Clinical trial results:
Phase III, Parallel-group, Placebo Controlled, Double-blind, Randomized, Multicenter International Study to Investigate the Safety and Efficacy of Propionyl-L-Carnitine (ST261) Modified Release Tablets in Patients Affected by Mild Ulcerative Colitis under Oral Stable Treatment.

Summary

EudraCT number	2011-004770-28
Trial protocol	ES HU LV DE LT AT PL
Global end of trial date	13 August 2013

Results information

Result version number	v1 (current)
This version publication date	09 August 2020
First version publication date	09 August 2020

Trial information

Trial identification

Sponsor protocol code	ST261-DM-11-006

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alfasigma S.p.A
Sponsor organisation address	Via Ragazzi del '99, 5, Bologna, Italy,
Public contact	Serena Principe, Alfasigma S.p.A, serena.principe@alfasigma.com
Scientific contact	Giovanni Valentini, Alfasigma S.p.A, giovanni.valentini@alfasigma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	10 October 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 August 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to compare the two treatment groups (ST 261 modified release tablets 1g/die vs. placebo) with respect to the proportion of patients with disease remission at the end of the 8 weeks of treatment.
Evaluation of safety and tolerability of ST 261 were also primary objectives of the study.

Protection of trial subjects:

The study was conducted in compliance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline for Good Clinical Practice (GCP) and the applicable national regulations so as to assure that the rights, safety, and wellbeing of the participating study patients were protected consistent with the ethical principles that have their origin in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 June 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 64
Country: Number of subjects enrolled	Spain: 16
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Hungary: 11
Country: Number of subjects enrolled	Latvia: 23
Country: Number of subjects enrolled	Lithuania: 7
Worldwide total number of subjects	150
EEA total number of subjects	150

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	143
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 55 sites in Austria (3 sites), France (9 sites), Germany (11 sites), Hungary (8 sites), Latvia (4 sites), Lithuania (4 sites), Poland (9 sites) and Spain (7 sites).

Pre-assignment

Screening details:

The study consisted of a screening period of up to 2 weeks. Patients with a diagnosis of active mild ulcerative colitis, under stable oral therapy, were screened for entry in the study.

Pre-assignment period milestones

Number of subjects started	150
Number of subjects completed	150

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	ST 261

Arm description:

Patients randomized to this arm of the study were treated with ST 261 modified release tablets.

Arm type	Experimental
Investigational medicinal product name	ST 261 modified release tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Modified-release tablet
Routes of administration	Oral use

Dosage and administration details:

Patients randomized to this arm of the study were treated with ST 261 modified release tablets administered orally in one 0.5 g tablet twice a day (before breakfast and before dinner) for 8 weeks.

Arm title	Placebo

Arm description:

Patients randomized to this arm of the study were treated with placebo.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Modified-release tablet
Routes of administration	Oral use

Dosage and administration details:

Patients randomized to this arm of the study were treated with placebo administered orally in one tablet twice a day (before breakfast and before dinner) for 8 weeks.

Number of subjects in period 1	ST 261	Placebo
Started	76	74
Completed	62	60
Not completed	14	14
Sponsor's decision	4	-
Consent withdrawn by subject	4	5
Withdrawn by Sponsor	-	2
Study termination	3	3
Adverse event, non-fatal	-	1
Patient's decision	1	1
Withdrew from follow-up period	-	2
Lost to follow-up	1	-
Lack of efficacy	1	-

Baseline characteristics

Reporting groups	
Reporting group title	ST 261
Reporting group description:	
Patients randomized to this arm of the study were treated with ST 261 modified release tablets.	
Reporting group title	Placebo
Reporting group description:	
Patients randomized to this arm of the study were treated with placebo.	

Reporting group values	ST 261	Placebo	Total
Number of subjects	76	74	150
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	43.0	45.1	
standard deviation	± 14.08	± 12.38	-
Gender categorical Units: Subjects			
Female	32	35	67
Male	44	39	83

Subject analysis sets	
Subject analysis set title	ITT/Safety population Arm ST261
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Intention-to-treat	
Subject analysis set title	ITT/Safety population Arm Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Intentio-to-treat	

Reporting group values	ITT/Safety population Arm ST261	ITT/Safety population Arm Placebo	
Number of subjects	76	74	

Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	43.0	45.1	
standard deviation	± 14.08	± 12.38	
Gender categorical Units: Subjects			
Female	32	35	
Male	44	39	

End points

End points reporting groups

Reporting group title	ST 261
Reporting group description:	
Patients randomized to this arm of the study were treated with ST 261 modified release tablets.	
Reporting group title	Placebo
Reporting group description:	
Patients randomized to this arm of the study were treated with placebo.	
Subject analysis set title	ITT/Safety population Arm ST261
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Intention-to-treat	
Subject analysis set title	ITT/Safety population Arm Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Intentio-to-treat	

Primary: Clinical/endoscopic remission

End point title	Clinical/endoscopic remission
End point description:	
The primary endpoint was clinical/endoscopic remission, defined as a Disease Activity Index (DAI) ≤ 2 with rectal bleeding sub-score = 0 and no other individual sub-score > 1, at the end of the 8 weeks treatment period/early termination. DAI has four sub-scales (stool frequency, rectal bleeding, mucosal appearance and physician's overall assessment of the disease severity) scored using four levels (0, 1, 2, 3). The DAI was calculated by summing the four sub-scores.	
End point type	Primary
End point timeframe:	
8 weeks	

End point values	ITT/Safety population Arm ST261	ITT/Safety population Arm Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	76	74		
Units: Subjects	11	22		

Statistical analyses

Statistical analysis title	Conditional Power
Statistical analysis description:	
The Conditional Power is the probability, given the data observed at the information time t (0 < t < 1) of the interim analysis, that at the end of the 8 weeks period, the two-sided test verifying that the null hypothesis H0 versus the alternative hypothesis H1 is statistically significant at the level α (0.05 for the present studies). Unknown parameters were estimated with the observed data and under the H0 model. The Conditional Power threshold was estimated as 0.25.	
Comparison groups	ITT/Safety population Arm ST261 v ITT/Safety population Arm Placebo

Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.25 [1]
Method	Conditional Power

Notes:

[1] - Here the Conditional Power threshold is reported (see Analysis description)

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 12 weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups	
Reporting group title	ST 261
Reporting group description: Patients randomized to this arm of the study were treated with ST 261 modified release tablets.	
Reporting group title	Placebo
Reporting group description: Patients randomized to this arm of the study were treated with placebo.	

Serious adverse events	ST 261	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 76 (0.00%)	1 / 74 (1.35%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 76 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	ST 261	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 76 (18.42%)	21 / 74 (28.38%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Fibroadenoma of breast			
subjects affected / exposed	0 / 76 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Vascular disorders			

Hypertension			
subjects affected / exposed	1 / 76 (1.32%)	1 / 74 (1.35%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Haemoglobin Decreased			
subjects affected / exposed	2 / 76 (2.63%)	0 / 74 (0.00%)	
occurrences (all)	2	0	
Pyrexia			
subjects affected / exposed	1 / 76 (1.32%)	2 / 74 (2.70%)	
occurrences (all)	1	2	
Reproductive system and breast disorders			
Breast discomfort			
subjects affected / exposed	0 / 76 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Endometriosis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Galactorrhoea			
subjects affected / exposed	0 / 76 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 76 (1.32%)	2 / 74 (2.70%)	
occurrences (all)	1	2	
Productive Cough			
subjects affected / exposed	1 / 76 (1.32%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
subjects affected / exposed	1 / 76 (1.32%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 76 (1.32%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Investigations			

Haemoglobin Decreased			
subjects affected / exposed	2 / 76 (2.63%)	0 / 74 (0.00%)	
occurrences (all)	2	0	
Body Temperature Increased			
subjects affected / exposed	1 / 76 (1.32%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Eosinophil Count Increased			
subjects affected / exposed	1 / 76 (1.32%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Alanine Aminotransferase Abnormal			
subjects affected / exposed	0 / 76 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Aspartate Aminotransferase Abnormal			
subjects affected / exposed	0 / 76 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Blood alkaline phosphatase abnormal			
subjects affected / exposed	0 / 76 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
C-Reactive Protein Increased			
subjects affected / exposed	0 / 76 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Electrocardiogram T wave abnormal			
subjects affected / exposed	0 / 76 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Gamma-Glutamyltransferase Abnormal			
subjects affected / exposed	0 / 76 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Procedural Pain			
subjects affected / exposed	1 / 76 (1.32%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 76 (1.32%)	4 / 74 (5.41%)	
occurrences (all)	1	5	

Dysgeusia			
subjects affected / exposed	0 / 76 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	0 / 76 (0.00%)	2 / 74 (2.70%)	
occurrences (all)	0	3	
Migraine			
subjects affected / exposed	0 / 76 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 76 (1.32%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Scleritis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Colitis Ulcerative			
subjects affected / exposed	2 / 76 (2.63%)	1 / 74 (1.35%)	
occurrences (all)	2	1	
Abdominal Pain Upper			
subjects affected / exposed	2 / 76 (2.63%)	0 / 74 (0.00%)	
occurrences (all)	2	0	
Diarrhoea			
subjects affected / exposed	1 / 76 (1.32%)	1 / 74 (1.35%)	
occurrences (all)	1	1	
Flatulence			
subjects affected / exposed	1 / 76 (1.32%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	1 / 76 (1.32%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Toothache			
subjects affected / exposed	1 / 76 (1.32%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Abdominal Distension			

subjects affected / exposed	0 / 76 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Abdominal Mass			
subjects affected / exposed	0 / 76 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Hyperchlorhydria			
subjects affected / exposed	0 / 76 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 76 (1.32%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Hyperhidrosis			
subjects affected / exposed	1 / 76 (1.32%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 76 (1.32%)	1 / 74 (1.35%)	
occurrences (all)	1	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 76 (3.95%)	2 / 74 (2.70%)	
occurrences (all)	3	2	
Back Pain			
subjects affected / exposed	1 / 76 (1.32%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Muscle Tightness			
subjects affected / exposed	1 / 76 (1.32%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 76 (1.32%)	2 / 74 (2.70%)	
occurrences (all)	1	2	
Influenza			
subjects affected / exposed	1 / 76 (1.32%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			

subjects affected / exposed	1 / 76 (1.32%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Oral herpes			
subjects affected / exposed	0 / 76 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Increased Appetite			
subjects affected / exposed	0 / 76 (0.00%)	1 / 74 (1.35%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 February 2012	Main changes included the following: -The term "parallel-group" was added to the title of the study. -The name of the Sponsor's responsible physician was updated. -Expected times for site activation, recruitment and approximate total duration of the study were added to the protocol. -The required previous timeframe for patients to repeat the pancolonoscopy at screening was increased from six to twelve months. This would reduce the number of patients requested to undergo an invasive procedure if already done recently. -An exclusion criterion was added to exclude patients receiving treatment with drugs or products containing carnitine or carnitine derivatives during the three months preceding the screening. -The temperature at which the study medication should be maintained was reduced from 30ºC to 25ºC to be more conservative (according to the stability data) with the drug storage conditions. -Some procedural changes and clarifications of the text were made in response to recommendations from Ethics Committees.
09 July 2012	Main changes included the following: -Smoking history was added as a screening assessment to better characterize patients. -Due to the fluctuations in symptoms observed in mild patients over short periods of time, it was recommended by the DMB and the Steering Committee that the DAI sub-cores relevant to stool frequency and rectal bleeding be recorded twice during the screening period. -The timeframe of at least four weeks was removed from Inclusion Criterion 3 - Diaphragm and spermicidal agent were removed from Inclusion Criterion 7 as they were not considered to be reliable methods (Pearl Index > 1) and in order to fulfill the criterion of highly effective barrier method. -Patients who had been previously treated with biological agents were excluded from the study without taking any washout period into consideration (Exclusion Criterion 6). -Parasites were added in Exclusion Criterion 7. -Bleeding disorders were clarified in Exclusion Criterion 13: alterations of the coagulation factors or any concurrent other disease possibly causing digestive apparatus bleeding. -The decision to stop study treatment administration due to the use of disallowedmedications was left to the Investigators' judgment. -The limitation that no more than 150 patients should belong to each study for the interim analysis was changed to 200 patients regardless of their origin. Also, the Independent Statistician was added as being responsible for the interim statistical analysis. In addition, the conditional power threshold was changed from Bt = 0.30 as minimum acceptable value for continuing the trial with no additional evaluations to At = 0.25 threshold under which the trial would be stopped.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

04 July 2013	The present study was conducted in parallel with the Phase III study 2011-004765-32 . In order to early terminate both of the two studies in case of futility, an interim analysis was planned to be performed by combining the samples (first 25% of the total planned patients for each study) of the two studies. The results of this analysis would lead to one of the following scenarios: close the study for futility, or go ahead with the fixed sample size. No sample upsizing or downsizing was planned. This analysis was carried out as planned when 200 patients in total, regardless of which of the two studies they belonged to, were randomized and had reached the final efficacy evaluation (Week 8 or early termination), with no interruption in patient enrolment. The interim analysis was performed in an unblinded manner in the intention-to-treat (ITT) population by an Independent Reporting Statistician who was completely independent from the blinded study team and was not involved in any other duties relevant to the study. The results were given to the Data Monitoring Board (DMB) to review and provide the relevant recommendations according to pre-specified rules. The DMB reviewed the data summary from both studies dated 01 July 2013. Their conclusion was to stop the studies in accordance with the protocol and DMB Charter. This was on the basis of the conditional power as stated in the protocol. The primary reason for stopping the study was strong evidence of futility. The conditional power was 0.004 (below the 0.25 threshold indicated in the protocol). There were no clinical safety issues and no meaningful safety differences were seen.	-

Notes:

Limitations and caveats

None reported