SYNOPSIS

Title of the study: Double-blind, double-dummy, randomized, parallel group trial of SL650472 (three dose regimens versus placebo and cilostazol), for 24-week improvement of walking distance in patients with stage II peripheral arterial disease who benefit from optimal prevention strategy including clopidogrel (ACT4791, MASCOT).

This report presents the 1-year safety follow-up data collected post-treatment, per Amendment No. 4.

Investigator(s): [redacted]

Study center(s): 86 centers in 9 countries (Czech Republic, Russian Federation, Unites States, Ukraine, Canada, Mexico, Sweden, Belgium, and Germany)

Publications (reference): Not applicable.

Study period:

Date first patient enrolled: 16 February 2006 (date of first signed informed consent)

Date last patient completed: 03 December 2008 (date of last patient last visit)

Phase of development: II

Objectives: The primary objective was to investigate in patients suffering from intermittent claudication due to Fontaine stage II peripheral arterial disease (PAD) whether a 24-week treatment with SL650472 once daily (OD) on top of clopidogrel may result in an improvement of walking capacity by comparing 3 doses of SL650472 to placebo, and to calibrate such effect versus cilostazol.

Methodology: This was a multicenter, multinational, double-blind, double-dummy, randomized, placebo-controlled, 5-arm parallel group study. Following recommendations from the Data Monitoring Committee after preclinical phototoxicological and genototoxicological findings had been observed for SL650472, two additional visits 6 months and 12 months post-treatment were to be conducted (per protocol Amendment 4).

Number of patients:

Randomized: 220 patients participated in the 1-year safety follow-up

Treated: 51(placebo), 45 (SL650472 5 mg), 40 (SL650472 10 mg), 46 (SL650472 20 mg), 38 (cilostazol)

Efficacy: Not applicable

Safety : 220

Pharmacokinetics : Not applicable

Diagnosis and criteria for inclusion:

- Male or female patients >40 years
- Stable symptoms of intermittent claudication
- Confirmed PAD
- Appropriate background therapy, i.e., patients following a program of exercise training and smoking cessation (if smokers) and able to be treated with clopidogrel.

Investigational product: SL650472 5, 10, 20 mg capsules

Dose: 5, 10, 20 mg OD

Administration: Oral route, with breakfast

Batch numbers: [redacted]

Duration of treatment: 24 weeks

Duration of observation: 31 weeks maximum including a 2- to 5-week placebo run-in phase, a 24-week treatment phase, and a follow-up visit 7 to 10 days after last study drug intake. Per Protocol amendment 4, after preclinical phototoxicological and genotoxicological findings were reviewed by the Data Monitoring Committee and the Steering Committee, it was recommended that all patients had 2 additional post-treatment follow-up visits conducted 26 and 52 weeks after last study drug intake; thus the total duration of the study was of 83 weeks maximum.

Reference therapy: Placebo of SL650472 capsules	Cilostazol 100 mg Pletal® tablets	Placebo of cilostazol tablets
Dose: 0 mg	100 mg twice daily (BID)	0 mg
Administration: Oral route, with breakfast	Oral route, at least 30 minutes before breakfast or dinner	Oral route, at least 30 minutes before breakfast or dinner
Batch numbers: [redacted]	[redacted]	[redacted]

Background therapy: Clopidogrel 75 mg tablets

Dose: 75 mg OD

Administration: Oral route

Batch number: [redacted]

Criteria for evaluation: The current report is a synopsized report due to the Sponsor's decision to discontinue the SL650472 development program. The following safety criteria were evaluated, and analyzed using descriptive statistics: post-treatment adverse events (AEs) and abnormalities in sexual hormone data observed during the long-term follow-up period.

Statistical methods: Safety analyses were conducted in all randomized and treated patients who participated in the long-term follow-up period. The period of analysis was the post-treatment period i.e., from the end of treatment plus 4 days and up to Week 52 post-treatment visit date. Post-treatment AEs were summarized by system organ class and treatment group. Abnormalities in sexual hormone data were summarized.

Summary:

An overview of post-treatments AEs including serious AEs and AEs leading to death, which were reported during the 1-year follow-up period is provided in the table below.

Overview of post-treatment AEs - All randomized and treated patients who participated to the long-term follow-up period

		SL650472			
	Placebo (N=51)	**5 mg (N=45)**	**10 mg (N=40)**	**20 mg (N=46)**	**Cilostazol (N=38)**
Any post treatment AE	14 (27.5%)	8 (17.8%)	5 (12.5%)	9 (19.6%)	11 (28.9%)
Any post treatment serious AE	6 (11.8%)	4 (8.9%)	1 (2.5%)	6 (13.0%)	2 (5.3%)
Any post treatment AE leading to death	0	1 (2.2%)	0	0	0

Notes: Post treatment adverse event = adverse event that developed or worsened during the post treatment period
Post treatment period = from end of treatment + 4 days up to Week 52 post treatment visit date

There was one death reported: a 59-year-old smoker male patient who had been treated with SL650472 5 mg for 24 weeks, was diagnosed with lung carcinoma more than 5 months after the last study drug administration and leading to death 4 months later.

Summary (Continued):

A total of 19 serious post-treatment AEs were reported. The majority of serious post-treatments AEs were vascular disorders or cardiac disorders related to patients' underlying conditions (15/19 patients). Other serious AEs were cancer in 3 patients, including one patient who was diagnosed with thyroid cancer 8 months after last study treatment (SL650472 20 mg) administration, and infection (trichomoniasis) in 1 patient.

There were no AEs related to phototoxicity reactions or sexual hormone disorders reported during the 1-year post-treatment follow-up in patients who had been receiving SL650472.

The number of subjects presenting post-treatment abnormalities for sexual hormones is presented below. No abnormalities were observed for estradiol or prolactin in any treatment group. Increased luteinising hormone (LH) values above the upper limit of normal (ULN) were observed post treatment in all treatment groups but with a higher incidence in the cilosatzol group. Increased follicle stimulating hormone (FSH) values above ULN were observed post treatment in all treatment groups but with a higher incidence in the placebo group. Such increases can be explained by the loss of negative feedback by estrogens on gonadotropin production that is observed in ageing population (mean age 64.1 years).

No specific concerns were identified regarding sexual hormones in patients who had been receiving SL650472.

Summary of patients post treatment abnormalities in sexual hormonology - All randomized and treated patients who participated to the long-term follow-up period

		SL650472			
Laboratory Tests PCSA Criteria	**Placebo (N=51)**	**5 mg (N=45)**	**10 mg (N=40)**	**20 mg (N=46)**	**Cilostazol (N=38)**
Estradiol (pmol/l) (Female)					
< LLN	0/7	0/3	0/4	0/7	0/0
> ULN	0/7	0/3	0/4	0/7	0/0
LH (IU/l)					
< LLN	0/31	0/21	0/24	0/22	0/17
> ULN	5/31 (16.1%)	3/21 (14.3%)	3/24 (12.5%)	2/22 (9.1%)	6/17 (35.3%)
FSH (IU/l)					
< LLN	0/31	0/20	0/24	0/22	0/17
> ULN	11/31 (35.5%)	5/20 (25.0%)	4/24 (16.7%)	4/22 (18.2%)	4/17 (23.5%)
Prolactin (ug/l) (Female)					
< LLN	0/7	0/3	0/4	0/7	0/0
> ULN	0/7	0/3	0/4	0/7	0/0
Total Testosterone (nmol/l) (Male)					
< LLN	1/24 (4.2%)	1/18 (5.6%)	1/19 (5.3%)	1/14 (7.1%)	1/16 (6.3%)
> ULN	0/24	1/18 (5.6%)	0/19	0/14	1/16 (6.3%)

Notes : Abnormality is a Potentially Clinically Significant Abnormality (PCSA) or, when PCSA are not defined for a parameter, an out of reference value of the analytical laboratory.
% calculated using the number of patients with at least one event (n) over the number of patients having at least one post-baseline value (N). into account.

Conclusion: [redacted]

Date of report: 08-Jun-2009