Debio 4126, a new 12-week octreotide formulation, provides maintenance of disease control in patients with acromegaly switching from long-acting somatostatin analogues (SSAs) – preliminary results

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INTRODUCTION

Debiopharm International SA is developing Debio 4126, a 12-week octreotide formulation, for the treatment of patients with acromegaly. Preliminary results from acromegaly patients in an ongoing trial, Debio 4126-102, are presented here for the first time.

METHODS

The Debio 4126-102 trial (OXTEND-01) is a Phase 1b, open-label, multicenter trial in patients with acromegaly to characterize the pharmacokinetics (PK), pharmacodynamics (PD), safety, and tolerability of Debio 4126 administered intramuscularly (IM) every 12 weeks (Q12W); 4 administrations were planned (**Figure 1**).

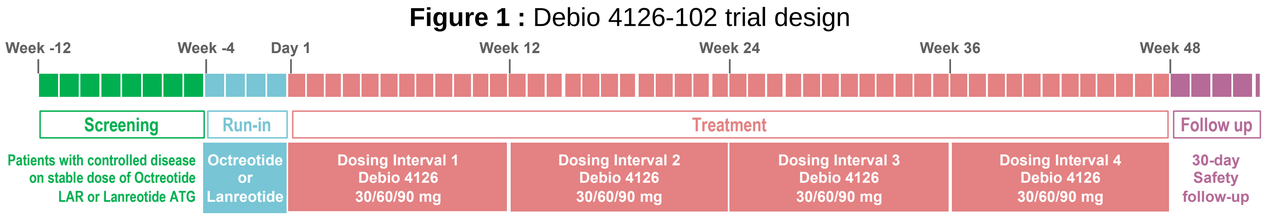
The trial was designed to investigate Debio 4126 in 2 parallel cohorts of patients with acromegaly and GEP-NETs (15 patients in each cohort). This poster discusses only the acromegaly cohort.

The acromegaly cohort enrolled adult patients with acromegaly controlled (insulin-like growth factor 1 [IGF-1] ≤1.3x upper limit of normal [ULN]) on a stable dose of octreotide or lanreotide as monotherapy.

The trial design is presented in **Figure 1**. At the beginning of the Run-in period, 4 weeks before Day (D)1, patients received a last dose of the somatostatin analog (SSA) they were receiving previously. On D1 of the treatment period, patients received Debio 4126 at a starting dose corresponding to the SSA dose (see **Table 2**).

Octreotide was measured centrally in plasma samples using a validated LC-MS/MS method. IGF-1 was measured centrally in serum samples using a validated chemiluminescence assay (IDS-iSYS). Abdominal ultrasounds were performed at least every 3 months to check for cholelithiasis.

Figure 1 : Debio 4126-102 trial design



RESULTS

Recruitment began in October 2022, and the last patient started Debio 4126 treatment in November 2023. The trial enrolled 16 patients with acromegaly. As of August 19th, 2024, 13 patients completed the trial per protocol. One patient discontinued the trial after 2 dosing intervals, due to inability to comply with the schedule of activities. The 2 ongoing patients received 4 Debio 4126 administrations. The last patient follow-up period completion is expected by the end of 2024.

Patient baseline parameters are presented in **Table 1**. Starting doses vs. treatment during the Run-in period are presented in **Table 2**.

During the trial, there was only 1 up-titration in a patient who had IGF-1 <1x ULN at screening, but whose IGF-1 increased up to 1.8x ULN during the Run-in period (on D-28, D-14, D-7, and on D1 of the first dosing interval [C1D1]). After administration of Debio 4126 30 mg on C1D1, corresponding to the 60 mg lanreotide dose the patient was receiving previously, the IGF-1 levels stabilized to between 1 and 1.3x ULN. Following the up-titration to Debio 4126 60 mg on C2D1, IGF-1 levels decreased slightly initially, but stayed above 1x ULN.

Table 1: Patient baseline characteristics

Parameter	Patients with acromegaly N=16
Age <65 years: n (%)	14 (87.5)
Age (years): minimum, **median**, maximum	33, **57.0**, 74
Females: n (%)	7 (43.8)
Height: mean (SD)	173.8 (12.4)
Weight: mean (SD)	87.2 (22.5)
BMI <30 kg/m²: n (%)	11 (68.8)
BMI (kg/m²): mean (SD)	28.6 (5.7)
Years from acromegaly diagnosis to Run-in: minimum, **median**, maximum	2.9, **9.37**, 33.3
Prior cholecystectomy: n (%)	4 (25.0)
IGF-1 at screening ≤1x ULN: n (%) >1x ULN ≤1.3x ULN: n (%)	 13 (81.3) 3 (18.8)
IGF-1 at baseline (last assessment prior to first dose) ≤1x ULN: n (%) >1x ULN ≤1.3x ULN: n (%) >1.3x ULN: n (%)	 12 (75.0) 3 (18.8) 1 (6.3)

IGF-1, insulin-like growth factor 1; N, overall number; n, number out of N; SD, standard deviation

Table 2: Starting dose vs. treatment during Run-in

Debio 4126 starting dose	N	SSA during the Run-in Period: Octreotide N (dose)	SSA during the Run-in Period: Lanreotide N (dose)
30 mg	3	1 (10 mg)	2 (60 mg)
60 mg	5	2 (20 mg)	3 (90 mg)
90 mg	8	6 (30 mg)	2 (120 mg)

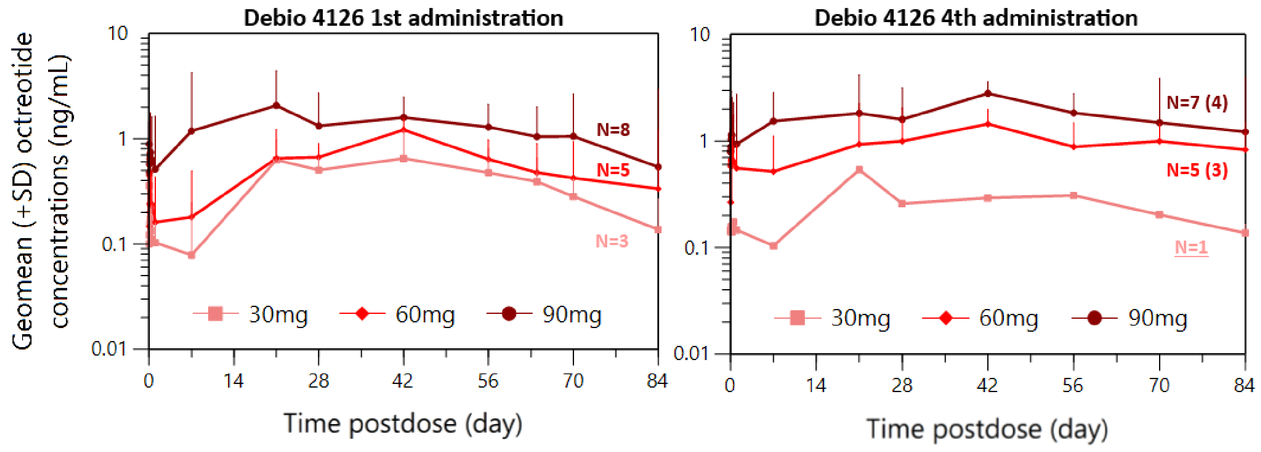
N, number; SSA, somatostatin analog

PK, PD AND SAFETY RESULTS

Preliminary PK results show sustained octreotide plasma concentrations over 84 days (12 weeks). Octreotide profiles after the first and fourth administrations are presented in **Figure 2.**

The results suggest dose-proportionality between 30, 60, and 90 mg Debio 4126, and limited accumulation after repeated administrations. The 24-hour initial release is lower than the C_{max} over the 12-week period.

Figure 2 : PK profiles after single and repeated administrations



Source data: May 6th, 2024. Abbreviations: N: number of total individual profiles (number of uncomplete profiles included in N). Underlined N: 1 patient profile and not a mean profile

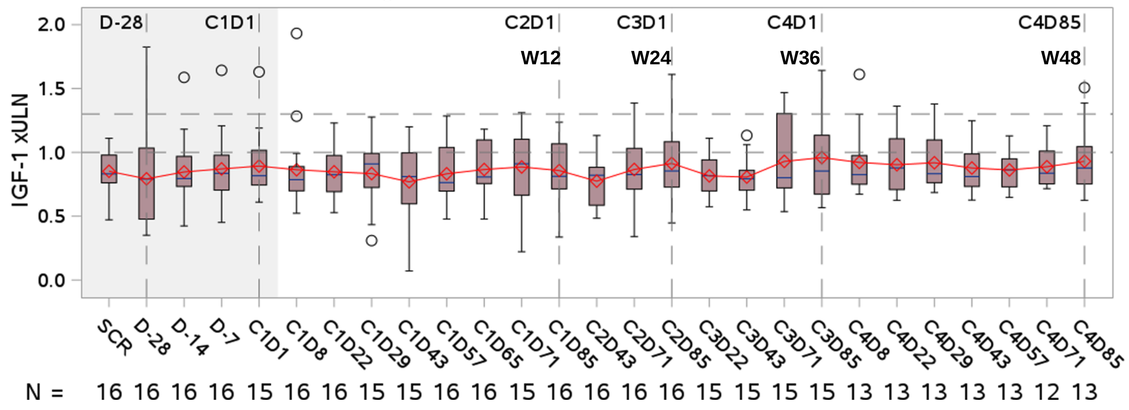
The PK profile is similar to that observed in healthy volunteers (see ref. 1).

IGF-1 data over time are presented in **Figure 3**. During the Run-in period, IGF-1 varied relative to screening (see **Table 1**, baseline vs. screening).

Of the 16 patients enrolled, 1 had IGF-1 >1.3x ULN at baseline and at the end of the fourth dosing interval (C4D85). Of the remaining 15 patients with baseline IGF-1 ≤1.3x ULN, 14 patients (93%), 95% confidence interval (CI) [68%; 99%], remained with IGF-1 ≤1.3x ULN at their last available assessment. Out of 12 with IGF-1 ≤1x ULN at baseline, 9 patients (75%), 95% CI [43%; 94%], maintained normal IGF-1 at their last available assessment.

Treatment-related treatment-emergent adverse events (TEAEs) are presented in **Table 3**. No deaths or serious adverse events (SAEs) were observed. Cholelithiasis was reported in 5 patients, all asymptomatic. In 1 assessment in 1 patient, a Grade 3 alanine aminotransferase per Common Terminology Criteria for Adverse Events (CTCAE) was observed. The event resolved spontaneously. All other TEAEs were Grade 1-2. All events were manageable. The overall safety profile corresponds to the safety profile expected for SSAs.

Figure 3 : PD profile over Run-in and treatment periods



Source data: August 19th, 2024. Abbreviations: CxDy, dosing interval x, Day y; IGF-1, insulin-like growth factor 1; SCR, Screening; ULN, Upper limit of normal; W, week.
Notes: The gray zone illustrates samples taken prior to any Debio 4126 dose. Dashed vertical lines mark dosing days and end of the treatment period. A red line connects the red diamonds representing the mean values for each visit. The box plots show the median, 1st quartile and 3rd quartile, and whiskers reach the furthest value from the median which is within 1.5 times the interquartile range from the lower or upper quartile. Data points outside this interval are plotted as outliers.

Table 3: Treatment-related TEAEs occurring in at least 2 patients by preferred term

System Organ Class Preferred Term	Debio 4126 30 mg N=3	Debio 4126 60 mg N=5	Debio 4126 90 mg N=8	Total N=16
Any treatment-related TEAE	3 (100)	3 (60.0)	5 (62.5)	11 (68.8)
General disorders and administration site conditions	**1 (33.3)**	**1 (20.0)**	**2 (25.0)**	**4 (25.0)**
Injection site erythema	1 (33.3)	0	1 (12.5)	2 (12.5)
Injection site induration	1 (33.3)	1 (20.0)	0	2 (12.5)
Injection site inflammation	0	0	2 (25.0)	2 (12.5)
Hepatobiliary disorders	**2 (66.7)**	**1 (20.0)**	**2 (25.0)**	**5 (31.3)**
Cholelithiasis	2 (66.7)	1 (20.0)	2 (25.0)	5 (31.3)
Nervous system disorders	**1 (33.3)**	**0**	**1 (12.5)**	**2 (12.5)**
Headache	1 (33.3)	0	1 (12.5)	2 (12.5)

Source data: July 12th, 2024. N, number; TEAE, treatment-emergent adverse event

Acknowledgements: The authors would like to thank all patients who accepted to participate in the trial as well as the medical and clinical staff who conducted the trial. Furthermore, the following persons significantly contributed to this work: Anna Perkio, Florilene Bouisset, Claudia Krolzig-Anyanwu, Catherine Dutreix, as well as Medpace, Q2S, and ICON staff.

Conflicts of interest: SIJ, AM, DRR, DB, MM, BG, CL, AB, and PCa are employees of Debiopharm; PW, MA, PCh, and TB are investigators in the Debio 4126 trial and received compensation from Debiopharm for the work performed

References: (1) Bellon A. *et al.,* ENEA 2022

CONCLUSIONS

Debio 4126 administered IM Q12W provides sustained release of octreotide over the 12-week dosing interval, with dose-proportionality between 30, 60, and 90 mg doses, and limited accumulation after repeating dosing. IGF-1 levels are maintained relative to baseline until the end of the 48-week treatment in a majority of patients with acromegaly. The safety profile is consistent with that of other SSAs.
These preliminary data support the potential of Debio 4126 administered Q12W to be an effective maintenance therapy for patients with acromegaly. The reduced injection frequency would decrease patient burden.
Debio 4126 efficacy and safety will be further assessed in a pivotal Phase 3 trial planned to start in 2025.

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