1 Study Synopsis

Name of Sponsor/Company: Helsinn Healthcare SA	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Test Drug /Investigational Product: Elsiglutide	Volume:	
Name of Active Ingredient: Elsiglutide (ZP1846)	Page:	
Title of Study: Phase II, Double-blind, Randomized, Two-stage, Placebo-controlled Proof of Concept Study in Colorectal Cancer Patients Receiving 5-FU-based Chemotherapy to Assess the Efficacy of Elsiglutide (ZP1846) Administered s.c. in the Prevention of Chemotherapy Induced Diarrhea (CID)		
Investigators: A list of the principal investigators for each site can be found in Appendix 16.1.4.		
Study Centre(s): The study was conducted in 19 study centers in 4 countries (Bulgaria, Hungary, Romania and Russia).		
Publication (Reference): none	**Phase of Development:** II	
Studied Period: Date of first patient first visit: 21 February 2012 Date of last patient last visit: 11 January 2013		
Objectives: The main objective of this proof of concept study was to obtain data on the efficacy of elsiglutide in preventing CID in patients with colorectal cancer receiving 5-FU based chemotherapy (FOLFOX4 or FOLFIRI regimen) in comparison to placebo. In addition, safety and tolerability of the administered repeated doses of elsiglutide were evaluated, and the pharmacokinetics (PK) of elsiglutide and its metabolites ZP2242 and ZP2712 were investigated in a subset of patients in each treatment arm.		
Methodology: This was a phase II, multicenter, double-blind, randomized, placebo-controlled, two-stage, proof of concept study with an interim futility analysis in colorectal cancer patients receiving 5-FU-based chemotherapy (FOLFOX4 or FOLFIRI) and administered elsiglutide subcutaneously (s.c.) for 4 consecutive days. Randomization was stratified by chemotherapy regimen. The patients were to receive a daily dose of 24 mg elsiglutide (or placebo) via a single s.c. injection for 4 consecutive days, starting from the first day of chemotherapy administration. The patients were to be hospitalized at least until Day 3. Further visits were scheduled for Days 4, 5 and 15 and for a Follow-up Visit on Day 28-32. Safety and tolerability were monitored throughout the study. The study was a two-stage trial with an interim futility analysis comparing elsiglutide and placebo. In the first stage, 29 patients were planned for each treatment, i.e. 29 patients were to receive 24 mg/day elsiglutide and 29 the matching placebo. The second stage was to be initiated at the same dose if more or the same number of responders (no-diarrhea patients) were seen in the elsiglutide arm compared to the placebo arm. Conversely, the null hypothesis could not be rejected, futility of the study was to be declared and the study was to be stopped. The Data Monitoring Committee (DMC) appointed for the study received the results of the interim analysis (including efficacy, safety and biomarker [citrulline] data) and provided a final recommendation as to continue the study.		

Number of Patients (Planned and Analysed):
Screened: 144 patients
Planned: 138 patients
Randomized and treated: 138 patients

	Number of patients		
	Placebo	24 mg/day Elsiglutide	Total
Safety set (SAF)	69	69	138
Intent-to-treat set (ITT)	69	69	138
Full analysis set (FAS)	69	69	138
Pharmacokinetic set (PK)	0	20	20

Diagnosis and Main Criteria for Inclusion: Female and male patients of at least 18 years of age with confirmed diagnosis of colorectal cancer and an Eastern Cooperative Oncology Group (ECOG) performance status ≤2, chemotherapy-naïve, and scheduled to receive a FOLFOX4 or FOLFIRI chemotherapy regimen.

Test Product, Dose and Mode of Administration, Batch Number:
Elsiglutide is a glucagon-like peptide 2 (GLP-2) agonist supplied as an acetate salt. A dose of 24 mg/day was administered via s.c. injection.
Batch number: [redacted]; expiry date: [redacted]

Duration of Treatment: Each patient received study medication for 4 consecutive days starting from the first day of chemotherapy administration.

Reference Therapy, Dose and Mode of Administration, Batch Number: Placebo (identical in composition to the active study drug except for elsiglutide and addition of acetic acid for pH adjustment) was administered in the same way as the active study drug.
Batch number: [redacted]; expiry date: [redacted]

Criteria for Evaluation:

Efficacy: The endpoint of primary interest was:

- Number of patients experiencing no diarrhea from Day 1 to Day 14

Secondary endpoints were:

- Proportion of patients experiencing grades ≥2 diarrhea at each day from Day 1 to Day 14 according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v. 4.03);
- Worst grade of diarrhea according to NCI-CTCAE at each day from Day 1 to Day 14;
- Time to occurrence of diarrhea, defined as the first day in which a grade ≥1 diarrhea was assessed (from Day 1 to day 14);
- Number of days with presence of grade ≥ 1 diarrhea (from Day 1 to Day 14);
- Number of days with presence of grade ≥ 2 diarrhea (from Day 1 to Day 14);
- Number of days with presence of at least one bowel movement accompanied by urgency (from Day 1 to 14);
- Number of days with presence of at least one episode of fecal incontinence (from Day 1 to 14);
- Proportion of patients who required i.v. fluids due to CID (from Day 1 to 14);

- Proportion of patients who required changes to the primary therapy (chemotherapy dose reduction, delay or change to regimen) due to CID as of Day 2, Day 14 and as of Day 28;
- Proportion of patients who used rescue medication (i.e. medication used for treatment of diarrhea) from Day 1 to Day 14.

To evaluate these endpoints, a patient diary was used. The patient diary was to be filled in daily from Day 1 to Day 14.

In addition, the proportion of patients who were limited concerning self-care Activities of Daily Living (ADL), the number of stools per day, the number of bowel movements accompanied by urgency per day, and the number of episodes of fecal incontinence per day were summarized for Day 1 to Day 14. Mean blood concentrations of citrulline (a biomarker for intestinal integrity, a decrease being indicative of an intestinal mucosal damage following chemotherapy) were summarized by treatment group for baseline, Day 5, and Day 15 including changes compared to baseline.

Pharmacokinetics: PK variables were assessed in a subset of patients in each treatment arm and included:

- Standard PK parameters to be determined for elsiglutide (ZP1846) and for its metabolites ZP2242 and ZP2712 (unless stated otherwise) for Day 1 and Day 4
- The effect of multiple dosing (dose linearity)
- Attainment of steady state based on trough plasma concentrations and accumulation

Safety: Safety was evaluated by monitoring:

- AEs
- Clinical laboratory parameters (hematology, blood chemistry, urinalysis)
- Vital signs (blood pressure [BP], pulse rate, body weight)
- Physical examination
- 12-lead electrocardiogram (ECG)
- Immunogenicity testing in a subset of patients

Statistical Methods:
The efficacy analysis (with the exception of citrulline data) was performed using patient diary entries from Day 1 to Day 14. Missing diary data were not imputed. The endpoint of primary interest for efficacy was the number of patients experiencing no diarrhea from Day 1 to Day 14 (defined as “responders”). The study hypothesis was that elsiglutide was superior to placebo with regard to the proportion of responders (i.e. no-CID patients) during Day 1 to Day 14. Superiority of elsiglutide over placebo was assumed if the difference in the number of patients without CID (elsiglutide – placebo) was larger than or equal to 5. The main primary efficacy analysis was conducted on the ITT set.
Descriptive statistical analyses for secondary efficacy endpoints were performed using the FAS. The statistics for continuous variables included number of available observations, mean, standard deviation (SD) and median (where applicable), minimum, and maximum. For categorical variables, the number and percentage of patients with a specific level of the variable were presented. All data were listed.

All safety analyses were performed for the SAF set descriptively. All data were summarized and listed. Treatment emergent AEs (TEAEs) were analyzed by system organ class (SOC) and preferred term (PT), relationship to study drug, relationship to chemotherapy, and intensity.
Laboratory data (hematology, blood chemistry and urinalysis) and immunogenicity data were summarized using frequency tables and shift tables. Frequency tables were prepared for physical examination data. Vital signs were summarized descriptively by visit and by differences compared to baseline. ECG data were summarized descriptively by visit and by differences compared to baseline and by using frequency tables.
PK parameters were derived by non-compartmental analysis of the plasma concentration data. Plasma concentrations, the effect of multiple dosing, accumulation and attainment of steady state were also evaluated graphically. All PK data were listed.

Summary – Conclusions:

Efficacy Results:
The study was a two-stage trial with an interim futility analysis comparing elsiglutide and placebo. In the first stage, a total of 58 patients were randomized to receive placebo (28 patients) or elsiglutide (30 patients). The interim analysis of the efficacy and safety data after Stage 1 yielded positive results, i.e. more responders (patients without diarrhea) were seen in the elsiglutide group (22 patients, 73.3%) compared to the placebo group (14 patients, 50.0%). Consequently, the DMC recommended continuing the study at the same dose.
For the overall trial, i.e. Stage 1 and Stage 2, (69 patients in each treatment group), superiority of elsiglutide to placebo was to be concluded if the difference in the number of responders (elsiglutide – placebo) was larger than or equal to 5. More patients were responders, i.e. had no diarrhea, in the elsiglutide group (43 patients) than in the placebo group (39 patients). As the difference between the treatment groups was <5 patients, superiority of elsiglutide over placebo could not be concluded.

Number of Responders[1] in the Period from Day 1 to Day 14
Intent-to-treat Set

	Placebo N = 69		24 mg/day Elsiglutide N = 69	
	n	**(%)**	**n**	**(%)**
Responder	39	(56.5)	43	(62.3)
Non-responder	30	(43.5)	26	(37.7)

[1]Responder was defined as a patient experiencing no diarrhea
N = number of patients in treatment group, n = number of patients with data available, % = percentage based on N.

The majority of patients did not have any diarrhea throughout the study. Overall, 6 more patients in the elsiglutide group than the placebo group had grade 1 diarrhea as worst grade during the study, but 10 more patients in the placebo group than the elsiglutide group had grade 2 diarrhea. Only 1 patient in each group had grade 3 diarrhea. The higher frequency of diarrhea grade ≥2 in the placebo group compared to the elsiglutide group was mostly due to differences at Days 5, 6, and 7.

Grade of Diarrhea According to NCI-CTCAE version 4.03 (Day 1 to Day 14)
Full Analysis Set

	Placebo N = 69		24 mg/day Elsiglutide N = 69	
Grade[1]	**n**	**(%)**	**n**	**(%)**
Grade 0	39	(56.5)	43	(62.3)
Grade 1	15	(21.7)	21	(30.4)
Grade 2	14	(20.3)	4	(5.8)
Grade 3	1	(1.4)	1	(1.4)
Grade <2	54	(78.3)	64	(92.8)
Grade ≥2	15	(21.7)	5	(7.2)

[1] Worst grade of diarrhea Day 1 to Day 14
NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events, % = percentage based on N.

In both treatment groups, the incidence of diarrhea increased on Day 2 and remained high up to Day 9. Diarrhea occurred most often 5 to 8 days after the first administration of chemotherapy. No clear differences between the treatment groups were observed.
While in the elsiglutide group the patients most often had diarrhea on 1 or 2 days, in the placebo group the likelihood of diarrhea on 3 or 4 days was as high as for 1 or 2 days. More than 4 days with diarrhea per patient were rare and similarly frequent in both treatment groups. No differences between treatments were detected for the number of days with bowel movements accompanied by urgency, number of days with fecal incontinence, patients requiring i.v. fluids, patients limited concerning ADL, patients requiring changes to primary therapy due to CID, patients needing rescue medication, and patients with diarrhea from Day 15 to follow-up.
Mean citrulline levels were similar in the treatment groups at baseline (placebo, 32.7 µmol/L; elsiglutide, 33.5 µmol/L). Mean levels decreased between Day 1 and Day 5 in both treatment groups, with a less pronounced decrease in the elsiglutide group than in the placebo group. Between Day 5 and Day 15, mean citrulline levels increased again in both treatment groups, with a more pronounced increase in the elsiglutide group than the placebo group. In the elsiglutide group, mean citrulline levels at Day 15 had even improved to above the baseline values (Day 15: placebo, 29.7 µmol/L; elsiglutide, 36.5 µmol/L).

Pharmacokinetic Results:
The mean elsiglutide (ZP1846) curves for Day 1 and Day 4 were similar. Scrutiny of the individual curves revealed that the Day 4 concentration curves were on the whole lower than those on Day 1 in 5 of the 20 patients. The mean ZP2242 curves for Days 1 and 4 were overall similar with possibly slightly higher concentrations on Day 4 than on Day 1, although in half of the patients the individual concentration curves were on the whole lower on Day 4 than on Day 1. The mean ZP2712 curve for Day 4 was slightly lower than for Day 1, particularly during the first few hours after dosing.

Summary of PK Parameters, PK set

Analyte	Statistic	t_{max} (h)	C_{max} (nM)	AUC_{0-t} (h*nM)	$AUC_{0-\infty}$ (h*nM)	λ_z (1/h)	$t_{1/2z}$ (h)
Elsiglutide (N=20)	n	20	20	20	7	7	7
Day 1	Mean	3.20	5.332	12.420	2.669	0.3600	2.14
	Median	2.00	0.6410	2.603	2.121	0.3933	1.76
	GeoMean	-	0.7621	3.044	2.438	-	-
	GeoCV (%)	-	180.6	181.5	49.0	-	-
Elsiglutide (N=19)	n	19	19	19	7	7	7
Day 1	Mean	3.26	0.639	3.273	2.669	0.3600	2.14
Excluding	Median	2.00	0.5970	2.538	2.121	0.3933	1.76
Patient 6088	GeoMean	-	0.5914	2.451	2.438	-	-
	GeoCV (%)	-	43.2	85.5	49.0	-	-
Elsiglutide (N=20)	n	20	20	20	6	7	7
Day 4	Mean	2.09	4.266	8.234	20.510	0.1458	5.99
	Median	2.00	0.7580	3.414	3.816	0.1293	5.36
	GeoMean	-	0.8049	3.390	6.169	-	-
	GeoCV (%)	-	162.1	131.9	284.6	-	-
Elsiglutide (N=19)	n	19	19	19	5	6	6
Day 4	Mean	2.10	0.6854	3.289	4.032	0.1571	5.52
Excluding	Median	2.00	0.7500	3.250	3.683	0.1575	4.55
Patient 6010	GeoMean	-	0.6352	2.833	3.514	-	-
	GeoCV (%)	-	44.0	68.6	68.4	-	-
ZP2242 (N=20)	n	20	20	20	17	18	18
Day 1	Mean	4.80	9.544	102.5	111.2	0.1056	7.04
	Median	4.00	7.105	79.60	84.18	0.1045	6.64
	GeoMean	-	8.223	84.85	89.28	-	-
	GeoCV (%)	-	57.8	68.3	73.8	-	-
ZP2242 (N=20)	n	20	20	20	9	11	11
Day 4	Mean	5.00	9.473	120.0	183.9	0.09172	9.15
	Median	4.00	7.945	98.61	144.0	0.06910	10.03
	GeoMean	-	7.709	101.2	154.3	-	-
	GeoCV (%)	-	71.2	66.4	73.5	-	-
ZP2712 (N=20)	n	20	20	20	6	6	6
Day 1	Mean	2.70	1.726	13.69	18.37	0.1457	5.32
	Median	2.00	1.635	12.23	20.26	0.1283	5.41
	GeoMean	-	1.646	11.86	16.33	-	-
	GeoCV (%)	-	32.8	60.7	66.9	-	-
ZP2712 (N=20)	n	20	20	20	7	7	7
Day 4	Mean	3.19	1.441	14.47	14.34	0.09530	8.33
	Median	2.00	1.315	10.89	13.82	0.08399	8.25
	GeoMean	-	1.300	12.57	13.00	-	-
	GeoCV (%)	-	50.4	58.8	54.0	-	-

AUC_{0-t} = area under the plasma concentration vs. time curve from time 0 to the time t of the last quantifiable concentration, or to t=24 h post-dose, whichever comes first; $AUC_{0-\infty}$ = AUC from time 0 to infinity; C_{max} = maximum plasma concentration; GeoCV = coefficient of variation for geometric mean; GeoMean = geometric mean; λ_Z = terminal elimination rate constant; N = number of patients in specified treatment group; n = number patients with data available; NA = not applicable; $t_{1/2Z}$ = apparent terminal elimination half-life; t_{max} = time of C_{max}; - = statistics not relevant

The t_{max} for elsiglutide (ZP1846) was most frequently observed at 2 h to 4 h post-dose, and for ZP2242 and ZP2712 most frequently at 2 h to 6 h post-dose.
Exposure, both in terms of AUC_{0-t} and $AUC_{0-\infty}$, to the metabolite ZP2242 was approximately 30-fold higher than exposure to the parent elsiglutide (ZP1846); exposure to ZP2712 was approximately 4-fold higher than exposure to the parent compound.
Examination of the data with regard to effects of multiple dosing on the pharmacokinetics did not result in a definitive outcome. In some patients, the exposure on Day 4 (for any or all of the analytes) was very low compared to that on Day 1 while for others the exposure was much higher, indicating that there was much variation between the patients.
Examination of the data with regard to accumulation upon multiple dosing did not result in a definitive outcome. Elsiglutide (ZP1846) geometric mean AUC_{0-t} values were slightly higher for Day 4 than for Day 1; 14 of the 20 patients had higher AUC_{0-t} values on Day 4 than on Day 1, suggesting that modest accumulation occurred. ZP2242 AUC_{0-24} values were available on both Day 1 and Day 4 for 13 patients. Of these, 9 patients had higher AUC_{0-24} values on Day 4 than on Day 1, suggesting that modest accumulation occurred. ZP2712 AUC_{0-24} values were available on both Day 1 and Day 4 in only 5 patients. Of these, 3 patients had higher AUC_{0-24} values on Day 4 than on Day 1. Considering that all patients had quantifiable pre-dose concentrations on Day 4, which suggests that accumulation occurs, it was expected that all patients would have higher AUC_{0-24} values on Day 4 than on Day 1.
The shape of the elsiglutide (ZP1846), ZP2242, and ZP2712 trough curves did not show a consistent pattern for all patients and in some cases initial peaks were followed by declines. The mean trough concentrations for elsiglutide (ZP1846) were close to or below the LLOQ of 50 pM throughout the study. A steady increase in mean ZP2242 trough concentrations was observed up to the last measurement on Day 5. A small increase in mean ZP2712 trough concentrations was observed up to the last measurement on Day 5.

Safety Results:
Altogether, 26.1% of patients in the placebo group and 36.2% of elsiglutide treated patients experienced at least 1 TEAE. Most TEAEs were of mild or moderate intensity. Three (3) AEs of severe intensity were reported for 2 patients in the placebo group and 2 AEs of severe intensity were reported by 2 patients in the elsiglutide group; of these, 1 AE (constipation) in the elsiglutide group was assessed as drug related by the investigator.
Gastrointestinal disorders was the most commonly reported SOC in the placebo group (15.9%), followed by blood and lymphatic system disorders, nervous system disorders and vascular disorders (4.3% each). Gastrointestinal disorders was also the most commonly reported SOC in the elsiglutide group (21.7%), followed by general disorders and administration site conditions, and nervous system disorders (both 8.7%). The percentages of patients reporting gastrointestinal disorders, general disorders and administration site conditions, and nervous system disorders were higher in the elsiglutide group than in the placebo group. At the PT level, events occurring in more than 1 patient in the placebo group were nausea (in 9 patients, 13.0%), headache (in 3 patients, 4.3%), and neutropenia, diarrhea, pyrexia, and phlebitis (each one in 2 patients, 2.9%). Events occurring in more than 1 patient in the elsiglutide group were nausea (in 11 patients, 15.9%), diarrhea (in 3 patients, 4.3%), constipation, injection site erythema, neuropathy peripheral and peripheral sensory neuropathy (each in 2 patients, 2.9%).
In the placebo group no patient had TEAEs assessed as related to study drug. In the

elsiglutide group, 8 patients (11.6%) had TEAEs assessed as related to study-drug. These were, mostly injection site events (injection site erythema in 2 patients, injection site nodule, injection site pruritus, injection site warmth, and rash each in 1 patient), but also constipation in 2 patients and nausea in 1 patient were reported.
A total of 7 SAEs occurred in 6 patients. Two patients in the placebo group had serious neutropenia. Four patients in the elsiglutide group experienced 5 SAEs (venous thrombosis, diarrhea, intestinal stenosis, neutropenia, tonsilitis). None of the SAEs were considered related to study medication. All patients recovered from their SAEs.
None of the patients died and none of the TEAEs led to discontinuation form the study.
The majority of clinical laboratory test results were within the reference ranges, with few isolated out-of-range results. No noteworthy differences between placebo and the elsiglutide group were detected for any laboratory parameter. There were no relevant changes between baseline and the respective visits in the mean and median values for systolic and diastolic BP and pulse rate. ECG evaluations did not show relevant differences between the treatment groups.
No indication for the development of anti-elsiglutide or anti-metabolite antibodies was seen in the elsiglutide group.

Conclusion:

- Four more patients were responders in the elsiglutide group (43 patients) than in the placebo group (39 patients). However, the study failed to show superiority of elsiglutide to placebo, as this was to be concluded if the difference in the number of responders, i.e. patients with no diarrhea, was larger than or equal to 5.
- A clear difference in favor of elsiglutide was observed for the proportion of patients experiencing diarrhea of grade ≥2 (elsiglutide: 5 patients vs placebo: 15 patients).
- No clear treatment differences were detected for other secondary efficacy endpoints.
- Citrullin levels suggested a protective effect of elsiglutide on the intestinal mucosa.
- The pharmacokinetics of elsiglutide and its metabolites ZP2242 and ZP2712 varied considerably across patients and over multiple days. An effect of multiple dosing cannot be excluded
- Exposure, both in terms of AUC_{0-t} and $AUC_{0-\infty}$, to the metabolite ZP2242 was approximately 30-fold higher than exposure to the parent elsiglutide (ZP1846); exposure to ZP2712 was approximately 4-fold higher than exposure to the parent compound.
- The safety profiles of elsiglutide and placebo were generally similar. Injection site reactions were the most frequently observed TEAEs assessed as related to elsiglutide. No serious or severe injection site reactions were observed.
- No indication for the development of immunity to elsiglutide was detected.
- Generally, it can be concluded that elsiglutide showed signs of efficacy and was well tolerated by the study patients.

Date of Report: 07 October 2013