2. SYNOPSIS

Sponsor/company Orion Corporation Orion Pharma	**Individual study table referring to a specific part of the dossier**	(for National Competent Authority use only)
Finished product: Not applicable	**Volume:**	
Active ingredient: ORM-12741	**Page**	
Study code: 3098009		
Study title: Efficacy of ORM-12741 for prevention of cold-induced vasospasm; a randomised, double-blind, placebo-controlled, single centre crossover study in patients with Raynaud's phenomenon secondary to systemic sclerosis		
Investigator and study centre: Ariane Herrick, MD. Rheumatic Disease Centre Salford Royal Hospital, Salford, United Kingdom.		
Development phase: IIa	**Study period:** 22 Jun 2011- 14 Dec 2011	
Objectives: The primary objective of the study was to evaluate the efficacy of ORM-12741 in the attenuation of a cold-induced reduction in finger blood flow and temperature in subjects with Raynaud's phenomenon (RP) secondary to systemic sclerosis in a controlled environment. The secondary objectives of the study were to evaluate the safety and tolerability of ORM-12741 in subjects with RP secondary to systemic sclerosis, and to assess the dose-response relationship in terms of the effect on finger blood flow and temperature.		
Methodology: This study was a phase IIa, randomised, double-blind, crossover, single dose placebo-controlled, single centre study. Subjects with RP secondary to systemic sclerosis were allocated to 1 of 6 treatment sequences according to the Williams crossover design to receive the study treatments in different order. Each subject had a screening visit, 3 treatment periods separated by at least 1 week long wash-out period and an end-of-study visit 1-2 weeks after the last study treatment administration. The duration of study was about 8 weeks for each subject.		
Sample size: A total of 18 subjects were planned to be enrolled. After interim analysis the number of subjects was reduced to 12 subjects, this was documented in the Amendment 2.		
Diagnosis and main criteria for inclusion: Male or female patients with a diagnosis of active RP secondary to systemic sclerosis, age of 18-75 years, body mass index (BMI) between 18-30 kg/m^2 fulfilling all of the inclusion criteria and none of the exclusion criteria, written informed consent (IC) obtained. The subjects had to have stable symptoms for RP and medication requirements for 2 months prior to screening, and negative pregnancy test for females of childbearing potential.		
Investigational product, dose and mode of administration, batch numbers: ORM-12741 was provided as 30 mg or 100 mg capsules for oral administration. The subjects received 2 dose levels of ORM-12741: 30 mg and 100 mg. Batch number for ORM-12741 30 mg capsule was 11A20/1 and for ORM-12741 100 mg capsule NA102L1.		
Duration of treatment: A single dose was administered during each of the 3 periods.		
Reference product, dose and mode of administration, batch numbers: Placebo capsules for ORM-12741 for oral administration. Batch number for placebo capsules used as study treatment was MM002L1 and for placebo capsules used in swallow test MI001L1.		
Bioanalytical method: ORM-12741 and ORM-13720 were determined using a validated liquid chromatography-tandem mass spectrometry (LC/MS/MS) method.		
Variables and methods of assessments:		

Efficacy variables: Effects of treatments on finger blood flow was assessed by measuring finger temperature, skin blood flow index by laser Doppler imaging (LDI), and skin temperature by infrared imaging. The subject's subjective feeling of response to the study treatment was assessed.

Pharmacodynamic (PD) variables: Plasma adrenaline and noradrenaline levels were analysed to assess response to the cold challenge and the study treatments.

Pharmacokinetic (PK) variables: Concentrations of ORM-12741 and its metabolite ORM-13720 in plasma were determined.

Safety variables: Safety was assessed by adverse events (AEs), heart rate (HR), blood pressure (BP), 12-lead electrocardiogram (ECG), physical examination and laboratory safety assessments.

Statistical methods:

Evaluation of efficacy: All efficacy variables were summarised using descriptive statistics and appropriate figures. The comparisons between treatment groups and placebo group were performed using analysis of variance (ANOVA) model for the Williams crossover design with 95% confidence intervals. The main outcome variables were the time to recovery of 70% of the baseline finger temperature, the area under the time-LDI curve for 40 min from the end of cold challenge and the rate of finger temperature change during the cold challenge and the recovery steps. Subjective feeling scores were described and summarised.

Evaluation of PD: The profiles of adrenaline and noradrenaline concentrations over the sampling period were constructed using both measured actual concentrations and their changes from baseline. Statistical analyses for these variables were similar as for finger temperature, including sampling time-point as repeated factor.

Evaluation of PK: All plasma concentrations of ORM-12741 and ORM-13070 were summarised using descriptive statistics.

Evaluation of safety: The AEs were displayed in a frequency table. The number and proportion of subjects having each AE were given, and severity of AEs and causality to the drug were given. Serious adverse events (SAEs) and other significant AEs were to be evaluated case by case.

The actual values and corresponding changes from baseline for HR and BP, and 12-lead ECG variables were summarised using descriptive statistics.

The abnormal physical examination findings were summarised using descriptive statistics.

Laboratory safety variables were summarised using descriptive statistics.

Summary-Conclusions

Demography and other baseline characteristics: A total of 28 study subject candidates were screened and 15 entered into the study. In total 12 subjects completed the study. None of the subjects who received study treatment discontinued the study. 3 subjects were randomised but did not receive any study treatment. All 12 subjects were Caucasian, with a mean age of 58 years (range 36-69). 10 (83.3%) subjects were females and 2 (16.7%) males. All subjects had RP secondary to systemic sclerosis (preferred terms systemic sclerosis, scleroderma or systemic sclerosis pulmonary) at screening.

Efficacy results: There was no evidence of improved recovery from cold challenge during the active treatment periods as compared to the placebo period in any of the efficacy evaluations. Instead, the area under LDI curve during recovery (right index finger) was statistically significantly smaller after both ORM-12741 dose levels as compared to placebo and there was a trend towards slower recovery also in most of the other efficacy variables during the active treatment periods as compared to the placebo period. In addition, the rate of change in temperature (cooling) during the cold challenge was significantly quicker after ORM-12741 30 mg treatment than placebo.

PD results: plasma noradrenaline levels were statistically significantly increased after both ORM-12741 dose levels at 91 min timepoint. Plasma adrenaline concentrations were not significantly affected by ORM-12741 treatment.

PK results: At pre-dose, 31 and 91 min timepoints plasma concentrations of ORM-12741 and ORM-13720 were comparable to corresponding concentrations in healthy subjects after similar dose levels.

Safety results: A total of 26 AEs were reported in 10 subjects (83.3%) after start of study treatment. There

were no deaths, other SAEs or other significant AEs during the study. 1 subject discontinued the study due to an AE before receiving any study treatment. The most common AE was headache with 8 events reported in 4 subjects. There were no clinically significant changes in laboratory, HR, BP, 12-lead ECG or physical examination results. Thus, in the present study ORM-12741 was safe and well tolerated. **Conclusion:** The main finding of the study is that patients having RP secondary to systemic sclerosis do not recover from cold challenge faster during active ORM-12741 treatment than during placebo period. Instead, there is some evidence of slower recovery during the active treatment periods.
Date of report: 27 Apr 2012