Debio 4126, a new 3-month octreotide formulation, provides sustained release of octreotide, as well as enhanced bioavailability and similar suppression of insulin-like growth factor 1 (IGF-1), compared to monthly Sandostatin LAR® in healthy volunteers - interim results

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INTRODUCTION

Debio 4126-101 trial is an open-label, active-controlled, parallel-group, single site Phase 1 study in healthy volunteers with flexible design. The aim is to characterize the pharmacokinetics (PK), pharmacodynamics (PD), and safety and tolerability of a single administration IM or SC of two formulations in two solvents of a 3-month sustained-release octreotide formulation, Debio 4126.

METHODS

- All enrolled subjects received a single dose of 200 µg octreotide immediate-release (Sandostatin IR) and were followed up for a week to confirm tolerability before long-acting form is administered
- Each cohort is composed of 7 to 15 subjects, including 2 sentinel subjects.
- 75 subjects were enrolled in 1 of the 6 Debio 4126 cohorts and received a single administration of 30 or 90 mg Debio 4126 formulations (A or B), in one of two tested solvents, either intramuscularly (IM) or subcutaneously (SC) (Figure 1).
- 14 subjects were enrolled in the reference cohort and received 3 injections of 30 mg Sandostatin LAR® every 28 days.
- Of the 90 subjects enrolled, 88 completed at least 84 days post first administration. Enrolment in additional cohorts is ongoing.
- Plasma octreotide and serum IGF-1 levels were measured using validated LC-MS/MS methods.
- PK parameters were derived from non compartmental analysis using Phoenix WinNonlin®

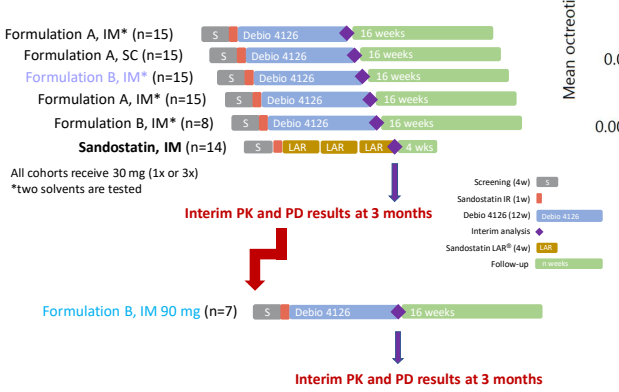

Figure 1 : Debio 4126-101 study design

RESULTS

In all Debio 4126 cohorts, octreotide levels are sustained over the intended dosing interval of 84 days (data not shown).

As with other octreotide long-acting, a short drug burst is observed, followed by a valley and a plateau phase, reached at approximately Day 28 for all doses tested (Figure 2).

After IM administration of a single dose of 90 mg Debio 4126, the mean octreotide plasma level stays above the target of 1 ng/mL, considered therapeutic in patients[1], until the end of the dosing interval. The PK profile of a single dose of Debio 4126 is similar to the PK profile following 3 administrations of Sandostatin LAR®, but bioavailability appears higher for Debio 4126 (Figure 2).

A reduction in serum IGF-1 levels over 84 days is seen in all cohorts and is comparable between the 90 mg Debio 4126 dose and 3 doses of 30 mg Sandostatin LAR® (Figure 3).

The PK of Debio 4126 appears dose-proportional within the tested dosing range (Table 1). The 90 mg dose is associated with a faster IGF-1 reduction compared to 30 mg Debio 4126 (Figure 3).

The safety profile of Debio 4126 is consistent with that of Sandostatin LAR®, regardless of Debio 4126 formulation, solvent or route of administration. Most frequent adverse reactions are those described for other somatostatin analogues (SSAs), i.e., gastrointestinal disorders, biliary disorders and injection site reactions.

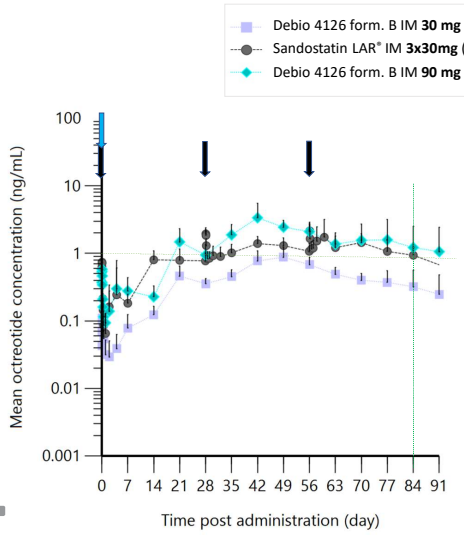

Figure 2 : Mean (+SD) octreotide levels

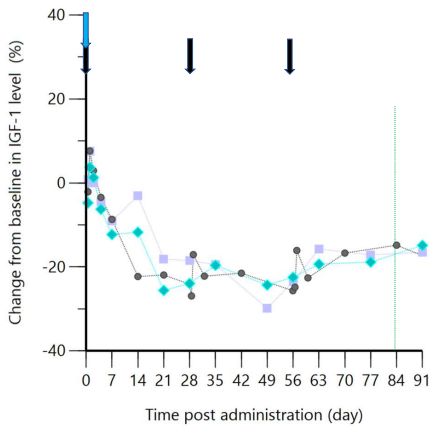

Figure 3: Mean change from baseline in IGF-1 levels

	Cohort	Number of subjects (at time of analysis)	Geometric Mean (Geo CV%)	Min	Max
AUC_{84days} (ng·day/mL)	Sandostatin LAR® IM 3x30mg	14	80.4 (29%)	50.9	136.8
	Debio 4126 IM 30 mg	15	35.9 (17%)	26.7	46.6
	Debio 4126 IM 90 mg	7	122.5 (27%)	75.9	187.9
C_{max} (ng/mL)	Sandostatin LAR® IM 3x30mg	14	1.0 (35%)	0.6	1.9
	Debio 4126 IM 30 mg	15	0.9 (34%)	0.5	1.8
	Debio 4126 IM 90 mg	7	3.8 (38%)	2.6	7.7

Table 1 : Descriptive statistics of main PK parameters

[1] FDA CDER Clinical pharmacology and biopharmaceutics review Sandostatin LAR®

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CONFLICTS OF INTEREST

AB, DS, MM, DRR, AM, BP, LM, CB, BD, BG, SIJ are employees of Debiopharm ; LT was an employee of Debiopharm at the time the data were generated ; JK and FF received compensation from Debiopharm for the work performed on the study

DISCUSSION

Debio 4126 provides sustained release of octreotide over the dosing interval of 84 days at a level considered adequate for treatment of patients with acromegaly. Bioavailability appears higher after Debio 4126 administration compared to Sandostatin LAR®.
Debio 4126 administered in healthy volunteers has a safety profile consistent with that of Sandostatin LAR® and demonstrates IGF-1 reduction over 84 days.

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