1 TITLE PAGE

1.1 Title Page

Summary of Clinical Study
Norgine Study NPJ5004-04/2011 (SDS)
EUDRACT-N° 2011-004474-29

A Multicentre, Randomised, Double-Blind, Placebo-Controlled Study to Evaluate the Safety of TZP-101 (IV Ulimorelin) Administered Post-Operatively in Patients Who Have Undergone Partial Bowel Resection

Protocol Number:	NPJ5004-04/2011 (SDS)
Name of Investigational Product:	Ulimorelin (TZP-101)
Indication Studied:	To accelerate recovery of GI motility in patients who have undergone partial bowel resection
Study Sponsor:	Norgine Ltd. Norgine House, Widewater Place Moorhall Road Harefield, Uxbridge, UB9 6NS United Kingdom
Development Phase of Study:	Phase IIIb
Study Initiation Date:	13th Feb 2012
Study Completion Date:	13 Apr 2012
Report Date	30 Oct 2012

Final Version 1.0: Nov 2nd 2012 **Total number of pages: 6**

2 CLINICAL TRIAL SUMMARY

Name of Company: Norgine Ltd. **Name of Active Substance(s):** Ulimorelin (TZP-101)		(For National Authority Use only)
Title: A Multicentre, Randomised, Double-Blind, Placebo-Controlled Study to Evaluate the Safety of TZP-101 (IV Ulimorelin) Administered Post-Operatively in Patients Who Have Undergone Partial Bowel Resection		
Principal or Coordinating Investigator: [redacted] Spitalul Clinic Judetean de Urgenta Timisoara, Romania		
Study centre(s): The following nine investigators, based at study centres across Romania, enrolled patients during the study: [redacted] (site 951, n = 1 patient) [redacted] (site 952, n = 4 patients) [redacted] (site 953, n = 8 patients) [redacted] (site 954, n = 7 patients) [redacted] (site 955, n = 2 patients) [redacted] (site 956, n = 1 patient) [redacted] (site 959, n = 1 patient) [redacted] (site 960, n = 3 patients) [redacted] (site 966, n = 1 patient)		
Sponsor's Responsible Medical Officer: [redacted] Norgine Ltd. Norgine House, Widewater Place Moorhall Road Harefield, Uxbridge, UB9 6NS United Kingdom		
Publication (reference): No abstracts have been published on the results of this study		
Study period: 13 Feb 2012 (screening of 1st subject) – 13 Apr 2012 (end-of-trial in last subject).	**Clinical Phase:** IIIb	

Name of Company: Norgine Ltd. **Name of Active Substance(s):** Ulimorelin (TZP-101)		(For National Authority Use only)

GCP-compliance:

The investigators agreed to conduct the study in compliance with the study protocol, with the International Standard of Good Clinical Practice (GCP) procedures, and with the principles of the Declaration of Helsinki (1964) and relevant amendments.

Objectives of the study:

To evaluate the safety of TZP-101 in comparison with placebo when administered post-operatively in patients who had undergone partial bowel resection. This study aimed to increase the number of patients administered TZP-101 in the safety database to approximately 1110 patients.

Methodology:

This was a multicentre, multinational, randomised, parallel, double-blind, placebo-controlled study.

The study consisted of a screening period, an in-patient treatment period, a follow-up phone call performed 14 days (± 2 days) after the last study drug administration and a follow-up clinic visit performed 32 days after the last study drug administration. The overall study duration for each patient was not anticipated to exceed 63 days.

Patients who completed the screening procedures and met the eligibility criteria were randomised to treatment as close as possible to the time of surgery. Patients were randomised to receive a once-daily intravenous (IV) administration of 480 µg/kg TZP-101 or placebo in a 2:1 ratio. Each patient began receiving the first dose of study drug TZP-101 or matching placebo within 60 minutes of the conclusion of surgery, provided that the patient was still eligible following surgery. Dosing continued once daily at 24 hour intervals from the first dose (± 2 hours) until the first:

- bowel movement post-surgery (i.e. passage of faecal matter)
- hospital discharge
- seven days of administration of study drug.

Name of Company: Norgine Ltd. **Name of Active Substance(s):** Ulimorelin (TZP-101)		(For National Authority Use only)

Number of subjects:

It was planned to dose 330 patients. Given that an approximate 7% loss of eligible patients was expected between randomisation and dosing, due to unforeseen changes in surgical procedure or patient status, it was anticipated that approximately 355 patients would be required to be randomised into the study.

During the conduct of the study, results from two pivotal Phase III studies with TZP-101 failed to meet their primary and secondary efficacy endpoints. The proposed benefits of TZP-101 were not demonstrated and so the study was terminated early.

In total 32 patients were screened; 27 patients were dosed with study medication of which 25 patients completed. All 27 randomised patients were analysed in this report.

Diagnosis and main criteria for inclusion:

Male and female patients (non-pregnant and not breastfeeding; aged 18-80 years (inclusive), and weighing less than 200 kg (441 pounds) who underwent open bowel resection were eligible for this study.

Patients classified as American Society of Anesthesiologists (ASA) Class 4, 5, or 6 or who had complete bowel obstruction or who were scheduled to receive low rectal (i.e. below the anterior peritoneal reflection) or anal anastomosis or a laparoscopic or laparoscopic hand-assisted procedure or whose surgical procedure was considered an emergency procedure or who were anticipated to require prolonged post-operative ventilation were not eligible for this study. Patients were also excluded from the study if they had significant liver or renal function impairment, a psychiatric disorder or cognitive impairment that in the investigator's opinion may have interfered with their study participation, or who had a history of drug or alcohol abuse (within the previous year) or who were taking controlled substances (other than those prescribed by a medical professional or accounted for by concomitant medications). Patients diagnosed with Hepatitis B or Hepatitis C, or who may be hypersensitive to the study drug or had taken a study drug within 30 days of study initiation (including TZP-101) were not eligible to take part in this study.

Test product, dose, batch N°:

All patients were randomised to receive either once daily, IV, TZP-101 at a dose of 480 µg/kg or once daily, IV, placebo.

The TZP-101 product and placebo were each diluted up to a total volume of 50mL with Dextrose 5% in Water for Injection and administered by IV infusion over 30 minutes at an infusion rate of 1.67 mL/min. Subsequent infusions occurred daily (at 24-hour intervals) with the infusion beginning at the same time as the first dose (± 2 hours).

The batch numbers used in this study were:

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TZP-101: 00003

Placebo: P0002

Criteria for evaluation:

Primary endpoint: Safety:

The primary endpoint of this study was the assessment of the following safety parameters:

Incidence of adverse events (AEs); clinical laboratory assessments (haematology, serum chemistry, coagulation parameters, and urinalysis); physical examination; vital signs (systolic and diastolic blood pressure, heart rate, respiration rate and temperature); 12-Lead electrocardiogram (ECG); local injection site tolerability.

Quality of Life (QoL) Endpoint and Health Outcomes

The QoL endpoints and health outcomes assessments consisted of: European Quality of Life-5 Dimensions (EQ-5D) questionnaire; incidence of AEs reported as health outcomes; imaging studies (e.g. X-rays) obtained post-surgery during the study; use of total parenteral nutrition (TPN); number of emergency room (ER) visits (total and due to ileus) after the index surgery; number of hospitalisations (total and due to ileus) after the index surgery.

Statistical methods:

No formal statistical justification for the sample size was performed.

Since the development of TZP-101 was terminated with the premature close of this study and no additional safety concerns compared with placebo were raised from the two pivotal phase III studies, data listings were prepared and AEs and demographics tabulated. The analysis described in the protocol was not performed

SUMMARY – CONCLUSIONS

Safety Results

The safety data collected during this study indicated that TZP-101 was well-tolerated at a dose of 480 µg/mL and were generally consistent with data from previous studies. The majority of treatment emergent adverse events (TEAE) were considered unrelated to the study drug (55.6% for TZP-101 and 77.8% for placebo). Overall, gastrointestinal (GI) disorders, and metabolism and nutritional disorders were the most common type of TEAEs reported (n=14, 51.9%) which was to be expected in this patient population. The most frequently reported TEAEs were hypoproteinaemia (48.1%), hypoalbuminaemia (44.4%) and nausea (40.7%). The most typical AEs for the post-surgical population, nausea and vomiting, were noticeably decreased in the TZP-101 group (38.9% and 27.8%, respectively) compared with placebo (44.4% and 33.3%, respectively) which is consistent with promotility activity. The TEAEs

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relating to blood proteins (hypoproteinaemia and hypoalbuminaemia) as well as pyrexia and anaemia were reported across both treatment groups and are typically associated with the conduct of surgery.

No patient discontinued treatment due to an AE. A total of six serious TEAEs were reported by four patients (three from the TZP-101 group and one from the placebo group). The type and incidence of these serious TEAEs were consistent with the clinical profile of the studied population and reported historical data.

Clinically significant changes in haematology and chemistry parameters were seen in both the placebo and TZP-101 groups – the majority of which had resolved by follow-up. TEAEs relating to increased blood pressure, cardiac disorders and injection site abnormalities were observed in the TZP-101 group only. Cardiac disorders have not been reported in previous patient studies with TZP-101 but were all considered unrelated to the study drug.

Discussion and Conclusion

The current study did not raise any additional safety concerns for TZP-101 (ulimorelin) compared with placebo and compared with previous data collected during the development of TZP-101 (ulimorelin). QoL and health outcome results were listed.

During the conduct of the current study, results from two pivotal Phase III studies with TZP-101 (TZP-101-CL-P007 and TZP-101-CL-P008) were released and demonstrated that both studies failed to meet their primary and secondary efficacy endpoints. Although no additional safety concerns compared with placebo were raised, the proposed benefits of TZP-101 (ulimorelin) were not demonstrated and so the current study, which was collecting further data on the safety of TZP-101 (ulimorelin) for regulatory filing, was terminated by the sponsor.

Clinical Summary of Clinical Study Report (30 Oct 2012). Prepared 02 Nov 2012