AstraZeneca

Clinical Study Report Synopsis

Drug Substance	MEDI-578
Study Code	D2460C00001
Edition Number	1
Date	28 January 2011

A Phase I, Single Centre, Double-blind, Randomised, Placebo-controlled, Parallel-group Study to Assess the Safety, Tolerability, Pharmacokinetics and Efficacy of Intravenous Infusion of MEDI-578, an Anti-nerve Growth Factor Monoclonal Antibody, after Single Ascending Doses in Male and Non-fertile Female Patients with Painful Osteoarthritis of the Knee

Study dates:
First subject enrolled: 15 February 2010
Last subject last visit: 02 September 2010
Date of early study termination: 03 November 2010. The development plan of MEDI-578 had been amended, which meant that this study was no longer in line with the proposed clinical development for the compound.

Phase of development:
Clinical pharmacology (I)

International Co-ordinating Investigator:

Sponsor's Responsible Medical Officer:

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centres

The study was performed in three centres in the United Kingdom. One centre was performing all study procedures and two centres were consenting and screening patients.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The objectives and the associated variables are summarised in Table S 1.

Table S 1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To assess the safety and tolerability of single ascending intravenous doses of MEDI-578 in patients with OA of the knee.	Adverse events, laboratory variables, vital signs, ECG, physical and neurological examination	Safety
Secondary	**Secondary**	
To evaluate the PK of MEDI-578 and provisionally assess the dose proportionality of the PK following administration of single ascending doses of MEDI-578.	AUC, C_{max}, t_{max}, CL, V_z and $t_{1/2}$	PK
To evaluate the analgesic efficacy of MEDI-578 during the night and day.	NRS pain intensity and SPID	Efficacy
Exploratory	**Exploratory**	
To further explore the analgesic efficacy of MEDI-578 during the night and day	WOMAC pain, WOMAC stiffness, WOMAC physical function scores, PGIC, PGADS, usage of rescue medication.	Efficacy

Study design

This was a first time in man phase I, double-blind, randomised, placebo-controlled, parallel-group (ie, within sequential escalating dose cohorts) study to evaluate the safety, tolerability, PK and efficacy of MEDI-578, an anti-NGF monoclonal antibody (mAb) in male and non-fertile female patients with painful OA of the knee at increasing single doses.

Target subject population and sample size

Patients with painful OA of the knee, aged 40 to 80 years, males and females (post-menopausal/ surgically sterilized). Forty-eight (48) to 56 patients were planned to complete the study. For reasons not related to the results in this study, it was prematurely terminated after the first patient in Cohort 3 had completed the study.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Each patient received MEDI-578 or placebo by a single intravenous (IV) infusion. Dose was adjusted by body weight. Infusions were completed over a 1-hour period for all dose cohorts. Seven dose cohorts were planned, with an option to include an eighth dose cohort. The starting dose was 3 μg/kg. An IV infusion of placebo to match MEDI-578 was used as comparator.

Duration of treatment

Single dose.

Statistical methods

Given the exploratory nature, no formal statistical hypothesis testing was performed in this study. In general, the statistical analysis was descriptive. All safety and tolerability, efficacy and PK data are presented in subject listings. Continuous variables are summarised using descriptive statistics, which includes n, mean, standard deviation, min, median, max, by treatment group, as appropriate. Categorical variables are summarised in frequency tables (frequency and proportion) by treatment group, where applicable. Graphical representations are used as appropriate. Examples include line graphs showing individual or mean development over time. Data are presented by actual dose (not by cohort), and patients receiving placebo are pooled across dosing cohorts for summarised statistics.

Subject population

The first patient in the study was enrolled on 15 February 2010, and the last visit of the last patient occurred on 02 September 2010. The disposition of the subjects in this study is summarised in Table S 2.

Table S 2 Patient disposition (All patients)

	Number (%) of patients				
	Placebo	**3 ug/kg**	**10 ug/kg**	**30 ug/kg**	**Total**
Patients enrolled[a]					109
Patients randomized	2 (100.0)	2 (100.0)	3 (100.0)	1 (100.0)	8 (100.0)
Patients who were not randomized					101
Reason: Screen failure[b, c]					92
Inclusion criteria 6					20
Exclusion criteria 20					28
Reason: Other					9
Patients who received treatment	2 (100.0)	2 (100.0)	3 (100.0)	1 (100.0)	8 (100.0)
Patients who did not receive treatment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table S 2 Patient disposition (All patients)

	Number (%) of patients				
	Placebo	**3 ug/kg**	**10 ug/kg**	**30 ug/kg**	**Total**
Patients who completed study	2 (100.0)	2 (100.0)	3 (100.0)	1 (100.0)	8 (100.0)
Patients who discontinued study	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a] Informed consent received

[b] Patients with screen failure due to more than one criteria are counted in each of the inclusion or exclusion criteria.

[c] Screen failure due to inclusion or exclusion criteria with at least 10% of screen failure patients are displayed.

Summary of efficacy results

Individual evening NRS pain scores during the first 4 weeks after dosing were fluctuating over time, and there was no apparent indication of a dose related effect. Similarly, individual fluctuations over time were seen in morning assessments of NRS pain during the first 4 weeks after dosing. There was no apparent indication of a dose related effect in any of the WOMAC sub-scores (pain, stiffness, physical functioning).

Summary of pharmacokinetic (PK) results

PK parameters were estimated after a single IV administration of 3 µg/kg, 10 µg/kg and 30 µg/kg of MEDI-578 using non-compartmental analysis. Mean parameter values were not reported because of the low numbers of patients in each cohort and the wide variability in individual parameter values within each cohort. Serum concentrations decreased rapidly from peak to below quantifiable levels (LOQ=10 ng/ml) after 12 hours post dose, hence clearance, volume of distribution and half-life values were not estimable from the lowest dose cohort of 3 µg/kg.

MEDI-578 peak concentrations increased in a slightly more than dose proportional manner across the three dose levels. Individual peak concentrations ranged from 19-40 ng/mL, 172-242 ng/mL and 1069 ng/ml following 3 µg/kg, 10 µg/kg and 30 µg/kg doses, respectively. The area under the curve up to last measurable time point, AUC_{last}, increased in a more than dose proportional manner; 171-298 ng.hr/mL, 1162-13090 ng.hr/mL, and 68440 ng.hr/mL for 3 µg/kg, 10 µg/kg and 30 µg/kg dose, respectively. The more than proportional increase in AUC is indicative of non-linear PK for MEDI-578. Consistent with non-linear behaviour, serum clearance decreased from with increasing dose from 1.3-5.4 L/day following 10 µg/kg to 0.81 L/day following 30 µg/kg. Consequently, half-life increased from 0.84-6.3 days following 10 µg/kg to 14 days following 30 µg/kg. Consistent with limited distribution of monoclonal antibodies, steady state volume of distribution values were low and ranged from 6-14 L across the dose groups.

Summary of safety results

No deaths, serious adverse events (SAEs), or adverse events leading to discontinuation of treatment (DAEs) were reported in this study. Two patients administered MEDI-578 3 μg/kg and two patients administered MEDI-578 10 μg/kg experienced adverse events (AEs). No AEs were reported for the two patients receiving placebo or the single patient administered MEDI-578 30 μg/kg. In the patients administered 3 μg/kg, one event of vomiting and one event of headache were reported to be moderate in intensity, and one event of pain in extremity was reported as mild. In the patients administered 10 μg/kg, one event of pain in extremity was reported to be moderate in intensity, the other AEs (1 joint injury, 1 balance disorder, and 1 dizziness) were reported as mild. No dose related pattern in the occurrence of AEs could be detected.

There were no clinically relevant trends observed in haematology, clinical chemistry (including serum immunoglobulines) or urinalysis (including catecholamines in urine). No haematology values and few clinical chemistry values outside AstraZeneca's project specific extended reference ranges were reported after dosing with study drug, and no correlation to treatment or dose of MEDI-578 could be detected.

There were no clinically relevant trends observed in vital signs, including orthostatic challenge. Few values outside AstraZeneca's project specific extended reference ranges were reported after dosing with Investigational Product, and no correlation to treatment or dose of MEDI-578 could be detected.

There were no clinically relevant trends, or findings observed in the ECG data. There were no QTcF values <300 ms or >450 ms, and no changes in QTcF >30 ms were observed in this study.