SALSARULO Pharma

CLINICAL STUDY REPORT SYNOPSIS

Clinical Trial to Evaluate the Efficacy and Safety of MACRORANGE®
in Patients Suffering from Functional Constipation

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STUDY TITLE:	Clinical Trial to Evaluate the Efficacy and Safety of MACRORANGE® In Patients Suffering from Functional Constipation
INVESTIGATIONAL PRODUCT NAME:	MACRORANGE®
INDICATION STUDIED:	Functional Constipation
STUDY DESIGN:	Open-Label, explorative, non-comparative study
SPONSOR NAME:	SALSARULO Pharma
PROTOCOL NUMBER:	MACR001, Protocol v1.0 dated 24JUL18
DEVELOPMENT PHASE:	Phase II
EUDRACT NUMBER	2018-001914-13
STUDY INITIATION DATE	05 November 2018 (FPFV)
STUDY COMPLETION DATE:	26 March 2019 (LPLV)
PRINCIPAL INVESTIGATOR NAME:	
AFFILIATION-INSTITUTION OF INVESTIGATOR:	Advanced Technology Corporation (A.T.C.) University Hospital Center (CHU) from Liège, Belgium
MEDICAL OFFICER NAME:	
REPORT DATE:	04 September 2019

This study was performed in accordance with Good Clinical Practice, including the archiving of essential documents. This report has been prepared in accordance with the International Council for Harmonisation (ICH) Guideline on the Structure and Content of Clinical Study Reports.

SYNOPSIS

Study Title:	**Clinical Trial to Evaluate the Efficacy and Safety of MACRORANGE® In Patients Suffering from Functional Constipation (MACR001)**
Investigational Product Name:	12g single dose stick-pack of MACRORANGE® containing 42% of Macrogol 4000 (i.e. 5.04 g of macrogol 4000)
Principal Investigator:	
Study Centre(s):	Advanced Technology Corporation (A.T.C.) CHU of Liege, B35, Route 124 Avenue Hippocrate, 15 4000 Liege, Belgium
Study Period:	First subject first Visit: 05 Nov 2018 First Subject dosed: 19 Nov 2018 Last Subject last visit: 26 Mar 2019
Phase of Development:	Phase II
OBJECTIVES	Primary: • To assess the efficacy of MACRORANGE® in patients with functional constipation (according to Rome III criteria) after daily administration of MACRORANGE® up to 14 days. Secondary: • To describe the average daily dosage of MACRORANGE® from Day 3 up to End of Study. • To further evaluate the tolerance of MACRORANGE® in patients with functional constipation. • To evaluate the taste of MACRORANGE®.
METHODS	Number of Patients: 30 subjects enrolled • Screening period (within 14 days before the week of wash out), • 1 week of wash-out, • 2 weeks of treatment.
Diagnosis and Main Criteria for Inclusion:	• Age of the patients: > 18 years of age; • Male and female patients; • Stool frequency strictly less than 3 per week; • Functional constipation as defined in constipation module of Rome III.

Test Product, Dose and Mode of Administration, Lot/batch Number			
Study Drug	**Dose Strength**	**Mode of Administration**	**Drug Product Lot/Batch Number:**

MACRORANGE®	12g single dose stick-pack	Oral administration	C180901
Duration of Treatment:	D1: first day of treatment • 3 (three) single dose stick-packs of MACRORANGE® before bedtime, without any hot beverage before, after or int the same time. The 3 single dose stick-packs must be taken within 30 minutes. D2: second day of treatment • 2 (two) single dose stick-packs of MACRORANGE® to the patient before bedtime, without any hot beverage before, after or in the same time. D3 to D14 **Depending on the stool effect, the patient could take:** • Either 1 (one) single dose stick-pack of MACRORANGE® once a day before bedtime (without any hot beverage before, after or at the same time), if the patient defecated at least once during that day (whatever the type of stool is, cf. Bristol scale); • Or 2 (two) single dose stick-packs of MACRORANGE® once a day before bedtime (without any hot beverage before, after or at the same time), if the patient did not defecate at all during that day.		
CRITERIA FOR EVALUATION:	**Efficacy:** Stool frequency during treatment (diary), Stool consistency according to Bristol Scale (diary), Clinical Global Impression (CGI) questionnaire, Global efficacy as specified by the patient.		
	Safety: Adverse events, Physical examination, Vital signs (heart rate, systolic/diastolic blood pressure), Laboratory tests (complete blood count, sodium, potassium, calcium, glucose, creatinine, TSH (thyroid stimulating hormone), human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) infection as performed locally), Clinical Global Impression, Global tolerability as specified by the patient.		
	Tolerance: Constipation symptoms (bloating, pain, malaise, bowel movements, prolonged/excessive straining, unsatisfactory defecation).		

STATISTICAL METHODS: Safety Efficacy	This is an explorative open-label clinical trial to assess the efficacy and safety of MACRORANGE®. A sample size of 30 subjects was evaluated after a wash-out of one week and a total active treatment period of 2 weeks. Descriptive statistics were performed for safety and efficacy endpoints. Efficacy was assessed through the average number of complete spontaneous defecations per week for a total active treatment period of 2 weeks, compared from baseline values (after a wash-out of one week). This sample size was estimated to detected, with a power of 90% and alpha (α) of 5% (2-sided), a difference of at least 1.25 in the total number of defecations per week as change from baseline. Other inferential statistical analyses were performed both on efficacy and safety variables.
SUMMARY OF RESULTS:	**Efficacy:** The average number of complete spontaneous defecations increased significantly at the end of the 2 weeks treatment with MACRORANGE® from 2.95 ± 1.90 stools per week to 5.44 ± 2.08 stools per week, with a mean change of + 2.49 (± 2.54) stools per week as compared to baseline. This is almost a doubling from the baseline to the end of this 2-week treatment period with MACRORANGE®. There was a statistically significant improvement in pain intensity and excessive straining after the administration of MACRORANGE® as compared to baseline. In addition, there was a statistically significant improvement in the consistency of stools at the end of the 2-week treatment. Complete defecation was obtained by 11 patients (37%) within 15 hours after the first dose of MACRORANGE®. It has to be also noticed that 18 patients (60%) had complete defecation within 24 hours after the first dose of MACRORANGE®. The average daily dose of MACRORANGE® during the 2-week treatment period was 18.41 (± 2.41) grams of MACRORANGE®, equivalent to 7.73 (± 1.01) grams of macrogol 4000, suggesting a potential reduction in the daily dose of macrogol 4000, compared to other marketed macrogol products. Patient's and Investigator's global impression on MACRORANGE® was rated as good to very good by 60% of them. In addition, 93% of the patients rated the tolerance to MACRORANGE® as good or very good with no poor evaluation. About 30% of the patients "like very much" the taste of MACRORANGE® and 67% of the patients "like it slightly".

	Safety Results: The administration of MACRORANGE® for 2 weeks was very well tolerated in this population of patients with functional constipation. There was no serious adverse reaction. All reported treatment emerging adverse events (TEAEs) were transient, of mild to moderate intensity. There were no significant or relevant changes observed in laboratory safety parameters and vital signs at the end of the study compared to baseline.
CONCLUSIONS:	The results from this first exploratory clinical trial performed on 30 patients suffering from functional constipation, as defined per Rome III criteria, have shown that MACRORANGE® is effective, safe and well tolerated in the treatment of patients with functional constipation. Moreover, MACRORANGE® seems to require less daily amount of macrogol 4000 to treat functional constipation and might be faster to obtain complete defecation compared to marketed macrogol 4000 drugs. A randomized controlled clinical trial will confirm these promising results.
DATE OF REPORT:	04 SEP 2019