2 SYNOPSIS

Name of Sponsor/Company: Ipsen Pharma	Individual Study Table Referring to Part	*(For national authority use only)*
Name of Finished Product:	of the Dossier	
Name of Active Ingredient(s): BIM 23A760	Volume: Page:	

Title of study: A Phase II exploratory, ascending dose, multicentre study to investigate the pharmacodynamics, pharmacokinetics, safety and tolerability, of BIM 23A760 in acromegalic patients
Study number: 2-55-52060-002

Principal Investigator: Professor Annamaria Colao

Study centre(s): University Federico II Naples, Via S Pansini 5, 80131 Naples, Italy

Publication (reference): None.

Studied period (years): Date of first enrolment: 27 August 2008 Date of last completed: 24 February 2009	**Phase of development:** II

Objectives:
To investigate the pharmacodynamics (PD) of BIM 23A760, administered by single subcutaneous (s.c.) injection to patients with acromegaly.
To investigate the pharmacokinetics (PK), safety and tolerability of BIM 23A760, administered by single s.c. injection to patients with acromegaly.

Methodology: This was a Phase II, exploratory, multicentre, open, ascending dose study conducted at four centres in Europe. Patients were screened for eligibility within 21 days prior to BIM 23A760 administration (Day 1), and an octreotide test was performed on Day -8. The patients were hospitalised on the evening of Day -2 and baseline control assessments were performed on Day -1. Patients received a single dose of BIM 23A760 on the morning of Day 1; the first cohort received a 1 mg dose and the second cohort a 4 mg dose. A clinical safety committee (CSC) reviewed the data from the 1 mg cohort before progressing to 4 mg dose level. Patients receiving 1 mg BIM 23A760 completed a final study visit at Day 29. For the 4 mg dose level, patients were to complete a final study visit at Day 43.

Number of patients (planned and analysed):
At least 8, up to a maximum of 12 octreotide sensitive patients were to be included . In addition, a maximum of 12 patients nonsensitive to octreotide could be included. Each cohort was to contain 4 to 12 patients (4 of whom were sensitive to octreotide) and the total maximum number of patients to be treated was 24. A total of 11 patients were treated and included in the analysis (5 in the 1 mg cohort; 6 in the 4 mg cohort). One patient (in the 1 mg cohort) was not sensitive to octreotide.

Diagnosis and criteria for inclusion: Patients between 18 and 75 years with a diagnosis of acromegaly (supported by documentation of elevated growth hormone [GH] and/or insulin like growth factor 1 [IGF-1] levels), a mean serum GH >4 µg/L during a 5 hour profile and IGF-1 above normal during the screening period.

Test product, dose and mode of administration, batch number:
BIM 23A760 lyophilisate for reconstitution with water for injection to 5 mg/mL; doses 1 mg and 4 mg; subcutaneous injection; batch number TBL6.

Duration of treatment: Single dose.

Name of Sponsor/Company: Ipsen Pharma	Individual Study Table Referring to Part	*(For national authority use only)*
Name of Finished Product:	of the Dossier	
Name of Active Ingredient(s): BIM 23A760	Volume: Page:	

Reference therapy, dose and mode of administration, batch number: None.

Criteria for evaluation:
Pharmacodynamics (PD): GH, IGF-1, prolactin.
Pharmacokinetics (PK): Concentration of BIM 23A760 in serum. Concentration of octreotide in plasma.
Safety: Adverse events (AEs), vital signs, electrocardiogram (ECG), clinical laboratory evaluations, glucose tolerance (insulin/glucagon/glucose cycle and HbA1c), endocrine parameters (adrenocorticotropic hormone [ACTH], cortisol cycle, luteinising hormone [LH], follicle stimulating hormone [FSH], free thyroxine [FT_4], thyroid stimulating hormone [TSH], testosterone), physical examination, gallbladder echography, local tolerance, anti-BIM 23A760 antibodies.

Statistical methods: Summary statistics and figures were presented for PD, PK and safety data. Student's t-test and the Mann-Whitney test were to be used to compare log-transformed PK parameters between the two cohorts. PD modelling was used to analyse the correlation between PD variables and BIM 23A760 levels.

Summary - conclusions:
Pharmacodynamics:
The results of the primary PD analysis (observed percentage inhibition of GH) are presented in the table. One patient in Cohort 1 was classified as octreotide nonsensitive but had an octreotide sensitivity test result (41%) close to the defined threshold (50%), therefore the results for Cohort 1 are presented including this patient (all patients) and excluding this patient (octreotide sensitive). All patients in Cohort 2 were sensitive to octreotide.

	All Patients	**Octreotide Sensitive Patients**	
	Cohort 1 1 mg BIM 23A760 (N=5)	**Cohort 1 1 mg BIM 23A760 (N=4)**	**Cohort 2 4 mg BIM 23A760 (N=6)**
Maximum % inhibition of GH			
Mean ± SD	-66.4 ± 24.88	-66.8 ± 28.70	-74.2 ± 21.56
Median	-64.6	-71.4	-76.9
Range	-93.8, -30.7	-93.8, -30.7	-97.1, -48.6

Inhibition in serum GH was seen in all patients at both the 1 mg and 4 mg dose levels and was apparent from Day 1 following BIM 23A760 administration. Mean GH inhibition was >66% in both groups. Maximum percentage GH inhibition ranged from 31% to 97% across all patients. Based on the data for GH measured over 1 hour, there was a tendency for prolonged duration of GH inhibition in the 4 mg cohort, with mean serum GH over 1 hour reaching a minimum at Day 3 in Cohort 1 and Day 8 in Cohort 2.
It was not possible to make a meaningful comparison of the magnitude of the change in GH between the two dose levels due to large interpatient variability and imbalances between the 1 mg and 4 mg cohorts at baseline.
Reductions in IGF-1 levels were seen at both dose levels, with maximum reductions at Day 4.
A marked inhibition of PRL levels was observed from 24 hours after drug administration in both dose cohorts. This inhibition was sustained for up to 3 weeks in the 1 mg cohort, and for at least 4 weeks in the 4 mg cohort.

Name of Sponsor/Company: Ipsen Pharma	Individual Study Table Referring to Part	*(For national authority use only)*
Name of Finished Product:	of the Dossier	
Name of Active Ingredient(s): BIM 23A760	Volume: Page:	

Pharmacokinetics:

Parallel serum concentration profiles were observed for Cohorts 1 and 2 after administration of 1 and 4 mg BIM 23A760, respectively. The profile presented 2 peaks, one between 2 and 4 hours and a second peak around 72 hours (3 days after administration), both of them within the same order of magnitude. After the second peak, levels decreased slowly reaching a mean serum concentration lower than or close to the limit of quantification after 8 days of s.c. administration for Cohort 1 (1 mg) or 22 days for Cohort 2 (4 mg).

Mean ± SD C_{max} for Cohort 1 was 143.5 ± 37.90 pg/mL with a range between 92.81 and 182.7 pg/mL, and 340.6 ± 313.1 pg/mL for Cohort 2 with a range between 119.7 and 965.5 pg/mL. An increase of exposure expressed as AUC_t was observed, suggesting that there is no meaningful loss of bioavailability with increasing doses. No statistically significant differences were observed in AUC_t/D and MRT_t after Student's t-test application when comparing the administered doses of 1 and 4 mg. These results should be taken with caution because of the low number (5 and 6 patients for Cohorts 1 and 2, respectively) of statistically compared values. C_{max} values showed a trend towards a less than dose-proportional increase.

Half-life could be calculated for Cohort 2 (4 of 6 patients) and its value was 155.5 hours (6.5 days). The value of the half-life of 6.5 days after 4 mg supports a weekly administration dose schedule.

Pharmacokinetics/Pharmacodynamics:

Results from this PK/PD analysis should be considered with caution due to the limited data available (only PD data from 11 patients with acromegaly).

BIM 23A760 induces inhibition of GH, IGF-1 and prolactin. However, the study design allowed for only GH levels to be adequately correlated with BIM 23A760 concentrations.

The decrease of mean GH levels after BIM 23A760 administration was well described by a Simple Inhibitory Emax model, which allowed the possibility of an incomplete GH inhibition. The E_{max}, EC_{50} and E_0 were 94%, 80.8 pg/mL and 9.85 ng/mL, respectively. The tested covariates (gender, dose level, age, weight and GH baseline) were not identified as having a statistically significant influence on the PD response. A high degree of interindividual variability was found for EC_{50} and E_0 (160% and 117%, respectively). The median of the individual Bayesian estimates of BIM 23A760 serum level needed to decrease the GH to 2.5 ng/mL ($C_{2.5}$) was 120 pg/mL.

Name of Sponsor/Company: Ipsen Pharma	Individual Study Table Referring to Part	*(For national authority use only)*
Name of Finished Product:	of the Dossier	
Name of Active Ingredient(s): BIM 23A760	Volume: Page:	

Safety results:
BIM 23A760 was well tolerated after single doses of 1 mg and 4 mg in patients with acromegaly. All TEAEs were of mild or moderate intensity. There was one SAE (hospitalisation for pneumonia; unrelated to study medication) but there were no withdrawals due to AEs. Two patients reported AEs associated with decreased blood pressure after receiving BIM 23A760, one at each dose level. Two patients reported gastrointestinal AEs (moderate diarrhoea in one patient after 1 mg BIM 23A760; mild epigastric discomfort and mild abdominal distension in one patient after 4 mg BIM 23A760). There was only one report of local intolerance at the injection site (mild erythema).
There were mean decreases in blood pressure after both doses; the decreases in blood pressure were larger and lasted longer after 4 mg BIM 23A760 than after 1 mg BIM 23A760. Heart rate also showed small decreases from baseline in both cohorts at all visits, however, there was no particular pattern to these results, either over time or by dose. Three patients in the 4 mg cohort met the criteria for orthostatic hypotension, however, none of these patients had clinical symptoms or concurrent AEs associated with these blood pressure changes and all had concomitant compensatory increases in heart rate.
There were decreases in TSH at Day 2 but levels had returned to baseline by Day 8. Other endocrine hormones were unaffected by administration of BIM 23A760.
Glucose tolerance was good. Insulin, glucagon and glucose cycles, as well as HbA1c, showed no clinically significant changes after administration of BIM 23A760.
There were no clinically significant safety findings with respect to laboratory parameters, ECGs or gallbladder echography, and no anti-BIM 23A760 antibodies were detected.

Overall conclusions:
Single doses of 1 mg and 4 mg BIM 23A760 were pharmacologically active in patients with acromegaly, demonstrated by sustained inhibition of GH (maintained for at least one week at the 4 mg dose), reduction in IGF-1, and marked and prolonged inhibition of PRL.
The pharmacokinetic profile of single dose BIM 23A760 in patients with acromegaly was characterised by an initial peak within 2 to 4 hours and a second peak approximately 3 days after administration, with a half-life of 6.5 days for the 4 mg dose. PK/PD modelling showed a correlation between BIM 23A760 serum levels and GH levels.
BIM 23A760 was well tolerated, with no serious related AEs. The few AEs reported included decreases in blood pressure and GI events. Local tolerance was good. There were findings indicative of meaningful changes in laboratory test results.
The data support the initiation of multiple dose studies in patients and demonstrate that BIM 23A760 is suitable for weekly dosing.

Date of report: 01 December 2009