinical outcomes, clinical signs and symptoms, microbiological response data, and from the Bowel movement record and Bristol Stool Chart taken from the patient diary.

.

Test Product (s), Dose(s), and Mode(s) of Administration

The investigational drug, LFF571 100 mg capsules, was prepared by Novartis and supplied to the Investigator as open-labeled, individual patient bottles (22 or 42 capsules per bottle).

Statistical Methods

In the primary analysis (first interim analysis), the relationship between total daily dose and dosing regimen and clinical response (clinical cure) was explored by logistic regression. Covariates for total daily dose and dosing frequency were included. A dose-response model was used to characterize the smallest daily dose and associated dosing frequency at which the clinical cure rate is likely to exceed 90%. Data from study part 1 could be included in the dose-response analysis. In addition to the logistic regression analyses, 90% two-sided confidence intervals were formed for the clinical cure rates.

For secondary efficacy analysis, survival analysis was performed on the time to diarrhea resolution. Sustained clinical cure rate and clinical relapse rate at 30 days following completion of treatment and 90% two-sided confidence intervals were presented for each treatment regimen. All efficacy analyses were performed on the mITT and per-protocol populations.

After the first interim analysis, the study was terminated and further interim analyses as originally planned were not carried out.

Criteria for evaluation

Efficacy: The primary efficacy variable was the rate of Clinical Cure at end-of treatment in the mITT population. This parameter was derived from a summary of the clinical outcomes (clinical cure, clinical improvement, failure, or indeterminate) by treatment at EOT and at EOS visits of patients in the LFF571 treatment groups based on investigator assignment.

Secondary efficacy variables were sustained clinical cure, clinical relapse, microbiological response, time to diarrhea resolution and number of bowel movements. These variables were based on clinical outcomes, clinical signs and symptoms, microbiological response data, and from the Bowel movement record and Bristol Stool Chart taken from the patient diary.

Safety: Safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), with their severity (CTCAE Grade) and relationship to study drug (suspected or not suspected), and pregnancies. They included the regular monitoring of hematology, blood chemistry and urine, and regular assessments of vital signs, physical condition and body weight.

Bioanalytics: Samples were taken at each scheduled collection time-point during the study to measure the LFF571 serum concentrations. The associated serum PK parameters for individual patients were calculated. At the end-of-therapy, fecal samples were collected where possible on Day 12, and fecal concentrations measured; the associated fecal PK parameters were also calculated and presented by patient.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

- Males and females between 18 and 90 years of age, inclusive.
- Diagnosed with primary episode or first relapse of moderate C. difficile infection. Received ≤24 hours of therapy effective for C. difficile infection prior to enrollment.

Exclusion criteria

- Severe C. difficile infection •
- Expected to require more than 10 days of C. difficile infection treatment. •
- More than one prior episode of C. difficile infection within the prior 3 months. •
- Use of anti-peristaltic drugs (including tincture of opium, metoclopramide, loperamide),, cholestyramine, or colestipol Other protocol-defined inclusion/exclusion criteria may apply

Participant Flow

Patient disposition – n (%) of patients (Safety population)

	LFF571 100mg bid N=9 n (%)	LFF571 200mg bid N=10 n (%)	LFF571 400mg qd N=9 n (%)	LFF571 400mg bid N=10 n (%)	Total N=38 n (%)
Patients					
Completed	8 (88.9)	8 (80.0)	8 (88.9)	10 (100.0)	34 (89.5)
Discontinued	1 (11.1)	2 (20.0)	1 (11.1)	0	4 (10.5)
Main cause of discontinuation					
Adverse event(s)	0	0	1 (11.1)	0	1 (2.6)
Subject withdrew consent	0	1 (10.0)	0	0	1 (2.6)
Administrative problems	0	1 (10.0)	0	0	1 (2.6)
Death	1 (11.1)	0	0	0	1 (2.6)

Baseline Characteristics

Demographic summary by treatment group (all randomized patients)

Parameter		LFF571 100mg bid N=9	LFF571 200mg bid N=10	LFF571 400mg qd N=9	LFF571 400mg bid N=10	Total N=38
Age (years)	Mean (SD)	60.7 (25.2)	59.4 (21.2)	63.1 (17.2)	65.4 (15.7)	62.2 (19.4)
	Median	75.0	62.0	65.0	68.5	65.5
	Range	20, 86	28, 89	27, 83	34, 87	20, 89
Gender – n (%)	Male	3 (33.3)	2 (20.0)	3 (33.3)	3 (30.0)	11 (28.9)
	Female	6 (66.7)	8 (80.0)	6 (66.7)	7 (70.0)	27 (71.1)
Race - n(%)	Caucasian	9 (100.0)	10 (100.0)	9 (100.0)	10 (100.0)	38 (100.0)
Ethnicity - n(%)	Other	9 (100.0)	10 (100.0)	9 (100.0)	10 (100.0)	38 (100.0)
Weight (kg)	Mean (SD)	67.1 (19.0)	67.8 (22.5)	70.9 (10.9)	81.4 (20.7)	72.1 (19.5)
	Median	63.0	67.7	71.0	81.9	70.0
	Range	47.9, 108.6	41.0, 112.3	55.8, 90.0	49.9, 122.7	41.0, 122.7
Height (cm)	Mean (SD)	166.1 (8.7)	164.1 (9.5)	169.4 (6.7)	166.0 (8.3)	166.2 (8.3)
	Median	166.6	164.3	167.6	163.9	165.1
	Range	152, 179	150, 178	162, 178	155, 180	150, 180
BMI (kg/m^2)	Mean (SD)	24.2 (5.8)	25.3 (8.1)	24.6 (2.3)	29.5 (7.3)	26.1 (6.7)
	Median	23.0	27.0	24.0	28.4	25.7
	Range	18.1, 33.9	13.5, 38.8	21.3, 28.4	20.0, 46.4	13.5, 46.4

Safety Results

Number of patients with AEs by primary system organ class (Safety analysis set)

	LFF571 100mg bid N=9 n (%)	LFF571 200mg bid N=10 n (%)	LFF571 400mg qd N=9 n (%)	LFF571 400mg bid N=10 n (%)	Total N=38 n (%)
Patients with any AE(s)	6 (66.7)	7 (70.0)	6 (66.7)	9 (90.0)	28 (73.7)
System organ class					
Gastrointestinal disorders	2 (22.2)	4 (40.0)	4 (44.4)	4 (40.0)	14 (36.8)
Nervous system disorders	2 (22.2)	2 (20.0)	1 (11.1)	4 (40.0)	9 (23.7)
Infections and infestations	1 (11.1)	1 (10.0)	0	5 (50.0)	7 (18.4)
General disorders and administration site conditions	0	1 (10.0)	3 (33.3)	1 (10.0)	5 (13.2)
Investigations	1 (11.1)	1 (10.0)	1 (11.1)	1 (10.0)	4 (10.5)
Respiratory, thoracic and mediastinal disorders	1 (11.1)	1 (10.0)	0	1 (10.0)	3 (7.9)
Cardiac disorders	0	0	2 (22.2)	0	2 (5.3)
Eye disorders	1 (11.1)	0	1 (11.1)	0	2 (5.3)
Injury, poisoning and procedural complications	1 (11.1)	0	1 (11.1)	0	2 (5.3)
Metabolism and nutrition disorders	0	0	1 (11.1)	1 (10.0)	2 (5.3)
Musculoskeletal and connective tissue disorders	1 (11.1)	0	0	1 (10.0)	2 (5.3)
Psychiatric disorders	1 (11.1)	0	1 (11.1)	0	2 (5.3)
Renal and urinary disorders	0	0	0	2 (20.0)	2 (5.3)
Blood and lymphatic system disorders	0	0	0	1 (10.0)	1 (2.6)
Ear and labyrinth disorders	1 (11.1)	0	0	0	1 (2.6)
Skin and subcutaneous tissue disorders	0	1 (10.0)	0	0	1 (2.6)

Arranged in descending order of frequency in total column / alphabetically

Number of patients with frequent AEs (>5% patients in total) by preferred term (Safety analysis set)

	LFF571 100mg bid N=9 n (%)	LFF571 200mg bid N=10 n (%)	LFF571 400mg qd N=9 n (%)	LFF571 400mg bid N=10 n (%)	Total N=38 n (%)
Patients with any AE(s)	6 (66.7)	7 (70.0)	6 (66.7)	9 (90.0)	28 (73.7)
Preferred term					
Nausea	1 (11.1)	2 (20.0)	1 (11.1)	3 (30.0)	7 (18.4)
Headache	2 (22.2)	1 (10.0)	0	2 (20.0)	5 (13.2)
Diarrhoea	0	1 (10.0)	2 (22.2)	1 (10.0)	4 (10.5)
Constipation	0	1 (10.0)	1 (11.1)	1 (10.0)	3 (7.9)
Abdominal pain	0	1 (10.0)	1 (11.1)	0	2 (5.3)
Back pain	1 (11.1)	0	0	1 (10.0)	2 (5.3)
Clostridium difficile infection	0	0	0	2 (20.0)	2 (5.3)
Fatigue	0	1 (10.0)	1 (11.1)	0	2 (5.3)
Oedema peripheral	0	0	1 (11.1)	1 (10.0)	2 (5.3)
Renal failure acute	0	0	0	2 (20.0)	2 (5.3)
Urinary tract infection	0	0	0	2 (20.0)	2 (5.3)
Vomiting	0	0	1 (11.1)	1 (10.0)	2 (5.3)

Arranged in descending order of frequency in total column / alphabetically

Overview of treatment-emergent adverse events (Safety analysis set)

	LFF571 100mg bid N=9 n (%)	LFF571 200mg bid N=10 n (%)	LFF571 400mg qd N=9 n (%)	LFF571 400mg bid N=10 n (%)	Total N=38 n (%)
Any adverse event	6 (66.7)	7 (70.0)	6 (66.7)	9 (90.0)	28 (73.7)
Any adverse event possibly related to study drug	3 (33.3)	2 (20.0)	1 (11.1)	6 (60.0)	12 (31.6)
Study drug discontinuation due to an adverse event	0	0	2 (22.2)	0	2 (5.3)*
Any serious adverse event	1 (11.1)	0	2 (22.2)	2 (20.0)	5 (13.2)
Any serious adverse event possibly related to study drug	0	0	1 (11.1)	2 (20.0)	3 (7.9)
Death	1 (11.1)	0	0	0	1 (2.6)**

*Both events were SAEs, no non-serious AEs led to discontinuation of study drug
**One further death (pat.400/112 in 400 mg bid group) was reported on Day 42 after study completion on Day 35, so does not appear on the end of study status listing 16.2.1-1.1
N = total number of patients; n = number of patients at least one adverse event in each category.

Other Relevant Findings

Deaths

One patient died during the study. The death was not suspected to be related to study drug. One further patient who completed the study on Day 35 was later reported to have died on

Day 42. Because the death was outside the study follow-up period, this event does not appear on the clinical database listings. Both deaths occurred in patients who had experienced SAEs

Conclusion

In conclusion, LFF571 was effective for the treatment of C. difficile infections. LFF571 treatment was well tolerated.

Date of Clinical Trial Report

26 June 2014

Date Inclusion on Novartis Clinical Trial Results Database

8 July 2014

Date of Latest Update