Name of sponsor/company:	InfectoPharm GmbH, Von-Humboldt-Str. 1, 64646 Heppenheim
Name of finished product:	InfectoDiarrstop® LGG® Mono Beutel
Name of active substance:	Lactobacillus rhamnosus GG (LGG®)

Title of study:

Multicentre, prospective, double-blind, two-armed, placebo-controlled phase III study to evaluate the efficacy and safety of the treatment of diarrhoea with Lactobacillus rhamnosus GG (InfectoDiarrstop® LGG® Mono) in infants and toddlers

Study code:

DIALAGG

EudraCT-No.: 2012-002291-13

Investigators / study centres:

8 active centres, i.e. centres which screened at least one patient, in Germany (4) and Poland (4).

Studied period:

First patient first visit: January 11, 2013

Last patient last visit: November 25, 2013

Phase of development:

Phase III study

Objectives:

The primary objective of the study was the duration of diarrhoea (time until therapeutic success, i.e. end of the diarrhoea, defined as ≤ 3 watery and/or loose stools per day during the past 2 days without recurrence of the diarrhoea until completion of the treatment).

Secondary objectives of the study were:

- Therapeutic success at the control visit on Day 5
- Therapeutic success at the final examination on Day 10
- Termination due to inefficacy on Day 2 and until Day 10
- Number of watery and/or loose stools on each day during the treatment phase
- Number of bloody stools on each day during the treatment phase
- Number of patients with vomiting analysed for each day during the treatment phase
- Grade of dehydration (mild/moderate/severe)
- Dropout cases (number and reasons)
- Adverse events (AEs) (including seriousness and relationship to study drug)

Methodology:

This study was designed as a multicentre, prospective, double-blind, two-armed, placebo-controlled phase III study with parallel group design.

The study consisted of a start visit (V0) at day 0 (start of treatment), two control visits at day 2 (V2) and day 5 (V5) as well as a final visit (V10) at day 10 (end of treatment).

Number of patients (planned, enrolled and analysed):

A total of 150 patients (2 x 66 + 2 x 9 in reserve) were planned to be enrolled in order to permit 132 evaluable patients (66 per treatment group). Overall, 150 patients were treated in the study, 73 in the verum group (treatment with LGG®) and 77 in the reference group (treatment with placebo). A total of 151 patients were enrolled and, except for one screening dropout, all received at least one dose of the study medication.

An overview of the analysis populations is given below.

Analysis population	LGG®	Placebo	Total
Safety	73	77	150
Full Analysis Set (FAS)	73	77	150
Per Protocol (PP)	70	76	146

Diagnosis and main criteria for inclusion:

Male or female infants and toddlers, aged 28 days to 24 months, with clinically diagnosed diarrhoea (> 3 watery and/or loose stools during the past 24 hours).

Main exclusion criteria:

- Diarrhoea for more than 3 days (72 hours)
- Diarrhoea after a stay abroad
- Bloody stools
- Fever
- Dehydration > 5% (loss in weight)
- Systemic treatment with antibiotics (currently or during the past 24 hours)
- Malnutrition (according to clinician's assessment)
- Severe or chronic disease of the gastrointestinal tract
- Short bowel syndrome
- Phenylketonuria
- Clinically relevant primary or secondary immunodeficiency
- Malignant tumour, chemotherapy, or radiotherapy (currently or during the past 6 months)
- Other severe diseases that the investigator assesses as conflicting with the participation Premature infants (gestational age < 38 weeks)
- Lactose intolerance
- Hypersensitivity to the active pharmaceutical ingredient or any other ingredient of the study medication
- Intake of highly dosed probiotics (> 109 colony forming units (CFU)/day during the past 7 days before inclusion)
- Other antidiarrhoeal medical therapies (currently or during the past 7 days)
- Inability of the parents to understand the instructions of the study Obvious unreliability of the parents or missing willingness to cooperate

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

Lactobacillus rhamnosus GG (InfectoDiarrstop® LGG® Mono), 1 sachet twice a day (morning and evening) for 10 days, suspended in as little water as possible – in addition to initially started oral rehydration solution (ORS) according to ESPGHAN recommendations. Batch number: D061201 (blinded on study medication).

Duration of treatment:

The study medication was to be administered for a maximum of 10 days.

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

Placebo, 1 sachet twice a day (morning and evening) for 10 days, suspended in as little water as possible – in addition to initially started ORS according to ESPGHAN recommendations.

Criteria for evaluation:

Efficacy:

The primary efficacy endpoint of the study was the duration of diarrhoea, i.e. the time until therapeutic success (end of diarrhoea), defined as ≤ 3 watery and/or loose stools per day during the past 2 days without recurrence of the diarrhoea until the end of the treatment. The first day without diarrhoea was classed as the end day of diarrhoea.

The number of diarrhoeal (watery and/or loose) stools were determined from the parent's recordings in the diary and transferred into the CRF by the investigator.

Secondary efficacy endpoints:

- Therapeutic success at the control visit on Day 5
- Therapeutic success at the final examination on Day 10
- Termination due to inefficacy on Day 2 and until Day 10
- Number of watery and/or loose stools on each day during the treatment phase
- Number of bloody stools on each day during the treatment phase
- Number of patients with vomiting analysed for each day during the treatment phase.

The number of diarrhoeal (watery and/or loose) stools, bloody stools, and vomiting events were determined from the parent's recordings in the diary and transferred into the CRF by the investigator. The grade of dehydration was determined by the investigator at each visit as mild (< 5 %), moderate (5-10 %), or severe (> 10 %).

Safety:

Safety endpoints were:

- Incidence and type of AEs and adverse drug reactions (ADRs) during the study
- Number of patients who drop out during the study including the reasons
- Vital signs comprising arterial blood pressure and heart rate.

Statistical methods:

Continuous variables were described using the following summary statistics: Number of patients with data (N), mean and standard deviation (SD), minimum (min), 1st quartile (Q1), median, 3rd quartile (Q3) and maximum (max). For ordered categorical data and nominal data, absolute and relative frequencies (in %) were calculated.

Demographic data and baseline characteristics were summarised descriptively for all patients in the FAS and PP population. To detect a possible imbalance between the two treatment groups, descriptive statistics were conducted stratified by the two groups LGG® and placebo.

All efficacy analyses were based on the FAS population as well as the PP population. For the confirmatory analysis of the primary efficacy variable, "duration of diarrhoea" was compared between the treatment groups using the t test at the one-sided significance level of 2.5 %. If the patient prematurely terminated the treatment without response, "duration of diarrhoea" was the treatment duration so far plus three (3) days. The confirmatory analysis was conducted on the FAS population. A sensitivity analysis was performed using the PP population. The secondary efficacy parameters were analysed using descriptive statistics. They were also tested one-sided for superiority of InfectoDiarrstop® LGG® Mono to placebo in an exploratory manner.

All safety analyses were carried out on all observed data throughout the entire safety population in a descriptive manner. No statistical tests were performed. The safety and tolerability of the study medication was assessed mainly by incidence and type of (serious) adverse events (S)AEs and (serious) adverse drug reactions (S)ADRs, respectively. AEs were displayed in summary tables, grouped on a coding term basis (MedDRA system organ class (SOC) and preferred term (PT)). The AEs were analysed with regard to their seriousness, intensity, relationship to study treatment, outcome, and action taken. Continuously distributed safety variables were analysed descriptively; categorically distributed variables were displayed in frequency tables.

No subgroup analyses or interim analyses were planned.

Summary / Conclusions:

Patient disposition:

	LGG®	Placebo	Total
Screened			151
Treated	73	77	150
Completed (up to day 10)	68	76	144

Efficacy results:

The primary objective of the study was the duration of diarrhoea (time until therapeutic success, i.e. end of the diarrhoea, defined as ≤ 3 watery and/or loose stools per day during the past 2 days without recurrence of the diarrhoea until completion of the treatment).

In the FAS the mean duration of diarrhoea was distinctly lower in the LGG® group (2.7 (SD: ± 2.5) days) than in the placebo group (3.9 (± 2.9) days). In the PP population the mean duration of diarrhoea in the LGG® group was 2.6 (± 2.5) days vs. 3.9 (± 3.0) days in the placebo group. The median was calculated as 2.0 days in the LGG® group for the FAS and PP population vs. 4.0 days and 3.5 days in the placebo group for the FAS and PP population, respectively. The difference between the two treatment groups was -1.22 days (95 % confidence interval: -2.10 to -0.35 days) in the FAS and -1.27 days (95 % confidence interval: -2.16 to -0.37 days) in the PP population, each in favour of LGG®.

The confirmatory analysis of the study, comparing the duration of diarrhoea between the treatment groups in the FAS, yielded a p value of 0.0066, two-sided t test. The result is significant one-sided at the 0.025 significance level and thus proves the superiority of LGG® compared to placebo.

Therefore, the alternative hypothesis (H_1), that the mean duration of diarrhoea for InfectoDiarrstop® LGG® Mono is shorter than that for placebo, can be accepted and the null hypothesis (H_0), that the mean duration of diarrhoea for InfectoDiarrstop® LGG® Mono is equal to or longer than that for placebo, can be rejected. This result was confirmed by a sensitivity analysis, performed for the PP population: Here, the comparison of the duration of diarrhoea between the treatment groups yielded a p value of 0.0061 (two-sided t test).

This effect of LGG® is also reflected by some of the secondary efficacy endpoints, e.g. the number of diarrhoeal stools and the incidence of vomiting, which is known to be often associated with acute diarrhoea.

At study day 5 and day 10, there was a high proportion of patients without diarrhoea in both treatment groups. At day 5 therapeutic success was slightly better in the LGG® group (80.8 % vs. 71.4 % in the placebo group) whereas at day 10 this small difference could no longer be observed (94.5 % vs. 96.1 % in the LGG® and placebo groups, respectively). Accordingly, the comparison of treatment groups by Fisher's exact test revealed no significant difference at both time points. Thus, the beneficial effect of LGG® treatment shown for the primary efficacy endpoint seems to take effect mainly before day 5, whereas after 5 to 10 days the natural course of the disease only allows a less pronounced benefit from LGG® treatment. None of the patients terminated the study prematurely due to inefficacy of study treatment on day 2.

The mean number of watery and/or loose stools decreased distinctly and continuously during the treatment phase from day 0 (6.0 and 6.3 in the LGG® and placebo groups, respectively) to day 10 (0.4 and 0.8 in the LGG® and placebo groups, respectively). It could be observed that from the first day of treatment until day 8 patients treated with LGG® had approximately one diarrhoeal stool less per day than patients in the placebo group. Accordingly, except for day 2, the comparison of the treatment groups using a t test yielded a significant difference in favour of the LGG® group at all time points (p-values < 0.05, two-sided). Only a few bloody stools were documented during the study, i.e. in 1 patient in the LGG® group at day 0 and day 2 and in 1 patient in the placebo group at day 8, day 9 and day 10.

Starting from comparable values at day 0 (45.2 % vs. 40.3 % of patients in the LGG® and placebo groups, respectively), the decrease in the number of patients with vomiting events during the treatment phase was distinctly stronger in the LGG® group, where already at day 5 only 1 patient (1.4 %) still had vomiting events. In the placebo group 22.1 % of patients still suffered from vomiting at day 5. During the first days of treatment the incidence of vomiting was remarkably reduced under LGG® treatment when compared to the incidence in the placebo group (-35 % at day 2, -63 % at day 3, -86 % at day 4). Also in the further progress until day 10, there was virtually no occurrence of vomiting in the LGG® group, whereas in the placebo group there was still a relevant proportion of patients with persistent vomiting until the end of treatment. Accordingly, the comparison of the treatment groups using Fisher's exact test yielded significant differences (p-values < 0.05, two-sided) in favour of the LGG® group at all time points from day 3 to day 9. This beneficial effect of LGG® on the incidence of vomiting corresponds very well to its effect on the duration of diarrhoea, as it is well-known that acute diarrhoea (e.g. caused by rotavirus) is often accompanied by vomiting.

Safety results:

Once the study drug administration had started, 21 AEs in 16 (21.9 %) of the 73 patients in the LGG® group and 23 AEs in 18 (23.4 %) of the 77 patients in the placebo group were reported. It can therefore be stated, that the frequency of patients who suffered from at least 1 AE during the study was similar in the two treatment groups.

Except for the MedDRA SOCs 'gastrointestinal disorders' (mainly vomiting) and 'infections and infestations' which were most frequently reported in both treatment groups, there were no MedDRA SOC or PT categories showing a particular frequency of events.

Only 1 of the AEs was judged by the investigators as potentially related to the study medication. This applied to an event of obstipation (MedDRA PT constipation) to a patient in the placebo group. The event was assessed as unexpected. It was of moderate intensity and required no study drug action or other action. At study end, the patient had not yet recovered. However, the obstipation was not present consistently but occurred from time to time. Except for this one event in the placebo group the patients had recovered from all other AEs at the end of the study.

The number of AEs which led to an exclusion of the patient from the study was low, i.e. 2 AEs (MedDRA PT diarrhoea and pyrexia) in 1 patient in the LGG® group and 2 AEs (MedDRA PT urinary tract infection and dehydration) in 1 patient in the placebo group. The investigators assessed all these AEs as not related to the study drug.

No patient died and no other SAEs occurred in the present study.

Regarding vital signs, only minimal changes between baseline and the following visits were observed with no relevant differences found between the two treatment groups.

Conclusion:

In summary, the results of the present study further confirm the efficacy and safety of InfectoDiarrstop® LGG® Mono in the treatment of acute diarrhoea in infants and toddlers, which is known from several previously performed clinical trials. Administration of LGG® in addition to ORS according to ESPGHAN significantly shortens the duration and, referring to the number of watery and/or loose stools, decreases the severity of diarrhoea. This beneficial effect is further substantiated by the analysed secondary parameters, e.g. the significant decrease of vomiting events and diarrhoeal stools over time. No serious AEs occurred in both treatment groups, no ADRs occurred under LGG® treatment, and the number of non-serious AEs did not differ between LGG® and placebo treatment. Therefore, InfectoDiarrstop® LGG® Mono and its active ingredient Lactobacillus rhamnosus GG can be considered as an effective and safe treatment option for the therapy of diarrhoea in infants and toddlers.

Date of (original) report:

14 November 2014