SYNOPSIS

Name of Sponsor: Amgen Inc. Mountain View, California

Name of Finished Product: AMG 220 (previously C326, Avimer® protein inhibitor of interleukin-6).

Name of Active Ingredient: AMG 220

Title of Study: A Placebo-Controlled, Phase 1, Single and Multiple IV Dose Escalation Study of the Safety, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of AMG 220 in Adults with Crohn's Disease

Investigators and Study Centers: This study was conducted at 2 sites in Australia:

[redacted], MD, [redacted]

[redacted], MD, [redacted]

Publication: No publications to date.

Study Period: 14 September 2006 (first subject enrolled) to 5 January 2007 (last subject visit)

Development Phase: 1

Introduction and Objectives: AMG 220 is an Avimer™ protein that was developed as treatment for inflammatory disorders including Crohn's disease (CD) based on its ability to bind to and inhibit interleukin-6.

The primary objective of the study was to examine the safety of single and multiple doses of AMG 220 in subjects with stable, mildly to moderately active CD. Secondary objectives were to characterize the pharmacokinetic and pharmacodynamic profiles, and immunogenicity of AMG 220 in subjects with stable, mildly to moderately active CD. [redacted]

Methodology: In Part A of this 2-part study, a sentinel subject in each cohort was to receive unblinded AMG 220 (0.03, 0.1, 0.3, 1.0, or 3.0 mg/kg) before treatment of the remainder of the cohort. The remaining subjects were to be randomized (2:1) to receive a single dose of intravenous (IV) AMG 220 (0.03, 0.1, 0.3, 1.0, or 3.0 mg/kg) or placebo. In Part B, subjects were to be randomized (3:1) to receive IV AMG 220 (0.03, 0.1, 0.3, or 1.0 mg/kg) or placebo twice weekly for 4 weeks. In Parts A and B, dose escalation was to be based on a review of safety data before the enrollment of the subsequent cohort. The results of this study are reported in a synopsis format because Amgen terminated further development of AMG 220 for reasons not related to subject safety. Amgen suspended enrollment after part of cohort 3 (0.1 mg/kg) in Part A was enrolled. This report summarizes the results of Part A (cohort 1 [0.03 mg/kg], cohort 2 [repeat 0.03 mg/kg], and cohort 3 [0.1 mg/kg]).

Pharmacokinetic, pharmacodynamic, and serum samples for anti-AMG 220 antibodies were collected at various time points up to the end-of-study visit (day 29). For the schedule of assessments see Section 7 of the protocol (Attachment 1 of this report).

Number of Subjects Planned: Approximately 52 subjects (Part A: approximately 20 subjects; Part B: approximately 32 subjects)

Number of Subjects Enrolled: 11 subjects in Part A; 0 subjects in Part B

Sex: [redacted] women [redacted] men [redacted]

Age: [redacted] years, inclusive

Ethnicity (Race): [redacted]

Diagnosis and Main Criteria for Eligibility: Men and women 18 to 65 years of age, diagnosed with stable, mildly to moderately active CD.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Subjects were to receive a single dose of IV AMG 220 (0.03, 0.1, 0.3, 1.0, or 3.0 mg/kg). AMG 220 was supplied as a frozen liquid preparation consisting of 20.3 mg/ml AMG 220 in [redacted] mM Tris-HCl (tromethamine hydrochloride), [redacted] mM NaCl, [redacted] mM $CaCl_2$, and [redacted]% (w/v) polysorbate-80 at pH [redacted]. Investigational product was manufactured and supplied by Boeringher Ingelheim Austria. The batch number was [redacted].

Duration of Treatment: Single dose.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: Placebo was administered IV and was identical to AMG 220 formulation, with the exception of the active protein. Placebo was manufactured and supplied by Boeringher Ingelheim Austria. The batch number was [redacted].

Study Endpoints

Safety Endpoints: The principal safety endpoints were the incidence of serious adverse events and adverse events. All subjects were tested for presence of antibodies to AMG 220.

Pharmacokinetic Endpoints: The following parameters were determined: area under the plasma drug concentration versus time curve (AUC) extrapolated to infinity ($AUC_{0\text{-}inf}$), maximum observed plasma concentration (C_{max}), time to C_{max} (T_{max}), volumes of distribution at steady state (V_{ss}), clearance (CL), mean residence time calculated as area under the moment curve AUMC/AUC (MRT), and terminal half life ($t_{1/2,Z}$).

Pharmacodynamic Endpoints: The principal pharmacodynamic marker was C-reactive protein (CRP). [redacted]

Efficacy Endpoints: [redacted]

Statistical Methods: Because the study was terminated early, actual analyses were limited to selected data listings (Attachment 5). For pharmacokinetic analysis, noncompartmental analysis was conducted using WinNonlin Professional v. 4.1e (Pharsight Corp., Mountain View, CA). Nominal sampling times and doses were used. The area under the concentration time curve was estimated using an infusion model with the log-linear trapezoidal method.

Summary of Results:

Subject Disposition: In Part A, although 5 cohorts of escalating dosing were initially planned (0.03, 0.1, 0.3, 1.0, or 3.0 mg/kg), Amgen suspended enrollment after part of cohort 3 (0.1 mg/kg) was enrolled. A total of 11 subjects (9 AMG 220, 2 placebo) enrolled and received 1 dose of investigational product (Listing 1). All subjects completed the study and the 28 days of follow-up after receiving a single dose of investigational product. In cohort 1 (0.03 mg/kg), the sentinel subject [redacted] had a serious adverse event of CD exacerbation and a grade 3 adverse event

of hypophosphatemia (Listing 1, Listing 2, and Listing 4.1). Although the investigator considered these events unrelated to investigational product, the Safety Review Committee (SRC) recommended to not escalate dose for cohort 2 because of the hypophosphatemia; the enrollment of cohort 2 was initiated at the same (0.03 mg/kg) dose level. All 4 subjects in cohort 2 received 0.03 mg/kg AMG 220, and after review of emerging data, the SRC recommended to escalate dose for cohort 3 to the 0.1 mg/kg dose level (Listing 1). In cohort 3, only 3 of 4 subjects were enrolled and received investigational product before further enrollment was terminated by Amgen.

Safety Results: AMG 220 was well tolerated at all doses administered during the study. No deaths, treatment-related serious adverse events, and adverse events leading to change in investigational product administration or early discontinuations were reported. One subject ([redacted]) receiving 0.03 mg/kg AMG 220 had a serious adverse event of CD exacerbation that was considered unrelated to investigational product (Listing 3). A narrative for this subject is provided in Attachment 4.

All subjects reported ≥ 1 adverse event (Listing 2). The most common adverse events (reported by ≥ 2 subjects receiving AMG 220) were: headache, nausea, dizziness, upper respiratory tract infection, and catheter site hematoma. Most adverse events were mild to moderate. Treatment-related adverse events were reported in 3 subjects (1 subject [0.03 mg/kg], 2 subjects [0.1 mg/kg]) (Listing 2). These events were considered mild and included dizziness, blurry vision, nausea, and headache.

Other Safety Findings: No trend was apparent in chemistry laboratory abnormalities (Listing 4.1). Due to the underlying medical condition and concomitant medications, chemistry laboratory abnormalities were present in most subjects before enrollment. One subject ([redacted]) reported a Common Terminology Criteria of Adverse Events (CTCAE) grade 3 abnormality of hypophosphatemia that was considered by the investigator to be severe, but unrelated to investigational product; this adverse event resolved on day 63, after the last scheduled study visit, and occurred in association with the subject's serious adverse event of CD exacerbation (Listing 2, Listing 3). A narrative for this subject is provided in Attachment 4.

No trends in variations in the proportions of B and T cells were observed over time (Listing 4.2). Hematology assessments showed that 2 subjects ([redacted]) in the 0.03 mg/kg AMG 220 group had grade 3 lymphopenia at a single time point (Listing 4.3). It should be noted that subject [redacted] was taking [redacted] and subject [redacted] was taking [redacted] (data on file). In microscopy and urinalysis, no trends were observed in the mild treatment-emergent abnormalities (Listing 4.4 and Listing 4.5, respectively). No subjects had prolonged P-R, QRS, or QTc intervals and no subjects had abnormal ECGs (Listing 6). No notable changes in postural vital signs were reported (Listing 7).

Antibody Results: Eleven subjects had ≥ 1 postdose sample and were analyzed for anti-AMG 220 antibodies. All subjects were negative for anti-AMG 220 antibodies. The full antibody report for this study including the methodology used to test the serum samples is presented in Attachment 7.

Pharmacokinetic Results: AMG 220 exhibited linear pharmacokinetics between 0.03 and 0.1 mg/kg doses after single IV administration (Figure 1). After a single IV dose of AMG 220, CL, V_{ss}, $t_{1/2,z}$, and MRT did not change between 0.03 and 0.1 mg/kg doses (Table 1).

The half-life of AMG 220 was unexpectedly short and averaged 10.6 and 11.1 hours in the 0.03 and 0.1 mg/kg groups, respectively; this half-life compares to the 28 hour-half-life observed in cynomolgus monkeys.

Figure 1. Mean (+SD) AMG 220 Serum Concentration-time Profiles After IV Administration of 0.03 and 0.1 mg/kg AMG 220 to Humans

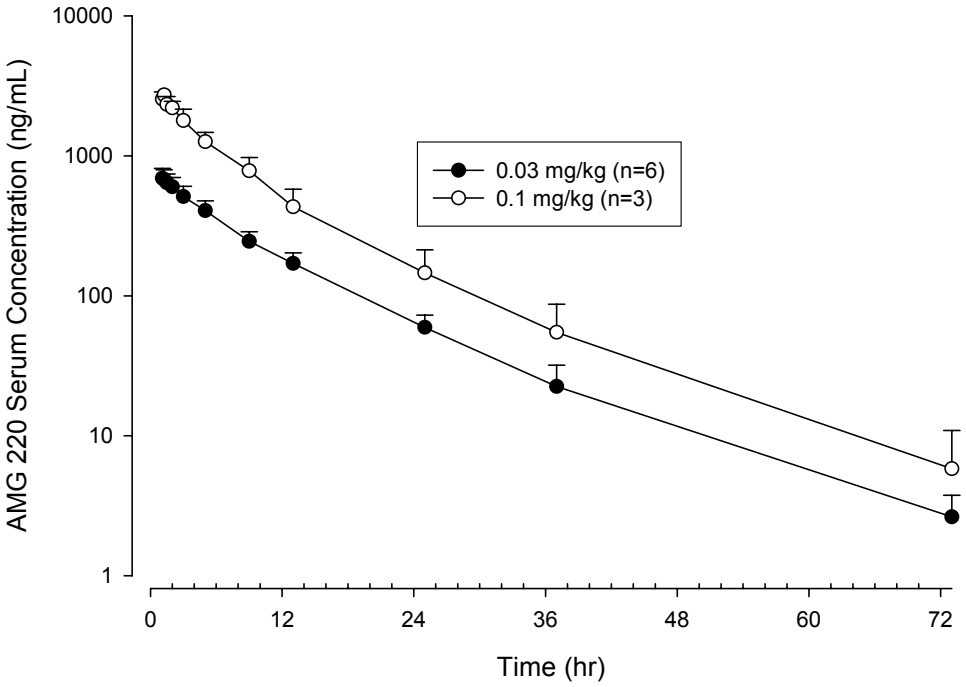

Table 1. Pharmacokinetic Parameters After an IV dose of AMG 220 to Humans

Dose (mg/kg)	Subject ID	T_{max} (hr)	C_{max} (ng/mL)	$AUC_{0\text{-inf}}$ (hr•ng/mL)	CL (mL/hr/kg)	V_{ss} (mL/kg)	$t_{1/2,Z}$ (hr)	MRT (hr)
0.03	[redacted]	1.25	574	5440	5.51	60.0	9.79	10.9
		1.25	753	6850	4.38	50.6	11.2	11.6
		1.08	631	6200	4.84	59.1	10.2	12.2
		1.08	754	7150	4.20	49.8	10.6	11.9
		1.08	899	8800	3.41	42.8	11.8	12.5
		1.08	595	5350	5.61	57.3	10.3	10.2
	N	6	6	6	6	6	6	6
	Mean	1.14	701	6630	4.66	53.3	10.6	11.5
	SD	0.0861	124	1290	0.839	6.71	0.717	0.868
	Median	1.08	692	6520	4.61	54.0	10.4	11.7
	CV%	7.6	17.7	19.4	18.0	12.6	6.7	7.5
Dose (mg/kg)	Subject ID	T_{max} (hr)	C_{max} (ng/mL)	$AUC_{0\text{-inf}}$ (hr•ng/mL)	CL (mL/hr/kg)	V_{ss} (mL/kg)	$t_{1/2,Z}$ (hr)	MRT (hr)
0.10	[redacted]	1.08	2710	20100	4.96	44.9	8.97	9.04
		1.08	2180	14900	6.70	56.1	9.72	8.38
		1.25	2800	25200	3.97	48.1	14.7	12.1
	N	3	3	3	3	3	3	3
	Mean	1.14	2560	20100	5.21	49.7	11.1	9.84
	SD	0.0962	336	5120	1.38	5.80	3.13	1.99
	Median	1.08	2710	20100	4.96	48.1	9.72	9.04
	CV%	8.4	13.1	25.5	26.5	11.7	28.1	20.2

$AUC_{0\text{-inf}}$ = area under the concentration-time curve from zero to infinity; CL = clearance; C_{max} = maximum observed concentration; MRT = mean residence time; $t_{1/2,Z}$ = half-life associated with the terminal phase; T_{max} = time at which C_{max} is observed; V_{ss} = volume of distribution at steady-state
All values except for CV% reported to 3 significant figures. CV% reported to 1 decimal place.

Pharmacodynamic Results: Mean serum CRP decreased numerically post dose in all treatment groups; however, the decrease was numerically greater in the AMG 220 group than in the placebo group at multiple time points (data on file). The difference was greatest between days 2 and 4 (data on file). Assays of total plasma IL-6 were not performed because of technical difficulties in the design of an assay for IL-6 in the presence of AMG 220. [redacted]

[redacted]

Conclusions: AMG 220 appeared to be well tolerated at the doses tested. No deaths, treatment-related serious adverse events, and adverse events leading to change in investigational product administration or early discontinuations were reported. One serious adverse event (CD exacerbation) was reported and was typical of CD. Pharmacokinetic results indicated a shorter half-life in humans than had been predicted based on the findings in cynomolgus monkeys.

Attachments:

[redacted]