1. TITLE PAGE

CLINICAL STUDY REPORT

IPI-504-06

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study Evaluating the Efficacy and Safety of IPI-504 in Patients with Metastatic and/or Unresectable Gastrointestinal Stromal Tumors Following Failure of at Least Imatinib and Sunitinib

Protocol Number:	IPI-504-06
Name of Test Drug:	IPI-504
Indication:	Metastatic and/or Unresectable Gastrointestinal Stromal Tumors
Phase:	3
Methodology:	Randomized, Double-Blind, Placebo-Controlled
First Patient Enrolled:	20 October 2008
Last Patient Enrolled:	14 April 2009
Date of Report:	1 April 2010
Sponsor:	Infinity Pharmaceuticals, Inc. 780 Memorial Drive Cambridge, MA 02139 Telephone: 617.453.1000 Fax: 617.453.1012
Responsible Medical Officer:	David Grayzel, MD Infinity Pharmaceuticals, Inc. Telephone: 617.453.1146 Fax: 617.453.1012
GCP Statement:	This study was performed in accordance with Good Clinical Practices (GCP), including the archiving of essential documents.

APPROVAL SIGNATURE PAGE

PREPARED BY:

Barbara E. Balser, VMD — On behalf of Barbara Balser — 2 April 2010

Consultant Medical Writer
Veristat, Inc

Signature — Date

Rodney Sleith — 2 April 2010

Consultant Biostatistician
Veristat, Inc

Signature — Date

REVIEWED/APPROVED BY:

Eduardo Rodenas, MD — April 1st, 2010

Senior Director,
Clinical Oncology
Infinity Pharmaceuticals, Inc.

Signature — Date

Leslie Williams, DVM, MPH — April 1, 2010

Senior Director, Clinical Development and
Pharmacovigilance
Infinity Pharmaceuticals, Inc.

Signature — Date

David S. Grayzel, MD — April 1, 2010

Vice President
Clinical Development and Medical Affairs
Infinity Pharmaceuticals, Inc.

Signature — Date

Imogene Grimes, PhD — Imogene M. Grimes — 01 APRIL 2010

Vice President
Data Management and Biostatistics
Infinity Pharmaceuticals, Inc.

Signature — Date

2. STUDY SYNOPSIS

Name of Company: Infinity Pharmaceuticals, Inc.	**Name of Finished Product:** IPI-504	**Name of Active Ingredient:** 17-allylamino-17-demethoxygeldanamycin hydroquinone, hydrochloride
Title of Study: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study Evaluating the Efficacy and Safety of IPI-504 in Patients with Metastatic and/or Unresectable Gastrointestinal Stromal Tumors Following Failure of at Least Imatinib and Sunitinib		
Investigators and/or Study Centers: Patients were enrolled in this study at 19 study sites in the United States (US), Canada, European Union (EU), and Rest of World (ROW).		
Publication (reference): Demetri GD, LeCesne A, Von Mehren M, Chmielowski B, Bauer S, Chow WA, et al. Final results from a phase III study of IPI-504 (retaspimycin hydrochloride) versus placebo in patients with gastrointestinal stromal tumors (GIST) following failure of kinase inhibitor therapies. Gastrointestinal Cancers Symposium. Orlando, FL. January 22-24, 2010. Abstract #64.		
Study Period: 07 October 2008 through 24 August 2009		**Phase of development:** Phase 3
Objectives: The primary objective of the study was to compare the progression-free survival (PFS) following administration of IPI-504 plus best supportive care versus placebo plus best supportive care in patients with metastatic and/or unresectable gastrointestinal stromal tumors (GIST) following failure of at least imatinib and sunitinib The secondary objectives of the study were to: 1. Compare the disease control rate (DCR) in both arms of the study. 2. Compare the time to progression (TTP) in both arms of the study. 3. Compare the overall survival (OS) in both arms of the study. 4. Evaluate the safety and tolerability of IPI-504 in this patient population.		
Methodology This was a randomized, double-blind, placebo-controlled, multi-center Phase 3 study designed to evaluate the efficacy and safety of IPI-504 compared with placebo in patients with metastatic and/or unresectable GIST who were receiving treatment with standard of care following failure of at least imatinib and sunitinib. The study was comprised of 2 parts: a double-blind period, during which patients received IPI-504 or placebo in a blinded fashion; and an open-label period for eligible patients with confirmed disease progression during double-blind treatment, during which patients received open label IPI-504. All patients received best standard of care throughout the study in combination with study drug. Screening for study eligibility was conducted within 28 days before the first dose of study drug and included documentation of disease progression by Response Evaluation Criteria in Solid Tumors (RECIST) or World Health Organization (WHO) criteria, medical history, physical examination, Eastern Cooperative Oncology Group (ECOG) performance status, vital signs, triplicate 12-lead		

Name of Company: Infinity Pharmaceuticals, Inc.	**Name of Finished Product:** IPI-504	**Name of Active Ingredient:** 17-allylamino-17-demethoxygeldanamycin hydroquinone, hydrochloride

electrocardiograms (ECGs), clinical laboratory tests , and ophthalmology/optometry examinations. Assessment of disease burden via computed tomography (CT) or magnetic resonance imaging (MRI) scans of the chest, abdomen, and pelvis was performed within 7 days before the first dose. Eligible patients were randomized in a 2:1 ratio to receive IPI-504 or placebo. Randomization was stratified based on TTP on imatinib (< 6 months versus ≥6 months or intolerance to imatinib) and geographic region (US/Canada versus EU/ROW).

During treatment, patients attended study center visits on each dosing day. Imaging assessments for evaluation of response to treatment and disease progression occurred at Weeks 2, 5, 8, 14 and 20 of treatment, every 6 weeks thereafter for patients who continued on treatment, and at the end of treatment. Tumor measurements were based on RECIST. All images were read locally at the site; in addition, an independent central assessment of imaging exams was conducted for determination of response to treatment and date of progression.

Safety was assessed via documentation of adverse events (AEs), routine clinical laboratory evaluations, heart rate, 12-lead ECGs (in triplicate), and ophthalmology/optometry examinations (as required based on symptoms). To assure the safety of patients, an Independent Data Monitoring Committee (IDMC) reviewed cumulative safety data on a quarterly or ad hoc basis as required in order to make recommendations regarding the further conduct of the study.

All patients were evaluated within 30 days after their last study drug dose. Thereafter, patients were to be followed every 2 months (±2 weeks) for survival and documentation of subsequent anticancer therapy until death or the end of the study, whichever was sooner.

This study was terminated early by the Sponsor due to an imbalance in deaths in the IPI-504 treatment group compared with the placebo treatment group.

Number of Patients (Planned and Analyzed):
The protocol was designed to enroll approximately 195 patients over a planned accrual period of 12 months in order to observe 148 patients with progressive disease or death by the end of the 6-month follow-up period.

At the time the study was terminated, 47 patients had been treated, including 32 patients randomized to IPI-504 and 15 patients randomized placebo. Six of the placebo patients had received IPI-504 during open-label treatment; thus a total of 38 patients had received at least 1 dose of IPI-504 during the study.

Diagnosis and Main Criteria for Inclusion:
Male or female patients 18 years of age or older with histologically confirmed metastatic and/or unresectable GIST, ECOG performance status ≤1, clinical failure of their most recent prior therapy for GIST, and documented radiographic progression or intolerance to imatinib and sunitinib were specific candidates for the study.

Name of Company: Infinity Pharmaceuticals, Inc.	**Name of Finished Product:** IPI-504	**Name of Active Ingredient:** 17-allylamino-17-demethoxygeldanamycin hydroquinone, hydrochloride

Test Product, Dose and Mode of Administration, Batch Number(s):
IPI-504 was supplied as a white-to-tan lyophilized powder in sterile, single-use vials containing 844.5 mg of IPI-504.

IPI-504 was to be administered at a dose of 400 mg/m^2 by intravenous (IV) infusion (in 250 mL of Sodium Chloride Injection, USP) over approximately 30 minutes twice weekly for 2 weeks followed by 1 week off. Study drug was not to be administered at doses >1000 mg. Doses were to be administered approximately 72 hours apart. All patients were also to receive best supportive care.

Lot numbers of IPI-504 for injection: 004I0108, 021I0208, 1529821, 1576137, 1597479

Lot numbers of IPI-504 diluent: 005I0108, 022I0208, 1489149, 1529822, 1599202

Reference Therapy, Dose and Mode of Administration, Batch Number(s):
Placebo was supplied as a white-to-tan lyophilized powder in sterile, single-use vials containing 255 mg of mannitol.

Placebo was to be administered in the same manner and on the same schedule as IPI-504. All patients were also to receive best supportive care.

Lot numbers of placebo: 361-01-001, 1489146

Lot number of placebo diluent: 361-02-002, 1489151

Duration of Treatment:
There was no predetermined maximum number of cycles of therapy in this study.

Criteria for Evaluation:
Efficacy:

Efficacy was assessed by serial tumor measurements based on RECIST conducted at Weeks 2, 5, 8, 14 and 20 of treatment, every 6 weeks thereafter for patients who continued on treatment, and at the end of treatment.

Safety:

Safety was assessed throughout the study by documentation of AEs, heart rate, clinical laboratory evaluations, 12-lead ECGs, and concomitant medications.

Statistical Methods:
Due to the early termination of the trial, efficacy analyses of PFS and TTP, and all exploratory efficacy analyses planned in the protocol were not conducted.

All AEs were coded and summarized by the Medical Dictionary for Regulatory Activities (MedDRA) (version 10.1) according to system organ class (SOC) and preferred term. Tabulations were produced for treatment-emergent AEs (TEAEs), TEAEs considered to be at least possibly related, TEAEs by severity, serious adverse events (SAEs), treatment-related SAEs, and AEs leading to treatment discontinuation. Actual values and changes from baseline over time on study were produced for clinical laboratory parameters, heart rate, and continuous ECG parameters. Shift analyses based on the Common Toxicity Criteria for AEs (CTCAE) were conducted for selected laboratory parameters.

Analyses were conducted on the Intent-to-treat (ITT) population, which included all patients who received at least 1 dose of study treatment.

Name of Company:	**Name of Finished Product:**	**Name of Active Ingredient:**
Infinity Pharmaceuticals, Inc.	IPI-504	17-allylamino-17-demethoxygeldanamycin hydroquinone, hydrochloride

Summary and Conclusions:

Baseline Characteristics:

The IPI-504 and placebo groups were similar with regard to demographic and baseline characteristics. In the ITT population, the majority of patients were male (66% and 73% in the IPI-504 and placebo groups, respectively) and white (75% and 87%, respectively). Mean age was 58 years in the IPI-504 group and 57 years in the placebo group with a range of 21 to 86 years across all 47 patients. As required by the protocol entry criteria, ECOG performance status at screening was 0 or 1 in all patients.

Mean duration since diagnosis of GIST was 5.3 years in the IPI-504 group and 6.4 years in the placebo group and ranged from 1.1 to 11.0 years across the 47 patients. The most common histopathologic type of GIST in both treatment groups was spindle cell, reported in 59% and 33% of patients in the IPI-504 and placebo groups, respectively.

All 47 patients had received prior treatment with imatinib and sunitinib. Mean duration from the end of the last prior treatment to enrollment in this study was 1.6 and 1.7 months in the IPI-504 and placebo groups, respectively. A higher proportion of patients who received IPI-504 had undergone prior hepatic surgery (22%) compared with patients who received placebo (13%).

Summary of Efficacy:

At the time of early study termination, 8 (25%) of the 32 patients in the IPI-504 group and 3 (20%) of the 15 patients in the placebo group had died within 30 days of the last dose of study drug (n=6) or in the follow-up period more than 30 days post treatment (n=5). None of the 47 patients achieved a CR or PR; stable disease of at least 6 weeks duration was observed in 3 patients (9%) and 2 patients (13%) in the IPI-504 and placebo groups, respectively.

Summary of Safety:

All 47 (100%) study patients experienced at least 1 TEAE during the double-blind treatment period. The most common TEAEs (i.e., occurring in >20% of IPI-504 patients) during the double-blind period were diarrhoea [19 (59%) IPI-504 patients and 3 (20%) placebo patients], fatigue [16 (50%) and 6 (40%) patients, respectively], nausea [13 (41%) and 5 (33%) patients, respectively), urine colour abnormal [13 (41%) and 0 patients, respectively], abdominal pain [11 (34%) and 3 (20%) patients, respectively], headache [11 (34%) and 3 (20%) patients, respectively], infusion site pain [10 (31%) and 1 (7%) patients, respectively], anorexia [9 patients (28%) and 3 patients (20%), respectively], and myalgia [7 patients (22%) and 0 patients, respectively].

A higher proportion of patients in the IPI-504 group (15 patients, 47%) experienced TEAEs of Grade 3 or higher severity during the double-blind period compared with the placebo group (5 patients, 33%). In addition, 3 patients randomly assigned to placebo who entered the open-label period experienced ≥Grade 3 events during treatment with IPI-504. TEAEs of ≥Grade 3 severity occurring in >10% of patients during any treatment with IPI-504 were diarrhoea (18% vs. 0% in the placebo group), renal failure/renal failure acute (13% vs. 0% in the placebo group), abdominal pain (11% vs. 0% in the placebo group), vomiting (11% vs. 0% in the placebo group), and aspartate aminotransferase increased (11% vs. 0% in the placebo group).

Two patients died during screening (prior to dosing) and 11 patients died during the treatment or post-treatment periods. Among these 11 patients, 6 died on study within 30 days of the last study drug dose,

Name of Company: Infinity Pharmaceuticals, Inc.	**Name of Finished Product:** IPI-504	**Name of Active Ingredient:** 17-allylamino-17-demethoxygeldanamycin hydroquinone, hydrochloride

and 5 died more than 30 days after the last dose. Among the 6 patients who died within 30 days after the last dose of study drug, 5 received IPI-504 and 1 received placebo. The events leading to death among the 5 IPI-504-treated patients were: renal failure, cardiorespiratory arrest, hepatic failure, disseminated intravascular coagulation with metabolic acidosis, and disease progression. The cause of death in the patient in the placebo group was disease progression.

Serious adverse events (SAEs) during double-blind therapy occurred more often in the IPI-504 group (13 patients, 41%) than in the placebo group (5 patients, 33%). In addition, 3 patients randomized to placebo who entered the open-label period experienced SAEs during treatment with IPI-504. SAEs occurring in more than 2 patients during any treatment with IPI-504 were diarrhoea (7 patients, 18%), renal failure/renal failure acute (6 patients, 16%), vomiting (4 patients, 11%), abdominal pain (3 patients, 8%), nausea (3 patients, 8%), aspartate aminotransferase increased (3 patients, 8%), and blood alkaline phosphatase increased (3 patients, 8%).

During the double-blind treatment period, 7 patients (22%) treated with IPI-504 and 1 patient (7%) treated with placebo were discontinued from treatment due to AEs. In addition, 1 patient randomized to placebo who entered the open-label period discontinued IPI-504 treatment due to AEs. Adverse events leading to discontinuation of IPI-504 were aspartate aminotransferase increased (2 patients, 5%), renal failure (2 patients, 5%), cardiorespiratory arrest (1 patient, 3%), myocardial infarction (1 patient, 3%), vomiting (1 patient, 3%), gastrointestinal fistula (1 patient, 3%), hepatic failure (1 patient, 3%), disseminated intravascular coagulation (1 patient, 3%) and metabolic acidosis (1 patient, 3%).

A higher proportion of patients who received IPI-504 experienced ≥Grade 3 elevations in liver function tests during the double-blind period than patients who received placebo as assessed by the following laboratory data: aspartate aminotransferase (AST: 16% vs 0%); alanine aminotransferase (ALT: 9% vs. 0%); and alkaline phosphatase (16% vs 0%). All patients with ≥Grade 3 elevations in liver enzyme levels had normal or Grade 1 values for these parameters at study baseline.

Treatment with IPI-504 led to a small decrease in mean heart rate compared with placebo; no clinically meaningful differences were observed in other ECG parameters. None of the patients receiving IPI-504 had a treatment-emergent QTc interval >450 msec.

Conclusions:
The trial was prematurely terminated by the Sponsor based on safety observations. IPI-504 at the dose and schedule evaluated in this study of 400 mg/m^2 twice weekly for 2 weeks followed by 1 week off treatment was not tolerated by this patient population. Serious adverse events including deaths, ≥Grade 3 TEAEs, ≥Grade 3 elevations in liver function tests, and discontinuations due to TEAEs occurred more frequently in patients receiving IPI-504 when compared with patients in the placebo group. Although the types of adverse events observed were not unexpected, the severity, including the outcome of death, and incidence of the events was greater than expected.

Date of the Report: 1 April 2010

3. TABLE OF CONTENTS

Section **Page**

TABLES INCLUDED IN THE TEXT

FIGURES INCLUDED IN THE TEXT

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
17-AAG	17-allylamino, 17-demethoxy geldanamycin
17-AG	17-amino, 17-demethoxy geldanamycin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APTT	Activated Partial Thromboplastin Time
AST	Aspartate aminotransferase
ATC	Anatomic therapeutic class
ATP	Adenosine triphosphate
$AUC_{0-\infty}$	AUC from time 0 extrapolated to infinity
AUC_{0-6h}	Area under the concentration by time curve from time 0 to 6 hours
BPI-sf	Brief Pain Inventory – Short Form
bpm	Beats per minute
BSA	Body surface area
BUN	Blood urea nitrogen
C	Centigrade
CFR	Code of Federal Regulations
CI	Confidence interval
CRF	Case report form
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CYP3A	Cytochrome P450 isoenzyme 3A
dL	Deciliter(s)
DMAG	17-dimethylaminoethylamino-17-demethoxy-geldanamycin
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
EBMT	European Bone Marrow Transplant
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EORTC-QLQ Core 30	European Organization and Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
F	Fahrenheit
FDA	Food and Drug Administration

Abbreviation	Definition
g	Gram(s)
GCP	Good Clinical Practice
GI	Gastrointestinal
h	Hour(s)
hCG	Human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart rate
ICH	International Conference on Harmonisation
ID	Identity
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IPI	Infinity Pharmaceuticals, Inc.
IRB	Institutional Review Board
IV	Intravenous(ly)
LBBB	Left bundle branch block
m	Meter(s)
µg	Microgram(s)
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
mL	Milliliter(s)
MRI	Magnetic imaging resonance
MTD	Maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PBO	Placebo
PD	Progressive disease
PDGFR-α	Platelet-derived growth factor receptor alpha
PET	Positron emission tomography
PFS	Progression-Free Survival
PK	Pharmacokinetic
PR	Partial response
Pt	Patient
PT	Prothrombin time
PTT	Partial thromboplastin time

Abbreviation	Definition
QTc	Corrected QT interval
QTcF	QT interval corrected using Fridericia's formula
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
ROW	Rest of the world
SAE	Serious adverse event
SD	Stable disease
SOC	System, organ, class
SD	Standard deviation
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
TTP	Time to progression
UK	United Kingdom
ULN	Upper limit of normal
US	United States
USP	United States Pharmacopoeia
WBC	White blood cell
WHO	World Health Organization

5. ETHICS

5.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The protocol, patient informed consent form, and any advertising used to recruit patients for the study were reviewed and approved by an appropriately constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC) at each study site before the study began.

Any documents that the IRB/IEC needed to fulfill its responsibilities, such as protocol amendments, and information concerning patient recruitment, payment, or compensation procedures, or information from the Sponsor was to be submitted to the IRB/IEC. The IRB/IEC's written unconditional approval of the study protocol and the informed consent form was to be in the possession of the Investigator and the Sponsor before the study was initiated. The IRB/IEC's unconditional approval statement was to be transmitted by the Investigator to the Sponsor prior to shipment of study drug supplies to the site.

The Investigator was responsible for informing the IRB/IEC of all amendments to the protocol. Progress reports and notifications of serious adverse events were to be provided to the IRB/IEC according to regulations and guidelines.

The IRB/IEC was to be informed by the Investigator of informed consent changes or revisions of other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study; new information that may adversely affect the safety of the patients or the conduct of the study; an annual update and/or request for re-approval; and when the study was completed.

A list of all IRBs/IECs consulted for this study is included in Appendix 16.1.3.

5.2. Ethical and Regulatory Conduct of the Study

The study was conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 Code of Federal Regulations [CFR] 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312) and ICH Harmonised Tripartite Guideline, Guideline for Good Clinical Practice E6(R1) (June 1996). These practices included: IRB/IEC procedures, informed consent, protocol adherence, administrative documents, drug supply accountability, data collection, patient records (source documents), adverse event recording and reporting, inspection and audit preparation, and records retention. The Investigator was made aware that regulatory authorities and representatives of the Sponsor could inspect the documents and patient records at any time.

All patient identities were kept confidential. Each patient was assigned a unique patient number, which in turn was used on the case report form (CRF) in place of the patient's name.

5.3. Patient Information and Consent

Before initiation of the study, the informed consent form to be used was submitted for approval to both the Sponsor and to the relevant IRB/IEC.

Prior to the conduct of any pre-entry tests not performed routinely in the treatment of the patient, the Investigator or a member of his/her staff was to explain the nature of the study, its purpose and associated procedures, the expected duration of participation, and the potential risks involved to the patient. The explanation was to be sufficiently detailed to allow for an informed decision to participate to be made by the patient. The informed consent form also was to explain that study data were to be stored in a database, maintaining confidentiality in accordance with national data legislation.

The Investigator or designee was to obtain written, informed consent from each participating patient. The patient was to have ample time and opportunity to ask questions and was to be informed about the voluntary nature of their study participation and their right to withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Following this discussion, the patient was to be asked if they were willing to sign and personally date a statement of informed consent.

The original signed informed consent form was to remain in the Investigator's file. A copy of the signed informed consent was to be provided to the patient.

The informed consent form and any other written information provided to the patients was to be revised whenever important new information became available that may have been relevant to the patient's consent, or if there was an amendment to the protocol which necessitated a change to the content of the patient's informed consent. The Investigator was to inform the patient of any changes in a timely manner and was to ask the patient to confirm continuation of their participation in the study by their signature on the revised informed consent form (if applicable). Any written informed consent form and written information was to receive the IRB's/IEC's approval/favorable opinion in advance of use.

To maintain confidentiality, all laboratory specimens, evaluation forms, reports, and other records were to be identified by a coded number (Europe) or by a coded number and initials (ROW). Sites were instructed to keep all study records in a locked file cabinet and to store code sheets linking a patient's name to a patient identification number separately in another locked file cabinet. Clinical information was not to be released without written permission of the patient, except as necessary for monitoring by applicable regulatory authorities and the Sponsor of the clinical trial or its representatives. The Principal Investigator also was to comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

Representative patient information used in the informed consent procedure is included in Appendix 16.1.3.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

6.1. Investigators and Study Centers

A list participating Investigators and study centers is provided in Table 6-1. The study was initiated at 44 investigational sites in the United States (US), Canada, European Union (EU), and throughout the rest of the world (ROW); a total of 19 sites enrolled and treated at least 1 patient at the time the study was terminated. Each Investigator's curriculum vitae is provided in Appendix 16.1.4.

Table 6-1 Primary Investigators and Study Centers by Country

Country	Site No.	Investigator	Organization	City, State
Australia	5*	McArthur, Grant	Peter MacCallum Cancer Institute	Melbourne, Victoria
	16	Goldstein, David	Prince of Wales Hospital	Randwick
	23	Kotasek, Dusan	Adelaide Cancer Centre	Ashford
	39	Karapetis, Christos	Flinders Medical Centre	Adelaide
	72*	Eliadis, Paul	Hematology and Oncology Clinics of Australasia	Auchenflower
Belgium	38*	Humblet, Yves	Hopital Universitaires S. Luc Ucl	Brussels
	60	Dirix, Luc	Sint - Augustinus	Wilrijk
Canada	49	Mulder, Karen	Cross Cancer Institute, University of Alberta	Edmonton
France	6*	Le Cesne, Axel	Institut Gustave Roussy	Villejuif Cedex
	56	Bompas, Emmanuelle	Centre Rene Gauducheau	Nantes
	92	Adenis, Antoine	Centre Oscar Lambret	Lille
Germany	8*	Reichardt, Peter	HELIOS Klinikum	Bad Saarow
	10	Hohenberger, Peter	Klinikum der Stadt Mannheim	Mannheim
	11*	Schlemmer, Markus	Klinikum der Universitaet Muenchen-Grosshadern	Muenchen
	50	Gruenwald, Viktor	Medical School Hannover	Hannover
	51*	Bauer, Sebastian	West German Cancer Center	Essen
Israel	44	Shacham-Shmueli, Einat	Sourasky Medical Center	Tel Aviv
	58	Brenner, Baruch	Oncology Institute - Rabin Medical Center	Petach Tikva
	61	Idelevitch, Efraim	Kaplan Medical Center	Rehovot
Italy	3	Casali, Paolo	Istituto Nazionale Tumori	Milan
Korea (South)	53*	Kang, Yoon-Koo	Asian Medical Center	Seoul
	55	Park, Joon Oh	Samsung Medical Center	Seoul

Country	Site No.	Investigator	Organization	City, State
Sweden	12	Eriksson, Mikael	Lund University Onkologiska Klinken	Lund
	83	Erlandsson, Martin	Kirurgiska Kliniken, Norrlands Universitetssjukhus	Umeå
United States	1/31*	Demetri, George	Dana-Farber Cancer Institute Massachusetts General Hospital Cancer Center	Boston, MA
	9*	von Mehren, Margaret	Fox Chase Cancer Center	Philadelphia, PA
	20*	Chow, Warren	City of Hope Medical Center	Duarte, CA
	21	Kaiser, Pamela	Lutheran General Hospital	Park Ridge, IL
	22	Kindler, Hedy L.	University of Chicago Medical Center	Chicago, IL
	24*	Chiorean, Elena	Indiana University Cancer Center	Indianapolis, IN
	25*	Elias, Anthony	University of Colorado	Aurora, CO
	27*	Priebat, Dennis	Washington Hospital Center	Washington, DC
	28*	Chmielowski, Bartosz	UCLA	Los Angeles, CA
	29*	Forscher, Charles A.	Cedars-Sinai Medical Center	Los Angeles, CA
	33	Samuels, Brian	Kootenai Cancer Center	Coeur d'Alene, ID
	34	Skubitz, Keith	University of Minnesota	Minneapolis, MN
	40*	Picus, Joel	Washington University	St. Louis, MO
	41*	Gorman, Richard	New Bern Cancer Care	New Bern, NC
	64	Heinrich, Michael	Oregon Health and Science University	Portland, OR
	65	Thornton, Katherine	Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins	Baltimore, MD
	66*	Pizzolato, Joseph	Mount Sinai Hospital	Miami Beach, FL
	70	Chen, Lei L.	University of Utah Huntsman Cancer Institute	Salt Lake City, UT
	71	Rosen, Gerald	St. Vincent's Cancer Center	New York, NY

*Study sites that enrolled and treated at least one patient prior to study termination.

6.2. Study Sponsor

The study was sponsored by Infinity Pharmaceuticals, Inc., 780 Memorial Drive, Cambridge, MA. Key Sponsor personnel are identified in Table 6-2.

Investigational product was supplied by the Sponsor.

Table 6-2 Key Sponsor Personnel

Study Role	Name / Title / Affiliation
Global Medical Monitor:	Eduardo Rodenas, MD Infinity Pharmaceuticals, Inc.
North American Medical Monitor:	Rob Shepard, MD Consultant to Infinity Pharmaceuticals, Inc.
Clinical Project Manager:	Travis Quigley Infinity Pharmaceuticals, Inc.
Global Project Manager:	Krista McKee, MPH Infinity Pharmaceuticals, Inc.
Clinical Research Associate:	Patricia Pimentel, CCRA Infinity Pharmaceuticals, Inc.
Regulatory Affairs Manager:	Laura DiMarzio Infinity Pharmaceuticals, Inc.

6.3. Clinical Monitoring

Study center and medical monitoring was conducted under the direction of the Sponsor by a contract research organization (CRO), Quintiles, 4820 Emperor Blvd, Durham, NC 27703, USA. Key CRO personnel are identified in Table 6-3.

Table 6-3 Key CRO Study Personnel

Study Role	Name / Title / Affiliation
EU Medical Advisor:	Adrien Tinetti, MD Quintiles Rue Jean Dominique Cassini 67404 Illkirch Cedex France
Asia-Pacific Medical Advisor:	Maria Teresa Sanchez, MD Quintiles 89 Science Park Drive, Lobby B#03-08 The Rutherford, Science Park One 118261 Singapore
Latin American Medical Advisor:	Gonzalo Rubio, MD Quintiles Torre Ducilio, E. Madero 1020, Floor 20 Buenos Aires, Argentina South America
Global Project Manager:	Laura Sandler Quintiles 10612 Montrose Ave, #204 Bethesda, Maryland 20814 United States
European Project Manager:	Gillian West Quintiles Ltd, The Pyramids Business Park Easter Inch Bathgate West Lothian EH48 2EH United Kingdom
Global Clinical Team Lead:	Kristina Johnson Quintiles 30 Justin Street Haverhill, Massachusetts 01832 United States
Global Regulatory Lead:	Shalu Ramrakha, PhD Quintiles Ltd, The Pyramids Business Park, Easter Inch Bathgate West Lothian EH48 2EH United Kingdom

6.4. Laboratory Facilities

The central study assessment facilities used in this study are listed in Table 6-4.

Table 6-4 Central Study Assessment Facilities

Study Assessment	Facility
Pharmacokinetics analyses:	Covance Laboratories, Inc. 3301 Kinsman Boulevard Madison, Wisconsin, USA 53704
Central electrocardiograms:	Biomedical Systems 77 Progress Parkway St. Louis, Missouri, USA 63043
Central imaging review:	Perceptive Informatics, Inc. 200 West Street Waltham, Massachusetts, USA 02451

Clinical safety laboratory testing was performed by each center's local laboratory. Pharmacokinetic analysis was conducted by Covance Laboratories, Inc. Central independent reviews of electrocardiograms (ECGs) were performed by Biomedical Systems.

Perceptive Informatics, Inc. provided an independent assessment of imaging exams for the study. A minimum of 3 qualified, board-certified radiologists were to assess the images for this study. Two radiologists conducted independent reads of each case (double read) with a third radiologist serving as adjudicator, when necessary. The independent radiologists were to assess study imaging to determine overall tumor response at each time point based on RECIST.

6.5. Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) was chartered for this study; the IDMC was responsible for assessing safety and futility during the conduct of the double-blind portion of the trial. The primary responsibility of the IDMC was to assure the ongoing safety of study participants. The IDMC was also charged with recommending to the Sponsor whether to continue the study, continue the study with suggested modifications, or terminate the study based on quarterly safety evaluations, ad hoc safety evaluations, and on a planned interim analysis of futility. The IDMC was administered by Veristat, Inc., 1750 Washington Street, Holliston, MA, USA.

The IDMC was a multidisciplinary group independent of the Sponsor. Members of the IDMC had no involvement in this trial outside their role on the IDMC and were not to act as Investigators or Sub-investigators on trials of the same or related products. The IDMC was comprised of 3 members, including 2 medical oncologists and a biostatistician; collectively, all 3 members had experience with the conduct and monitoring of randomized clinical trials. The IDMC members are identified in Table 6-5.

Table 6-5 Independent Data Monitoring Committee Members

Committee Member	Affiliation
Ronald H. Blum, MD	Beth Israel Medical Center 10 Union Square East, 4A-17 New York, New York, USA 10003
Jerald P. Radich, MD	Clinical Research Division Fred Hutchinson Cancer Research Center D4-100; 1100 Fairview Ave. North Seattle, Washington, USA 98109
Joseph Massaro, PhD	34 Robinson Drive Bedford, Massachusetts, USA 01730

The Committee was to review cumulative safety data on a quarterly basis throughout the study and make recommendations regarding the further conduct of the study. Additional IDMC meetings were to be convened on an ad hoc basis by the Sponsor or by the IDMC if there were immediate concerns regarding observations made during the course of the study. The purpose of the quarterly and ad hoc safety evaluations was to determine if the trial should be terminated based on safety concerns.

In addition to the safety evaluations, one unblinded interim analysis of futility was to be conducted when the 74th patient had documentation of progressive disease or had died.

A total of 4 meetings were held with the IDMC. The organizational meeting was conducted on 03 September 2008. The first patient was enrolled in the study in 14 October 2008. The initial quarterly safety review was conducted on 30 January 2009. The IDMC recommended that the study continue without modification at this meeting.

Between 6 and 9 April 2009, 3 serious adverse events (SAEs) resulting in death were reported to the Sponsor. The cases were reviewed by the Sponsor and an ad hoc IDMC meeting was convened. The meeting took place on 14 April 2009 and included the IDMC members, representatives from the Sponsor and George Demetri, MD as a representative for the Investigators. At the meeting, data from a total of 4 patients who had died were reviewed. Unblinding by the IDMC revealed that all 4 deaths had occurred in the IPI-504 group while no deaths occurred in the placebo group. Based on the imbalance in deaths between the IPI-504 and placebo groups, the IDMC recommended that the Sponsor stop patient enrollment in the trial and remove all patients currently receiving treatment.

On 15 April 2009, Infinity terminated the trial and announced that enrollment in Study IPI-504-06 was stopped and that all ongoing patients were to be removed from treatment. Between 17 and 28 April 2009, Infinity notified all Regulatory Authorities and Ethics Committees of the trial termination.

The final close-out meeting of the IDMC was held on 11 December 2009.

6.6. Data Analysis and Reporting

Statistical analyses were performed by Veristat, Inc., who also was responsible for production of the final clinical study report.

7. INTRODUCTION

7.1. Gastrointestinal Stromal Tumors (GIST) – Disease State and Current Treatment

Gastrointestinal stromal tumors (GIST) are mesenchymal neoplasms thought to arise from the interstitial cells of Cajal. While they are most commonly found in the stomach and small intestine, GIST can occur anywhere in the gastrointestinal (GI) tract as well as within the omentum and mesenteric tissue. Unresectable or metastatic GIST is a uniformly fatal disease that is characterized by the expression of the receptor tyrosine kinase KIT (CD117) in the vast majority of cases. Approximately 90% of GIST tumors contain mutations in the KIT receptor leading to constitutive activation of this receptor tyrosine kinase. In addition, a small percentage of GIST neoplasms contain mutations in platelet-derived growth factor receptor alpha (PDGFR-α), another tyrosine kinase.[1,2,3,4] These "gain of function mutations" have been shown to play a critical role in tumor genesis and in determining responsiveness to current therapies.[5]

Prior to 2002, the response rate of GIST to conventional chemotherapy was less than 5%.[6] With the discovery of mutations in KIT and the advent of tyrosine kinase inhibitors (TKIs) as effective therapy for GIST, there has been a substantial and dramatic change in the management of these patients with significant improvements in overall survival. Imatinib mesylate (Gleevec/Glivec®, Novartis) is indicated for first-line therapy in the treatment of patients with KIT (CD117) positive unresectable and/or metastatic GIST. In 2006, sunitinib malate (Sutent®, Pfizer) was approved as second-line therapy for the treatment of unresectable and/or metastatic GIST after disease progression on or intolerance to imatinib mesylate.

Despite these recent advances in the treatment of GIST, nearly all patients experience disease progression with significant disruption in a patient's quality of life, and GIST remains a fatal disease. Therefore, novel therapies are needed for patients who have progressed on or are intolerant of the proven therapeutic agents, imatinib and sunitinib.

7.2. IPI-504

7.2.1. Overview

IPI-504 is a novel, potent, and selective small molecule inhibitor of heat shock protein 90 (Hsp90), a recently identified target for cancer therapy. Hsp90 is a "protein chaperone" that enables its "client" proteins to achieve their appropriate conformation and function. The function of Hsp90 is vital for regulating signal transduction pathways that control cell proliferation, growth, and survival.[7] Many of these client proteins, such as cytosolic KIT kinase (c-KIT), Akt, human epidermal growth factor receptor 2 (Her-2), epidermal growth factor receptor (EGFR), Bcr-Abl (breakpoint cluster region gene-Abelson kinase), and PDGFR-α, are oncoproteins[8] or important cell-signaling proteins. As signal transducers and molecular switches, these client proteins are inherently unstable. Hsp90 keeps unstable signaling proteins poised for activation until they are stabilized by conformational changes associated with the formation of signal transduction complexes.[9,10,11] In response to Hsp90 inhibition, these proteins, including both those in their natural state such as Her-2, as well as those in their

mutant forms such as EGFR, KIT, and PDGFR-α, are degraded by the proteasome. This results in potent in vitro cytotoxicity and antitumor activity in vivo in multiple tumor models.

There are several naturally occurring Hsp90 inhibitors representing different chemical classes that have helped elucidate the role of Hsp90.[12,13] These compounds have provided insight into how the modulation of this target could help effectively treat a variety of cancers. To date, many experiments and clinical trials have been conducted with 17-AAG (17-allylamino-17-demethoxygeldanamycin), a particular derivative of the natural product geldanamycin.[14] However, 17-AAG has very poor solubility and was originally administered to patients in dimethylsulfoxide / egg phospholipid and subsequently Cremophor EL®-based formulations. Since then, others have attempted to develop Hsp90 inhibitors that did not necessitate such noxious formulations.

One such compound is IPI-504, a potent, selective, and water-soluble Hsp90 inhibitor. IPI-504 is a water-soluble derivative of 17-AAG and interconverts in vivo with 17-AAG and has increased potency for Hsp90 inhibition compared with 17-AAG. Both IPI-504 and 17-AAG are converted to an active metabolite 17-amino-geldanamycin (17-AG), which also is a potent inhibitor of Hsp90. IPI-504 is >4000 times more soluble than 17-AAG in aqueous formulations, and has >200 mg/mL solubility.

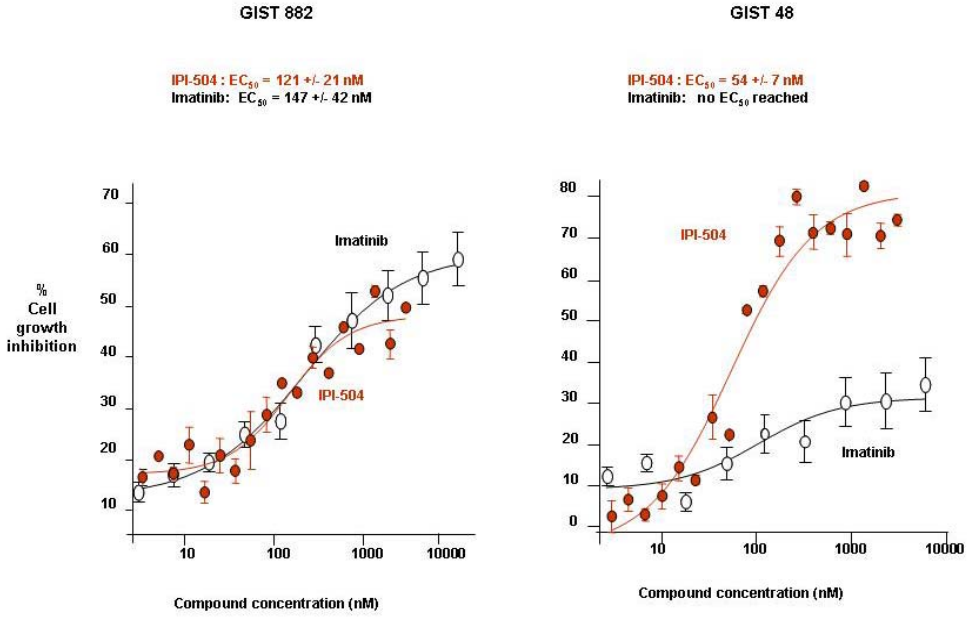
Following administration of 17-AAG in tumor-bearing mice, pharmacologically active levels of IPI-504 have been detected in the plasma. This important observation has been confirmed in other rodent and primate species. Therefore, not only is IPI-504 a water-soluble analog of 17-AAG, it is also a previously undescribed active metabolite of 17-AAG.[15] Based on the in vitro and in vivo interconversion of IPI-504 and 17-AAG demonstrated in cell cultures, animal models, and human clinical studies, it is likely that nonclinical studies and clinical studies previously published using 17-AAG demonstrate Hsp90 inhibition due to both 17-AAG and IPI-504 and their common active metabolite 17-AG. Similarly, studies with IPI-504 demonstrate the combined Hsp90 inhibitory effects of both IPI-504 and 17-AAG and their common active metabolite 17-AG.

There is a strong rationale for the therapeutic potential of IPI-504 in GIST. In this disease, there is a single molecular lesion driving tumor growth that is dependent on Hsp90. Mutated KIT is a client protein of Hsp90 that is dependent on Hsp90 for proper functioning. GIST tumor cells with mutated KIT are sensitive to Hsp90 inhibition by IPI-504. In addition, imatinib-resistant cells containing additional KIT mutations are even more sensitive to Hsp90 inhibition with IPI-504. Furthermore, biologic and anti-neoplastic effects of IPI-504 have been demonstrated in multiple human xenograft and murine orthotopic models of cancer. Several intravenous (IV) dose administration schedules (including IPI-504 administered daily and twice weekly) have been shown to significantly reduce tumor volume, delay tumor growth, and prolong survival in these animal models.

To determine whether IPI-504 could provide an alternative therapeutic strategy in imatinib-resistant GIST, in vitro studies were performed using imatinib-sensitive and imatinib-resistant, patient-derived GIST cell lines (GIST 882 and GIST 48, respectively). These two GIST cell lines were treated with increasing concentrations of IPI-504 and imatinib and the effects on cell viability were determined (Figure 7-1). As expected, imatinib was cytotoxic in GIST 882 cells

(EC_{50} = 147 nM) and it did not significantly affect the viability of GIST 48 cells. In contrast, IPI-504 inhibited the growth of both GIST cell lines with associated decreased levels of phosphorylated KIT as well as downstream signaling proteins. The imatinib-resistant cell line (GIST 48) was slightly more sensitive to IPI-504 (Figure 7-1). Thus, both imatinib-sensitive and imatinib-resistant GIST cell lines are sensitive to Hsp90 inhibition with IPI-504.

Figure 7-1 Effects of IPI-504 and Imatinib on the Viability of Imatinib-Sensitive and Imatinib-Resistant GIST Cell Lines



GIST 882 and GIST 48 were incubated with increasing concentrations of IPI-504 and imatinib for 72 hours and cell growth measured using Alamar blue.

IPI-504 has strong antiproliferative and proapoptotic effects in imatinib-resistant GIST cells at clinically achievable doses. IPI-504 abrogated oncogenic KIT signaling in imatinib-resistant cells, and by its mechanism of action may thus overcome the problem of genetic heterogeneity in imatinib-resistant GIST. Of note, preclinical data also indicate that Hsp90 inhibition may be effective in the subset of GIST patients with PDGFR-alpha mutations.[16,17,18] These data provide a rationale for the development of IPI-504 in the treatment of GIST.

7.2.2. Clinical Experience with IPI-504

At the time Study IPI-504-06 was initiated, over 140 patients with a variety of malignancies, including multiple myeloma, GIST, non-small cell lung cancer, prostate cancer, and other solid tumors had been treated with IPI-504 in clinical studies; of these 140 patients, 45 were patients with metastatic, refractory GIST. At study initiation, commonly occurring adverse events in patients treated with IPI-504 were generally similar across studies and tumor types and included fatigue, diarrhea, nausea, headache, anemia, infusion site pain, myalgia, vomiting, back pain, and increased aspartate aminotransferase (AST). The majority of adverse events were of Grade 1 or 2 in intensity.

The initial study designed to investigate IPI-504 in patients with GIST was Study IPI-504-02. This was an open-label, dose-escalation study designed to evaluate safety, identify the MTD and recommend a dose for subsequent clinical trials with IPI-504 for patients with either metastatic and/or unresectable GIST; patients with advanced or metastatic soft tissue sarcoma (STS) were also eligible.

Two 21-day dosing regimens were evaluated:

- Schedule A: IPI-504 twice weekly for 2 weeks followed by 1 week off treatment
- Schedule B: IPI-504 twice weekly for 3 weeks (without a break)

Patients treated according to Schedule A received doses ranging from 90 to 500 mg/m^2, establishing an maximum tolerated dose (MTD) of 400 mg/m^2. A total of 32 patients with GIST or STS were treated at the MTD of 400 mg/m^2 administered twice weekly for 2 weeks followed by 1 week off treatment.

Patients treated according to Schedule B received doses ranging from 150 to 225 mg/m^2. An MTD was not established for Schedule B in this study and further dose escalation was discontinued because of the greater ease of clinical implementation, increased patient compliance, and greater cumulative dose demonstrated with Schedule A.

Four dose-limiting toxicities occurred in patients treated according to Schedule A in Study IPI-504-02, including Grade 3 asymptomatic lipase elevation (90 mg/m^2), Grade 4 intra-cranial hemorrhage (400 mg/m^2), and Grade 3 headache and Grade 3 myalgia (500 mg/m^2). Only 1 DLT was seen with Schedule B: Grade 3 nausea and AST elevation (225 mg/m^2).

Overall, the most commonly occurring adverse events among patients with GIST/STS in Study IPI-504-02 included headache, nausea, diarrhea, myalgia, and infusion site pain. Adverse events of Grade 3 intensity occurred at a low incidence and primarily included clinical laboratory abnormalities (e.g., AST increased, alanine aminotransferase [ALT] increased, and alkaline phosphatase increased) and gastrointestinal (GI) symptoms (e.g., diarrhea, nausea, and vomiting).

18-fluorodeoxyglucose positron emission tomography (18-FDG-PET) was used in IPI-504-02 to evaluate biologic response. The rationale for the use of 18-FDG-PET arises from the growing medical literature which demonstrates that 18-FDG-PET response to TKI therapy with imatinib or sunitinib has been associated with clinical benefit.[19,20] 18-FDG-PET results were assessed using European Organization for Research and Treatment of Cancer (EORTC) PET response criteria.[21] This analysis demonstrated that 4 (22%) of 18 patients achieved partial responses (PR) by PET (>25% reduction in SUV_{max} [maximum standard uptake value]), and 12 (67%) of 18 patients achieved stable disease (SD). In addition to these PET responses, histologic and computed tomography (CT) changes in GIST patients consistent with biological activity were noted, including 76% of patients having SD as a best response by RECIST.

While this Phase 1 study was not designed to demonstrate efficacy, the biological activity signal with PET scans appears to correlate with a longer than expected median PFS of 11.9 weeks in patients receiving third-line therapy or greater. In a trial with sunitinib as second-line therapy for patients with metastatic GIST, the median PFS was 6.0 weeks in patients who received

treatment with placebo. While comparisons to historical control are inherently biased, this difference suggested that further clinical investigation of IPI-504 in patients with GIST was warranted.

7.3. Study Rationale

Despite recent advances in the treatment of GIST, nearly all patients eventually progress with resistance to the approved TKIs, imatinib and sunitinib causing significant disruption in a patient's quality of life. Following failure of these therapies, GIST remains a fatal disease. Therefore, novel therapies are needed for patients who have progressed on or are intolerant to the proven current therapies.

In the Phase 1 clinical trial (Study IPI-504-02), IPI-504 had an acceptable safety profile and encouraging biological activity in heavily pre-treated patients with GIST in whom prior therapies have failed. This randomized, double-blind, placebo-controlled, multi-center, multi-national study was designed to more fully evaluate the efficacy and safety of IPI-504 in patients with metastatic and/or unresectable GIST following treatment with imatinib and sunitinib.

8. STUDY OBJECTIVES

8.1. Primary Objective

The primary objective of this study was to compare the progression free survival (PFS) following administration of IPI-504 plus best supportive care versus placebo plus best supportive care in patients with metastatic and/or unresectable GIST following failure of at least imatinib and sunitinib.

8.2. Secondary Objectives:

The secondary objectives of this study were:

1. To compare the disease control rate (DCR) in both arms.
2. To compare the time to progression (TTP) in both arms.
3. To compare the overall survival (OS) in both arms.
4. To evaluate the safety and tolerability of IPI-504 in this patient population.

8.3. Exploratory Objectives

The exploratory objectives of this study were:

1. To evaluate the health-related quality of life (HRQoL) in both arms.
2. To compare severity and interference of pain in both arms.
3. To evaluate exposure levels of IPI-504 (and its metabolites) in this patient population and explore the correlation of plasma concentration with clinical outcomes and safety parameters.
4. To explore the correlation of clinical outcomes with tumor mutational status.

9. INVESTIGATIONAL PLAN

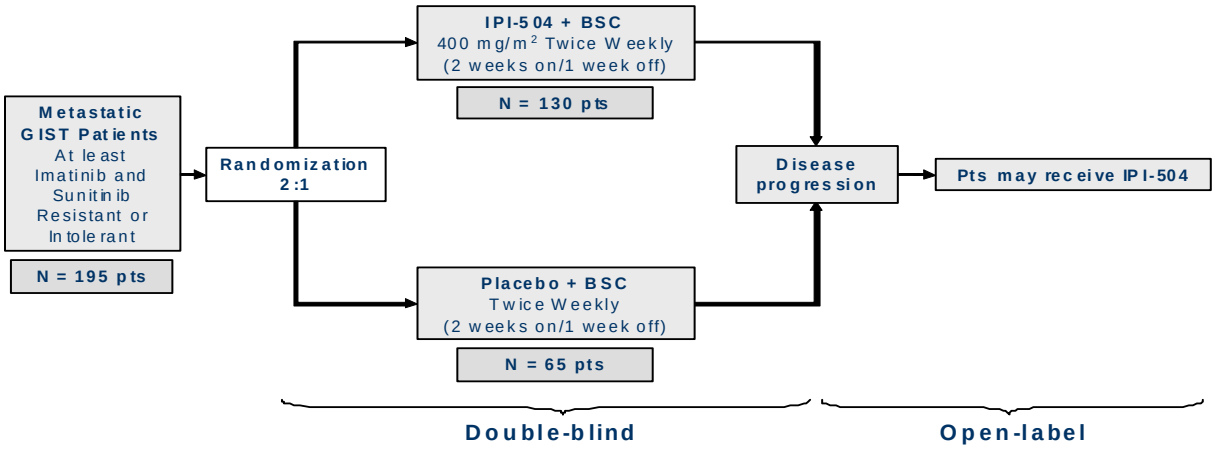
9.1. Overall Study Design and Plan

This was a randomized, double-blind, placebo-controlled, multi-center study to evaluate the efficacy and safety of IPI-504 compared with placebo in patients with metastatic and/or unresectable GIST following failure of at least imatinib and sunitinib who were receiving treatment with best standard of care (BSC). The primary objective was to compare PFS across the treatment groups. The study was to be conducted at approximately 75 study centers in the US, Canada, EU, and ROW. Approximately 195 patients aged 18 years or older with histologically confirmed metastatic and/or unresectable GIST with CT or magnetic resonance imaging (MRI) evidence of measurable disease, as determined by RECIST, and who had documented radiographic progression or intolerance to imatinib and sunitinib were to be enrolled in this study.

As described in Section 6.5, the study was terminated by the Sponsor on 15 April 2009 due to an imbalance in deaths between the treatment arms; at that time a total of 47 (24%) of the planned 195 patients had been enrolled.

The study contained 2 parts, a double-blind portion, during which patients received study drug in a blinded fashion, and, for patients who experienced confirmed disease progression during double-blind treatment, an open-label portion during which IPI-504 was administered. A schematic of the study design is provided in Figure 9-1.

Figure 9-1 Study Schematic



After provision of written informed consent, patients were screened for study eligibility within 28 days before baseline (Cycle 1, Day 1 [C1D1]). Screening assessments to be performed included documentation of disease progression by RECIST or World Health Organization (WHO) criteria, documentation of medical history, physical examination, Eastern Cooperative Oncology Group (ECOG) performance status, vital signs, ophthalmology or optometry examination, triplicate 12-lead electrocardiograms (ECGs), and clinical laboratory tests.

Assessment of disease burden via a CT or MRI scan of the chest, abdomen, and pelvis was to be performed within 7 days before C1D1. Collection of a tumor biopsy was optional.

Patients who were determined to be eligible, based on screening assessments, were to be randomly assigned to treatment via an interactive voice response system (IVRS) at a 2:1 ratio to receive IPI-504 plus best supportive care (N=130) or placebo plus best supportive care (N=65). Randomization was stratified based on time to progression (TTP) on imatinib (< 6 months versus ≥6 months or intolerance to imatinib) and geographic region (US/Canada versus EU/ROW).

Patients were to receive 400 mg/m^2 of IPI-504 or placebo as a 30-minute IV infusion twice weekly for 2 weeks followed by 1 week off treatment concurrent with best supportive care. Best supportive care was to be administered according to institutional standard, but was not to include administration of systemic cancer-specific therapies including chemotherapies, biologic therapies, investigational therapies, TKIs (e.g., imatinib, sunitinib, nilotinib, dasatinib), or local therapies such as surgery, radiotherapy, or lesion ablative therapies. IPI-504 and placebo doses were to be administered approximately 72 hours apart; doses greater than 1000 mg were not permitted.

There was no maximum duration of treatment in the blinded portion of the study. Patients who experienced disease progression, based on local site radiology review and confirmed by central radiology review, who met all other entrance criteria may have entered the open-label portion of the study and received treatment with IPI-504.

During treatment, patients were to attend study center visits and have evaluations performed on each dosing day (i.e., twice weekly for 2 weeks on an every 3-week basis). All patients were to be evaluated within 30 days after their last study drug dose. Thereafter, patients were to be followed every 2 months (±2 weeks) for survival and documentation of subsequent anticancer therapy until death or the end of the study, whichever was sooner.

Tumor measurements were based on RECIST. All images were to be read locally at the site; in addition, a central radiology review was conducted. The primary analysis for tumor response was to be based on the central review.

During treatment, safety was to be assessed via documentation of adverse events, routine clinical laboratory evaluations, heart rate, 12-lead ECGs (in triplicate), and ophthalmology/optometry examinations (if required based on symptoms). To assure the safety of patients, an IDMC was to review cumulative safety data on a quarterly or ad hoc basis, as required, to make recommendations regarding the further conduct of the study.

Blood samples for assessment of pharmacokinetic (PK) parameters of IPI-504 and its metabolites were to be collected at selected study sites. IPI-504, 17-AAG, and 17-AG plasma concentrations were to be determined.

Details of the Schedules of Assessments and Procedures for the double-blind and open-label periods are provided in Table 9-3 and Table 9-4.

9.2. Discussion of Study Design, Including Choice of Control Groups

This was a two-part, Phase 3 study, with the first part being a randomized, double-blind placebo-controlled evaluation and the second part allowing for open-label treatment with IPI-504.

The inclusion of a placebo group and the double-blind design was employed to avoid bias in the assessment of both efficacy and safety variables. Inclusion of a placebo group with best supportive care was considered feasible because there is no currently approved treatment for this patient population and no limit to the number of prior therapies a patient may have received prior to enrolling in this study. Patients who experienced disease progression in the double-blind portion of the study and met all eligibility criteria may have started treatment with IPI-504 in the open-label portion of the study.

Randomization avoids systematic differences between groups with respect to known or unknown baseline variables that could affect outcome. Randomization was stratified based on TTP with imatinib and geographic region. The stratification factor of time on imatinib attempted to balance patients with wild-type GIST between the 2 study arms. The rationale was that wild-type patients would not respond to imatinib, based on the mechanism of action, so these patients would be expected to discontinue imatinib < 6 months after they started this therapy.

The safety assessments conducted during this study, including monitoring for adverse events, physical examinations, vital signs assessments, and clinical laboratory tests, are widely used and generally recognized as reliable, accurate, and relevant. They represent the standard for Good Clinical Practice (GCP) to ensure the safety of each patient. In order to further ensure the safety of patients, an IDMC was established in conformance with FDA and the European Medicines Agency guidance, including 2 oncologists and a statistician with expertise in clinical research. Based on these reviews, the IDMC was to make a recommendation to the Sponsor whether to continue the study, continue the study with suggested modifications, or terminate the study.

9.3. Selection of Study Population

9.3.1. Double-Blind Portion

9.3.1.1. Double-Blind Inclusion Criteria

Patients were eligible for inclusion in the randomized, double-blind phase of the study if they met the following criteria:

1. At least 18 years of age at the time of study randomization.
2. Histologically confirmed metastatic and/or unresectable GIST.
3. Measurable disease on CT or MRI as defined by RECIST, with at least one measurable lesion.
4. Documented radiographic progression or intolerance to imatinib and sunitinib.

5. Clinical failure of the most recent prior therapy for GIST.

   Note: There was no limit to the number of prior therapies a patient may have received (e.g., patients may have received treatment with nilotinib, other TKIs, or chemotherapy, in addition to imatinib or sunitinib).

6. ECOG performance status: 0 or 1.
7. Administration of the last dose of imatinib or nilotinib ≥1 week, any other TKI ≥2 weeks, chemotherapy, radiotherapy, surgery, ablative therapy, biologic therapy (e.g., antibodies, vaccines), or any other investigational therapy ≥ 4 weeks prior to randomization.
8. Resolution of all toxic effects of imatinib, sunitinib, other TKIs, surgery, radiotherapy, chemotherapy, lesion ablative therapy, or investigational therapy to baseline or Grade 1 by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0.
9. Patients must have had acceptable organ and marrow function, as defined below:
   - Hemoglobin ≥8.0 g/dL (80 g/L).
   - Absolute Neutrophil Count (ANC) ≥1500/μL (1.5×10^9/L).
   - Platelets ≥ 100,000 /μL (100×10^9/L).
   - ALT and AST ≤ 2.5 x upper limit of normal (ULN), or ≤ 3.0 x ULN if considered secondary to liver metastases.
   - Alkaline phosphatase ≤ 2.5 x ULN, or ≤ 3.0 x ULN if considered secondary to liver metastases.
   - Serum bilirubin ≤ 1.5 x ULN.
   - Prothrombin time (PT) and partial thromboplastin time (PTT) ≤ 1.5 x ULN unless the patient was receiving warfarin. If the patient was receiving warfarin, the international normalized ratio (INR) must have been within therapeutic range.
   - Serum creatinine ≤ 1.5 x ULN.
   - Albumin ≥ 3.0 g/dL
10. Women of reproductive potential (defined as being less than 1 year post-menopausal) must have had a negative serum or urine β human chorionic gonadotropin (βHCG) pregnancy test; and men and women of reproductive potential must have agreed to practice an effective method of avoiding pregnancy while receiving study drug and for 30 days after the final dose of study drug. Effective contraception included use of oral contraceptives with an additional barrier method, double barrier methods (diaphragm with spermicidal gel or condoms with contraceptive foam), Depo-Provera, partner vasectomy, and total abstinence.
11. Written informed consent was to be obtained from the patient prior to receipt of any study medication or beginning study procedures.

9.3.1.2. Double-Blind Exclusion Criteria

Patients were to be excluded from the study if they met any of the following criteria:

1. Previous administration of 17-AAG, 17-dimethylaminoethylamino-17-demethoxygeldanamycin (17-DMAG), or other known Hsp90 inhibitors.
2. Surgery, radiotherapy, or lesion ablative procedure to the only area of measurable disease.
3. Use of a medication or food that was a clinically relevant CYP3A inhibitor or inducer within 2 weeks prior to administration of IPI-504 or placebo. Patients who were on a stable dose of drugs that are not listed in Protocol Appendix 2 but were known to alter CYP3A activity for > 2 weeks were eligible to enroll.
4. Patients with a history of any of the following within the last 6 months: cardiac disease such as acute coronary syndrome or unstable angina, symptomatic congestive heart failure, uncontrolled hypertension, cirrhotic liver disease, cerebrovascular accident, or any other significant co-morbid condition or disease which, in the judgment of the Investigator, would have placed the patient at undue risk or interfere with the study (e.g., psychiatric or other conditions).
5. Grade 3 or 4 hemorrhagic event within the last 6 months.
6. Known human immunodeficiency virus positivity.
7. Sinus bradycardia (resting heart rate < 50 bpm) secondary to intrinsic conduction system disease. Patients with sinus bradycardia secondary to pharmacologic therapy may have enrolled if withdrawal of the therapy resulted in normalization of the resting heart rate to within normal limits.
8. Baseline QT corrected using Fridericia's correction method (QTcF) ≥ 470 milliseconds (msec), or previous history of clinically significant QTc prolongation while taking other medications.
9. History of prior malignancies within the past 3 years other than non-melanomatous skin cancers that had been controlled, prostate cancer that had been treated and had not recurred, non-muscle-invasive bladder cancer, and carcinoma in situ of the cervix.
10. Active or recent history (within 3 months) of keratitis or keratoconjunctivitis confirmed by ophthalmology or optometry exam.
11. Presence of Left Bundle Branch Block, Right Bundle Branch Block plus left anterior hemiblock, bifascicular block, or 3rd degree heart block. This did not include patients with a history of these events with adequate control by pacemaker.
12. Patients with known central nervous system (CNS) metastases. Patients with symptoms indicative of CNS metastases must have had a head CT or brain MRI at screening.
13. Women who were pregnant or lactating.

9.3.2. Open-Label Portion

After unblinding, patients receiving either IPI-504 or placebo may have received IPI-504 in the open-label portion of the study if defined inclusion and exclusion criteria were met.

9.3.2.1. Open-Label Inclusion Criteria

Patients who had disease progression as defined in Section 9.5.1.2.2 were to meet the following criteria to be eligible for subsequent open-label treatment with IPI-504:

1. ECOG performance status 0, 1 or 2.
2. Resolution of all drug-related adverse events from blinded phase of study to baseline or Grade 1 by NCI CTCAE version 3.0.
3. Patients must have acceptable baseline organ and marrow function as defined below:
   - Hemoglobin ≥8.0 g/dL (80 g/L).
   - Absolute Neutrophil Count ≥1500/μL (1.5×10^9/L).
   - Platelets ≥ 100,000 /μL (100×10^9/L).
   - ALT and AST ≤ 2.5 x ULN, or ≤ 3.0 x ULN if considered secondary to liver metastases.
   - Alkaline phosphatase ≤ 2.5 x ULN, or ≤ 3.0 x ULN if considered secondary to liver metastases.
   - Serum bilirubin ≤ 1.5 x ULN.
   - Prothrombin time (PT) and partial thromboplastin time (PTT) ≤1.5 × ULN if the patient is not receiving warfarin. If the patient is receiving warfarin, the INR must be within therapeutic range.
   - Serum creatinine ≤ 1.5 x ULN.
   - Albumin ≥ 3.0 g/dL
4. Patients must be able to adhere to all protocol requirements.

9.3.2.2. Open-Label Exclusion Criteria

In order to continue into the open-label portion of the study, patients were not permitted to have any of the following:

1. Use of a medication or food that was a clinically relevant CYP3A inhibitor or inducer within 2 weeks prior to administration of IPI-504 or placebo. A list of clinically relevant CYP3A inhibitors and inducers was provided in Appendix 2 of the study protocol. Patients who were on a stable dose of a drug that was not listed in the protocol appendix but was known to alter CYP3A activity for > 2 weeks were eligible to enroll.
2. Patients with a history of any of the following within the last 6 months: cardiac disease such as acute coronary syndrome or unstable angina, symptomatic congestive heart failure, uncontrolled hypertension, cirrhotic liver disease, cerebrovascular accident, or any other significant co-morbid condition or disease which, in the judgment of the Investigator, would

have placed the patient at undue risk or interfere with the study (e.g., psychiatric or other conditions).

3. Grade 3 or 4 hemorrhagic event within 6 months.
4. Known human immunodeficiency virus positivity.
5. Sinus bradycardia (resting heart rate < 50 bpm) secondary to intrinsic conduction system disease. Patients with sinus bradycardia secondary to pharmacologic therapy may have enrolled if withdrawal of the therapy resulted in normalization of the resting heart rate to within normal limits.
6. QT corrected using Fridericia's correction method (QTcF) ≥ 470 milliseconds (msec).
7. History of prior malignancies within the past 3 years other than non-melanomatous skin cancers that had been controlled, prostate cancer that had been treated and had not recurred, non-muscle-invasive bladder cancer, and carcinoma in situ of the cervix.
8. Active or recent history of keratitis (confirmed within 3 months) or keratoconjunctivitis.
9. Presence of Left Bundle Branch Block, Right Bundle Branch Block plus left anterior hemiblock, bifascicular block, or 3rd degree heart block. This did not include patients with a history of these events with adequate control by pacemaker.
10. Patients with known CNS metastases. Patients with symptoms indicative of potential CNS metastases were to have a head CT or brain MRI at screening.
11. Women who were pregnant or lactating.

9.3.3. Removal of Patients from Therapy or Assessment

9.3.3.1. Discontinuation of Therapy at Any Time

An individual patient was not to receive IPI-504 or placebo if any of the following occurred:

- Withdrawal of consent;
- Unacceptable toxicity;
- Pregnancy or intent to become pregnant;
- Patient noncompliance;
- Physician decision;
- Event which in the opinion of the Investigator contraindicates further dosing such as intercurrent illnesses, significant drug toxicities, or complications;
- Administration of non-permitted concomitant medication including initiation of alternative anticancer therapy or treatment with another investigational agent; or
- End of the study.

Patients who were permanently discontinued from IPI-504 or placebo were to be followed for adverse events and SAEs through 30 days after the discontinuation of IPI-504 or placebo, including collection of blood specimens for safety laboratory data.

9.3.3.2. Discontinuation of the Study

Enrollment of additional patients into the study may have been discontinued if any of the following occurred:

- IDMC recommendation, based on safety or futility
- Events were determined by the Sponsor to be of overwhelming medical significance as to stop entrance into the study and immediately initiate an IDMC meeting to determine any necessary changes to the study and determine the further course of the study
- Extenuating circumstances (e.g., inability to accrue to the trial in a timely manner.)

If the Sponsor permanently discontinued the study for any of the above reasons, no further patients were to be randomized into the study.

9.4. Treatments Administered

9.4.1. Identity of Investigational Product

IPI-504 and placebo were supplied by the Sponsor as a sterile lyophilized powder in single-use vials containing 844.5 mg IPI-504 or 255 mg mannitol, respectively; the vials were to be stored at 2°C to 8°C. The drug product was formulated as lyophilized hydrochloride salt. Each vial of IPI-504 or placebo was to be reconstituted with 16 mL of the diluent.

Study drug was to be supplied to the sites by the Sponsor in the form of 2 different kits, as follows:

- IPI-504 or placebo and diluent with a blinded label.
- Open-label IPI-504 and diluent.

The following lot numbers were used:

- Lot numbers of IPI-504 for injection: 004I0108, 021I0208, 1529821, 1576137, 1597479
- Lot numbers of IPI-504 diluent: 005I0108, 022I0208, 1489149, 1529822, 1599202
- Lot numbers of placebo: 361-01-001, 1489146
- Lot number of placebo diluent: 361-02-002, 1489151

9.4.2. Method of Assigning Patients to Treatment Groups

Patients were to be screened by Investigators or qualified designees to assess eligibility for randomization into the study. Randomization was centralized using an IVRS. The IVRS assigned a unique patient identification number and provided the identifying numbers for the investigational product, either IPI-504 or placebo, to be dispensed to the patient. Administration of the first dose of IPI-504/placebo was to begin within 36 hours or on the next business day after randomization. A confirmatory communication with the blinded randomization information was to be sent to the Investigator/designee.

Patients were randomized using a 2:1 randomization procedure to 1 of the 2 study arms as follows:

- IPI-504 + best supportive care (N = 130)
- Placebo + best supportive care (N = 65)

The stratification factors in the central block randomization procedure were as follows:

- Stratification factor 1:
  - TTP on imatinib < 6 months
  - TTP on imatinib ≥ 6 months or intolerance to imatinib
- Stratification factor 2:
  - Geographic region USA/Canada
  - Geographic region EU/ROW

Time to progression on imatinib was defined as the time from the patient's first treatment with imatinib (regardless of dose) for metastatic disease until the first radiologic evidence of disease progression. Retreatment with imatinib after initial progression was not included in this calculation. Patients who had disease recurrence while receiving imatinib for adjuvant therapy after complete surgical resection were to be stratified similarly to those whose TTP on imatinib was < 6 months. If both disease progression by RECIST or WHO and intolerance were observed for imatinib, then disease progression was to be the entry criteria for the stratification factor in randomization. Detailed randomization procedures were provided in the IVRS manual.

9.4.3. Selection of Doses in the Study

The dose and schedule selected for this study, i.e., 400 mg/m^2 twice weekly for 2 weeks followed by 1 week off treatment, was that determined to be the MTD in the Phase 1 dose-finding study conducted in patients with GIST/STS (IPI-504-02) (see Section 7.2.2). The dose was not to exceed 1000 mg.

9.4.4. Selection and Timing of Dose for Each Patient

9.4.4.1. General Dose Administration Information

The IPI-504 dose for administration to a given patient was to be calculated based on the patient's body surface area (BSA) using the appropriate calculation, per institutional guidelines. BSA was to be calculated once prior to the start of study drug administration (at Screening or prior to Cycle 1, Dose 1) and per institutional guidelines, thereafter. Any patient whose BSA resulted in a calculated dose of greater than 1000 mg was to be given a total dose of 1000 mg at each study drug administration. Study drug was not to be administered at doses greater than 1000 mg.

The IPI-504 or placebo solution was to be administered via a peripheral IV catheter or central line using a 250 mL bag of 0.9% Sodium Chloride Injection; the line was to be flushed before

and after administration with sterile 5 to 10 mL 0.9% Sodium Chloride Injection, USP. Study drug administration was to be completed within 4 hours of reconstitution with supplied diluent.

The infusion duration may have been increased up to 60 minutes in the event of infusion-related pain or tingling. A 500 mL IV infusion bag may also have been used in the event of infusion-related pain or tingling. If a 500 mL IV bag was used, the infusion time was to have been approximately 60 minutes. Alternatively, additional normal saline may have been infused via a Y line to alleviate local symptoms.

During the double-blind period, doses were to be administered approximately 72 hours apart twice weekly for 2 weeks followed by 1 week off for a 21-day cycle. The patients' initial infusion was to occur on C1D1 within 36 hours or on the next business day after randomization. Time between doses may have varied; however, doses should not have been administered fewer than 66 hours or more than 104 hours apart.

Eligibility for the open-label portion of the study had to be confirmed prior to administration of the first open-label dose. Eligibility criteria and testing included confirmation of disease progression, pre-dose ECGs completed in triplicate within 5 minutes, and for women of child-bearing potential, a negative serum or urine ß-HCG pregnancy test result.

9.4.4.2. Dose Modifications

Patients were to be monitored continuously for toxicity while on study and the dose or regimen modified as detailed in Table 9-1 based on dose reduction levels as presented in Table 9-2. Toxicity was to be assessed using the NCI CTCAE version 3.0. For an individual patient, dose modifications may have been more conservative than indicated in Table 9-1, based on the clinical judgment of the Investigator, with notification of the Medical Monitor.

Table 9-1 IPI-504 Modifications for Toxicity

EVENT	GRADE	ACTION
NAUSEA, VOMITING OR DIARRHEA Regardless of relationship to study drug	2	For VOMITING or DIARRHEA: Dosing to be withheld until return to ≤ Grade 1 or baseline, then re-initiated at one dose level lower. For NAUSEA: Withholding/reducing dose was not required. Prophylactic therapies were to be administered as specified in the protocol.
	3	First AND Second occurrence: Dosing to be withheld until return to ≤ Grade 1 or baseline, then re-initiated at one dose level lower. Third occurrence: Patient was not to receive additional IPI-504/placebo.
	4	Patient was not to receive additional IPI-504/placebo.
ASYMPTOMATIC AMYLASE OR LIPASE Regardless of relationship to study drug	3	Grade 3 AMYLASE with Grade 2 LIPASE: Withheld until both return to ≤ Grade 1 or baseline, then dose reduced by one dose level. Grade 3 LIPASE with Grade 2 AMYLASE: Withheld until both return to ≤ Grade 1 or baseline, then dose reduced by one dose level. NOTE: Grade 3 AMYLASE/LIPASE without the presence of a Grade 2 LIPASE/AMYLASE did not require dose modification
	4	Withheld until return to ≤ Grade 1 or baseline, then re-initiated at one dose level lower.
PANCREATITIS Regardless of relationship to study drug	2	Withheld until return to ≤ Grade 1 or baseline, then re-initiated at one dose level lower.
	3	First occurrence: Withheld until return to ≤ Grade 1 or baseline, then re-initiated at one dose level lower. Second occurrence: Patient was not to receive additional IPI-504/placebo.
	4	Patient was not to receive additional IPI-504/placebo.
HYPERGLYCEMIA[a] Regardless of relationship to study drug	3	First AND Second occurrence: Withheld until return to ≤ Grade 1 or baseline level, then re-initiated at one dose level lower. Third occurrence: Patient was not to receive additional IPI-504/placebo.
	4	Patient was not to receive additional IPI-504/placebo.
HEPATIC INJURY (AST, ALT, alkaline phosphatase, and total bilirubin) Regardless of relationship to study drug	3	First AND Second occurrence: Withheld until return to ≤ Grade 1 or baseline level, then re-initiated at one dose level lower. Third occurrence: Patient was not to receive additional IPI-504/placebo.
	4	Patient was not to receive additional IPI-504/placebo.

EVENT	GRADE	ACTION
ALL OTHER STUDY DRUG-RELATED EVENTS Must be at least related to study drug	2	If dose reduction was felt to be clinically indicated, the Medical Monitor was to be contacted.
	3	First AND Second occurrence: Withheld until return to ≤ Grade 1 or baseline then re-initiated at one dose level lower. Third occurrence: Patient was not to receive additional IPI-504/placebo.
	4	Non-hematologic: Patients were not to receive additional IPI-504/placebo. Hematologic First Occurrence: Withheld until return to ≤ Grade 1 or baseline then re-initiated at one dose level lower. Hematologic Second Occurrence: Patients were not to receive additional IPI-504/placebo.

a. To meet the criteria for Grade 3 or 4 hyperglycemia, a fasting glucose must have been acquired. For Grade 3 non-fasting hyperglycemia, patients who had diabetes mellitus may have received the dose of IPI-504/placebo, but should have had a fasting glucose drawn prior to the next dose of IPI-504/placebo; however, patients who did not have diabetes mellitus should have had the dose of IPI-504/placebo held and a fasting glucose should have been drawn. For Grade 4 non-fasting hyperglycemia, patients should have had the dose of IPI-504/placebo held and a fasting glucose should have been drawn.

Table 9-2 Dose Reduction Table

Starting Dose	1st Dose Reduction	2nd Dose Reduction
400 mg/m^2	300 mg/m^2	225 mg/m^2

Note: Patients requiring a third dose reduction were to be discontinued from the study.

For any dose interruptions, dosing was to resume within 14 days of the scheduled Dose 1 of the next cycle. If the patient was unable to resume dosing within 14 days of the scheduled Dose 1 of the next study cycle, they were to be removed from the study. Patients who had their dose of study drug reduced due to toxicity were not to have subsequent dose increases. There were to be no attempts to make up for doses omitted due to toxicity.

9.4.5. Blinding

9.4.5.1. Overview

During the blinded phase of the study, both patients and Investigators, including site personnel, study nurses, coordinators, pharmacists, and pharmacy staff, were to be blinded to study arm assignments. In addition, all protocol-associated Sponsor personnel and its contractors, including the Medical Monitor, biostatistician, statistical programmer, project managers, site monitors, and data managers were to be blinded to study arm assignments. Serious adverse events that were both unexpected and thought by the Investigator and /or the Sponsor to be at least possibly related to study drug were to be unblinded for regulatory reporting. Sponsor employees and/or representatives may also have had access to unblinded safety reports due to regulatory reporting requirements; however, the number of these individuals was to be minimized and their interactions with other study team members were to be restricted.

Investigational product was to be supplied to the pharmacy as blinded, numbered kits containing IPI-504 or placebo and diluent. The clinical site staff was to order study drug from the pharmacy using the site's normal ordering procedures. The pharmacist (or designee) was to prepare the study drug from one or more of the appropriate vials (determined by the patient's weight, height, and randomization assignment). Once IPI-504 or placebo had been reconstituted with the supplied diluent and injected into the 0.9% sodium chloride IV bag, the pharmacist (or designee) was to cover the IV bag with the plastic sleeve provided for blinding. Further instructions on drug preparation methods required to maintain the blind, i.e., masking the IV bag, were to be included in the investigational product manual supplied by the Sponsor.

9.4.5.2. Unblinding

Unblinding may have occurred in the following instances:

- Disease progression. See Section 9.5.1.2.2 for definition of disease progression;
- An adverse event in which knowledge of the patient's treatment would have affected their ongoing medical care. Such events were to be discussed with the Medical Monitor prior to unblinding;
- Pregnancy.

In instances of unblinding for disease progression, the decision to unblind the patient was to be based on a real-time central review of the imaging assessment. Circumstances may have arisen in which real-time central review in a timely fashion was not possible and treatment decisions were made based on the local on-site review of the imaging assessment. The situation in which a local on-site radiology review may have been used to determine unblinding was defined as:

- At least 7 days had passed since receipt of the full imaging assessment by the independent central reviewers and the central review result was still pending, AND
- The patient was within 24 hours of their next scheduled dose of study drug.

In the event that both of the above circumstances were true, the local on-site radiologic review may have been used to determine if unblinding was required. In these cases, it was strongly encouraged that the imaging assessment be reviewed by at least two medical professionals who were not directly responsible for the care of the patient in question, at least one of whom was a radiologist. Disagreements were to be adjudicated by a third medical professional, ideally one not involved in the care of the patient. This assessment was to be based on the modified RECIST.

Patients who stayed on the blinded portion of the study based on the on-site radiology review and were subsequently deemed to have progressed by the central radiology review (which was delayed by extenuating circumstances) were to be unblinded at the time the central radiology review became available.

Based on the ad hoc IDMC meeting convened on 14 April 2009 (see Section 6.5), data were unblinded to the committee and Sponsor for 4 patient deaths that had been reported at that time. Based on this review, the study was prematurely terminated. Following the early termination of the trial, patients who were ongoing in the study at the time could have been unblinded to their treatment assignment.

9.4.6. Prior and Concomitant Therapy

IPI-504 was to be used with caution in combination with drugs that were strong inhibitors or inducers of CYP3A or with drugs that were metabolized primarily via CYP3A. Protocol Appendix 2 (see Appendix 16.1.1) provided a list of medications known to inhibit or induce CYP3A activity to a clinically relevant degree that were not to be taken by study patients. Other CYP3A inhibitors/inducers not on the list may have been used if the patient was on a stable dose for greater than 2 weeks prior to randomization. Questions about concomitant medications were to be discussed with the Medical Monitor.

All concomitant medications used by the patient from 30 days prior to the first dose of IPI-504/placebo through 30 days after the last dose of IPI-504/placebo were to be recorded.

Patients were not to receive the following while receiving study drug:

- Investigational agents or therapy with any other kinase inhibitor.
- Any antitumor therapy, such as cytostatic and/or cytotoxic drugs, hormonal therapy, radiation therapy, immunotherapy, or any biological response modifiers.

The Sponsor was to be notified if any patient received prohibited concomitant medications. Patients may have received medications to treat adverse events (AEs) as deemed necessary by the Investigator or the patient's physician.

9.4.6.1. Corticosteroids

Patients who required oral or IV corticosteroids (e.g., prednisone, dexamethasone, hydrocortisone) for longer than 24 hours were to have daily blood glucose monitoring for the first 7 days of treatment with the corticosteroid. Glucose monitoring may have been done by finger stick or serum glucose testing. Dose modifications for Grade 3 or 4 glucose elevations were to be made per Table 9-1. Patients who did not experience a Grade 3 or 4 glucose elevation after 7 days of treatment may have continued on corticosteroids with blood glucose monitoring intermittently as per local standard of care.

9.4.6.2. Other Concomitant Therapies

The following were suggested in the study protocol for prophylaxis of nausea and vomiting:

- Granisetron (Kytril®) 1 mg IV prior to administration of IPI-504/placebo
- Prochlorperazine 10 mg orally every 4-6 hours, as needed, for nausea

At the discretion of the Investigator, prophylactic therapies may have been administered prior to the first administration of the study drug or in response to adverse events. Other regimens and doses were acceptable as well.

Best supportive care was to be according to institutional standard, but was not to include administration of systemic cancer-specific therapies including chemotherapies, biologic therapies, investigational therapies, TKIs (e.g., imatinib, sunitinib, nilotinib, dasatinib), or local therapies such as surgery, radiotherapy, or lesion ablative therapies.

9.4.7. Treatment Compliance

The study pharmacist (or designee) was required to maintain accurate drug accountability records. Upon completion of the study, all study drug accountability records were to be returned to the Sponsor. All unused study kits were to be either returned to the assigned distribution centers or discarded at the sites according to their institutional drug destruction policies, as designated by the Sponsor. All materials or supplies provided by the Sponsor were to be returned to the Sponsor upon study completion. The Investigator was to notify the IRB/IEC when the study was completed.

9.5. Efficacy and Safety Variables

9.5.1. Efficacy and Safety Measurements Assessed and Flow Chart

9.5.1.1. Study Flow Chart

The Schedules of Assessments to be performed during the double-blind and open-label periods are shown in Table 9-3 and Table 9-4, respectively. The schedules are followed by descriptions of the study assessments.

The study was comprised of 2 parts, a double-blind portion during which patients were randomly assigned to receive IPI-504 or placebo concurrent with standard of care, and, for patients who experienced confirmed disease progression during double-blind treatment, an open-label portion during which IPI-504 was administered.

Each patient was to undergo a screening assessment within 28 days prior to receiving the first dose of study drug. Assessment of disease activity via a CT or MRI scan of the chest, abdomen, and pelvis was to be performed within 7 days before C1D1.

During treatment, patients were to attend study center visits and have evaluations performed on each dosing day (i.e., twice weekly for 2 weeks on an every 3-week basis). Assessments at the end of dosing in the double-blind period should have been obtained within 30 days after discontinuation from the study drug. If the patient was continuing on the open-label portion of the study, these assessments may have been combined with the required Dose 1 open-label assessments.

All patients were to be followed for survival on an every 2-month basis until death or the end of the study (3 years after the last patient was randomized), whichever was sooner.

Patients were considered to have completed the study if they were followed for survival until death or the end of the study. Patients were considered lost to follow-up only if no contact had been established by the time the study was completed such that there was insufficient information to determine the patient's status at the end of the study. Investigators were to document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient was re-established, follow-up was to resume according to the protocol.

Table 9-3 Schedule of Patient Evaluations/Blinded Study Period

PATIENT EVALUATIONS	Screening (Days)	Cycle 1 (twice weekly – 2 of 3 weeks)				Additional Cycles (twice weekly – 2 of 3 weeks)				End of Dose Admin.	30 Days Post Dose Administration (by Visit or Phone Call)	Survival Follow-up
	≤ 28	Dose 1	Dose 2	Dose 3	Dose 4	Dose 1	Dose 2	Dose 3	Dose 4			
Informed Consent	X											
Verify Eligibility Criteria[a]	X	X										
Medical History, Demographics	X											
Physical Examination	X	X[b]				X				X		
Vital Signs[c]	X	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X		
Eye Examination[e]	X											
Serum/Urine βHCG Pregnancy Test	X[f]	X[f]								X		
Study Randomization	X[g]											
ECG (12-lead)[h]	X	X										
Assessment of AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	
Serum Chemistry[i]	X	X[j]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X		
Hematology[l]	X	X[j]		X[k]		X[k]		X[k]		X		
Coagulation[m]	X[m]											
Urinalysis	X[n]											
BSA Calculation	X[o]	X[o]										
IPI-504 or Placebo administration		X[g]	X	X	X	X	X	X	X			
Pharmacokinetic (PK) Sample Collection[p]		X[p]							X[p]			
Imaging	See Table 9-5											
ECOG Performance Status	X	X				X				X		

PATIENT EVALUATIONS	Screening (Days) ≤ 28	Cycle 1 (twice weekly – 2 of 3 weeks) Dose 1	Dose 2	Dose 3	Dose 4	Additional Cycles (twice weekly – 2 of 3 weeks) Dose 1	Dose 2	Dose 3	Dose 4	End of Dose Admin.	30 Days Post Dose Administration (by Visit or Phone Call)	Survival Follow-up
Pain Assessment		X	X		X	X	X[q]		X	X		
HRQoL Assessment[r]		X	X		X	X			X	X		
Survival												X[s]
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	
Tumor Biopsy (optional)	X									X[t]		

a Screening/baseline CT/MRI may have been used to document disease progression on previous therapy if performed in accordance with study requirements.

b If the screening physical examination was completed within 7 days of Cycle 1, Dose 1, it did not need to be repeated at Cycle 1, Dose 1.

c Vital signs included temperature, blood pressure, pulse rate, and respiratory rate.

d Vital signs were to be performed prior to and following the completion of each study drug infusion. If there was a pulse of less than 50 bpm, or symptomatic sinus bradycardia, then pulse rate was to be confirmed with a pulse oximeter or ECG (ECG taken in triplicate). If a pulse rate of less than 50 bpm or symptomatic sinus bradycardia was confirmed, the heart rate was to be taken every 30 minutes until pulse normalized and patient was asymptomatic.

e Baseline screening ophthalmology or optometry exam was to include a slit lamp and funduscopic exam. At the beginning of each cycle, the clinic physician or designated surrogate was to conduct a review of systems and physical exam. The physician may have elected to withhold further dosing depending on eye-related complaints or initial findings. Any complaints or findings involving the eye were to be confirmed by an ophthalmology or optometry exam.

f For women of child-bearing potential only, serum or urine βHCG pregnancy test were to be negative at screening and prior to Dose 1. If the pregnancy test at screening was performed within 14 days of randomization, then the pregnancy test did not need to be performed at Cycle 1, Dose 1.

g The first study drug administration was to occur within 36 hours or on the next business day after randomization.

h See Section 9.5.1.4.

i Serum chemistries included sodium (Na), potassium (K), chloride (Cl), carbon dioxide (CO_2), lactate dehydrogenase, ALT, AST, total bilirubin, albumin, total protein, creatinine, blood urea nitrogen, alkaline phosphatase, uric acid, calcium, phosphorus, magnesium, glucose, amylase, and lipase.

j On Cycle 1, Dose 1, routine laboratory evaluations (hematology and serum chemistry) may have been performed within 5 days prior to study drug administration.

k Blood samples were to be drawn within the 24 hours prior to dose administration.

l Hematology laboratory parameters included complete blood cell count with differential and platelets and hemoglobin.

m PT and PTT were to be taken at baseline and as clinically indicated for patients who were not taking warfarin. Patients on warfarin were to have PT and the INR assessed at baseline and at least 1 time per cycle.

n After screening, urinalysis was to be performed as clinically indicated.

o BSA calculation was to be obtained prior to the start of study drug administration and per institutional guidelines, thereafter.

p See Section 9.5.4. To be performed only at selected centers.

q The Brief Pain Inventory-short form (BPI-sf) was to be assessed prior to Dose 1, 2, and 4 during Cycles 1 through 4 , and prior to Dose 1 and 4 every cycle thereafter.

r Health-related Quality of Life (HRQoL) was to be assessed using the EORTC-QLQ Core 30, a patient-assessed questionnaire, prior to Dose 1, 2, and 4 during Cycle 1, and prior to Dose 1 and 4 every cycle thereafter.

s Survival status and notation of subsequent anticancer therapy were to be documented every 2 months (± 2 weeks) after the last dose of IPI-504 or placebo by clinic visit or telephone contact until death or the end of the study. Follow-up assessments were to be done for all patients including those who did not continue IPI-504 in the open-label portion of the study.

t Additional tumor biopsies/samples or samples at a different time point on study could have been taken at the discretion of the study Investigator.

Table 9-4 Schedule of Patient Evaluations/Open-Label Period

	Cycle #				Discontinuation		
Patient Evaluation	**Dose 1**	**Dose 2**	**Dose 3**	**Dose 4**	**Last Study Drug Dose**	**30 Days Post Dose (by Visit or Phone Call)**	**Survival Follow-up**
Open-Label Inclusion Criteria	X[a]						
ECG (12-lead)	X[a]						
Serum/Urine βHCG Pregnancy Test	X[a]				X		
Physical Examination	X				X		
Vital Signs[b]	X[b]	X[b]	X[b]	X[b]	X[b]		
BSA Calculation	X						
Drug Administration	X	X	X	X			
Assessment of AE/SAEs	X	X	X	X	X	X	
Serum Chemistry[c]	X[d]	X[d]	X[d]	X[d]	X		
Hematology[e]	X[d]		X[d]		X		
Coagulation[f]	X[f]						
ECOG Performance Status	X				X		
Imaging							
Concomitant Medications	X	X	X	X	X	X	
Survival							X[g]

Note: Optional Tumor Biopsy may have been conducted during the open-label portion of the study (no more than 1 per patient) at the Investigator's discretion. Eye examination(s) and urinalysis were to be conducted as clinically indicated.

a For Cycle 1 only, Inclusion Criteria for open-label participation were to be confirmed prior to dose administration. Confirmation of eligibility included pre-dose ECGs completed in triplicate within 5 minutes and, for women of child-bearing potential, a negative serum or urine ßHCG.

b Vital signs included temperature, blood pressure, pulse rate, and respiratory rate. On days of dose administration, vital signs were to be performed prior to and following the completion of the infusion. If there was a pulse of less than 50 bpm, or symptomatic sinus bradycardia, then pulse was to be confirmed with a pulse oximeter or ECG (taken in triplicate). If a pulse rate of less than 50 bpm or symptomatic sinus bradycardia was confirmed, the heart rate was to be taken every 30 minutes until pulse normalized and patient was asymptomatic.

c Serum chemistries included sodium, potassium, chloride, CO2, lactate dehydrogenase, ALT, AST, total bilirubin, albumin, total protein, creatinine, blood urea nitrogen, alkaline phosphatase, uric acid, calcium, phosphorus, magnesium, glucose, amylase, and lipase.

d Blood samples were to be drawn within 24 hours prior to dose administration.

e Hematology laboratory parameters included complete blood cell count with differential and platelets and hemoglobin.

f Prothrombin time (PT) and partial thromboplastin time (PTT) were to be taken at baseline and as clinically indicated for patients who were not taking warfarin. Patients on warfarin were to have PT and INR assessed at least 1 time per cycle.

g Survival status and notation of subsequent anticancer therapy were to be documented every 2 months (± 2 weeks) after the last dose of IPI-504 by clinic visit or telephone contact until death or the end of the study.

9.5.1.2. Baseline Assessments

9.5.1.2.1. Demographics, Medical History and History of Prior Treatment for GIST

Demographic data, including age, sex, race, ethnicity, height, and weight, were to be captured at the screening assessment. Furthermore, a complete medical history was to be obtained from each patient, including documentation of GIST, documentation of treatment history, and documentation of any history of corneal irritation or dryness.

9.5.1.2.2. Documentation of Disease Progression or Intolerance to Imatinib or Sunitinib at Baseline

All patients were to have documented disease progression or intolerance to imatinib and sunitinib therapy. Documentation of disease progression by RECIST or WHO criteria was to be reviewed by the Investigator at the study site prior to enrollment; documentation was to include date of assessment, imaging technique, target lesion measurements, and non-target lesion assessments prior to therapy initiation and at radiographic disease progression. The location of new lesions was also to be documented. For patients intolerant of therapy with imatinib and/or sunitinib, the type and severity of intolerance were to be documented prior to enrollment.

Intolerance was defined as:

- Life-threatening adverse events (i.e., Grade 4 according to NCI CTCAE version 3.0), or
- Grade 2 or Grade 3 adverse event that was unacceptable to the patient and persisted despite appropriate medical management.

If both disease progression by RECIST or WHO and intolerance to imatinib and sunitinib therapy were observed, then disease progression was to be the entry criteria.

Patients who received imatinib as adjuvant therapy after complete surgical resection were to be divided into 2 groups:

- Group 1: Those who received imatinib as adjuvant therapy and had disease recurrence while receiving imatinib.
- Group 2: Those who received imatinib as adjuvant therapy and had disease recurrence after completing imatinib treatment course.

Patients in Group 1 met the criteria for disease progression on imatinib therapy. Patients in Group 2 did not meet the entry criteria based on their exposure to imatinib in the adjuvant setting and were to have documented progression or intolerance to imatinib during therapy for metastatic disease in order to be eligible.

If patients received other therapies for GIST after imatinib and sunitinib, patients must have had clinical failure of the most recent prior therapy for GIST. Clinical failure of the most recent therapy was to be defined by the treating physician and could have included radiographic progression, clinical progression, or patient intolerance.

9.5.1.3. Efficacy Assessments

Tumor Assessments

The timing of tumor imaging assessments is summarized in Table 9-5.

Table 9-5 Timing of Imaging Assessments

Timing of Assessment[a, b]	Study Day (From Start of Study Drug Administration)	Scheduling Window	Expected Cycle, Dose (If no dosing delay)[c]
Screening	-	≤ 7 days before randomization	-
Week 2	11	+3 days	Cycle 1, Dose 4
Week 5	32	±3 days	Cycle 2, Dose 4
Week 8	53	±3 days	Cycle 3, Dose 4
Week 14	95	±3 days	Cycle 5, Dose 4
Week 20 (and every 6 weeks thereafter)	Every 42 days from last scan	±7 days	Dose 4 of every other cycle
End of Dose Administration[d]	-	±7 days from study drug discontinuation	-

a Imaging was to be performed according to the study imaging acquisition guidelines. For each time point, a CT scan of chest, abdomen, and pelvis was to be performed. CT was the preferred modality; however, MRI may have been used. The use of chest x-ray was not encouraged; however, it may have been used when necessary to identify the presence or absence of disease. PET and any other imaging modalities were not acceptable for assessment of the primary endpoint.

b Unscheduled imaging assessments were to be avoided whenever possible; however, they may have been performed when clinically indicated.

c Tumor assessment was to be fixed by calendar date. Dosing delays should not have affected when imaging assessments were performed.

d The End of Dose Administration imaging assessment was only required for patients who discontinued IPI-504/ placebo for reasons other than progression by RECIST or death.

All images were to be read locally at the site and an independent central read was conducted. Blinded central independent imaging review of response and disease progression during the study was to be the basis for the primary analysis of tumor response and progression.

Details on response assessment based on RECIST are provided in the protocol included in Appendix 16.1.1 of this report; information is not detailed here as the study was terminated prematurely and analyses of efficacy were not conducted as planned.

Tumor biopsies conducted at screening and end of study drug administration were optional. Tumor samples were to be used to assay tumoral mutational status prior to and after study drug administration in order to evaluate the relationship between mutation status and outcome. Archived tissue samples may have been collected for analysis, if available.

Patient Reported Outcomes

The Brief Pain Inventory-short form (BPI-sf) was to be measured at Dose 1, 2, and 4 during Cycles 1 through 4, and on Dose 1 and 4 of each cycle thereafter.

The European Organization and Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) was to be measured at Dose 1, 2, and 4 during Cycle 1, and at Dose 1 and 4 during all cycles thereafter.

9.5.1.4. Safety Assessments

Physical Examination and Height, Weight, and Body Surface Area

Each patient was to undergo a complete physical examination at screening, including assessments of the head, eyes, ears, nose, and throat as well as the respiratory, cardiovascular, gastrointestinal, musculoskeletal, neurological, psychiatric, dermatological, hematologic/ lymphatic, and endocrine systems. A complete physical examination was also to be conducted at the C1D1 visit of the double-blind period (unless performed within 7 days prior), at the C1D1 visit of the open-label period, and at the end of dose administration (i.e., within 30 days after study drug discontinuation).

Height and weight were to be measured for BSA calculation prior to the start of study drug administration and per institutional guidelines, thereafter.

Ophthalmology/Optometry Examinations

A screening ophthalmology or optometry evaluation was be conducted to include a slit lamp and funduscopic exam. At the beginning of each cycle, the clinic physician or designated surrogate was to conduct a review of systems. Any complaints or findings involving the eye were to be confirmed by an ophthalmology or optometry exam. The physician may have elected to withhold further dosing depending on eye-related complaints or initial findings.

Vital Signs

Vital signs, including temperature, blood pressure, pulse rate, and respiratory rate, were to be measured at screening, prior to IPI-504/placebo administration, following the completion of IPI-504/placebo infusion, and at the end of dose administration (i.e., within 30 days after study drug discontinuation). If there was a pulse of less than 50 bpm, or symptomatic sinus bradycardia, then pulse was to be confirmed with a pulse oximeter or ECG (ECG taken in triplicate). If confirmed, the heart rate was to be taken every 30 minutes until pulse normalized and the patient was asymptomatic.

ECOG Performance Status

ECOG performance status was to be assessed for each patient at screening, on dose 1 of each cycle of the double-blind and open-label periods, and at the end of dose administration (i.e., within 30 days after study drug discontinuation).

Safety Laboratory Assessments

The following clinical laboratory assessments were to be obtained during the study. On Cycle 1, Dose 1, routine laboratory evaluations may have been performed within 5 days prior to study

drug administration. All other on-treatment blood samples were to be drawn within the 24 hours prior to dose administration.

- *Hematology*: Hematology laboratory parameters, including a complete blood cell count with differential and platelets and hemoglobin, were to be measured at screening; C1D1 and C1D3; Doses 1 and 3 of all subsequent cycles for the double-blind and open-label periods; and at the end of dose administration (i.e., within 30 days after study drug discontinuation).

  Hematology samples were to be drawn within 24 hours prior to each dose for which hematology samples were required. Hematology assessments were to be reviewed when available by the Investigator or designee to confirm that no dose modifications were required (see Section 9.4.4.2). Patients who required dose modification or required the withholding of study drug were to be monitored closely for the resolution of adverse events.

- *Serum chemistries*: Serum chemistries, including Na, K, Cl, CO_2, lactate dehydrogenase, ALT, AST, total bilirubin, albumin, total protein, creatinine, blood urea nitrogen (BUN), alkaline phosphatase, uric acid, calcium, phosphorus, magnesium, glucose, amylase, and lipase, were to be measured within 24 hours prior to dose administration at each visit and also at the end of dose administration (i.e., within 30 days after study drug discontinuation).

  Liver function test results, including ALT, AST, alkaline phosphatase and total bilirubin, were to be reviewed prior to each dose administration to determine if the dose should have been held or reduced (see Section 9.4.4.2). Similarly, lipase and amylase results were to be reviewed prior to dose administration in the presence of signs and symptoms of pancreatitis. When available, all other evaluations were to be reviewed by the Investigator or designee to confirm that no other dose modifications were required (see Section 9.4.4.2). Patients who required dose modification or required the withholding of study drug were to be monitored closely for the resolution of adverse events.

- *Coagulation*: PT and PTT were to be taken at screening and as clinically indicated for patients who were not taking warfarin. Patients on warfarin were to have PT and the INR assessed at baseline and at least 1 time per cycle.
- *Urinalysis*: Urinalysis was to be conducted as screening and thereafter as clinically indicated.
- *Serum or urine pregnancy test:* A serum or urine pregnancy test was required for all women of child-bearing potential at screening and prior to C1D1 of the double-blind and open-label periods and at the end of dose administration (i.e., within 30 days after study drug discontinuation). If the pregnancy test at screening was performed within 14 days of randomization for the double-blind period, then the pregnancy test did not need to be performed at C1D1 for that period.

Electrocardiograms/Cardiac Evaluation

All ECGs performed during the study were to be obtained in triplicate within approximately a 5-minute time period. ECGs were to be measured at screening and at pre-dose, end of infusion, and 30 (±10) minutes post-infusion on C1D1. For time points when both ECG and PK tests were required, ECGs were to be measured first, followed by PK sample collection.

All pre-dose ECGs were to be obtained within 3 hours prior to infusion and were to be reviewed by the Investigator or designee prior to dose administration for monitoring of the QTc interval. QTc was to be calculated using Fridericia's correction method for heart rate, where $QTcF=QT/RR^{1/3}$ and QT are expressed in milliseconds and RR in seconds.

The patient's baseline (pre-dose Day 1) QTcF interval was required to be <470 msec.

End-of-infusion ECGs were to be taken within 10 minutes prior to the end of the infusion. If a patient had an increase in QTcF of >60 msec or QTcF of >500 msec (Grade 3) after IPI-504 or placebo administration, the ECG (in triplicate) was to have been monitored every 30 minutes until resolution.

Patients who had heart rate or ECG-determined conduction changes were to have had pulse and/or ECG measurements every 30 minutes (± 10 minutes) until resolution. The threshold for continued monitoring included symptom-related concerns, heart rate < 50 bpm, QTcF >500 msec, or QTcF change of > 60 msec over pre-dose.

Adverse Events

All adverse events, including SAEs, were to be reported immediately following the signing of the informed consent through 30 days after the discontinuation of IPI-504 or placebo. Patients were to be instructed to report all adverse events and were to be asked a non-leading health status question at each visit. All events were to be collected and recorded in the CRF.

Definitions

An adverse event was defined as any untoward medical occurrence in a patient or clinical investigations subject administered a pharmaceutical product and which did not necessarily have to have a causal relationship with this treatment. An AE could, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE included, but was not limited to, the following:

- Any clinically significant worsening of a pre-existing condition;
- An AE occurring from overdose (i.e., a dose higher than that prescribed by a healthcare professional for clinical reasons, or a dose higher than that described on the marketed product label) of an investigational or marketed product, whether accidental or intentional;
- An AE occurring from abuse (e.g., use for non-clinical reasons) of an investigational or marketed product;
- An AE that was associated with the discontinuation of the use of an investigational or marketed product; and
- Adverse changes from baseline, which are listed in the NCI CTCAE V3.0 and available for downloading from the Cancer Therapy Evaluation Program website (http://ctep.info.nih.gov).

A protocol-related AE was an AE occurring during a clinical trial that was not related to the investigational product, but was considered by the Investigator or Medical Monitor (or designee) to be related to the research conditions, i.e., related to the fact that a patient was participating in the study. For example, a protocol-related AE may have been an untoward event occurring during a washout period or an event related to a medical procedure required by the protocol.

A SAE was defined as any adverse event that:

- Resulted in death
- Was life threatening
- Required in-patient hospitalization or prolongation of existing hospitalization
- Resulted in persistent or significant disability/incapacity
- Resulted in congenital anomaly/birth defect

Important medical events that were not immediately life-threatening of fatal, or did not require hospitalization may have been considered a serious adverse event, based upon appropriate medical judgment, if they jeopardized the patient or required medical or surgical intervention to prevent one of the outcomes listed in this definition.

Recording of Adverse Events

At each required visit during the trial, all adverse events that had occurred since the previous visit were to be recorded. The Investigator was required to determine the severity and relationship of each adverse event, possible etiologies, and whether the event met criteria as a SAE.

Relationship

The relationship of an adverse event to the study drug was to be determined by the Investigator based on his or her clinical judgment and the following definitions:

Assessments That Indicated a "Likely Relationship" to Study Product:

- Definitely related: An adverse event that followed a reasonable temporal sequence from administration of the study drug, had a plausible mechanism for the event to be related to the study product, and causes other than the study product had been ruled out and/or the event re-appeared on re-exposure to the study product.
- Probably related: An adverse event that followed a reasonable temporal sequence from administration of the study drug, had a plausible mechanism for the event to be related to the study product, and the event could not be reasonably explained by known characteristics of the patient's clinical state or an alternative etiology was not apparent.
- Possibly related: An adverse event that followed a reasonable temporal sequence from administration of the study drug, had a plausible mechanism for the event to be related to the

study product but there may also have been an alternative etiology, such as characteristics of the patient's clinical status or underlying disease.

Assessments That Indicated an "Unlikely Relationship" to Study Product:

- Not likely: The event was unlikely to be related to the study product and likely to be related to factors other than study product.
- Not related: The event was related to an etiology other than the study product (the alternative etiology was to be documented in the patient's medical record).

Severity

The severity of the adverse event was to be assessed according to the CTCAE v3.0. Severity categories were Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe), Grade 4 (Life-Threatening), and Grade 5 (Death).

Reporting of Adverse Events

All adverse events were to be recorded in the CRF.

The reporting period for SAEs was the period immediately following the signing of the informed consent through 30 days after the discontinuation of IPI-504/placebo. Serious adverse events were to be followed by the Investigator until resolution, even if this extended beyond the study reporting period. Resolution of an SAE was defined as the return to baseline status or stabilization of the condition with the expectation that it would remain chronic. At any time after completion of the SAE reporting period, if an Investigator became aware of an SAE that was suspected by the Investigator to be related to study product, the event was to have been reported to the study Sponsor or designee.

Any serious adverse event was to be reported to Infinity Pharmaceuticals, Inc. within 24 hours of the Investigator's first knowledge of the event by telephone, telefax, or e-mail transmission to the Sponsor (or designee). The initial report was to be as complete as possible. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) was to be documented on a follow-up form. For purposes of regulatory safety monitoring, the Investigator was required to follow the event to resolution and report to the Sponsor or designee the outcome of the event using the serious adverse event report form. Investigators were also to submit safety information provided by Infinity and/or designee to the IRB or IEC.

Pregnancy and death, regardless of causality, were to be reported within 24 hours by fax to Infinity Pharmaceuticals, Inc. or designee.

If the patient was receiving IPI-504 at the time of the pregnancy diagnosis, the study drug was to be discontinued immediately. All pregnancies of patients or their partners occurring while on study was to be followed for outcome, any premature terminations, and the health status of the mother and child up to 30 days after delivery. Any infant death, regardless of causality, within 30 days of birth was to be reported to Infinity or designee as well as infant deaths after 30 days that were suspected by the Investigator to be related to the in utero exposure of study drug.

In case of a death during the study or within 30 days after the administration of the last dose of study drug, every effort was to be made to establish a cause of death. If a post-mortem examination was performed, a copy of the results (with translation of important parts into English) was to be forwarded to the study Sponsor or designee within the usual timeframes. The report was to contain a comment regarding the co-involvement of progression of disease, if appropriate, and was to assign a single primary cause of death together with any contributory causes.

9.5.2. Appropriateness of Measurements

Demographic data, complete patient medical histories, including cancer treatment history, and baseline disease status were to be documented for all patients at baseline. Study drug administration data, including dose interruptions and modifications and the associated reason(s), also were to be documented.

Adverse events and serious adverse events were to be monitored in this study in accordance with ICH GCP guidelines to ensure the safety of patients. Additional parameters assessed during this study were standard parameters used to assess the safety of patients and included vital signs, clinical laboratory tests, and ECGs. All ECG assessments were read by a central laboratory to ensure consistency in readings and to utilize the expertise of the central laboratory cardiologists.

Patient's response to treatment was to be determined according to standard criteria, RECIST.

9.5.3. Primary Efficacy Variable

The primary efficacy endpoint defined in the study protocol was PFS measured in days from randomization until the first documentation of objective tumor progression or death due to any reason, whichever occurred first. As the study was prematurely terminated with only 24% of the planned sample size enrolled, analysis of the primary efficacy endpoint was not conducted.

9.5.4. Drug Concentration Measurements

PK sampling was to be conducted at selected sites. The timing of PK sample collection is summarized in Table 9-6.

Table 9-6 Blood Samples for PK Assessment

	Pre- study drug infusion	Study drug infusion	After EOI		
Time	**Pre-dose[a]**	**EOI[b]**	**30 minutes (± 15 min)**	**3.5 hours (± 30 min)**	**24 hours (± 2 h)**
Cycle 1, Dose 1[c]	X	X	X	X	X
Cycles 3 and 7, Dose 4	X		X		
Cycle 5, Dose 4		X		X[d]	

a Pre-dose PK sample should be collected within approximately 2 hours prior to IPI-504 or placebo infusion.

b EOI: End-of-infusion. Sample should be collected within approximately 5 minutes prior to infusion completion.

c PK sample collection should be done after ECGs are measured for time points in which both are required.

d Sample should be collected at 3.5 hours (± 30 min) or immediately before the patient leaves the clinic, whichever is earlier.

For time points when both PK and ECG tests were required (Cycle 1, Dose 1), PK samples were to be collected after ECGs were measured. Blood samples were to be collected from a site distal to the site of infusion or from a site on the non-infusion arm.

IPI-504, 17-AAG, and 17-AG plasma concentrations were to be assessed by the Sponsor or designee.

9.6. Data Quality Assurance

The primary source document for this study was the patient's medical record. If separate research records were maintained by the Investigator(s), both the medical records and the research records were to be considered source documents for the purposes of auditing the study. Data recorded on source documents were to be transcribed onto a validated data collection method provided by the Sponsor or designee. Collected data were to be reviewed by the Sponsor or designee, with a copy retained by the Investigator.

The study was monitored by the Sponsor or designee on a regular basis throughout the study period. All study documents (patient files, signed informed consent forms, copies of case report forms, Study File Notebook, etc.) were to be kept secured for a period of 2 years following marketing of IPI-504 or for 2 years after centers were notified that the Investigational New Drug application was discontinued.

SAEs regardless of causality were to be reported to the Sponsor and to the IRB/IEC, with the Investigator keeping the IRB/IEC informed as to the progress of the study.

Protocol violations were collected at the site as well as by the clinical research associate. The two sets of results were to be merged together; then, the medical monitor was to identify the major violations prior to database lock.

This report was audited by Infinity's designee (Veristat, Inc.) to determine accuracy and agreement of text and appendix tables and listings. All SAS® programs used to generate analytical results were developed and validated according to Infinity (or designee) SAS® programming standards and Infinity (or designee) SAS® validation procedures.

9.7. Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1. Statistical and Analytical Plans

The following statistical and analytical plans are based on the Statistical Analysis Plan (SAP) as amended on 19 March 2010; the document is included in Appendix 16.1.9.

It is noted that the SAP was modified to remove most efficacy analyses since the study was prematurely terminated and the efficacy analyses became less relevant due to the substantial reduction in sample size.

9.7.1.1. General Methods

All data were to be provided in data listings sorted by treatment group and patient number. All tabular summaries were to be presented by treatment group. Categorical data were to be summarized by the number and percentage of patients falling within each category. In general, continuous variables were to be summarized by descriptive statistics including N, mean, standard error or deviation, median, minimum, and maximum. All confidence intervals (CIs) were to be two-sided, unless stated otherwise.

All descriptive statistical analyses were to be performed using SAS statistical software (Version 8.2), unless otherwise noted.

All statistical comparisons and confidence intervals were to be based on two-sided tests unless otherwise specified. All p-values were to be considered descriptive and may not have been interpretable due to the small number of events observed.

9.7.1.2. Population Definitions

Due to the early termination of the study, only 2 populations were analyzed as follows:

- Intent-to-Treat (ITT) Population: all patients randomized into the study analyzed according to randomized treatment, regardless of treatment received.
- Safety Population: all patients who received at least 1 dose of study drug during the double-blind treatment period, analyzed according to the treatment patients actually received, regardless of randomized treatment.

The ITT population was the primary population for the analyses of efficacy and the Safety population was the primary population for the analyses of safety. Assuming all patients received treatment as randomized, the ITT and Safety populations would be identical.

9.7.1.3. Patient Disposition

A tabular summary of the number of patients in each patient population, those who received open-label treatment, who were alive and who had died at the end of the study, and who died due to GIST and the relationship of their death to study drug was to be presented. Reasons for

discontinuation were to be summarized for end of the double-blind portion of the study as well as the end of open-label portion.

Patient status at the end of study was to be summarized based on survival status. For the patients who had died, the cause of death (due to disease vs. not) and the relationship to study treatment were to be summarized by treatment group.

Summary statistics were to be presented for the stratification factors used at randomization: geographic region and TTP on Imatinib of <6 months or ≥6 months. The number of patients who were randomized at each site was to be summarized for all patient populations.

A by-patient listing of study completion information, including the reason for premature study withdrawal was to be presented.

9.7.1.4. Demographic and Baseline Characteristics

Demographic and baseline characteristics (disease and medical history) were to be summarized for all study populations. The following demographic characteristics were to be summarized by treatment group and for all patients combined: age, gender, ethnicity, race, height, and weight. Age was to be summarized both as a continuous variable and by predefined age categories (<20, 20-39, 40-65, and >65 years).

Disease history, to include time from initial diagnosis of GIST to randomization (years), specific tumor sites involved, number of tumor sites involved, and histology of GIST (Spindle Cell, Mixed Spindle and Epithelioid, Dedifferentianted, Rhabdomyoblastic, Other) were to be summarized.

Prior therapy for GIST was to be summarized for the following prior therapies: imatinib, sunitinib, nilotinib, AMG-706, sorafenib, dasatinib, everolimus, rapamycin, bevacizumab, gefitinib, erlotonib or other. In addition, the duration on imatinib and sunitinib, maximum dose on imatinib and sunitinib, number of adjuvant therapies, number of prior treatment regimens, number of unique treatments, months from last treatment to informed consent, reason for discontinuation from last prior treatment and best response on imatinib and sunitinib was to be summarized.

Patients who had any surgery, any hepatic surgery, any radiation, or any abdominal radiation and the total number of prior surgeries were to be tabulated. Since type of surgery and radiation locations were free text fields in the CRF, these were to be categorized by the medical monitor prior to database lock.

Medical history was to be coded using MedDRA (version 10.1) and summarized by system organ class (SOC) and preferred term.

All demographic and baseline data were to be provided in Listings.

9.7.1.5. Efficacy Analyses

Due to the early termination of this trial, efficacy analyses were limited to the evaluation of overall survival and best overall response. The following planned analyses were omitted:

- All analyses of PFS and TTP, including subgroup analyses, and modeling procedures
- Summary of mutational status and clinical outcome by mutational status
- All other exploratory efficacy analyses (i.e., quality of life analyses)
- Summary of subsequent cancer treatments while on trial

Overall Survival

Overall survival (OS) was to be determined as the time from randomization until death. For patients who were alive at the end of study or lost to follow-up, OS was to be censored on the last date when patients were known to be alive. OS was to be estimated using Kaplan-Meier methods and the 2 treatment groups were to be compared using a two-sided stratified log-rank test at the α=0.05 significance level. Because fewer than 25% of the planned enrollment was achieved, and because fewer than 25% of the patients in the study had deaths reported in the database, the Kaplan-Meier estimates are provided in the tables following text, but are not discussed within the text or used in discussion or conclusions.

Response to Treatment

The disease control rate (DCR), defined as the proportion of patients with confirmed CR, confirmed PR, or SD for at least 6 weeks from randomization, was to be calculated. Confirmed CR and PR were those that persisted on repeat imaging ≥4 weeks after the initial documentation of response. The response rate, including both confirmed and non-confirmed responses, also was to be summarized. For both response rates, results across the treatment groups were to be compared using Fisher's exact test. The 95% CI of the DCR for each treatment group was to be calculated based on an exact probability method. In addition to DCR, best overall response rate was to be summarized descriptively.

9.7.1.6. Pharmacokinetic Evaluations

Plasma concentrations of IPI-504, 17-AAG and 17-AG with nominal post-dose time and corresponding derived post-dose times were to be presented in a listing and summarized by nominal post-dose collection time. Concentrations that were below the quantitation level of the assay were to be set to zero prior to summarization in tables and were presented as reported in the listings.

The sparse samples collected in this study were intended to be used in a population PK analysis to estimate PK parameters of IPI-504 and its metabolites following single and multiple dose administration.

Correlations between baseline characteristics, plasma concentrations and efficacy RECIST outcomes and/or safety outcome variables may have been explored. There were no pharmacodynamic variables in this trial.

9.7.1.7. Safety Analyses

All safety parameters were to be summarized as follows:

- All patients by treatment group (IPI-504 and placebo) during the double blind portion of the study
- From the first IPI-504 dose onward for the subset of patients who were randomized to placebo and entered the open-label period
- From Dose 1 of IPI-504 onward for all patients (i.e., summarizes safety during all IPI-504 treatment including double-blind and open-label for patients who were randomized to and received placebo during the double-blind period).

Extent of Exposure

In order to summarize study drug exposure and subsequent anticancer therapy, including both ITT and safety population analyses, the following tables were created:

Duration and Intensity of Study Drug Exposure

The total dose and duration of study treatment were to be summarized using descriptive statistics by treatment group. The dose intensity of the study treatment was to be summarized where dose intensity was defined as a percent of actual total dose that a patient received during the study treatment period versus the intended dose for the same period according to the protocol based on the following equation.

$$100 \times \frac{\sum actual\ \ dose\ \ received\ \ (mg/m^2)}{400(mg/m^2)\ \times 4 \times\ \ treatment\ \ period\ \ (in\ \ cycles)}$$

Descriptive statistics for the number of cycles and doses received and the total dose of IPI-504 in mg/m^2 was to be presented for each treatment group.

A by-patient listing of dose administration information was to be provided.

Dose Modification and Discontinuation

Dose modifications of study drug were to be summarized according to the cause of the modifications. The number and percent of patients with dose modification and/or discontinuation of study drug were to be descriptively summarized by treatment group.

Adverse Events

Analyses of AEs and SAEs were to be performed for events that were considered treatment-emergent. Treatment-emergent AEs and SAEs were defined as new events occurring after

dose 1 of the double-blind portion of the study or worsening of a pre-existing condition after 1 dose and within 30 days of the last dose of study treatment (unless they were considered treatment related). All AEs and SAEs collected after dose 1 of the double-blind portion of the study were to be considered post-treatment, even if they occurred after the last dose of therapy.

TEAEs and treatment-emergent SAEs were to be summarized by MedDRA system organ class and preferred term, by severity grade according to NCI CTCAE, and by relationship to study drug. Patients were to be counted only once for each preferred term, once for each body system, and by the highest event severity, regardless of the number of events the patient experienced. All AEs that occurred for patients who were never treated were to be presented in a separate listing. SAEs that began more than 30 days after last dose administration were not to be summarized unless related to study drug; however, all SAEs that were recorded on the CRF were to be included in data listings.

Patients who died, had SAEs, discontinued due to an AE, or had a dose modification due to an AE were to be presented in data listings.

Laboratory Data

Descriptive statistics for blood chemistry and hematology parameters were to be provided by treatment group. The actual values of laboratory tests were to be presented by visit and by change from baseline. The last value collected prior to treatment was to represent the baseline value.

Laboratory abnormalities with toxicity grades according to the NCI CTCAE were to be derived based on reference to laboratory normal range values. Laboratory abnormalities occurring from the start of study drug administration through 30 days after the last dose of study drug were to be presented. Shift tables of grades at baseline to worst grades post-baseline were to be presented as well as a summary of grades over time.

All laboratory data were to be provided in data listings.

Physical Examination Abnormalities

All physical examination data were to be presented in data listings.

Vital Signs

Pre and post-infusion vital signs data were to be summarized over time. Change from pre-dose to post-dose within each visit was also to be presented.

By-patient listings of vital sign measurements were to be provided.

Electrocardiogram

Descriptive statistics for ECG parameters, including heart rate, PR, QRS, QT, QTcB, and QTcF, were to be provided by treatment group. If the comments for ECGs included the text

'Technically Poor Tracing' or 'Poor Data Quality', then the ECG value was not to be used for analysis. Change from the pre-treatment time point to each visit was also to be presented.

Concomitant Medications

Concomitant medications were to be coded using the WHO Drug dictionary (September 2006). If a concomitant medication was started in the double-blind portion of the study and stopped after open-label treatment, this medication was to appear in both the double-blind group and the open-label group. Results were to be tabulated by Anatomic Therapeutic Class (ATC) and drug name for patients overall as well as within treatment group.

ECOG

ECOG results were to be summarized over time as well as a shift from baseline to the highest ECOG score on study.

9.7.2. Determination of Sample Size

In a sunitinib Phase 3 trial, the median PFS for placebo patients was 6 weeks (95% confidence interval: 4.4 to 9.9 weeks). To account for potential improvement in standard of care over time and for the variation in the median PFS estimation for placebo patients in the sunitinib trial, 7 weeks was assumed as the median PFS for placebo patients in the current trial. Patients were randomized using 2:1 ratio to receive either IPI-504 or placebo. A total of 148 patients with disease progression or death were required in order to detect a 75% improvement in median PFS in IPI-504 patients from 7 weeks to 12.25 weeks, using a two-sided log-rank test and an overall significance level of 0.05 and power of 0.9. The hazard ratio in IPI-504 versus placebo patients was 0.57.

For the purpose of the sample size estimation, it is assumed that the lost-to-follow-up times were independent and exponentially distributed with a common parameter (λ=0.0744), which was determined under the expectation of 20% drop-out rate in 3 months. With a planned accrual period of 12 months and a minimum follow-up period of 6 months, it was estimated that a total of 195 patients (130 in the IPI-504 study arm and 65 in the placebo arm) needed to be enrolled in order to observe 148 patients with progressive disease or death by the end of the minimum follow-up period. The total number of patients to be enrolled was to be adjusted to achieve the required number of events if the underlying assumptions changed significantly on the patient accrual and drop-out rate during the study.

9.8. Changes in the Conduct of the Study or Planned Analyses

9.8.1. Changes in the Conduct of the Study

As described in Section 6.5, the study was terminated by the Sponsor on 15 April 2009 due to an imbalance in deaths between the treatment arms; at that time a total of 47 (24%) of the planned 195 patients had been enrolled.

9.8.1.1. Amendments to the Protocol

There were 3 amendments to the original study protocol, dated 19 May 2008. A summary of the key changes made with each of these amendments is provided below; complete details can be found in Appendix 16.1.1.

Amendment 1, dated 16 July 2008:

- Inclusion criteria changes: The inclusion criterion for AST, ALT, and alkaline phosphatase was changed from "≤ 5.0 x ULN if considered secondary to liver metastases" to "≤ 3.0 x ULN". An inclusion criterion was added for albumin (albumin ≥ 3.0 g/dL).
- Introduction: A statement in the introduction regarding the biological activity of IPI-504 in GIST was corrected.
- New section regarding treatment criteria prior to each study drug administration: This included drawing blood samples for chemistry and hematology/coagulation analysis and reviewing these results within the 24 hours prior to study drug administration. (The Schedules of Assessments were modified accordingly and also the laboratory evaluations section.) Language was added requiring confirmation that no other dose modifications were required prior to study drug administration.
- Dose modification: The dose modification section was updated to delineate dose modifications to be made for AEs with or without known relationship to study drug.
- Blood chemistries were added for Dose 2 and Dose 4 for all additional cycles and open-label cycles.
- The instructions for reporting of laboratory/vital sign abnormalities were clarified to avoid reporting such abnormalities as both laboratory findings and AEs.
- An incorrect reason for study drug discontinuation in individual patients was removed.
- The definition of measurable disease was updated to reflect that confirming the neoplastic nature of a solitary lesion was not feasible in this patient population.

Amendment 2, dated 15 September 2008:

- The tumor biopsy section clarified that that biopsies/samples could have been done at the Investigator's discretion with the patient's consent, archived tissue samples could have been collected for analysis, if available, and the laboratory manual contained instructions on the disposal of tissue samples.
- A second manufacturer, Ben Venue Laboratories was added.

Amendment 3, dated 12 February 2009:

- The definition of disease recurrence during adjuvant imatinib therapy was clarified.
- Inclusion Criterion #9 was clarified.
- Exclusion Criterion #3 was clarified.
- Open-label inclusion criteria were modified. Changes included, but were not limited to, the addition of an inclusion criteria requiring resolution of drug-related AEs that occurred during the blinded phase, and the addition of open-label exclusion criteria for sinus bradycardia and for the use of medications or foods that are clinically relevant CYP3A inhibitors or inducers.
- The criteria for treatment prior to study drug administration were clarified.
- The procedure for dose modification due to Grade 3 or 4 hyperglycemia was clarified.
- The procedures pertaining to routine laboratory evaluations, coagulation assessment, and vital signs collection were clarified.
- The assessments to be performed at 30 days post dose administration were clarified.
- Guidelines for reporting laboratory/vital signs abnormalities as AEs were expanded.
- Description of the IDMC was expanded.

9.8.1.2. Other Changes

Although listed in the schedule of assessments, vital signs of temperature, respiratory rate and blood pressure were not captured in the eCRF; data collected included only heart rate. Further, only physical examination findings that represented clinically significant changes from baseline were to be recorded on the AE CRF; complete details for post-baseline physical examinations were not captured.

9.8.2. Changes in the Planned Statistical Analyses

Due to the early termination of the trial with only 47 (24%) of the planned 195 patients randomized into the study, many of the planned efficacy analyses were eliminated as detailed in Section 9.7.1.5.

10. STUDY PATIENTS

10.1. Disposition of Patients

Patient disposition is summarized by treatment group and overall in Table 10-1. A tabular summary of patient disposition by treatment group and population is presented in Table 14.1.1. Patient disposition for all screened patients for both the double-blind and open-label periods is provided in Listing 16.2.1.1.

Table 10-1 Patient Disposition

Disposition	IPI-504 n (%)	Placebo n (%)	Overall n (%)
Screened			68
Randomized	32 (100.0)	15 (100.0)	47 (100.0)
Treated in the Double-Blind Period	32 (100.0)	15 (100.0)	47 (100.0)
Reason for Termination from Double-Blind			
Early Termination of the Study	13 (40.6)	7 (46.7)	20 (42.6)
RECIST Disease Progression	10 (31.3)	6 (40.0)	16 (34.0)
Adverse Event	4 (12.5)	0	4 (8.5)
Death[1]	3 (9.4)	0	3 (6.4)
Patient request to discontinue study drug	1 (3.1)	0	1 (2.1)
Symptomatic Deterioration	1 (3.1)	0	1 (2.1)
Other	0	2 (13.3)	2 (4.3)
Treated in the Open-Label Period[2]	2 (6.3)	6 (40.0)	8 (17.0)
Reason for Termination from Open-Label[2,3]			
Early Termination of the Study	1 (50.0)	5 (83.3)	6 (75.0)
RECIST Disease Progression	1 (50.0)	0	1 (12.5)
Adverse Event	0	1 (16.7)	1 (12.5)

Note: Percents are based on the number of patients randomized by treatment group or overall

1 Six deaths occurred within 30 days of the last dose of study treatment, including 4 patients in IPI-504 group, 1 patient during treatment with placebo, and 1 patient randomized to placebo who received open-label IPI-504. For 3 of these patients, the reason for study termination was reported as a reason other than death: for 1 patient in the IPI-504 group (006-001), the reason for study termination was reported as adverse event (renal failure) and for the 2 patients randomized to placebo, the reason for study termination was reported as RECIST disease progression (024-001; patient continued in the open-label period prior to death) or early termination of the study (028-001).

2 All patients received IPI-504 during the open-label period.

3 Percents for reasons for termination from the open-label period are calculated based on the number of patients who entered this study period.

Source: Table 14.1.1 and Listing 16.2.1.1.

Prior to premature termination of the study by the Sponsor, a total of 68 patients were screened for entry. Eleven (16%) patients did not meet eligibility requirements and 10 (15%) were in the screening period at the time of study termination (Listing 16.2.4.1).

The remaining 47 (69%) patients were randomized in the double-blind portion of the study at 19 study sites in the US, Australia, Belgium, France, Germany, and South Korea, including 32

patients randomized to receive IPI-504 and 15 randomized to receive placebo. Eight of these 47 patients were eligible for and went on to enter the open-label portion of the study, 2 from the IPI-504 group and 6 from the placebo group.

The number of patients randomized at each study site is provided in Table 14.1.4. One study site randomized and treated a total of 14 (30%) of the 47 patients; all other study sites randomized 4 patients or fewer.

The most common reason for early withdrawal from the study was premature termination of the study by the Sponsor. At the time of early study termination, a total of 26 patients were on study and thus were withdrawn, including 20 patients in the double-blind period [13 (41%) in the IPI-504 group and 7 (47%) in the placebo group] and 6 patients in the open-label period.

During the double-blind period, other reasons for study withdrawal that were reported for more than 1 patient were RECIST disease progression (31% and 40% of IPI-504 and placebo patients, respectively), adverse event (13% and 0%, respectively), and death (9% and 0%, respectively). During the open-label period, other reasons for withdrawal were RECIST disease progression (1 patient initially in the IPI-504 group) and adverse event (1 patient initially in the placebo group). A discussion of adverse events leading to withdrawal from treatment is provided in Section 12.3.3.

Randomization was stratified based on TTP on imatinib (< 6 months versus ≥ 6 months or intolerance) and geographic region (US/Canada versus EU/ROW). As shown in Table 10-2, within each strata, the number of patients treated with IPI-504 was approximately twice that of placebo based on the 2:1 randomization scheme. A slightly higher ratio (i.e., >2:1) of patients treated with IPI-504 in the US had TTP on imatinib ≥6 months compared with patients who received placebo. By-patient information on strata is provided in Listing 16.2.4.3.

Table 10-2 Number of Patients by Region and Time to Progression on Imatinib (IVRS, ITT Population)

	Region Stratum			
	USA/Canada (N=32)		**EU/ROW (N=15)**	
TTP on Imatinib Stratum:	**IPI-504 (N=22) n (%)**	**Placebo (N=10) n (%)**	**IPI-504 (N=10) n (%)**	**Placebo (N=5) n (%)**
<6 months	6 (60.0)	4 (40.0)	2 (66.7)	1 (33.3)
≥6 months or Intolerance	16 (72.7)	6 (27.3)	8 (66.7)	4 (33.3)

Note: percents are based on the row total within each geographic region.

Source: Table 14.1.5.

10.2. Protocol Deviations

10.2.1. Eligibility Violations

A by-patient listing of the eligibility status of all screened patients is presented in Listing 16.2.4.1. Details on eligibility status and entry into the open-label period are included in Listing 16.2.4.13.

Among the 47 randomized patients, 3 were reported not to have met all inclusion and exclusion criteria at study baseline. Patient 025-001 in the IPI-504 group failed to meet Exclusion Criterion 10 requiring ophthalmology examination within 3 months of study entry to rule out keratitis or keratoconjunctivitis; an exemption was granted for enrollment. Patients 029-001 and 001-004 in the IPI-504 and placebo groups, respectively, failed to meet Inclusion Criterion 4 requiring documented radiographic evidence of progression or intolerance to imatinib and sunitinib. Exemptions were not granted for these patients.

10.2.2. Protocol Deviations

Listing 16.2.2.1 identifies protocol deviations for all randomized patients.

In general, the majority of protocol deviations were minor, primarily related to missed study visits or procedures not conducted on time, and did not have an impact on the assessment of efficacy or safety.

Major protocol deviations were identified for 3 patients, 2 in the IPI-504 group and 1 in the placebo group. Of the 2 patients treated with IPI-504, 1 patient as detailed above (Patient 029-001) had missing source documentation verifying radiographic disease progression on imatinib and sunitinib and 1 (Patient 040-001) was administered IPI-504 when liver function tests showed elevated values and, per protocol, the dose should have been held. The patient later died (see Section 12.3.3). In addition, 1 placebo patient as detailed above (Patient 001-004) had no radiographic evidence of disease progression on imatinib and sunitinib.

11. EFFICACY EVALUATION

11.1. Data Sets Analyzed

The ITT population includes all 47 patients randomized into the study; all patients received treatment as randomized.

11.2. Demographic and Other Baseline Characteristics

11.2.1. Demographics

The demographic characteristics for all 47 patients in the ITT population are provided in Table 11-1. Demographic data and ECOG performance status are provided for each patient in Listing 16.2.4.4 and Listing 16.2.9.8, respectively.

Table 11-1 Demographic and Baseline Characteristics (ITT Population)

Parameter	IPI-504 (N=32)	Placebo (N=15)	Overall (N=47)
Sex, n (%)			
Males	21 (65.6)	11 (73.3)	32 (68.1)
Females	11 (34.4)	4 (26.7)	15 (31.9)
Age (years)			
Mean (SD)	58 (11.2)	57 (14.9)	57 (12.4)
Median	58	57	58
Minimum, Maximum	29, 75	21, 86	21, 86
Age Category (years), n (%)			
20-39	1 (3.1)	1 (6.7)	2 (4.3)
40-65	23 (71.9)	10 (66.7)	33 (70.2)
>65	8 (25.0)	4 (26.7)	12 (25.5)
Race, n (%)			
White	24 (75.0)	13 (86.7)	37 (78.7)
Asian	6 (18.8)	1 (6.7)	7 (14.9)
Black or African American	2 (6.3)	1 (6.7)	3 (6.4)
Screening ECOG Status, n (%)			
0	17 (53.1)	8 (53.3)	25 (53.2)
1	15 (46.9)	7 (46.7)	22 (46.8)

Source: Table 14.1.3 and Table 14.3.6.16.

The two treatment groups were similar with regard to demographic and baseline characteristics. The majority of patients were male (66% and 73% in the IPI-504 and placebo groups, respectively) and white (75% and 87%, respectively). Mean age was 58 years in the IPI-504 group and 57 years in the placebo group with a range of 21 to 86 years across all 47 patients. As required by the protocol entry criteria, ECOG performance status at screening was 0 or 1 in all patients.

11.2.2. Baseline Disease Characteristics

A summary of baseline disease characteristics, including duration of GIST, histology of the disease, and tumors sites involved is provided in Table 11-2; these data are provided for each patient in Listing 16.2.4.6.

Table 11-2 GIST Disease Characteristics (ITT Population)

Parameter	IPI-504 (N=32)	Placebo (N=15)	Overall (N=47)
Years Since Diagnosis of GIST			
Mean (SD)	5.3 (2.46)	6.4 (2.41)	5.7 (2.48)
Median	5.0	6.3	5.5
Minimum, Maximum	1.1, 11.0	1.6, 10.5	1.1, 11.0
Histology			
Spindle Cell	19 (59.4)	5 (33.3)	24 (51.1)
Mixed Spindle and Epithelioid	5 (15.6)	4 (26.7)	9 (19.1)
Epithelioid	2 (6.3)	3 (20.0)	5 (10.6)
Other	2 (6.3)	0	2 (4.3)
Not Available/Unknown	4 (12.5)	3 (20.0)	7 (14.9)
Tumor Sites Involved			
Small Bowel	16 (50.0)	7 (46.7)	23 (48.9)
Stomach	11 (34.4)	4 (26.7)	15 (31.9)
Omentum/Mesentery	5 (15.6)	3 (20.0)	8 (17.0)
Colon	1 (3.1)	1 (6.7)	2 (4.3)
Esophagus	1 (3.1)	1 (6.7)	2 (4.3)
Other	5 (15.6)	2 (13.3)	7 (14.9)

Source: Table 14.1.7

Mean duration since diagnosis of GIST was 5.3 years in the IPI-504 group and 6.4 years in the placebo group and ranged from 1.1 to 11.0 years across the 47 patients. The most common histopathologic type of GIST in both treatment groups was spindle cell, reported in 59% and 33% of patients in the IPI-504 and placebo groups, respectively. The site of tumor involvement was most commonly the small bowel (50% and 47% of patients in the IPI-504 and placebo groups, respectively). Most patients had only 1 tumor site involved (84% and 87% of patients in the IPI-504 and placebo groups, respectively); a total of 7 patients, including 5 IPI-504 patients and 2 placebo patients, had more than 1 site involved (Table 14.1.7).

A summary of the number and types of prior therapies for GIST is provided in Table 11-3; these data are listed for each patient in Listing 16.2.4.7 (prior surgery), Listing 16.2.4.8 (prior radiation therapy), and Listing 16.2.4.9 (prior systemic therapy).

Table 11-3 Number and Types of Prior Therapies (ITT Population)

Parameter	IPI-504 (N=32)	Placebo (N=15)	Overall (N=47)
≥3 Unique Prior Systemic Treatments, n (%)	20 (62.5)	10 (66.7)	30 (63.8)
Most Common Prior Systemic Therapy, n (%)			
Imatinib	32 (100.0)	15 (100.0)	47 (100.0)
Sunitinib	32 (100.0)	15 (100.0)	47 (100.0)
Nilotinib	12 (37.5)	4 (26.7)	16 (34.0)
Sorafenib	6 (18.8)	4 (26.7)	10 (21.3)
Dasatinib	4 (12.5)	4 (26.7)	8 (17.0)
Prior Surgery for GIST, n (%)	32 (100.0)	15 (100.0)	47 (100.0)
Prior Hepatic Surgery for GIST, n (%)	7 (21.9)	2 (13.3)	9 (19.1)
Prior Radiation Therapy, n (%)	4 (12.5)	0	4 (8.5)

Source: Table 14.1.6 and Table 14.1.8.

Nearly two-thirds of the patients in both treatment groups had received 3 or more unique prior treatments for GIST (63% and 67% in the IPI-504 and placebo groups, respectively). Mean numbers of prior treatments were 5.1 and 6.4 in the IPI-504 and placebo groups, respectively (Table 14.1.6).

All 47 patients had received prior treatment with imatinib and sunitinib and failed to respond or experienced disease progression following treatment. Other commonly administered prior treatments for GIST were nilotinib (38% and 27% in the IPI-504 and placebo groups, respectively), sorafenib (19% and 27%, respectively), and dasatinib (13% and 27%, respectively).

All 47 patients had undergone prior surgery for the treatment of GIST. A higher proportion of patients who received IPI-504 had undergone prior hepatic surgery (22%) compared with patients who received placebo (13%) (Table 11-3). Prior radiation therapy for the disease had been administered to 4 patients, all were in the IPI-504 treatment group.

Mean durations from the end of the last prior treatment to enrollment in this study were 1.6 and 1.7 months in the IPI-504 and placebo groups, respectively (Table 14.1.6). Reason for discontinuation from the last prior treatment was progressive disease in the majority of patients (81% and 80% in the IPI-504 and placebo groups, respectively) (Table 14.1.6).

Table 11-4 details the intensity of prior imatinib and sunitinib therapy; these data are provided for each patient in Listing 16.2.4.9.

Table 11-4 Prior Imatinib and Sunitinib Treatments (ITT Population)

Treatment	IPI-504 (N=32)	Placebo (N=15)	Overall (N=47)
Imatinib			
Duration (years), Median (range)	1.50 (0.2, 6.28)	2.59 (0.12, 7.36)	1.72 (002, 7.36)
Maximum Dose Received, n (%)			
800 mg	18 (56.3)	8 (53.3)	26 (55.3)
600 mg	3 (9.4)	4 (26.7)	7 (14.9)
400 mg	11 (34.4)	3 (20.0)	14 (29.8)
Sunitinib			
Duration (years), Median (range)	0.90 (0.17, 307)	0.88 (0.12, 2.25)	0.89 (0.12, 3.07)
Maximum Dose Received, n (%)			
50 mg	25 (78.1)	11 (73.3)	36 (76.6)
37.5 mg	7 (21.9)	3 (20.0)	10 (21.3)
Other	0	1 (6.7)	1 (2.1)

Source: Table 14.1.6.

Prior treatment with sunitinib was comparable in both treatment groups. The median number of years on sunitinib was approximately 0.9 in both treatment groups (0.90 and 0.88 years in the IPI-504 and placebo groups, respectively). A similar proportion of patients in both treatment groups received a maximum dose of 37.5 mg (approximately 20-22%) and 50 mg (approximately 73-78%).

Prior treatment with imatinib was more varied between the treatment groups. Placebo patients received imatinib, on average, for a longer period of time (median: 2.59 years) compared with IPI-504 patients (median: 1.50 years). Approximately half of the patients in both groups received a highest maximum dose of 800 mg (56% and 53% in the IPI-504 and placebo groups, respectively).

Evidence of disease progression on prior imatinib and sunitinib is summarized in Table 14.1.9 and listed for each patient in Listing 16.2.4.10; details on intolerance to these prior therapies are provided in Listing 16.2.4.11.

11.2.3. Other Medical History

Medical history is summarized by MedDRA SOC and preferred term in Table 14.1.11. A by-patient listing of medical history is presented in Listing 16.2.4.5.

All 47 patients in the ITT population had at least 1 medical condition other than their primary cancer at screening. Overall, the body systems in which patients most frequently reported a history of medical conditions were GI disorders (88% and 80% in the IPI-504 and placebo groups, respectively), vascular disorders (63% and 47%, respectively), and general disorders (56% and 60%, respectively). Renal and urinary tract disorders were reported in 11 (34%) and 7 (47%) patients) in the IPI-504 and placebo groups, respectively, and hepatobiliary disease was reported in 3 (9%) and 1 (7%) patients, respectively.

The most commonly reported medical conditions (>20% of all patients) were hypertension (59% and 33% of IPI-504 and placebo patients, respectively), gastroesophageal reflux disease (47% and 27%, respectively), abdominal pain (28% and 53%, respectively), fatigue (34% and 40%, respectively), nausea (31% and 27%, respectively), depression (22% and 40%, respectively), diarrhoea (19% and 27%, respectively), and anemia (19% and 27%, respectively).

11.3. Measurements of Treatment Compliance

Study drug exposure is summarized in Table 14.3.6.13; data are provided for each patient in Listing 16.2.5.1 and Listing 16.2.5.2. A complete discussion on extent of exposure to the study drug is provided in Section 12.1.

In general, compliance with the treatment regimen was good. Mean dose intensity during the double-blind treatment period was 87% in the IPI-504 treatment group and 94% in the placebo group.

11.4. Efficacy Results and Tabulations of Individual Patient Data

11.4.1. Analysis of Efficacy

As the study was terminated prematurely with only 47 (24%) of the planned 195 patients enrolled, efficacy analyses were limited to overall survival and best response on treatment.

11.4.1.1. Overall Survival

In this study with fewer than a fourth of the planned enrollment and with fewer than a fourth of the enrollees having data on death, estimates from the overall survival analysis require cautious interpretation.

At the time of early study termination, 8 (25%) of the 32 patients in the IPI-504 group and 3 (20%) of the 15 patients in the placebo group had died within 30 days of the last dose of study drug (n=6) or in the follow-up period more than 30 days post treatment (n=5).

11.4.1.2. Best Overall Response

Table 11-5 summarizes best overall response to treatment for the ITT population based on the central independent radiology assessments. These data are listed for each patient in Listing 16.2.6.1.1.

Table 11-5 Best Overall Response based on Central Read (ITT Population)

Response	IPI-504 (N=32)	Placebo (N=15)
Best Overall Response		
CR or PR	0	0
SD <6 weeks	19 (59.4)	10 (66.7)
SD ≥6 weeks	3 (9.4)	2 (13.3)
PD	2 (6.3)	2 (13.3)
Unknown[1]	8 (25.0)	1 (6.7)

1 Patients without post-baseline disease assessments.

Source: Table 14.2.2.1.

None of the 47 patients achieved a CR or PR during the study; SD of any duration was reported as the best response for 22 (69%) of 32 IPI-504 patients and 12 (80%) of 15 placebo patients. Stable disease of at least 6 weeks duration was observed in 3 patients (9%) and 2 patients (13%) in the IPI-504 and placebo groups.

11.4.2. Statistical and Analytical Issues

The majority of planned efficacy analyses were not conducted as the study was terminated with only 47 (24%) of the planned sample of 195 patients randomized and treated.

11.4.3. Tabulation of Individual Response Data

All tabulations of efficacy data are provided in Section 14.2; no individual response data were summarized.

11.4.4. Drug Dose, Drug Concentration, and Relationship to Response

Descriptive statistics for plasma concentrations are summarized in Section 14.3.5, Table 14.4.1; data are provided for each patient in Listing 16.2.5.3. The bioanalytical report is provided in Appendix 16.2.5.

During the double blind portion of the study, pharmacokinetic samples were collected from 20 patients who were administered IPI-504 and 10 patients who were administered placebo. Individual plasma concentrations of IPI-504, 17-AAG and 17-AG on C1D1 are presented graphically in Section 14.3.6, Figure 2.1, Figure 2.2 and Figure 2.3, respectively. Analysis of the samples collected at the end of the infusion from patients who received placebo revealed no measurable concentrations of IPI-504, 17-AAG or 17-AG. No additional analyses were performed on these data, given early study termination.

11.4.5. Drug-Drug and Drug-Disease Interactions

Not applicable to the present study.

11.4.6. By-Patient Displays

By-patient listings of patient response assessed by central reads are presented in Listing 16.2.6.1.1, Listing 16.2.6.1.3, Listing 16.2.6.1.5, and Listing 16.2.6.2.1. By-patient listings of patient response, assessed by the Investigator, are presented in Listing 16.2.6.1.2, Listing 16.2.6.1.4, Listing 16.2.6.1.6, and Listing 16.2.6.2.2.

11.4.7. Efficacy Conclusions

Due to the early termination of the study leading to a sample size of only 47 patients, no efficacy conclusions can be drawn from this study.

12. SAFETY EVALUATION

Tabulations of safety data are provided for all patients who received at least 1 dose of blinded study treatment, either IPI-504 (n=32) or placebo (n=15), and across all IPI-504 treated patients (n=38). The latter analysis includes data on the 32 patients who were randomized to IPI-504 and the 6 patients who were randomized to placebo and entered the open-label extension period to receive IPI-504 following disease progression. Note that the appendix tables included in Section 14.3 also present results separately for treatment during the open-label period for these 6 patients.

12.1. Extent of Exposure

12.1. Extent of Exposure

Descriptive statistics for extent of exposure are provided in Table 12-1.

Table 12-1 Exposure to Study Drug (ITT Population)

	Patients Receiving Treatment during the DB Period		All Patients Receiving IPI-504 (DB+OL) (N=38) n (%)
Parameter	**Placebo (N=15) n (%)**	**IPI-504 (N=32) n (%)**	
Total Dose (mg)			
Mean (SD)	2733.1 (1444.21)	2413.7 (1892.95)	2491.2 (1996.75)
Median	2526.9	1686.7	1686.7
Minimum, Maximum	1185.3, 6000.0	400.00, 8016.1	400.00, 8016.1
Duration (days)			
Mean (SD)	30.4 (22.74)	26.3 (24.39)	27.5 (25.40)
Median	29.0	22.0	22.0
Minimum, Maximum	7, 84	1, 95	1, 95
Number of Doses			
Mean (SD)	7.1 (3.65)	6.2 (4.70)	6.4 (5.00)
Median	7.0	4.5	4.5
Minimum, Maximum	3, 15	1, 20	1, 20
Dose Intensity (%)[1]			
Mean (SD)	93.9 (12.49)	87.46 (20.54)	87.4 (21.37)
Median	99.4	100.0	100.0
Minimum, Maximum	52.6, 102.5	37.0, 100.2	31.3, 100.2
Dose Decreased, N (%)			
No	14 (93.3)	28 (87.5)	32 (84.2)
Yes	1 (6.7)	4 (12.5)	6 (15.8)
300 mg	1 (6.7)	4 (12.5)	5 (13.2)
225 mg	1 (6.7)	1 (3.1)	2 (5.3)

1 Dose Intensity = [actual dose received in mg/m^2 / ($(400mg/m^2)x(4)x$(treatment period in cycles))]x100.

Source: Table 14.3.6.13.

Mean and median duration of treatment were shorter in the IPI-504 group (26.3 and 22.0 days, respectively) compared with the placebo group (30.4 and 29.0, respectively). Consistent with these results, median number of doses administered was lower in the IPI-504 group (4.5 doses) compared with the placebo group (7.0 doses). Most patients (38 of 47) received only 1 or 2 cycles of treatment in this study (Listing 16.2.5.1).

Four (13%) patients in the IPI-504 group (Patients 001-008, 001-014, 001-015, and 53-004) required a dose reduction during the double-blind period due to adverse events compared with 1 (7%) patient in the placebo group (Patient 020-001). All 5 patients had their dose reduced to 300 mg; 2 of these patients (Patients 001-008 and 020-001) required further dose reductions to 225 mg. In addition, during the open-label period, 2 patients had dose reductions (Patients 001-004 and 009-003). A discussion of adverse events leading to dose reduction is provided in Section 12.3.3.3.

12.2. Adverse Events

12.2.1. Brief Summary of Adverse Events

An overall summary of TEAE rates is provided in Table 12-2.

Table 12-2 Overall Summary of Treatment-Emergent Adverse Events (ITT Population)

	Patients Receiving Treatment during the DB Period		Patients Receiving IPI-504 (DB+OL) (N=38) n (%)
Patients with at least one of the following:	**Placebo (N=15) n (%)**	**IPI-504 (N=32) n (%)**	
TEAEs	15 (100.0)	32 (100.0)	37 (97.4)
Related TEAEs	10 (66.7)	31 (96.9)	36 (94.7)
Grade ≥ 3 TEAEs	5 (33.3)	15 (46.9)	18 (47.4)
Grade ≥ 4 TEAEs	1 (6.7)	8 (25.0)	10 (26.3)
Deaths within 30 days of Last Dose	1 (6.7)	4 (12.5)	5 (13.2)
SAEs	5 (33.3)	13 (40.6)	16 (42.1)
Related SAEs	0	10 (31.3)	12 (31.6)
TEAEs Resulting in Discontinuation[1]	1 (6.7)	7 (21.9)	8 (21.1)
TEAEs Resulting in Dose Reduction	1 (6.7)	4 (12.5)	5 (13.2)
TEAEs Resulting in Held Dose	3 (20.0)	9 (28.1)	10 (26.3)

1 Includes adverse events leading to treatment discontinuation and adverse events with outcome of death.

Source: Table 14.3.1.1.

All 47 (100%) study patients experienced at least 1 TEAE during the double-blind period. Compared with the placebo group, patients in the IPI-504 group experienced higher rates of all categories of TEAEs during the double-blind period, including study drug-related TEAEs (97% vs. 67%), grade 3 or higher TEAEs (47% vs. 33%), SAEs (41 vs. 33%), related SAEs (31% vs. 0%), TEAEs that led to treatment discontinuation (22% vs. 7%), TEAEs that led to a held dose (28% vs. 20%), and TEAEs that led to a dose reduction (13% vs. 7%).

12.2.2. Display of Adverse Events

All tabulations of adverse events are provided in Section 14.3.1.

12.2.2.1. Treatment-emergent Adverse Events

Table 12-3 summarizes TEAEs occurring in ≥10% of the 38 patients who received at least 1 dose of IPI-504 regardless of relationship to study treatment, by MedDRA SOC and preferred term, and by study period.

Table 12-3 Treatment-Emergent Adverse Events Occurring in ≥10% of Patients who Received IPI-504 by MedDRA SOC and Preferred Term, and by Study Period (ITT Population)

MedDRA SOC Preferred Term	Patients Receiving Treatment during the DB Period Placebo (N=15) n (%)	Patients Receiving Treatment during the DB Period IPI-504 (N=32) n (%)	Patients Receiving IPI-504 (DB+OL) (N=38) n (%)
At Least 1 TEAE	***15 (100.0)***	***32 (100.0)***	***37 (97.4)***
Gastrointestinal Disorders	*12 (80.0)*	*25 (78.1)*	*30 (78.9)*
Diarrhoea	3 (20.0)	19 (59.4)	23 (60.5)
Nausea	5 (33.3)	13 (40.6)	16 (42.1)
Abdominal Pain	3 (20.0)	11 (34.4)	12 (31.6)
Vomiting	1 (6.7)	6 (18.8)	8 (21.1)
Constipation	6 (40.0)	5 (15.6)	5 (13.2)
Abdominal Pain Upper	0	5 (15.6)	5 (13.2)
Abdominal Distension	0	2 (6.3)	4 (10.5)
General Disorders and Administration Site Conditions	*8 (53.3)*	*23 (71.9)*	*28 (73.7)*
Fatigue	6 (40.0)	16 (50.0)	17 (44.7)
Infusion Site Pain	1 (6.7)	10 (31.3)	11 (28.9)
Oedema Peripheral	1 (6.7)	6 (18.8)	7 (18.4)
Pyrexia	2 (13.3)	5 (15.6)	6 (15.8)
Investigations	*2 (13.3)*	*20 (62.5)*	*25 (65.8)*
Urine Colour Abnormal	0	13 (40.6)	16 (42.1)
Aspartate Aminotransferase Increased	0	5 (15.6)	7 (18.4)
Blood Alkaline Phosphatase Increased	0	3 (9.4)	5 (13.2)
Alanine Aminotransferase Increased	0	2 (6.3)	4 (10.5)
Haemoglobin Decreased	0	3 (9.4)	4 (10.5)
Metabolism and Nutrition Disorders	*3 (20.0)*	*16 (50.0)*	*20 (52.6)*
Anorexia	3 (20.0)	9 (28.1)	12 (31.6)
Musculoskeletal and Connective Tissue Disorders	*1 (6.7)*	*12 (37.5)*	*17 (44.7)*
Myalgia	0	7 (21.9)	9 (23.7)
Arthralgia	0	5 (15.6)	9 (23.7)
Back Pain	0	4 (12.5)	6 (15.8)

(continued)

MedDRA SOC Preferred Term	Patients Receiving Treatment during the DB Period Placebo (N=15) n (%)	Patients Receiving Treatment during the DB Period IPI-504 (N=32) n (%)	Patients Receiving IPI-504 (DB+OL) (N=38) n (%)
Nervous System Disorders	*7 (46.7)*	*12 (37.5)*	*14 (36.8)*
Headache	3 (20.0)	11 (34.4)	13 (34.2)
Renal and Urinary Disorders	*1 (6.7)*	*6 (18.8)*	*10 (26.3)*
Renal Failure[1]	0	4 (12.5)	6 (15.8)
Respiratory, Thoracic and Mediastinal Disorders	*2 (13.3)*	*5 (15.6)*	*7 (18.4)*
Dyspnoea	0	2 (6.3)	4 (10.5)

1 Includes reports of acute pre-renal failure, renal failure and renal failure acute (see Listing 16.2.7.1)

Source: Table 14.3.1.2.

The most commonly occurring TEAEs (i.e., occurring in >20% of IPI-504 patients) during the double-blind period were diarrhoea [19 (59%) IPI-504 patients and 3 (20%) placebo patients], fatigue [16 (50%) and 6 (40%) patients, respectively], nausea [13 (41%) and 5 (33%) patients, respectively), urine colour abnormal [13 (41%) and 0 patients, respectively], abdominal pain [11 (34%) and 3 (20%) patients, respectively], headache [11 (34%) and 3 (20%) patients, respectively], infusion site pain [10 (31%) and 1 (7%) patients, respectively], anorexia [9 patients (28%) and 3 patients (20%), respectively], and myalgia [7 patients (22%) and 0 patients, respectively].

12.2.2.2. Treatment-emergent Adverse Events by Severity

Table 12-4 summarizes TEAEs of Grade 3 or greater severity occurring in 2 or more patients during the study by MedDRA SOC and preferred term, and by study period.

Table 12-4 Treatment-Emergent ≥Grade 3 TEAEs Occurring in Two or More Patients by Severity, MedDRA SOC and Preferred Term, and by Study Period (ITT Population)

MedDRA SOC Preferred Term	Patients Receiving Treatment during the DB Period						Patients Receiving IPI-504 (DB+OL) (N=38) n (%)		
	Placebo (N=15) n (%)			IPI-504 (N=32) n (%)					
	Gr 3	Gr 4	Gr 5	Gr 3	Gr 4	Gr 5	Gr 3	Gr 4	Gr 5
At Least 1 TEAE by Severity	***4 (26.7)***	***0***	***1 (6.7)***	***7 (21.9)***	***4 (12.5)***	***4 (12.5)***	***8 (21.1)***	***5 (13.2)***	***5 (13.2)***
Gastrointestinal Disorders	*0*	*0*	*0*	*9 (28.1)*	*1 (3.1)*	*0*	*11 (28.9)*	*1 (2.6)*	*0*
Diarrhoea	0	0	0	6 (18.8)	0	0	7 (18.4)	0	0
Abdominal Pain	0	0	0	3 (9.4)	0	0	4 (10.5)	0	0
Vomiting	0	0	0	2 (6.3)	1 (3.1)	0	3 (7.9)	1 (2.6)	0
Nausea	0	0	0	2 (6.3)	0	0	3 (7.9)	0	0
Investigations	*0*	*0*	*0*	*4 (12.5)*	*3 (9.4)*	*0*	*4 (10.5)*	*4 (10.5)*	*0*
Aspartate Aminotransferase Increased	0	0	0	1 (3.1)	2 (6.3)	0	1 (2.6)	3 (7.9)	0
Blood Alkaline Phosphatase Increased	0	0	0	3 (9.4)	0	0	3 (7.9)	0	0
Alanine Aminotransferase Increased	0	0	0	1 (3.1)	0	0	2 (5.3)	0	0
Lipase Increased	0	0	0	1 (3.1)	1 (3.1)	0	1 (2.6)	1 (2.6)	0
Metabolism and Nutrition Disorders	*1 (6.7)*	*0*	*0*	*3 (9.4)*	*1 (3.1)*	*1(3.1)*	*3 (7.9)*	*2 (5.3)*	*1 (2.6)*
Dehydration	0	0	0	1 (3.1)	0	0	2 (5.3)	0	0
Hyperglycaemia	1 (6.7)	0	0	1 (3.1)	0	0	1 (2.6)	0	0
Renal and Urinary Disorders	*1(6.7)*	*0*	*0*	*1 (3.1)*	*1 (3.1)*	*1(3.1)*	*3 (7.9)*	*1 (2.6)*	*1 (2.6)*
Renal Failure Acute	0	0	0	1 (3.1)	0	0	3 (7.9)	0	0
Renal Failure	0	0	0	0	1 (3.1)	1 (3.1)	0	1 (2.6)	1 (2.6)
General Disorders and Administration Site	*2 (13.3)*	*0*	*1 (6.7)*	*3 (9.4)*	*0*	*0*	*3 (7.9)*	*0*	*1 (2.6)*
Fatigue	0	0	0	2 (6.3)	0	0	2 (5.3)	0	0
Disease Progression	0	0	1 (6.7)	0	0	0	0	0	1 (2.6)
Respiratory, Thoracic and Mediastinal	*0*	*0*	*0*	*1 (3.1)*	*0*	*0*	*2 (5.3)*	*0*	*0*
Dyspnoea	0	0	0	1 (3.1)	0	0	2 (5.3)	0	0

Source: Table 14.3.1.3, Table 14.3.1.4

A total of 15 (47%) of 32 patients in the IPI-504 group experienced TEAEs of Grade 3 or higher severity during the double-blind period, including 4 patients (13%) with Grade 4 events and 4 patients (13%) with Grade 5 events, compared with 5 (33%) of 15 patients who received placebo, including 1 patient (7%) with a Grade 5 event. In addition, 3 patients randomized to placebo who entered the open-label phase experienced ≥Grade 3 events during treatment with IPI-504, including 1 patient each with Grade 4 and Grade 5 TEAEs.

TEAEs of ≥Grade 3 severity occurring in >10% of patients during any treatment with IPI-504 were diarrhoea (18% vs. 0% in the placebo group), renal failure/renal failure acute (13% vs. 0% in the placebo group), abdominal pain (11% vs. 0% in the placebo group), vomiting (11% vs. 0% in the placebo group), and aspartate aminotransferase increased (11% vs. 0% in the placebo group).

12.2.2.3. Treatment-related Adverse Events

Table 12-5 summarizes treatment-related TEAEs occurring in ≥10% of the 38 patients who received at least 1 dose of IPI-504 by MedDRA SOC and preferred term, and by study period.

Table 12-5 Treatment-Related Adverse Events Occurring in ≥10% of Patients who Received IPI-504 by MedDRA SOC and Preferred Term, and by Study Period (ITT Population)

MedDRA SOC Preferred Term	Patients Receiving Treatment during the DB Period		Patients Receiving IPI-504 (DB+OL) (N=38) n (%)
	Placebo (N=15) n (%)	IPI-504 (N=32) n (%)	
At Least 1 Related TEAE	***10 (66.7)***	***31 (96.9)***	***36 (94.7)***
Gastrointestinal Disorders	*7 (46.7)*	*24 (75.0)*	*29 (76.3)*
Diarrhoea	3 (20.0)	17 (53.1)	20 (52.6)
Nausea	4 (26.7)	10 (31.3)	13 (34.2)
Vomiting	1 (6.7)	6 (18.8)	7 (18.4)
Abdominal Pain	0	5 (15.6)	5 (13.2)
Investigations	*2 (13.3)*	*16 (50.0)*	*21 (55.3)*
Urine Colour Abnormal	0	13 (40.6)	16 (42.1)
Aspartate Aminotransferase Increased	0	5 (15.6)	7 (18.4)
Blood Alkaline Phosphatase Increased	0	3 (9.4)	5 (13.2)
Alanine Aminotransferase Increased	0	2 (6.3)	4 (10.5)
General Disorders and Administration Site Conditions	*4 (26.7)*	*20 (62.5)*	*24 (63.2)*
Fatigue	3 (20.0)	14 (43.8)	15 (39.5)
Infusion Site Pain	1 (6.7)	10 (31.3)	11 (28.9)
Oedema Peripheral	0	4 (12.5)	4 (10.5)
Nervous System Disorders	*4 (26.7)*	*9 (28.1)*	*11 (28.9)*
Headache	2 (13.3)	9 (28.1)	11 (28.9)

(continued)

MedDRA SOC Preferred Term	Patients Receiving Treatment during the DB Period Placebo (N=15) n (%)	Patients Receiving Treatment during the DB Period IPI-504 (N=32) n (%)	Patients Receiving IPI-504 (DB+OL) (N=38) n (%)
Musculoskeletal and Connective Tissue Disorders	*1 (6.7)*	*9 (28.1)*	*13 (34.2)*
Arthralgia	0	5 (15.6)	9 (23.7)
Myalgia	0	7 (21.9)	9 (23.7)
Metabolism and Nutrition Disorders	*1 (6.7)*	*11 (34.4)*	*12 (31.6)*
Anorexia	1 (6.7)	7 (21.9)	7 (18.4)

Source: Table 14.3.1.6, Table 14.3.1.9.

The most commonly occurring treatment-related TEAEs (i.e., occurring in >20% of IPI-504 patients) during the double blind period were diarrhoea [17 (53%) IPI-504 patients and 3 (20%) placebo patients], fatigue [14 (44%) and 3 (20%) patients, respectively], urine colour abnormal [13 (41%) and 0 patients, respectively], nausea [10 (31%) and 4 (27%) patients, respectively], infusion site pain [10 (31%) and 1 (7%) patients, respectively], and headache [9 (28%) and 2 (13%) patients, respectively].

During the double blind period, 10 (31%) patients in the IPI-504 group experienced a Grade 3 or higher treatment-related TEAE; none of patients in the placebo group experienced treatment-related TEAEs ≥Grade 3 in severity (Table 14.3.1.7). Grade 3 or higher treatment-related TEAEs occurring in more than 2 patients during any IPI-504 treatment (Table 14.3.1.8) included diarrhoea (7 patients, 18%), vomiting (4 patients, 11%), aspartate aminotransferase increased (4 patients, 11%), nausea (3 patients, 8%), blood alkaline phosphatase increased (3 patients, 8%), renal failure/renal failure acute (2 patients, 5%), and alanine aminotransferase increased (2 patients, 5%).

12.2.3. Analysis of Adverse Events

12.2.3.1. Gastrointestinal Disorders

The most commonly occurring TEAEs during the study, in both the IPI-504- and placebo-treated patients, were GI disorders, which occurred in 25 (78%) of 32 IPI-504 patients and 12 (80%) of 15 placebo patients during the double-blind study period. Across all IPI-504 treated patients, GI events occurred in 30 (79%) of 38 patients.

The most common GI disorders in the IPI-504-treated group during the double-blind period (i.e., occurring in >20% of IPI-504 patients) were diarrhoea (59% vs. 20% in the placebo group), nausea (41% vs 33% in the placebo group), and abdominal pain (34% vs. 20% in the placebo group). In the placebo group, the most common GI disorder was constipation (40% vs 16% in the IPI-504 group).

Across all IPI-504 treatment, the incidences of diarrhoea, nausea, and abdominal pain were similar to those occurring during the double-blind period (61%, 42%, and 32%, respectively). Other GI disorders occurring in ≥10% of patients during any IPI-504 treatment were vomiting

(21% vs 7% in the placebo group), abdominal pain upper (13% vs. 0% in the placebo group) and abdominal distension (11% vs. 0% in the placebo group).

The majority of GI adverse events occurring during IPI-504 treatment were assessed as treatment related. Overall, 29 (76%) of the 38 patients who received IPI-504 experienced a treatment-related GI disorder. Treatment-related GI disorders occurring in ≥10% of patients during any IPI-504 treatment were diarrhoea (53% vs 20% in the placebo group), nausea (34% vs. 27% in the placebo group), vomiting (18% vs 7% in the placebo group) and abdominal pain (13% vs 0% in the placebo group).

The majority of GI disorders were Grade 1 or 2 in severity; 12 (32%) of the 38 patients who received IPI-504 experienced at least 1 GI disorder that was Grade 3 (11 patients, 29%) or Grade 4 (1 patient, 3%) in severity. None of the patients in the placebo group experienced Grade 3 or 4 GI disorders during double-blind treatment. No Grade 5 GI events were reported during the study.

The most commonly occurring Grade 3 or 4 GI disorders during any IPI-504 treatment (i.e., occurring in >2 patients) were diarrhoea (7 patients, 18%), abdominal pain (4 patients, 11%), vomiting (4 patients, 11%), and nausea (3 patients, 8%). One patient with Grade 4 vomiting discontinued IPI-504 due to the event. The only other GI event leading to discontinuation of IPI-504 treatment was Grade 3 gastrointestinal fistula.

12.2.3.2. General Disorders and Administration Site Conditions

Adverse events in the General Disorders and Administration Site Conditions SOC occurred in 23 (72%) of 32 patients in the IPI-504 group and in 8 (53%) of 15 patients in the placebo group during the double-blind period. Across all IPI-504 treated patients, general disorders occurred in 28 (74%) of 38 patients.

The most common general disorders in the IPI-504 treatment group during the double-blind period (i.e., occurring in >20% of IPI-504 patients) were fatigue (50% vs. 40% in the placebo group) and infusion site pain (31% vs. 7% in the placebo group).

Across all IPI-504 treatment, the incidences of fatigue and infusion site pain were similar to the incidence during double-blind treatment (45% and 29%, respectively). Other general disorders occurring in 10% or more of patients during any IPI-504 treatment were oedema peripheral (18% vs 7% in the placebo group) and pyrexia (16% vs. 13% in the placebo group).

General disorders assessed as treatment-related by the Investigators occurred in 24 (63%) of the 38 patients who received IPI-504, including fatigue (40% vs. 20% in the placebo group), infusion site pain (29% vs 7%), and oedema peripheral (11% vs 0% in the placebo group).

The majority of general disorders and administration site conditions were Grade 1 or 2 in severity. Four (11%) of the 38 patients who received IPI-504 during the study experienced general disorders that were ≥Grade 3 in severity. During the double-blind period, 3 (20%) of 15 placebo patients experienced general disorders ≥Grade 3 in severity.

Grade 3 general disorders during IPI-504 treatment were fatigue (2 patients, 5%) and asthenia (1 patient, 3%). Grade 3 disorders during placebo treatment in the double-blind period were oedema peripheral (1 patient, 7%) and performance status decreased (1 patient, 7%). No Grade 4 events were reported in this SOC. The oedema peripheral led to discontinuation of placebo treatment; no other patients discontinued due to general disorders or administration site conditions.

Disease progression was reported as the cause of death in 2 patients, including 1 placebo patient during the double-blind period (Patient 028-001) and 1 patient randomized to placebo who experienced disease progression and entered the open-label phase and subsequently died following treatment with IPI-504 (Patient 024-001). Narratives for these patients are provided in Section 12.3.3.1.

12.2.3.3. Investigations

TEAEs in the Investigations SOC occurred in 20 (63%) of 32 patients who received IPI-504 during the double-blind period compared with 2 (13%) of 15 patients who received placebo. Across all IPI-504 treatment, the incidence of events in this SOC was 66% (25 of 38 patients).

The most common TEAE in the Investigations SOC during double-blind treatment (i.e., occurring in >20% of IPI-504 patients) was urine colour abnormal in 13 (41%) of 32 patients in the IPI-504 group and 0% of 15 patients in the placebo group. The incidence of urine colour abnormal during any IPI-504 treatment was 42% (16 of 38 patients).

Other laboratory abnormalities occurring in the Investigations SOC in 10% of more of patients during any IPI-504 treatment were aspartate aminotransferase increased (18% vs 0% in the placebo group), blood alkaline phosphatase increased (13% vs 0% in the placebo group) alanine aminotransferase increased (11% vs 0% in the placebo group), and haemoglobin decreased (11% vs 0% in the placebo group).

Most adverse events in the Investigations SOC were assessed as treatment-related. Overall, 21 (55%) of the 38 patients who received IPI-504 experienced a treatment-related event in this SOC. All occurrences of urine colour abnormal, aspartate aminotransferase increased, blood alkaline phosphatase increased, and alanine aminotransferase increased were assessed as treatment related.

The majority of TEAEs in the Investigations SOC were Grade 1 or 2 in severity. Overall, 8 (21%) of the 38 patients who received IPI-504 had Grade 3 (4 patients, 11%) or Grade 4 (4 patients, 11%) events in the Investigations SOC. None of the patients in the placebo group experienced ≥Grade 3 events in the Investigations SOC during double-blind treatment. No Grade 5 events were reported.

Grade 3 or 4 events during IPI-504 treatment in the Investigations SOC included aspartate aminotransferase increased (4 patients, 11%), blood alkaline phosphatase increased (3 patients, 8%), alanine aminotransferase increased (2 patients, 5%), and lipase increased (2 patients, 5%). Two patients (Patients 001-004 and 001-014) discontinued from treatment due to a Grade 4

aspartate aminotransferase increased; no other discontinuations were reported for events in the Investigations SOC.

A more detailed discussion of liver enzyme elevations based on review of laboratory data is provided in Section 12.4.2.

12.2.3.4. Metabolism and Nutrition Disorders

Disorders of metabolism and nutrition occurred in 16 (50%) of 32 IPI-504 patients compared with 3 (20%) of 15 placebo patients during the double-blind period. Across all IPI-504 treatment, 20 (53%) of 38 patients experienced an event in this SOC.

The most commonly occurring metabolism and nutrition disorder (i.e., occurring in >20% of IPI-504 patients) during double-blind therapy was anorexia in 28% and 20% of patients in the IPI-504 and placebo groups, respectively. All other events in this SOC occurred with incidence <10% of IPI-504 patients. Anorexia was assessed as treatment-related in 7 (18%) of the 38 patients who received treatment with IPI-504 compared with 1 (7%) of the 15 patients during treatment with placebo.

Overall, 6 (16%) of the 38 patients who received IPI-504 had a ≥Grade 3 metabolism and nutrition disorders. During treatment with placebo in the double-blind period, 1 patient (7%) had a ≥Grade 3 event in this SOC.

Grade 3 or 4 events in this SOC during any IPI-504 treatment included dehydration (2 patients, 5%), hyperglycaemia (1 patient, 3%), anorexia (1 patient, 3%), diabetic ketoacidosis (1 patient, 3%), hyperuricaemia (1 patient, 3%), and hypokalaemia (1 patient, 3%). In the placebo group, Grade 3 hypercalcaemia, hyperglycaemia, and hypernatraemia occurred in 1 patient (7%).

Patient 066-001 in the IPI-504 treatment group experienced metabolic acidosis; the event was reported as a cause of death in this patient; a narrative is provided in Section 12.3.3.1.

12.2.3.5. Musculoskeletal and Connective Tissue Disorders

Musculoskeletal and connective tissue disorders occurred in 12 (38%) of 32 patients in the IPI-504 group compared with 1 (7%) of 15 patients in the placebo group during double-blind treatment. Across all IPI-504 treatment, 17 (45%) of 38 patients experienced at least 1 musculoskeletal disorder.

The most commonly occurring events in this SOC across all IPI-504 treatment were myalgia (24% vs 0% in the placebo group), arthralgia (24% vs. 0% in the placebo group), and back pain (16% vs. 0% in the placebo group). All occurrences of myalgia and arthralgia and 1 report of back pain were assessed as treatment-related.

Reports of arthralgia and myalgia in 1 patient in the IPI-504 group (Patient 001-008) were assessed as Grade 3 in severity; all other events in this SOC were Grade 1 or 2 in severity. None of the musculoskeletal system events led to treatment discontinuation.

12.2.3.6. Nervous System Disorders

Nervous system disorders, primarily reports of headache, occurred in 12 (38%) of 32 patients in the IPI-504 group and 7 (47%) of 15 patients in the placebo group during the double-blind period; overall the incidence of nervous system disorders was 37% (14 patients) during treatment with IPI-504. Headache occurred during double-blind treatment in 11 (34%) and 3 (20%) patients in the IPI-504 and placebo groups, respectively. Across all IPI-504 treatment, 13 (34%) of the 38 patients experienced headache; in 11 patients (29%), the headache was assessed as treatment related.

The majority of nervous system disorders were Grade 1 or 2 in severity; 2 events, including migraine in 1 patient in the IPI-504 group and lethargy in 1 patient in the placebo group, were reported as Grade 3 in severity. No Grade 4 or 5 nervous system disorders were reported during the study and none of these events led to treatment discontinuation.

12.2.3.7. Renal and Urinary Disorders

Renal and urinary disorders occurred in 6 (19%) of 32 IPI-504 patients and in 1 (7%) of 15 placebo patients during double-blind treatment. Across all IPI-504 treatment, 10 (26%) of 38 patients experienced a renal or urinary disorder.

The most commonly occurring renal disorder was renal failure, including reports of acute prerenal failure, renal failure and renal failure acute, occurring in 6 (16%) of the 38 patients who received any IPI-504; none of the patients in the placebo group experienced renal failure.

Renal disorders were reported as treatment related in 5 (13%) of the 38 patients who received IPI-504; none of the patients in the placebo group had treatment-related renal disorders. Treatment-related renal disorders during IPI-504 treatment included 3 patients (8%) with renal failure and 1 patient each (3%) with chromaturia and nocturia.

Renal failure or acute renal failure was reported as Grade 3 or 4 in severity in 4 patients (11%) (Patients 001-004, 011-001, 024-001, and 053-004). In Patient 006-001, renal failure was reported as a cause of death; a narrative for this patient is provided in Section 12.3.3.1. In 4 of the 5 patients with ≥Grade 3 renal failure, GI disorders including nausea, vomiting or diarrhoea occurred concurrent with the renal failure, indicating that dehydration may have played a role in the development of renal failure.

12.2.3.8. Respiratory, Thoracic and Mediastinal Disorders

Respiratory disorders occurred in 5 (16%) of 32 IPI-504 patients and in 2 (13%) of 15 placebo patients during double-blind treatment. Across all IPI-504 treatment, 7 (18%) of 38 patients experienced a respiratory system disorder. None of these events were assessed as related to treatment with IPI-504.

The most commonly occurring event in this SOC was dyspnoea in 4 (11%) of the 38 patients who received any IPI-504; none of the patients in the placebo group experienced dyspnoea.

Two reports of dyspnoea, 1 in an IPI-504 patient during the double-blind period (Patient 001-014) and 1 in a patient during the open-label period who was randomized to placebo (Patient 024-001) were reported as Grade 3 in severity. No Grade 4 or 5 respiratory system disorders were reported during the study and none of these events led to treatment discontinuation.

12.2.3.9. All Other Body Systems

Adverse events in all other MedDRA SOC occurred in < 10% of patients during treatment with IPI-504.

A total of 7 (22%) of the 32 IPI-504 patients and 2 (13%) of the 15 placebo patients experienced cardiac disorders. The cardiac events in the IPI-504 group were generally Grade 1 or 2 and occurred in a single patient each. One patient suffered cardiorespiratory arrest and died (Patient 009-001) and 1 patient experienced myocardial infarction assessed as Grade 4 in severity. The only cardiac event occurring in more than 1 IPI-504 patient was sinus bradycardia [2 (6%) patients]; both events were Grade 1.

Other Grade 3, 4 or 5 events reported during treatment with IPI-504 in other body systems included 1 report each of reactive psychosis (Patient 001-014), sepsis (Patient 006-001), bacteraemia (Patient 020-002), hepatic failure (Patient 040-001), disseminated intravascular coagulation (Patient 066-001), and deep vein thrombosis, operative haemorrhage, and haematoma infection (Patient 001-011).

12.2.4. Listings of Adverse Events by Patient

A by-patient listing of all AEs is presented in Listing 16.2.7.1. A by-patient listing of all AEs assessed as CTCAE Grade 3 or higher is presented in Listing 16.2.7.2.

12.3. Deaths, Other Serious Adverse Events and Other Significant Adverse Events

12.3.1. Listings of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Table 14.3.2.1, Table 14.3.2.2, Table 14.3.2.3, Table 14.3.2.4 and Table 14.3.2.5 present by-patient listings for adverse events leading to withdrawal, dose reductions, and dose holds; patient deaths; and serious adverse events; respectively. Information on the survival status of patients during the follow-up phase is provided in Listing 16.2.6.3.

12.3.2. Narratives of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

Complete narrative summaries for all SAEs that occurred within 30 days of the last dose of study treatment and for withdrawals due to AEs are presented in Section 14.3.3.

12.3.3. Analysis of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

12.3.3.1. Deaths

Two patients died during the screening period prior to study drug initiation (Patients 005-001, 056-001). In addition, 11 patients died during the study, including 6 patients who died within 30 days after administration of the last study drug dose (Patients 006-001, 009-001, 024-001, 028-001, 040-001, and 066-001), and 5 patients who died more than 30 days after treatment (Patients 001-004, 008-001, 009-003, 020-002, and 029-001).

During the screening process, Patient 005-001 and Patient 056-001 died of rapid disease progression prior to randomization in the study.

Table 12-6 presents a listing of the 6 randomized patients who died within 30 days of the last dose of study treatment, including 4 patients randomized to IPI-504 who died following double-blind treatment, 1 patient randomized to placebo who died following treatment with IPI-504 in the open-label phase, and 1 patient randomized to placebo who died following double-blind treatment. Brief narratives for each of these deaths follow the table.

Table 12-6 Listing of Patient Deaths within 30 Days of the Last Dose of Study Treatment (ITT Population)

Pt ID (Age/Sex)	Medical and Disease History	No. of Doses/ Cycles[1]	Cause of Death (Reported AE)	Relation -ship	Relative Day[2]
Deaths Following Treatment with IPI-504					
006-001 (72 yo M)	5 yr Hx of GIST; Hx of MI, nephritis, hypertension and hypercholesterolemia	1/1 (DB)	Renal Failure	Possible[3]	+11
009-001 (74 yo M)	9 yr Hx of GIST; Hx of hypertension, GI hemorrhage, grand mal seizure, anemia, manic depression	2/1 (DB)	Cardiorespiratory Arrest	Possible	+2
024-001[4] (57 yo M)	8 yr Hx of GIST; Hx of hypertension, elevated LFTs, insomnia, dyspnea	4/1 (DB)[4] 5/2 (OL)	Disease Progression	Possible	+23
040-001 (64 yo M)	6 yr Hx of GIST; Hx of hypertension, hypothyroidism, gout, anemia	4/1 (DB)	Hepatic Failure	Probable	+2
066-001 (71 yo F)	10 yr Hx of GIST; Hx of hypertension, chronic renal failure, diabetes, depression, anemia, pancreatitis	2/1 (DB)	Disseminated Intravascular Coagulation, Metabolic Acidosis	Possible	+2
Deaths Following Treatment with Placebo					
028-001 (86 yo M)	8 yr Hx of GIST; Hx of hypertension, pulmonary embolism, depression, hypercholesterolemia, diabetes	15/5 (DB)	Disease Progression	None	+20

Note: F=female, Hx=history, LFT=liver function test, M=male, MI=myocardial infarction, yo=year old, yr=years

1 Data presented in parentheses represents the study period: DB=double-blind; OL=open-label

2 Days from last dose to death.

3 Relationship was reported as remote by the Investigator but was upgraded to possible by the Sponsor

4 Patient was randomized to placebo and died following open-label treatment with IPI-504

Source: Listing 16.2.4.4, Listing 16.2.4.5, Listing 16.2.4.6, Listing 16.2.5.1, Listing 16.2.7.1

Patient 006-001 (Renal Failure)

A 72 year old man with GIST diagnosed in May 2004 died of renal failure after receiving 1 dose of IPI-504. Relevant disease history included myocardial infarction and nephritis. The patient's baseline serum creatinine was 85 µmol/L (normal range 80 -125 µmol/L). One day after dose administration the patient was hospitalized for diarrhoea. In the following 3 days, creatinine ranged from 110 to 115 µmol/L. Diarrhoea resolved, however the planned IPI-504 dose was held due to renal insufficiency (creatinine reported at that time was 110 µmol/L). Grade 3 AST, Grade 1 ALT, and Grade 1 bilirubin were noted during hospitalization; renal insufficiency worsened to Grade 3 (creatinine 385 µmol/L on Day +6). Renal insufficiency was considered secondary to contrast media administration, dehydration, ascites and tumor lysis syndrome. Creatinine remained elevated reaching a maximum of 473 µmol/L 8 days post-treatment. Positive blood cultures at that time indicated sepsis. Dialysis was

initiated, but was poorly tolerated. The patient subsequently died 11 days after receiving a single dose of IPI-504.

Patient 009-001 (Cardiopulmonary arrest)

A 74 year old man with GIST diagnosed in November 1999 died 6 days after receiving 2 doses of IPI-504. Relevant disease history included grand mal seizure, hypertension, GI hemorrhage, and multiple surgeries, including resection of liver segments 5 and 6. After the second dose of IPI-504, the patient experienced worsening nausea, mild diarrhoea, weakness and restlessness. The patient was subsequently found unresponsive, and was transported to the hospital. Resuscitation was unsuccessful. The patient was pronounced dead; cause of death was reported as cardiopulmonary arrest.

Patient 040-001 (Hepatic Failure)

A 64 year old man with GIST diagnosed in May 2003 died of hepatic failure 2 days after receiving his fourth dose IPI-504. Hepatic failure occurred after receiving IPI-504 in the setting of Grade 3 transaminitis. Relevant disease history included liver metastases with prior hepatic resection. Baseline ALT and AST were 48 and 47 U/L, respectively (ULN of 53 and 47 U/L, respectively). Prior to Dose 4, Grade 3 ALT and AST were noted (431 and 582 U/L, respectively), however IPI-504 was administered in violation of the protocol. Two days after receiving Dose 4, the patient presented with nausea and purple emesis. Liver function tests included Grade 4 AST (1257 U/L), Grade 3 ALT (357 U/L), Grade 3 alkaline phosphatase (829 U/L), normal bilirubin and prolonged prothrombin time. The patient was diagnosed with sepsis and diabetic ketoacidosis secondary to increased lactic acid. While hospitalized, AST and ALT worsened; bilirubin remained normal. Renal function declined and respiratory distress was noted. The patient's status deteriorated leading to death; cause of death was reported as liver failure. The patient's death summary attributed death to cardiac arrest due to severe metabolic acidosis secondary to multiorgan failure.

Patient 066-001 (Disseminated Intravascular Coagulation and Metabolic Acidosis)

A 71 year old woman with GIST diagnosed in February 1999 died of metabolic acidosis and disseminated intravascular coagulation (DIC) 2 days after receiving her second dose of IPI-504. Relevant disease history included recurrences in the liver with left hepatectomy, chronic renal failure, diabetes, and pancreatitis. One day after receiving IPI-504, the patient presented with nausea, vomiting, diarrhoea, and abdominal pain. Renal function was worsening in the setting of dehydration. While hospitalized, AST increased to Grade 3; ALT was Grade 1, alkaline phosphatase and bilirubin were within normal ranges. Lactic acidosis and acute kidney injury, secondary to vomiting, were diagnosed. The patient experienced melena and subsequently became hypotensive and unresponsive with respiratory distress. Lactic acidosis continued. Laboratory results showed worsening AST and ALT to Grade 4 with bilirubin within normal limits. Blood gas results showed worsening acidosis. The patient required resuscitation twice and active bleeding was noted. Disseminated intravascular coagulation was subsequently diagnosed, and the patient was determined to be critically ill due to ischemic bowel or

rapid turnover in necrosis of large gastrointestinal mass. Comfort measures were administered and the patient subsequently died; cause of death was reported as metabolic acidosis and DIC.

Patient 024-001 (Disease Progression)

A 57 year old man diagnosed with GIST in January 2001 died of disease progression approximately 3 weeks after treatment. The patient had received 4 doses of placebo during the double-blind period and entered the open-label period following disease progression and received 5 doses of IPI-504 prior to study closure. Four days later, the patient was hospitalized with Grade 3 abdominal pain and acute renal failure secondary to nausea and dehydration. Scans showed increasingly significant tumor burden, and the patient was offered comfort care. He was discharged to hospice, where he subsequently died due to disease progression. The death due to disease progression was reported as possibly related to study treatment based on the clinical deterioration after discontinuation of IPI-504, rather than on direct drug toxicity.

Pt 028-001 (Disease Progression)

An 86 year old man diagnosed with GIST in August 2001 died 20 days post-treatment of disease progression after receiving 15 doses of placebo.

Four of the 6 patients who died on study were 70 years of age or older and 5 of the 6 were male. All 6 patients had a history of GIST for 5 or more years with 4 patients having had GIST for 8 or more years. Among the 5 patients who died who received IPI-504, 3 had received only 1 or 2 doses of IPI-504, 1 had received 4 doses and 1 had received 5 doses of IPI-504.

Review of the 4 fatal cases not associated with disease progression indicated that although the patients had different reported causes of death, there was a similar clinical pattern among these cases: IPI-504 dose of 400 mg/m^2 (4 of 4 patients), death within 2 days post-dose (3 of 4), prior hepatic resection (3 of 4), and hepatotoxicity (2 of 4).

Unblinded review of patient deaths in Study IPI-504-06 in April 2009 by the IDMC revealed an imbalance of deaths in the IPI-504 treatment group (4 deaths) compared with the placebo treatment group (0 deaths). Based on these findings, the IDMC recommended stopping Study IPI-504-06; Infinity concurred and ended the trial prematurely on 15 April 2009.

Among the 5 patients who died more than 30 days post-treatment, disease progression was reported as the cause of death in all 5 patients (Patients 001-004, 008-001, 009-003, 020-002, and 029-001 (Listing 16.2.6.3).

12.3.3.2. Other Serious Adverse Events

Table 12-7 presents treatment-emergent SAEs reported in 2 or more patients by MedDRA SOC and preferred term.

Table 12-7 Treatment-Emergent Serious Adverse Events Occurring in Two or More Patients by MedDRA SOC and Preferred Term, and by Study Period (ITT Population)

MedDRA SOC Preferred Term	Patients Receiving Treatment during the DB Period Placebo (N=15) n (%)	Patients Receiving Treatment during the DB Period IPI-504 (N=32) n (%)	Patients Receiving IPI-504 (DB+OL) (N=38) n (%)
At Least 1 Treatment-Emergent SAE	***5 (33.3)***	***13 (40.6)***	***16 (42.1)***
Gastrointestinal Disorders	*0*	*10 (31.3)*	*12 (31.6)*
Diarrhoea	0	6 (18.8)	7 (18.4)
Vomiting	0	3 (9.4)	4 (10.5)
Abdominal Pain	0	2 (6.3)	3 (7.9)
Nausea	0	2 (6.3)	3 (7.9)
Renal and Urinary Disorders	*1 (6.7)*	*4 (12.5)*	*6 (15.8)*
Renal Failure[1]	0	4 (12.5)	6 (15.8)
Metabolism and Nutrition Disorders	*1 (6.7)*	*3 (9.4)*	*4 (10.5)*
Metabolic Acidosis/Ketoacidosis[2]	0	2 (6.3)	2 (5.3)
Hyperglycaemia	1 (6.7)	1 (3.1)	1 (2.6)
Investigations	*0*	*2 (6.3)*	*3 (7.9)*
Aspartate Aminotransferase Increased	0	2 (6.3)	3 (7.9)
Blood Alkaline Phosphatase Increased	0	2 (6.3)	3 (7.9)
Alanine Aminotransferase Increased	0	1 (3.1)	2 (5.3)
Vascular Disorders	*0*	*1 (3.1)*	*2 (5.3)*
Deep Vein Thrombosis	0	1 (3.1)	2 (5.3)

1 Renal failure combines the preferred terms renal failure acute, acute prerenal failure, and renal failure.

2 Metabolic Acidosis/Ketoacidosis combines the preferred terms of metabolic acidosis and diabetic ketoacidosis.

Source: Table 14.3.1.10

During the double-blind period, 13 (41%) of 32 patients in the IPI-504 group experienced at least 1 SAE compared with 5 (33%) of 15 patients in the placebo group. Overall, 16 (42%) of the 38 patients who received IPI-504 in either the double-blind or open-label periods experienced at least 1 SAE during the study.

The most commonly occurring types of SAEs in the IPI-504 group were GI events, including diarrhoea, vomiting, abdominal pain, and nausea; none of the patients in the placebo group had serious GI events. Overall, the incidence of serious diarrhoea, vomiting, abdominal pain and nausea among IPI-treated patients at any time during the study was 18%, 11%, 8% and 8%, respectively.

Renal failure was reported as a SAE in 4 IPI-504 patients during the double-blind period and in 2 additional patients during the open-label period for an overall incidence of 16%. In 3 patients (8%), the serious renal failure was assessed as treatment-related. In most cases, renal failure occurred in patients with nausea, vomiting, and diarrhoea, and was likely associated with dehydration. Renal failure was reported as the cause of death in 1 of these patients (Patient 006-001; see Section 12.3.3.1). Renal failure was not reported as a serious event in any patient during treatment with placebo.

Metabolism and nutrition disorders were reported as SAEs in 4 patients (11%) during treatment with IPI-504, and included metabolic acidosis, diabetic ketoacidosis, dehydration and hyperglycemia in 1 patient each. Hyperglycaemia was reported as an SAE in 1 patient during treatment with placebo.

Other SAEs occurring among IPI-504-treated patients included aspartate aminotransferase increased (3 patients, 8%), blood alkaline phosphatase increased (3 patients, 8%), alanine aminotransferase increased (2 patients, 5%), and deep vein thrombosis (2 patients, 5%). A discussion of liver function test results is provided in Section 12.4.2.

Table 12-8 presents a summary of treatment-related SAEs reported in 2 or more patients by MedDRA SOC and preferred term.

Table 12-8 Treatment-Related Serious Adverse Events Occurring in Two or More Patients by MedDRA SOC and Preferred Term, and by Study Period (ITT Population)

MedDRA SOC Preferred Term	Patients Receiving Treatment during the DB Period Placebo (N=15) n (%)	Patients Receiving Treatment during the DB Period IPI-504 (N=32) n (%)	Patients Receiving IPI-504 (DB+OL) (N=38) n (%)
At Least 1 Treatment-Emergent SAE	***0***	***10 (31.3)***	***12 (31.6)***
Gastrointestinal Disorders	*0*	*7 (21.9)*	*8 (21.1)*
Diarrhoea	0	6 (18.8)	7 (18.4)
Vomiting	0	3 (9.4)	4 (10.5)
Nausea	0	2 (6.3)	3 (7.9)
Renal and Urinary Disorders	*0*	*3 (9.4)*	*3 (7.9)*
Renal Failure[1]	0	3 (9.4)	3 (7.9)
Metabolism and Nutrition Disorders	*0*	*3 (9.4)*	*3 (7.9)*
Metabolic Acidosis/Ketoacidosis[2]	0	2 (6.3)	2 (5.3)
Hyperglycaemia	0	1 (3.1)	1 (2.6)
Investigations	*0*	*2 (6.3)*	*3 (7.9)*
Aspartate Aminotransferase Increased	0	2 (6.3)	3 (7.9)
Blood Alkaline Phosphatase Increased	0	2 (6.3)	3 (7.9)
Alanine Aminotransferase Increased	0	1 (3.1)	2 (5.3)

1 Renal failure combines the preferred terms renal failure acute, acute prerenal failure, and renal failure.

2 Metabolic Acidosis/Ketoacidosis combines the preferred terms of metabolic acidosis and diabetic ketoacidosis.

Source: Table 14.3.1.14

During the double-blind period, 10 (31%) of 32 patients in the IPI-504 group experienced at least 1 treatment-related SAE compared with 0 (0%) of 15 patients in the placebo group. Overall, 12 (32%) of the 38 patients who received IPI-504 in either the double-blind or open-label periods experienced at least 1 treatment-related SAE during the study. The most commonly occurring types of treatment-related SAEs were GI events, including diarrhoea, vomiting, and nausea. All serious reports of metabolic acidosis/ketoacidosis, aspartate aminotransferase increased, and blood alkaline phosphatase increased were reported as related to IPI-504.

12.3.3.3. Other Significant Adverse Events

Adverse Events Leading to Treatment Withdrawal

Table 12-9 summarizes patients who discontinued from study treatment due to adverse events.

Table 12-9 Listing of Patients Discontinued from the Study Due to Adverse Events (ITT Population)

Pt ID	Preferred Term	Study Period	Relative Day[1]	CTCAE Grade	Relation	SAE	Outcome
			During Treatment with IPI-504				
001-004[2]	Aspartate Aminotransferase Increased	OL[2]	20	4	Definite	Yes	Change in Grade
001-014	Aspartate Aminotransferase Increased	DB	33	4	Definite	Yes	Change in Grade
006-001	Renal Failure	DB	3	5	Possible[3]	Yes	Fatal
009-001	Cardio-Respiratory Arrest	DB	5	5	Possible	Yes	Fatal
011-001	Myocardial Infarction	DB	16	4	Probable	Yes	Resolved
	Renal Failure	DB	16	4	Probable	Yes	Resolved
	Vomiting	DB	16	4	Probable	Yes	Resolved
020-002	Gastrointestinal Fistula	DB	10	3	Remote	Yes	Resolved w Sequelae
040-001	Hepatic Failure	DB	13	5	Probable	Yes	Fatal
066-001	Disseminated Intravascular Coagulation	DB	6	5	Possible	Yes	Fatal
	Metabolic Acidosis	DB	6	5	Possible	Yes	Fatal
			During Treatment with Placebo				
005-002	Oedema Peripheral	DB	32	3	None	Yes	Ongoing

1 Day relative to the first dose of IPI-504 or placebo, as applicable.

2 Patient was randomized to placebo and discontinued following open-label treatment with IPI-504

3 Relationship was reported as remote by the Investigator but was upgraded to possible by the Sponsor

Source: Table 14.3.2.1.

Overall, a total of 9 patients had TEAEs leading to discontinuation from the study, including 8 (21%) of 38 patients treated with IPI-504 (including 1 patient assigned to placebo during the

double-blind period) and 1 (7%) of 15 patients during treatment with placebo. All events reported for the IPI-504 group were assessed by the Investigator as CTCAE Grade ≥ 3 and possibly, probably, or definitely related to study drug. All TEAEs leading to discontinuation were also reported as SAEs.

Events leading to discontinuation of IPI-504 were aspartate aminotransferase increased (2 patients, 5%), renal failure (2 patients, 5%), cardiorespiratory arrest (1 patient, 3%), myocardial infarction (1 patient, 3%), vomiting (1 patient, 3%), gastrointestinal fistula (1 patient, 3%), hepatic failure (1 patient, 3%), disseminated intravascular coagulation (1 patient, 3%), and metabolic acidosis (1 patient, 3%).

Adverse Events Leading to Dose Modifications

Dose modifications due to AEs, including dose reductions and doses held, were more common in the IPI-504 group compared with the placebo group. Overall, 11 (29%) of 38 patients receiving IPI-504 (including 1 open label patient previously assigned to the placebo group during double-blind) had at least one dose held or had a dose reduction due to TEAEs compared with 3 (20%) of 15 patients during treatment with placebo.

Commonly occurring TEAEs that led to dose modifications in IPI-504-treated patients included diarrhoea (5 patients, 13%), increased AST (4 patients, 11%), increased alkaline phosphatase (3 patients, 8%), renal failure (3 patients, 8%), nausea (2 patients, 5%) and vomiting (2 patients, 5%).

12.4. Clinical Laboratory Evaluation

12.4.1. Listings of Individual Laboratory Measurements by Patient and Each Abnormal Laboratory Value

By-patient listings of hematology and clinical chemistry results, including identification of laboratory values outside the normal range, are presented in Listing 16.2.8.1 (Hematology), Listing 16.2.8.2 (Clinical Chemistry), and Listing 16.2.8.3 (Other Laboratory Tests).

12.4.2. Evaluation of Each Laboratory Parameter

Hematology and coagulation data are summarized in Table 14.3.4.1 (CTCAE Grade ≥3, by patient), Table 14.3.6.1 (Change from baseline, Double-blind), Table 14.3.6.3 (Change from baseline, patients treated with IPI-504), Table 14.3.6.5 (CTCAE grades by visit), and Table 14.3.6.7 (Shift Tables by Highest CTCAE Grade).

Clinical chemistry data are summarized in Table 14.3.4.2 (CTCAE Grade ≥3, by patient), Table 14.3.6.2 (Change from baseline, Double-blind), Table 14.3.6.4 (Change from baseline, patients treated with IPI-504), Table 14.3.6.6 (CTCAE grades by visit), and Table 14.3.6.8 (Shift Tables by Highest CTCAE Grade).

12.4.2.1. Laboratory Values over Time

Hematology

Table 12-10 presents actual values and changes from baseline over time for white blood cell count, hemoglobin, and platelet count during the first 2 treatment cycles; thereafter there were too few patients in the analysis; complete results are provided for all visits and all hematology parameters in Table 14.3.6.1.

Table 12-10 Selected Hematology Parameters: Descriptive Statistics for Actual Values and Changes from Baseline Over Time during the First Two Cycles of Treatment during the Double-blind Period (ITT Population)

		Patients Receiving Treatment during the DB Period			
		Placebo (N=15) n (%)		IPI-504 (N=32) n (%)	
Visit	Statistic	Actual Values	Change from BL	Actual Values	Change from BL
		White Blood Cell Count ($x10^9$/L)			
Cycle 1 Dose 1	N	14		25	
	Mean (SD)	9.5 (4.10)		7.5 (3.33)	
	Min, Max	3.8, 19.4		2.8, 14.8	
Cycle 1 Dose 3	N	15	15	26	26
	Mean (SD)	10.3 (5.80)	0.8 (4.09)	9.1 (5.09)	2.0 (2.94)
	Min, Max	3.6, 26.21	-4.4, 14.4	3.6, 23.2	-1.3, 10.9
Cycle 2 Dose 1	N	10	10	19	19
	Mean (SD)	10.2 (4.20)	0.5 (1.93)	9.6 (5.81)	2.2 (3.54)
	Min, Max	4.9, 17.9	-2.6, 2.7	4.3, 27.3	-0.9, 14.5
Cycle 2 Dose 3	N	7	7	16	16
	Mean (SD)	9.3 (5.98)	0.7 (1.61)	10.6 (5.08)	3.0 (3.55)
	Min, Max	5.0, 21.9	-2.7, 2.5	4.9, 22.5	-0.0, 15.0
		Hemoglobin (g/L)			
Cycle 1 Dose 1	N	14		25	
	Mean (SD)	115.9 (16.16)		120.6 (16.50)	
	Min, Max	90, 140		94, 157	
Cycle 1 Dose 3	N	15	15	26	26
	Mean (SD)	113.6 (17.84)	-1.4 (4.88)	121.7 (16.60)	0.8 (6.06)
	Min, Max	87, 144	-9, 9	94, 169	-11, 13
Cycle 2 Dose 1	N	10	10	19	19
	Mean (SD)	115.4 (20.19)	-2.4 (10.49)	125.3 (17.53)	3.4 (9.22)
	Min, Max	88, 156	-23, 16	97,169	-11, 19
Cycle 2 Dose 3	N	7	7	16	16
	Mean (SD)	120.7 (19.82)	2.3 (8.28)	125.4 (14.68)	1.4 (14.40)
	Min, Max	101, 154	-11, 14	108, 162	-30, 27

		Patients Receiving Treatment during the DB Period			
		Placebo (N=15) n (%)		IPI-504 (N=32) n (%)	
Visit	**Statistic**	**Actual Values**	**Change from BL**	**Actual Values**	**Change from BL**
		Platelet Count ($x10^9$/L)			
Cycle 1 Dose 1	N	14		25	
	Mean (SD)	344.6 (151.25)		313.7 (151.08)	
	Min, Max	161, 719		130, 569	
Cycle 1 Dose 3	N	15	15	26	26
	Mean (SD)	310.3 (136.28)	-17.1 (67.16)	343.1 (173.21)	25.8 (66.33)
	Min, Max	134, 617	-122, 158	89, 722	-116, 218
Cycle 2 Dose 1	N	10	10	19	19
	Mean (SD)	307.9 (134.77)	-17.6 (96.42)	426.3 (230.08)	98.4 (118.77)
	Min, Max	155, 525	-194, 122	196, 851	-129, 343
Cycle 2 Dose 3	N	7	7	16	16
	Mean (SD)	235.1 (72.91)	-20.0 (70.43)	366.1 (191.50)	17.9 (108.63)
	Min, Max	157, 362	-158, 55	177, 799	-132, 344

Note: Doses 1 and 3 were selected as they included the largest number of patients within each of the first 2 cycles.
Source: Table 14.3.6.1.

Mean changes over time for white blood cell count, hemoglobin, and platelet count were small at all assessments through Cycle 2 and were similar in the IPI-504 and placebo groups. Results were similar when assessed across all 38 patients who received IPI-504 (Table 14.3.6.3). Mean changes over time for other hematology parameters also were small and the changes were similar in the active and placebo groups.

Coagulation Parameters

Mean changes over time for coagulation parameters, including PTT, PT, and INR are presented in Table 14.3.6.1 (double-blind period) and Table 14.3.6.3 (across all IPI-504 treatment). Review of the data showed no apparent differences between the treatment groups for changes from baseline for any of these parameters; however, the number of patients in each post-baseline analysis was small making evaluation of these data difficult to interpret.

Clinical Chemistry

Table 12-11 presents actual values and changes from baseline over time for ALT, AST, total bilirubin, serum creatinine and bicarbonate, during the first 2 treatment cycles; thereafter there were too few patients in the analysis; complete results are provided for all visits and all clinical chemistry parameters in Table 14.3.6.2.

Table 12-11 Selected Chemistry Parameters: Descriptive Statistics for Actual Values and Changes from Baseline Over Time during the First Two Cycles of Treatment during the Double-blind Period (ITT Population)

		Patients Receiving Treatment during the DB Period			
		Placebo (N=15) n (%)		IPI-504 (N=32) n (%)	
Visit	Statistic	Actual Values	Change from BL	Actual Values	Change from BL
		ALT (U/L)			
Cycle 1 Dose 1	N	14		25	
	Mean (SD)	25.1 (18.03)		24.0 (14.09)	
	Min, Max	9, 80		4, 61	
Cycle 1 Dose 4	N	14	14	26	26
	Mean (SD)	21.2 (8.95)	-3.4 (15.65)	54.9 (82.89)	30.2 (76.16)
	Min, Max	10, 44	-54, 13	5, 431	-21, 383
Cycle 2 Dose 1	N	9	9	19	19
	Mean (SD)	26.4 (10.68)	-3.8 (13.06)	28.0 (21.31)	5.9 (18.53)
	Min, Max	13, 44	-36, 6	5, 99	-18, 58
Cycle 2 Dose 4	N	8	8	14	14
	Mean (SD)	29.4 (19.12)	5.0 (16.31)	28.7 (14.16)	7.4 (11.63)
	Min, Max	12, 64	-13, 40	6, 55	-24, 27
		AST (U/L)			
Cycle 1 Dose 1	N	14		25	
	Mean (SD)	33.5 (18.86)		30.1 (14.54)	
	Min, Max	15, 67		14, 78	
Cycle 1 Dose 4	N	14	14	26	26
	Mean (SD)	30.4 (8.84)	-1.8 (11.83)	62.5 (109.94)	35.3 (105.70)
	Min, Max	19, 48	-28, 11	15, 582	-13, 540
Cycle 2 Dose 1	N	9	9	19	19
	Mean (SD)	38.4 (18.93)	-0.4 (11.91)	30.2 (19.53)	5.7 (16.12)
	Min, Max	22, 72	-28, 17	15, 85	-8, 56
Cycle 2 Dose 4	N	8	8	14	14
	Mean (SD)	43.8 (28.96)	8.1 (24.03)	29.4 (9.89)	5.6 (8.51)
	Min, Max	22, 107	-30, 56	15, 50	-15, 21

		Patients Receiving Treatment during the DB Period			
		Placebo (N=15) n (%)		IPI-504 (N=32) n (%)	
Visit	**Statistic**	**Actual Values**	**Change from BL**	**Actual Values**	**Change from BL**
		Total Bilirubin (µmol/L)			
Cycle 1 Dose 1	N	12		25	
	Mean (SD)	7.8 (3.31)		9.6 (4.63)	
	Min, Max	3, 15		3, 21	
Cycle 1 Dose 4	N	14	14	26	26
	Mean (SD)	7.2 (2.19)	0.2 (2.15)	10.5 (4.91)	1.9 (4.57)
	Min, Max	2, 10	-5, 4	3, 22	-5, 15
Cycle 2 Dose 1	N	9	9	19	19
	Mean (SD)	7.4 (1.74)	-0.1 (2.42)	9.6 (4.28)	1.0 (2.52)
	Min, Max	4, 10	-5, 2	3, 19	-4, 7
Cycle 2 Dose 4	N	8	8	14	14
	Mean (SD)	7.4 (1.77)	-0.3 (2.31)	9.4 (4.38)	1.3 (3.10)
	Min, Max	4, 10	-5, 2	5, 22	-2, 10
		Creatinine (µmol/L)			
Cycle 1 Dose 1	N	14		24	
	Mean (SD)	91.4 (22.83)		78.9 (21.99)	
	Min, Max	62, 155		53, 141	
Cycle 1 Dose 4	N	14	14	26	26
	Mean (SD)	89.5 (15.92)	1.4 (13.32)	85.4 (24.97)	6.2 (13.70)
	Min, Max	62, 111	-22, 24	48, 159	-18, 36
Cycle 2 Dose 1	N	10	10	19	19
	Mean (SD)	83.2 (15.64)	-1.9 (11.75)	82.5 (27.41)	1.3 (14.25)
	Min, Max	63, 115	-17, 18	44, 159	-18, 44
Cycle 2 Dose 4	N	8	8	14	14
	Mean (SD)	81.0 (11.16)	-3.3 (13.74)	91.1 (29.80)	6.8 (16.47)
	Min, Max	62, 97	-28, 17	53, 168	-27, 45

		Patients Receiving Treatment during the DB Period			
		Placebo (N=15) n (%)		IPI-504 (N=32) n (%)	
Visit	**Statistic**	**Actual Values**	**Change from BL**	**Actual Values**	**Change from BL**
		Bicarbonate (mmol/L)			
Cycle 1 Dose 1	N	12		22	
	Mean (SD)	26.94 (2.790)		26.42 (2.762)	
	Min, Max	21.0,31.0		22.0,32.0	
Cycle 1 Dose 4	N	12	12	24	24
	Mean (SD)	27.49 (2.238)	0.22 (2.548)	26.25 (2.420)	-0.50 (1.971)
	Min, Max	23.0,31.0	-5.0,5.0	21.0,32.0	-4.2,2.0
Cycle 2 Dose 1	N	10	10	19	19
	Mean (SD)	26.00 (2.789)	-1.30 (3.057)	26.34 (2.190)	0.02 (2.045)
	Min, Max	22.0,30.0	-4.0,6.0	23.0,30.0	-4.5,3.0
Cycle 2 Dose 4	N	8	8	14	14
	Mean (SD)	26.75 (3.412)	-0.63 (2.066)	25.81 (2.677)	-0.10 (2.662)
	Min, Max	23.0,32.0	-5.0,2.0	20.0,31.0	-6.0,3.0

Source: Table 14.3.6.2.

Mean changes from pre-dose on C1D1 to C1D4 for ALT and AST were greater in the IPI-504 group (30.2 and 35.3 U/L, respectively) compared with the placebo group (-3.4 and -1.8 U/L, respectively). This is likely due to a single patient (Patient 040-001) who had changes from baseline of 383 and 540 U/L for ALT and AST, respectively, at the C1D4 visit. This patient incorrectly received IPI-504 in the setting of Grade 3 AST and subsequently died of hepatic failure. Detailed information on patients with clinically significant elevations in liver function tests is provided in Section 12.4.2.3. By C2D4, mean changes from C1D1 in the IPI-504 and placebo groups were similar for ALT (7.4 and 5.0 U/L in the IPI-504 and placebo groups, respectively) and AST (5.6 and 8.1 U/L, respectively). Mean changes from C1D1 in total bilirubin were slightly greater in the IPI-504 group compared with the placebo group to C1D4 and C2D4; however most patients in both groups had total bilirubin values within or just outside the normal range at all time points assessed.

Mean changes from C1D1 to C1D4 and C2D4 in alkaline phosphatase were greater in the IPI-504 group (107.8 and 69.0 U/L, respectively) compared with the placebo group (4.7 and 8.5 U/L, respectively) (Table 14.3.6.2); this appeared to be due to several patients (Patients 001-014, 001-016, 029-001 and 053-004) (see Section 12.4.2.3).

Mean changes in serum creatinine from C1D1 to C1D4 and C2D4 were 6.2 and 6.8 µmol/L, respectively, in the IPI-504 group and 1.4 and -3.3 µmol/L, respectively, in the placebo group. For urea nitrogen, mean changes from C1D1 to C1D4 and C2D4 were 0.3 and 0.8 mmol/L, respectively, in the IPI-504 group and -0.4 and 0.3 mmol/L, respectively, in the placebo group (Table 14.3.6.2).

For serum bicarbonate (CO_2), mean changes from baseline to C1D4 were -0.50 and 0.22 mmol/L in the IPI-504 and placebo groups, respectively, and to C2D4 were -0.10 and

-0.63 mmol/L, respectively. Mean changes from C1D1 to C1D4 and C2D4 were similar between the IPI-504 and placebo groups for sodium, potassium, chloride, calcium, magnesium and phosphate (Table 14.3.6.2).

12.4.2.2. Individual Patient Changes

Hematology and Coagulation Parameters

Shift analyses from baseline CTCAE grade to maximum CTCAE grade on study are summarized for hematology and coagulation parameters in Table 14.3.6.7. A summary of shifts to Grade 3 or 4 values for these parameters is provided in Table 12-12.

Table 12-12 Hematology and Coagulation Shifts to Grade 3 or 4 Abnormalities Based on the Maximum Post-baseline Value (ITT Population)

	Patients Receiving Treatment during the DB Period		Patients Receiving IPI-504
Parameter	**Placebo (N=15) n/N[1] (%)**	**IPI-504 (N=32) n/N[1] (%)**	**(DB+OL) (N=38) n/N[1] (%)**
Hemoglobin	0/15	1/29 (3.4)	2/35 (5.7)
White blood cell count	0/15	0/29	0/35
Lymphocytes	2/15 (13.3)	3/29 (10.3)	5/35 (14.3)
Neutrophils	0/15	0/29	0/35
Platelets	0/15	0/29	0/35
Partial thromboplastin time (PTT)	1/8 (12.5)	3/14 (21.4)	4/19 (21.1)
International Normalized Ratio (INR)	1/5 (20.0)	0/12	0/14

1 Number of patients with shift to Grade 3 or 4 divided by the number of patients with baseline and post-baseline results.
Source: Table 14.3.6.7.

Shifts to CTCAE Grade 3 or 4 hematologic abnormalities were uncommon during the study and the incidence in the proportion of patients with shifts was similar in the IPI-504 and placebo groups. A higher proportion of patients in the IPI-504 group had a shift to Grade 3 or 4 PTT (21%) compared with patients in the placebo group (13%); however, the number of patients with data included in the analysis was small. For INR, none of the 12 patients in the IPI-504 group who had baseline and post-baseline results for this parameter had a shift to a Grade 3 or 4 value compared with 1 (20%) of 5 patients in the placebo group.

A discussion of patients with Grade 3 or 4 abnormalities in hemoglobin and PTT is provided in Section 12.4.2.3.

Clinical Chemistry

Shift analyses from baseline CTCAE grade to maximum CTCAE grade on study are summarized for clinical chemistry parameters in Table 14.3.6.8. A summary of shifts to Grade 3 or 4 values for these parameters is provided in Table 12-13.

Table 12-13 Clinical Chemistry Shifts to Grade 3 or 4 Abnormalities Based on the Maximum Post-baseline Value (ITT Population)

Parameter	Patients Receiving Treatment during the DB Period: Placebo (N=15) n/N[1] (%)	Patients Receiving Treatment during the DB Period: IPI-504 (N=32) n/N[1] (%)	Patients Receiving IPI-504 (DB+OL) (N=38) n/N[1] (%)
AST	0/15	5/32 (15.6)	6/37 (16.2)
ALT	0/15	3/32 (9.4)	4/37 (10.8)
Alkaline Phosphatase	0/15	5/32 (15.6)	5/37 (13.5)
Total Bilirubin	0/15	0/32	0/37
Albumin	0/15	1/32 (3.1)	1/37 (2.7)
Creatinine	0/15	1/32 (3.1)	1/37 (2.7)
Sodium (Hypernatremia)	0/15	0/32	0/37
Sodium (Hyponatremia)	0/15	3/32 (9.4)	5/37 (13.5)
Potassium (Hyperkalemia)	0/15	1/32 (3.1)	1/37 (2.7)
Potassium (Hypokalemia)	0/15	1/32 (3.1)	2/37 (5.4)
Calcium (Hypercalcemia)	1/15 (6.7)	0/32	0/37
Calcium (Hypocalcemia)	0/15	2/32 (6.3)	3/37 (8.1)
Glucose (Hyperglycemia)	1/15 (6.7)	4/31 (12.9)	4/36 (11.1)
Glucose (Hypoglycemia)	0/13	0/31	0/36
Phosphorus (Hypophosphatemia)	1/14 (7.1)	2/32 (6.3)	3/37 (8.1)
Serum Bicarbonate	0/15	2/29 (6.9)	2/34 (5.9)
Lipase	0/15	3/32 (9.4)	3/38 (7.9)
Amylase	0/15	1/32 (3.1)	1/38 (2.6)

1 Number of patients with shift to Grade 3 or 4 divided by the number of patients with baseline and post-baseline results.
Source: Table 14.3.6.8.

Serum ALT and AST levels were normal in the majority of patients at study entry (Table 14.3.6.8). Serum ALT at baseline was normal in 30 (94%) of 32 patients randomized to receive IPI-504 and in 14 (93%) of 15 patients randomized to receive placebo and serum AST levels were normal in 26 (81%) and 11 (73%) patients, respectively. Any shift from baseline in AST CTCAE grade to the highest grade during the double-blind treatment period was noted in 17 (53%) of the 32 patients randomized to IPI-504 compared with 5 (33%) of the 15 patients randomized to placebo. Similarly, 14 patients (44%) randomized to IPI-504 had shifts in ALT CTCAE grade during the double-blind period compared with 3 patients (20%) randomized to placebo. A higher proportion of patients who received IPI-504 during the study had shifts to Grade 3 or 4 AST, ALT, and alkaline phosphatase during the study compared with patients who received placebo. Overall, 6 (16%), 4 (11%) and 5 (14%) patients who received IPI-504 had a shift from baseline to a Grade 3 or 4 AST, ALT or alkaline phosphatase value, respectively; none of the patients who received placebo had shifts to Grade 3 or 4 liver function tests. In 3 patients in the IPI-504 treatment group (Patients 001-004, 001-014, and 040-001) shifts to Grade 4 AST were observed, and in 1 patient (Patient 066-001) shifts to Grade 4 ALT and AST were noted; no shifts to Grade 4 alkaline phosphatase were observed. No patients had Grade 3

or 4 elevations in total bilirubin. A discussion of patients with Grade 3 or 4 elevations in ALT, AST, and alkaline phosphatase is provided in Section 12.4.2.3.

The majority of patients in both treatment groups had normal serum creatinine results [28 (88%) patients in IPI-504 group and 14 (93%) patients in placebo group] at study baseline (Table 14.3.6.8). A total of 4 (13%) of the 32 patients randomized to IPI-504 had a shift to Grade 2 creatinine and 1 (3%) had a shift to Grade 3 creatinine during the double-blind treatment period, compared with no patients with Grade 2 or 3 creatinine results in the placebo group. A discussion of the patient with Grade 3 serum creatinine is provided in Section 12.4.2.3.

Shifts to Grade 3 or 4 low electrolyte values during the double-blind period, including sodium, potassium and calcium, were more common in the IPI-504 group compared with the placebo group, as were shifts to low serum bicarbonate (CO_2). Shifts to elevated levels of lipase also occurred more often in patients receiving IPI-504. Shifts to low phosphorus occurred in a similar proportion of patients in the two treatment groups.

12.4.2.3. Individual Clinically Significant Abnormalities

Hematology

A summary of hematology and coagulation parameter abnormalities reported as TEAEs is provided in Table 12-14.

Table 12-14 Hematologic and Coagulation Parameter Abnormalities Reported as TEAEs (ITT Population)

	Patients Receiving Treatment during the DB Period		Patients Receiving IPI-504 (DB+OL) (N=38) n (%)
MedDRA Preferred Term	Placebo (N=15) n (%)	IPI-504 (N=32) n (%)	
Haemoglobin Decreased	0	3 (9.4)	4 (10.5)
Anaemia	2 (13.3)	1 (3.1)	2 (5.3)
WBC Increased	0	2 (6.3)	2 (5.3)
Leukocytosis	1 (6.7)	0	0
Coagulation time prolonged	0	1 (3.1)	1 (2.6)

Source: Table 14.3.1.2.

Consistent with the laboratory data, very few patients in the study had TEAEs related to hematologic findings or coagulation parameters. The most common hematologic abnormality reported as an adverse event during the double-blind phase was haemoglobin decreased/anaemia reported in 4 (13%) patients in the IPI-504 group and 2 (13%) patients in the placebo group; WBC increased/leukocytosis occurred in 2 (6%) and 1 (7%) patients, respectively. All but one of these events were Grade 1 or 2 in severity; 1 patient, Patient 053-004 experienced Grade 3 haemoglobin decreased; the event was transient and resolved during continued treatment.

Table 14.3.4.1 presents a listing of all patients with ≥Grade 3 hematology test results. As summarized in Table 12-12, 2 patients in the IPI-504 group had treatment-emergent Grade 3 hemoglobin and 4 patients had treatment-emergent Grade 3 PTT.

Patient 053-004 in the IPI-504 group, with a baseline hemoglobin of 105 g/L (Grade 1; LLN 116 g/L), had a decrease in hemoglobin to 74 g/L 2 days after the C1D4 dose. At the end of study visit, the patient's hemoglobin had improved to 82 g/L (Grade 2). Decreased hemoglobin was reported as an adverse event in this patient; this patient also had Grade 3 acute renal failure on study.

Patient 001-011 who was randomized to placebo had a baseline hemoglobin level of 107 g/L (Grade 1; LLN 116 g/L). The patient experienced disease progression and elected to enter the open-label phase; hemoglobin at that time had decreased to 94 g/L (Grade 2). Approximately 2 weeks after starting IPI-504 treatment the patient's hemoglobin had decreased to 68 g/L (Grade 3); hemoglobin levels remained in the Grade 1 to 2 severity range throughout the rest of IPI-504 treatment. Anemia was reported as an adverse event in this patient.

Three patients had Grade 3 PTT elevations during double-blind treatment with IPI-504 and 1 had a Grade 3 PTT elevation during open-label treatment, all were in the setting of a more serious condition including myocardial infarction with renal failure in Patient 011-001, hepatic failure in Patient 040-001, disseminated intravascular coagulation in Patient 066-001 and renal failure and Grade 4 elevation in AST in Patient 001-004. One of these patients, Patient 011-001, was reported to have received heparin at the time of the PTT elevation.

Clinical Chemistry

Clinical chemistry abnormalities reported as treatment-emergent AEs are summarized in Table 12-15.

Table 12-15 Clinical Chemistry Abnormalities Reported as TEAEs (ITT Population)

	Patients Receiving Treatment during the DB Period		Patients Receiving IPI-504 (DB+OL) (N=38) n (%)
MedDRA Preferred Term	Placebo (N=15) n (%)	IPI-504 (N=32) n (%)	
Aspartate aminotransferase increased	0	5 (15.6)	7 (18.4)
Blood alkaline phosphatase increased	0	3 (9.4)	5 (13.2)
Alanine aminotransferase increased	0	2 (6.3)	4 (10.5)
Blood amylase increased	1 (6.7)	1 (3.1)	2 (5.3)
Lipase increased	0	2 (6.3)	2 (5.3)
Hyperuricaemia	0	0	2 (5.3)
Hypokalaemia	1 (6.7)	2 (6.3)	2 (5.3)
Hypomagnesaemia	0	2 (6.3)	2 (5.3)
Blood creatinine increased	2 (13.3)	0	1 (2.6)
Blood glucose increased	0	1 (3.1)	1 (2.6)
Blood potassium increased	0	1 (3.1)	1 (2.6)
Blood urea increased	0	0	1 (2.6)
Blood uric acid increased	0	0	1 (2.6)
Hyperglycaemia	1 (6.7)	1 (3.1)	1 (2.6)
Hyperkalaemia	0	1 (3.1)	1 (2.6)
Hyperphosphataemia	0	0	1 (2.6)
Hypoalbuminaemia	0	1 (3.1)	1 (2.6)
Hypernatraemia	1 (6.7)	0	0
Hypercalcaemia	1 (6.7)	0	0
Hypophosphataemia	1 (6.7)	0	0

Source: Table 14.3.1.2

The most common clinical chemistry abnormalities reported as TEAEs were aspartate aminotransferase increased, blood alkaline phosphatase increased, and alanine aminotransferase increased occurring in 7 (18%), 5 (13%), and 4 (11%) of the IPI-504-treated patients; none of the placebo-treated patients had these laboratory abnormalities reported as TEAEs. Four patients had Grade 3 or 4 elevations in AST and/or ALT reported as TEAEs (Patients 001-004, 001-14, 001-016 and 066-001). Two of these patients also had Grade 3 elevations in alkaline phosphatase reported (Patients 001-014 and 001-016); one additional patient (Patient 029-001) had a Grade 3 elevation in blood alkaline phosphatase reported as a TEAE.

A summary of patients with CTCAE Grade ≥3 clinical chemistry abnormalities based on laboratory data is provided in Table 14.3.4.2. Table 12-16, summarizes patients with at least one ≥ Grade 3 AST, ALT, alkaline phosphatase, or serum creatinine value during the study.

Table 12-16 Patients with Grade ≥3 Elevations in ALT, AST, Alkaline Phosphatase or Serum Creatinine (ITT Population)

Patient No. (Doses)	Parameter (Normal Range)	Baseline Value (Grade)	Maximum on Study Value (Grade, Day)	Last Value (Grade, Day)
001-004[1] (2 doses)	ALT U/L (7-52)	13 (G0)[2]	269 (G3; 5x ULN) 2 days post treatment	26 (G0) 16 days post treatment
	AST U/L (9-30)	19 (G0)[2]	901 (G4; 30x ULN) 2 days post treatment	28 (G0) 16 days post treatment
001-014 4 doses	ALT U/L (7-52)	17 (G0)	419 (G3; 8x ULN) 2 days post treatment	58 (G1) 7 days post treatment
	AST U/L (9-30)	15 (G0)	869 (G4; 29x ULN) 1 day post treatment	19 (G0) 7 days post treatment
	Alkaline Phosphatase U/L (36-118)	126 (G1)	715 (G3; 6x ULN) 4 days after Dose 2	298 (G2) 7 days post treatment
001-016 (2 doses)	AST U/L (9-30)	49 (G1)	231 (G3; 8x ULN) 1 day post treatment	71 (G1) 63 days post treatment
	Alkaline Phosphatase U/L (36-118)	276 (G1)	1025 (G3; 9x ULN) 7 days post treatment	657 (G2) 63 days post treatment
006-001 (1 dose)	AST U/L (0-35)	78 (G1)	257 (G3; 7x ULN) 3 days post treatment	112 (G2) 8 days post treatment
	Creatinine µmol/L (80-125)	85 (G0)	473 (G3; 4x ULN) 8 days post treatment	424 (G3) 9 days post treatment
029-001 (4 doses)	Alkaline Phosphatase U/L (0-124)	212 (G1)	1501 (G3; 12x ULN) 11 days post treatment	511 (G2) 45 days post treatment
040-001 (4 doses)	ALT U/L (7-53)	48 (G0)	661 (G3; 12x ULN) 2 days post treatment	661 (G3) 2 days post treatment
	AST U/L (11-47)	42 (G0)	2326 (G4; 49x ULN) 2 days post treatment	2326 (G4) 2 days post treatment
	Alkaline Phosphatase U/L (36-126)	198 (G1)	885 (G3; 7x ULN) 2 days post treatment	840 (G3) 2 days post treatment
053-004 (3 doses)	Alkaline Phosphatase U/L (40-120)	279 (G1)	907 (G3; 8x ULN) 6 days after Dose 2	679 (G3) 7 days post treatment
066-001 (2 doses)	ALT U/L (9-52)	8 (G0)	2292 (G4; 35x ULN)[3] 2 days post treatment	2292 (G4)[3] 2 days post treatment
	AST U/L (14-36)	18 (G0)	4340 (G4; 117x ULN)[3] 2 days post treatment	4340 (G4)[3] 2 days post treatment

1 Patient was randomized to placebo; data presented are during open-label treatment with IPI-504

2 Immediately prior to dosing with IPI-504

3 Normal range for these assessments were: ALT 30-65 U/L; AST 15-37 U/L.

Source: Table 14.3.4.2, Listing 16.2.5.2, Listing 16.2.8.2.

Based on review of the laboratory data, 6 patients had Grade 3 or 4 elevations in ALT and or AST during treatment with IPI-504, 3 who also had Grade 3 elevations in alkaline phosphatase and 1 who also had a Grade 3 elevation in serum creatinine. Two additional patients had Grade 3 elevations in alkaline phosphatase. All 8 patients had normal or Grade 1 values for these parameters at study baseline. The maximum elevations occurred after 1 to 4 doses of IPI-504. Three of these patients died: 006-001, 040-001 and 066-001; narratives for these patients are provided in Section 12.3.3.1. In 4 of the remaining 5 patients, the Grade 3 or 4 abnormalities had improved to Grade 2 or better as of the last on study assessment.

A summary of worst LFT abnormality (ALT, AST, alkaline phosphatase) relative to the upper limit of normal, e.g., between 2 and 3x ULN, between 3 and 5x ULN, between 5 and 10x ULN, between 10 and 20x ULN and >20x ULN is provided in Table 14.3.6.10; results are presented by cycle and dose in Table 14.3.6.9. These data correlate with the patient listing provided in Table 12-16. Four patients had ALT and or AST elevations >10x ULN (Patients 001-004, 001-014, 040-001 and 066-001); in all 4 patients, at least one of the elevations was >20x ULN. One patient had an elevation in alkaline phosphatase >10x ULN (Patient 029-001).

12.5. Vital Signs, Physical Findings, and Other Observations Related to Safety

12.5.1. Vital Signs

Descriptive statistics for heart rate are summarized in Table 14.3.5.1 (double-blind only) and Table 14.3.5.2 (all patients treated with IPI-504, double-blind and open-label); a by-patient display is provided in Listing 16.2.9.1. A summary of actual values and changes from pre-infusion to the end of the infusion following doses in Cycle 1 (double-blind period) is provided in Table 12-17.

Table 12-17 Descriptive Statistics for Actual Values and Changes from Pre- to End of infusion for Heart Rate during Cycle 1 (ITT Population)

		Patients Receiving Treatment during the DB Period			
		Placebo (N=15) n (%)		IPI-504 (N=32) n (%)	
Visit Timepoint	Statistic	Actual Values	Change from BL	Actual Values	Change from BL
Cycle 1 Dose 1					
Pre-infusion	N	14		32	
	Mean (SD)	77.5 (17.31)		75.6 (13.17)	
	Min, Max	55, 113		54,98	
End of Infusion	N	13	12	30	30
	Mean (SD)	71.0 (11.47)	-2.2 (11.61)	62.0 (10.71)	-13.8 (9.05)
	Min, Max	57, 94	-27, 22	44, 84	-33, 4
Cycle 1 Dose 2					
Pre-infusion	N	14		28	
	Mean (SD)	77.9 (18.06)		78.1 (18.17)	
	Min, Max	51, 106		48.0,125.0	
End of Infusion	N	13	12	22	22
	Mean (SD)	72.3 (15.07)	-3.8 (8.27)	66.1 (11.21)	-9.5 (16.20)
	Min, Max	47, 104	-22, 11	47, 92	-57, 20
Cycle 1 Dose 3					
Pre-infusion	N	15		25	
	Mean (SD)	78.5 (15.56)		79.5 (11.78)	
	Min, Max	61, 109		64, 109	
End of Infusion	N	12	12	17	17
	Mean (SD)	73.0 (16.93)	-3.8 (5.57)	61.2 (9.40)	-15.2 (5.78)
	Min, Max	55, 101	-10, 8	48, 82	-29, -5
Cycle 1 Dose 4					
Pre-infusion	N	14		25	
	Mean (SD)	78.7 (17.75)		82.4 (18.87)	
	Min, Max	56, 110		52, 130	
End of Infusion	N	12	12	16	16
	Mean (SD)	73.3 (13.30)	-3.9 (7.70)	68.4 (15.23)	-13.3 (9.45)
	Min, Max	56, 100	-27, 2	52, 112	-31, 3

Source: Table 14.3.5.1

On average, IPI-504 patients experienced greater decreases from baseline to the end of infusion in heart rate compared with placebo patients. Mean changes to the end of the IPI-504 infusion were -13.8, -9.5, -15.2 and -13.3 bpm for Doses 1, 2, 3 and 4 of Cycle 1, respectively, corresponding changes following dosing with placebo were -2.2, -3.8, -3.8 and -3.9 bpm, respectively. Similar results were noted in subsequent cycles.

Vital sign abnormalities reported as TEAEs are summarized in Table 12-18.

Table 12-18 Vital Signs Abnormalities Reported as TEAEs (ITT Population)

	Patients Receiving Treatment during the DB Period		Patients Receiving IPI-504 (DB+OL) (N=38) n (%)
MedDRA Preferred Term	Placebo (N=15) n (%)	IPI-504 (N=32) n (%)	
Pyrexia	2 (13.3)	5 (15.6)	6 (15.8)
Heart Rate Increased	0	2 (6.3)	2 (5.3)
Tachycardia	1 (6.7)	1 (3.1)	1 (2.6)
Hypertension	1 (6.7)	1 (3.1)	1 (2.6)
Hypotension	0	1 (3.1)	1 (2.6)

Source: Table 14.3.1.2.

The most common vital sign abnormalities reported as a TEAE was pyrexia occurring in a similar proportion of patients in both treatment groups during the double-blind period (16% and 13%, in the IPI-504 and placebo groups, respectively). Other vital sign abnormalities reported as TEAEs included increased heart rate (2 patients, 5%), tachycardia (1 patient, 3%), hypertension (1 patient, 3%), and hypotension (1 patient, 3%). All of these events were reported as Grade 1 or 2 in severity and none led to treatment discontinuation.

12.5.2. ECOG Performance Status

ECOG PS is summarized by cycle in Table 14.3.6.16; a shift analysis from baseline to worst PS on study is provided in Table 14.3.6.17. By-patient listings of ECOG PS are presented in Listing 16.2.9.8.

During double-blind treatment, 4 (15%) of 27 IPI-504 patients with baseline and post-baseline ECOG PS results had a shift from a baseline value of 0 or 1 to PS of 2 (n=3) or 3 (n=1). In the placebo group, 4 (29%) of 14 patients with data available had a shift to PS of 2 (n=1) or 3 (N=3).

12.5.3. Electrocardiogram Findings

Tabulations of ECG findings are provided in Table 14.3.6.11 (double-blind treatment) and Table 14.3.6.12 (all IPI-504 treatment). Results of ECG assessments are provided for each patient in Listing 16.2.9.2 (mean of triplicate measurements, including changes from pre-infusion) and Listing 16.2.9.3 (all triplicate assessments, including ECG comments).

Table 12-19 presents actual values and changes from baseline prior to, at the end of, and 30 minutes following the C1D1 infusion for ECG parameters, including heart rate, QT interval and the corrected QT based on both Bazett's and Fridericia's formulae.

Table 12-19 ECG Actual Values and Changes from Baseline to End of Infusion and Post-Infusion on C1D1 of the Double-Blind Period (ITT Population)

Parameter	Placebo (N=15)		IPI-504 (N=32)	
Time Point	Actual Value	Change from BL	Actual Value	Change from BL
Heart Rate (beats/min)				
Prior to Infusion	72.7 (12.54)		73.2 (12.34)	
End of Infusion	71.6 (13.01)	-0.1 (4.28)	62.0 (10.72)	-11.2 (6.76)
30 Min Post Infusion	70.6 (13.26)	-1.6 (4.63)	59.6 (9.95)	-14.0 (8.50)
QT (msec)				
Prior to Infusion	387.8 (36.17)		378.0 (39.27)	
End of Infusion	393.2 (35.00)	1.2 (13.47)	403.7 (40.21)	25.8 (21.71)
30 Min Post Infusion	399.6 (40.04)	10.3 (38.35)	401.5 (36.46)	24.2 (22.90)
QTcB (msec)				
Prior to Infusion	422.2 (17.22)		412.9 (25.87)	
End of Infusion	424.9 (19.46)	1.4 (12.98)	405.6 (21.24)	-7.2 (13.98)
30 Min Post Infusion	429.5 (44.76)	7.0 (39.97)	396.1 (23.00)	-17.0 (13.66)
QTcF (msec)				
Prior to Infusion	410.3 (19.89)		400.9 (27.26)	
End of Infusion	414.0 (19.80)	1.3 (12.23)	404.9 (24.07)	4.2 (14.15)
30 Min Post Infusion	419.3 (39.20)	8.2 (39.23)	397.9 (23.74)	-2.9 (12.94)

Source: Table 14.3.6.11.

As was observed with the vital signs assessments, a larger mean decrease was observed in heart rate for patients receiving IPI-504 compared with patients receiving placebo at both the end of infusion and the 30 minute post-infusion time point.

Mean decreases from pre-infusion were observed for QTcB at both the end of infusion and 30 minutes post-infusion for the IPI-504 treatment group. For QTcF, a small mean increase was observed at the end of infusion in the IPI-504 group that was similar to the placebo group and a mean decrease from baseline was observed at the 30 minute post infusion time point for the active treatment group.

The ECG data were reviewed for QTc intervals >450 msec; both QTcF and QTcB measurements were assessed; results are provided in Listing 16.2.9.4 (QTcF) and Listing 16.2.9.5 (QTcB).

None of the patients in either the IPI-504 group or the placebo group had treatment-emergent QTcF or QTcB intervals >450 msec that were obtained from adequate ECG tracings.

12.5.4. Concomitant Medications

Concomitant medications are summarized in Table 14.3.6.18; a summary of the most commonly reported concomitant medications by ATC class is provided in Table 12-20. A by-patient

listing of concomitant medications is presented in Listing 16.2.9.9. By-patient listings of subsequent cancer therapies post treatment are presented in Listing 16.2.9.11.

The most commonly reported types of concomitant medications in IPI-504-treated patients included serotonin ($5HT_3$) antagonists (24 patients, 63%), proton pump inhibitors (19 patients, 50%), natural opium alkaloids (16 patients, 42%), and anilides (15 patients, 39%). The most commonly reported concomitant medications in placebo patients during the double-blind period included serotonin ($5HT_3$) antagonists (7 patients, 47%), proton pump inhibitors (5 patients, 33%), and propulsives, contact laxatives, selective beta blocking agents, and emollients/softeners (each 4 patients, 27%).

Table 12-20 Concomitant Medications Reported in ≥10% of Patients During Treatment with IPI-504 (ITT Population)

WHO Anatomic Therapeutic Class	Patients Receiving Treatment during the DB Period: Placebo (N=15) n (%)	Patients Receiving Treatment during the DB Period: IPI-504 (N=32) n (%)	Patients Receiving IPI-504 (DB+OL) (N=38) n (%)
Serotonin (5HT3) Antagonists	7 (46.7)	21 (65.6)	24 (63.2)
Proton Pump Inhibitors	5 (33.3)	17 (53.1)	19 (50.0)
Natural Opium Alkaloids	3 (20.0)	14 (43.8)	16 (42.1)
Anilides	2 (13.3)	13 (40.6)	15 (39.5)
Benzodiazepine Derivatives	2 (13.3)	11 (34.4)	12 (31.6)
Propulsives	4 (26.7)	11 (34.4)	12 (31.6)
Antipropulsives	1 (6.7)	9 (28.1)	10 (26.3)
Propionic Acid Derivatives	2 (13.3)	9 (28.1)	10 (26.3)
Heparin Group	1 (6.7)	6 (18.8)	9 (23.7)
Contact Laxatives	4 (26.7)	7 (21.9)	8 (21.1)
Sulfonamides, Plain	1 (6.7)	6 (18.8)	8 (21.1)
Ace Inhibitors, Plain	2 (13.3)	7 (21.9)	7 (18.4)
Dihydropyridine Derivatives	1 (6.7)	7 (21.9)	7 (18.4)
Multivitamins, Plain	3 (20.0)	7 (21.9)	7 (18.4)
Beta Blocking Agents, Selective	4 (26.7)	6 (18.8)	6 (15.8)
Fluoroquinolones	1 (6.7)	5 (15.6)	6 (15.8)
Other Antiemetics	2 (13.3)	6 (18.8)	6 (15.8)
Glucocorticoids	0	5 (15.6)	5 (13.2)
H2-Receptor Antagonists	0	4 (12.5)	5 (13.2)
Imidazole Derivatives	0	4 (12.5)	5 (13.2)
Osmotically Acting Laxatives	2 (13.3)	3 (9.4)	5 (13.2)
Platelet Aggregation Inhibitors Excl. Heparin	1 (6.7)	5 (15.6)	5 (13.2)
Potassium	0	4 (12.5)	5 (13.2)
Preparations Inhibiting Uric Acid Production	0	3 (9.4)	5 (13.2)
Selective Serotonin Reuptake Inhibitors	2 (13.3)	5 (15.6)	5 (13.2)
Softeners, Emollients	4 (26.7)	3 (9.4)	5 (13.2)
Thiazides, Plain	1 (6.7)	5 (15.6)	5 (13.2)
Thyroid Hormones	1 (6.7)	5 (15.6)	5 (13.2)
Aldosterone Antagonists	1 (6.7)	2 (6.3)	4 (10.5)
Appetite Stimulants	1 (6.7)	3 (9.4)	4 (10.5)
Benzodiazepine Related Drugs	0	3 (9.4)	4 (10.5)
Blood And Related Products	2 (13.3)	2 (6.3)	4 (10.5)
Carbapenems	0	4 (12.5)	4 (10.5)
Electrolyte Solutions	1 (6.7)	3 (9.4)	4 (10.5)
HMG CoA Reductase Inhibitors	0	4 (12.5)	4 (10.5)
Magnesium Compounds	1 (6.7)	4 (12.5)	4 (10.5)
Opioid Anesthetics	0	3 (9.4)	4 (10.5)
Other Drugs For Functional Bowel Disorders	1 (6.7)	4 (12.5)	4 (10.5)
Selective Beta-2-Adrenoreceptor Agonists	2 (13.3)	3 (9.4)	4 (10.5)
Solutions For Parenteral Nutrition	0	4 (12.5)	4 (10.5)

Source: Table 14.3.6.18.

12.5.5. Concomitant Procedures

A by-patient listing of concomitant procedures is provided in Listing 16.2.9.10. Thirteen IPI-504 patients required at least 1 concomitant procedure during the study. The most commonly reported concomitant procedure was a safety monitoring procedure, typically an ECG or chest x-ray to monitor an AE.

12.6. Safety Conclusions

12.6.1. Deaths

From randomization through the 30-day follow-up period, 6 deaths occurred in the study, 5 deaths in patients who received blinded or open-label IPI-504 and 1 death in a patient who received only placebo. The death in the placebo patient was attributed to disease progression.

All 5 deaths in the IPI-504 treatment group were assessed as treatment related. In one of these 5 patients, death was attributed to disease progression and was reported as related to IPI-504 based on clinical deterioration after discontinuation of IPI-504, rather than on direct drug toxicity. Among the remaining 4 patients, the causes of death were reported as cardiopulmonary arrest, metabolic acidosis and DIC, renal failure, and hepatic failure. The latter event occurred following administration of IPI-504 in the setting of Grade 3 AST and ALT elevations in violation of the protocol. Three of these 4 patients died on Day 2 following dosing; the fourth patient died 11 days post-treatment. Review of these 4 cases indicated that, although the patients had different reported causes of death, there were similarities in their clinical presentation prior to death. Three of the 4 patients had undergone prior hepatic surgery and 2 of the 4 experienced hepatotoxicity on study.

12.6.2. Hepatoxicity

Elevated AST and ALT are expected events with IPI-504, and are described in the known safety profile of the investigational drug. Additionally, GIST is known to be associated with hepatic involvement. Among all patients treated in this study, 3 patients (9%) in the IPI-504 group and 1 (7%) in the placebo group had a history of hepatobiliary disease other than their malignancy, based on medical history information. Serum ALT and AST levels were normal in the majority of patients at study entry. Serum ALT at baseline was normal in 30 (94%) of 32 patients randomized to receive IPI-504 and in 14 (93%) of 15 patients randomized to receive placebo, and serum AST levels were normal in 26 (81%) and 11 (73%) patients, respectively.

During the course of the blinded treatment period, a higher incidence of elevated transaminases occurred in the IPI-504 group compared with the placebo group. AST shifts in CTCAE grade occurred in 17 patients (53%) in the IPI-504 group compared with 5 patients (30%) in the placebo group; ALT shifts occurred in 14 (44%) and 3 (20%) patients, respectively. The magnitude of the transaminase elevations also differed between the 2 treatment groups. No patients in the placebo group experienced a Grade 3 or 4 elevated AST or ALT. In the IPI-504 treated group, 6 (16%) patients experienced a Grade 3 or 4 elevated AST and/or ALT during treatment with IPI-504; in 3 of these patients Grade 3 elevations in alkaline phosphatase were also noted. Two additional patients had Grade 3 elevations in alkaline phosphatase on study.

These findings indicate that the elevations in serum hepatic transaminases seen in patients treated with IPI-504 are unlikely to be attributed to GIST alone.

One of the patients with Grade 3/4 elevations in ALT and AST in the IPI-504 treatment group died of hepatic failure (Patient 040-001), 2 patients experienced serious adverse events of elevated serum transaminase levels during the blinded period (Patients 001-014 and 001-016), and an additional patient experienced serious transaminase elevations during the open-label period (Patient 001-004). Two other patients had elevated ALT and AST levels at the time of death, one due to renal failure (Patients 006-001) and one with metabolic acidosis and DIC (Patient 066-001).

All patients received IPI-504 at a starting dose of 400 mg/m^2; 6 patients discontinued, reduced the dose and/or held drug due to elevations in serum liver enzymes, including 5 with hepatic transaminase elevations (Patients 001-004, 001-014, 001-016, 040-001 and 066-001) and 1 with an elevation in alkaline phosphatase (Patient 29-001). Five of the dose modifications occurred in the blinded period, and 1 in the open-label period. Of these 6 patients, 4 had prior liver surgery, 1 had a history of hepatitis, and 1 experienced disease progression. The occurrences of Grade 3 or 4 elevations in transaminases occurred after the patients had received 1 to 4 doses of IPI-504. Among the 5 patients whose IPI-504 dosing was reduced during treatment for elevations in serum liver enzymes, 2 had serum enzymes increase again following rechallenge with lower doses of IPI-504; 1 patient with the dose reduced to 300 mg/m^2 (Patient 001-014) and 1 patient with the dose reduced to 225 mg/m^2 (Patient 001-004).

In summary, IPI-504-treated patients had a higher incidence of hepatoxicity compared with the placebo group, as evidenced by more transaminase elevations, more Grade 3 or 4 AST and/or ALT laboratory findings, more serious hepatic events, and treatment-related fatalities with the presence of elevated liver function tests at the time of death.

12.6.3. Renal Failure

At baseline, the incidences of medical history reports of renal and urinary tract disorders were similar between the IPI-504 group [11 patients, (34%)] and the placebo group [7 patients, (47%)]. The most common pre-existing renal condition at baseline was nephrolithiasis. Additionally, the majority of patients in both treatment groups had normal serum creatinine results [28 patients (88%) in IPI-504 group and 14 patients (93%) in placebo group] at study baseline.

There was a higher incidence of adverse events associated with renal failure in the IPI-504 treated group compared with the placebo group: 6 (16%) of the 38 patients who received IPI-504 experienced renal failure, including reports of acute renal failure, renal failure and acute prerenal failure compared with no patients in the placebo group. Both treatment groups had a similar proportion of patients with any shifts from baseline in serum creatinine during the double-blind period [8 patients (25%) in IPI-504 group and 4 patients (27%) in placebo group]. However, the magnitude of these changes were greater in the IPI-504 group, where 6 (16%) patients who received IPI-504 during the study had a shift to Grade 2 creatinine and 1 (3%) had a shift to Grade 3 creatinine, compared with no patients with Grade 2 or 3 creatinine elevations in the placebo group.

In all patients with renal failure or pre-renal failure, the events were serious in nature. Five of the 6 patients with renal or pre-renal failure experienced serious GI events that may have led to dehydration with subsequent renal failure. It is likely that most reports of renal failure in patients receiving IPI-504 appeared to be due to dehydration, not to direct renal toxicity. The sixth patient with renal failure was experiencing disease progression concurrent with the renal failure. In one patient the event of renal failure along with sepsis resulted in death. In the other 5 cases, the renal failure was reported as resolved.

12.6.4. Gastrointestinal Disorders

It is not unexpected that heavily pre-treated GIST patients enrolled in this study would have underlying, pre-existing GI disorders at study enrollment, which is confirmed by medical history with 28 (88%) of 32 patients randomized to IPI-504 and 12 (80%) of 15 patients randomized to placebo having at least 1 GI disorder reported at baseline. The most common GI conditions present at study entry were gastro-oesophageal reflux disease [15 (47%) IPI-504 patients and 4 (27%) placebo patients], nausea [10 (31%) and 4 (27%) patients, respectively], abdominal pain [9 (28%) and 8 (53%) patients, respectively], and diarrhoea [6 (19%) patients and 4 (27%) patients], respectively.

During the study, GI disorders were the most commonly occurring TEAEs, with 25 (78%) of 32 IPI-504 patients and 12 (80%) of 15 placebo patients experiencing at least 1 GI disorder during the double-blind period. Although the overall incidence of GI events was similar between the treatment groups, the IPI-504-treated group experienced more severe GI events, with 12 (32%) of the 38 patients who received IPI-504 during the study experiencing a Grade 3 or higher GI event, compared with none of the patients in the placebo group. Grade 3 or higher GI events reported in more than 2 patients during IPI-504 treatment included diarrhoea (7 patients, 18%), abdominal pain (4 patients, 11%), vomiting (4 patients, 11%), and nausea (3 patients, 8%). In 5 patients, serious GI events of diarrhoea and/or vomiting were observed in patients subsequently diagnosed with renal or pre-renal failure. These events have been observed previously with IPI-504 and are described as expected events in the Investigator Brochure. However, the frequency of severe events compared with placebo-treated patients was different from the known safety profile of IPI-504.

12.6.5. Cardiac Disorders

Reversible cardiac disorders, including sinus bradycardia, have been observed with IPI-504 treatment and are not unexpected. During the study, 7 patients (22%) in the IPI-504 group and 2 patients (13%) in the placebo group experienced cardiac disorders. The cardiac events in the IPI-504 group were generally Grade 1 or 2 and occurred in a single patient each. One patient died of cardiorespiratory arrest (Patient 009-001). The only cardiac event occurring in more than 1 IPI-504 patient was sinus bradycardia [2 (6.3%) patients]; both events were Grade 1. ECG findings in the IPI-504 group were consistent with the known safety profile of IPI-504. Therefore, no new clinically significant cardiac findings were observed in the IPI-504 treated patients during the study.

12.6.6. Overall Safety Conclusions

IPI-504 at the dose and schedule evaluated in this study of 400 mg/m^2 twice weekly for 2 weeks followed by 1 week off treatment was not tolerated by the patient population enrolled.

Unblinded review of patient deaths in April 2009 by the IDMC revealed that 4 deaths had occurred in the IPI-504 treatment group compared with no death in the placebo treatment group. Based on these findings, the IDMC recommended stopping Study IPI-504-06; the Sponsor concurred and terminated the trial on 15 April 2009.

In summary, there was a higher incidence of SAEs, ≥Grade 3 TEAEs, and discontinuations due to TEAEs in the IPI-504 treatment group compared with the placebo group. The qualitative nature of the observed events was not unexpected for this patient population, as evidenced by the most commonly occurring safety findings, including a higher incidence of hepatotoxicity and events of nausea, vomiting and diarrhoea in the IPI-504 group compared with the placebo group. However, the severity of these events, including the outcome of death, and the incidence of events, was greater than expected compared to the known safety profile of IPI-504. Based on these findings, it was concluded that IPI-504 at this dose and schedule was not tolerated in this patient population.

13. DISCUSSION AND OVERALL CONCLUSIONS

The current study was a randomized, double-blind, placebo-controlled, multi-center study designed to evaluate the efficacy and safety of IPI-504 compared with placebo in patients with metastatic and/or unresectable GIST who were receiving standard of care following failure of at least imatinib and sunitinib. The primary objective was to compare PFS between the IPI-504 and placebo groups.

The protocol was designed to enroll approximately 195 patients over a planned accrual period of 12 months in order to observe 148 patients with progressive disease or death by the end of the 6-month follow-up period. Enrollment began in October 2008. As of 14 April 2009, a total of 47 patients had been enrolled in the study at 20 study sites. By that date, a total of 4 on-study deaths had been reported to the Sponsor, including 3 deaths reported in a 3-day period between 6 and 9 April 2009. All 4 patients that had died on study had been treated with IPI-504 during the double-blind portion of the study. Based on these events, the IDMC recommended that enrollment of additional patients be stopped and study drug administration be discontinued for all patients ongoing in the study. In accordance with the IDMC's recommendation, the Sponsor terminated the study.

After all data were available for review, a total of 11 deaths had been reported during the study; additionally, 2 patients died of rapidly progressive disease during the screening process. Among the 11 patients who died on study, 6 died within 30 days of double-blind (N=5) or open-label (N=1) treatment, and 5 died more than 30 days post-treatment. Four of the 6 patients who died on study were 70 years of age or older; all 6 had a history of GIST for 5 or more years with 4 patients having had GIST for 8 or more years. The causes of death were reported as disease progression, cardiopulmonary arrest, metabolic acidosis and DIC, renal failure, and hepatic failure. The latter event occurred following administration of IPI-504 in the setting of Grade 3 AST and ALT elevations in violation of the protocol. Of the patients who died within 30 days of treatment, 5 were receiving IPI-504 and 1 was receiving placebo. Three of the 5 IPI-504 patients died on Day 2 following dosing; the other patients died 11 and 23 days post-treatment. Review of the 4 deaths that were not associated with disease progression indicated that there were similarities in their clinical presentation prior to death. Three of the 4 patients had undergone prior hepatic surgery and 2 of the 4 experienced hepatotoxicity on study.

Patients receiving IPI-504 experienced higher rates of ≥Grade 3 TEAEs (46.9% vs. 33.3%) and SAEs (40.6 vs. 33.3%), higher rates of Grade 3 and 4 liver enzyme elevations, and were more likely to discontinue treatment due to AEs (21.9% vs. 6.7%).

Overall, the most commonly reported types of TEAEs were GI disturbances, reported in 78% and 80% of patients during the double-blind treatment phase in the IPI-504 and placebo groups, respectively. Although the overall incidence of GI events was similar between the treatment groups, the IPI-504 treated group experienced more severe GI events, with 12 (32%) of the 38 patients who received IPI-504 during the study experiencing a Grade 3 or higher GI event, compared with none of the patients in the placebo group. The most common Grade ≥3 GI events were diarrhoea (18%), abdominal pain (11%), vomiting (11%), and nausea (8%). These events have been observed previously during treatment with IPI-504; however, the frequency of

severe events compared to placebo-treated patients was different from the known safety profile of IPI-504.

IPI-504-treated patients had a higher incidence of hepatotoxicity compared to the placebo group, as evidenced by more transaminase elevations, more Grade 3 or 4 AST and/or ALT laboratory findings, more serious hepatic events, and treatment-related fatalities in the presence of elevated liver function tests at the time of death. None of the patients in the placebo group experienced a Grade 3 or 4 elevated AST or ALT. A total of 6 patients had Grade 3 or 4 elevations in ALT and or AST during treatment with IPI-504, 3 of these patients also had Grade 3 elevations in alkaline phosphatase. Two additional patients had Grade 3 elevations in alkaline phosphatase. All 8 patients had normal or Grade 1 values for these parameters at study baseline. The maximum elevations occurred after 1 to 4 doses of IPI-504. Three of these patients died: 006-001 (renal failure), 040-001 (hepatic failure) and 066-001 (metabolic acidosis with DIC). In 4 of the remaining 5 patients, the Grade 3 or 4 abnormalities had improved to Grade 2 or better as of the last on study assessment.

There was a higher incidence of adverse events associated with renal failure in the IPI-504 treated group compared to the placebo group. In all patients with renal failure or pre-renal failure, the events were serious in nature. Five of the 6 patients with renal or pre-renal failure experienced serious GI events that may have led to dehydration with subsequent renal failure. Therefore, it is likely that most reports of renal failure in patients receiving IPI-504 were related to underlying dehydration and not to direct renal toxicity.

Given the notable reduction in sample size, with only 24% of the planned study population enrolled, many of the planned efficacy analyses were not performed and no efficacy conclusions can be drawn.

In conclusion, the trial was prematurely terminated by the Sponsor based on the safety observations. IPI-504 at the dose and schedule evaluated in this study of 400 mg/m^2 twice weekly for 2 weeks followed by 1 week off treatment was not tolerated by this patient population. Serious adverse events including deaths, ≥Grade 3 TEAEs, ≥Grade 3 elevations in liver function tests, and discontinuations due to TEAEs occurred more frequently in patients receiving IPI-504 when compared to patients in the placebo group. Although the types of adverse events observed were not unexpected, the severity, including the outcome of death, and incidence of the events was greater than expected.

14. TABLES, FIGURES AND GRAPHS REFERRED TO, BUT NOT INCLUDED IN THE TEXT

14.1. Demographic Data

The following statistical tables are included in this section:

Table 14.1.1	Patient Disposition
Table 14.1.2	Summary of Reasons for Not Being Randomized- Patients Who Were Screened and Not Randomized
Table 14.1.3	Demographic and Baseline Characteristics
Table 14.1.4	Number of Patients Randomized by Site
Table 14.1.5	Number of Patients by Stratification Factors
Table 14.1.6	Prior Therapy
Table 14.1.7	Disease History
Table 14.1.8	Prior Surgery or Radiation Therapy
Table 14.1.9	Evidence of RECIST/WHO Progression on Prior Treatments for Eligibility Confirmation
Table 14.1.10	Pre-Treatment Mutational Status
Table 14.1.11	Medical History by MedDRA System Organ Class (SOC) and Preferred Term (PT)

14.2. Efficacy Data

The following statistical tables are included in this section, numbering is not sequential due to the deletion of the majority of efficacy analyses based on the early trial termination:

Table 14.2.2.1:	Overall Disease Control Rate, Best Overall Response, Objective Response, and Duration of Objective Response from Randomization to Withdrawal from the Double-blind Portion of the Study: Central Reads (ITT Population)
Table 14.2.2.2:	Overall Disease Control Rate, Best Overall Response, Objective Response, and Duration of Objective Response from Randomization to Withdrawal from the Double-blind Portion of the Study: Central Reads (Per Protocol Population)
Table 14.2.2.7:	Overall Survival (ITT Population)
Table 14.2.2.8:	Overall Survival (Per Protocol Population)

14.3. Safety Data

14.3.1. Displays of Adverse Events

The following statistical tables are included in this section:

Table 14.3.1.1:	Treatment Emergent Adverse Events (TEAEs) (ITT Population)
Table 14.3.1.2:	Treatment Emergent Adverse Events (TEAEs) by MedDRA System Organ Class (SOC) and Preferred Term (PT) (ITT Population)
Table 14.3.1.3:	Treatment Emergent Adverse Events (TEAEs) by MedDRA System Organ Class (SOC), Preferred Term (PT) and Maximum Severity while on Double Blind Portion of the Study (ITT Population)
Table 14.3.1.4:	Treatment Emergent Adverse Events (TEAEs) by MedDRA System Organ Class (SOC), Preferred Term (PT) and Maximum Severity While on IPI-504 (ITT Population)
Table 14.3.1.5:	Summary of Most Frequent (>10% dose 1 of IPI-504 onward) Treatment Emergent Adverse Events (TEAEs) by MedDRA Preferred Term (PT) (ITT Population)
Table 14.3.1.6:	Drug Related Treatment Emergent Adverse Events (TEAEs) by MedDRA System Organ Class (SOC) and Preferred Term (PT) (ITT Population)
Table 14.3.1.7:	Drug Related Treatment Emergent Adverse Events (TEAEs) by MedDRA System Organ Class (SOC), Preferred Term (PT), and Maximum Severity for Blinded Portion of the Study (ITT Population)
Table 14.3.1.8:	Drug Related Treatment Emergent Adverse Events (TEAEs) While on the Open Label Portion of the Study only by MedDRA System Organ Class (SOC), Preferred Term (PT) and Maximum Severity While on IPI-504 (ITT Population)
Table 14.3.1.9:	Summary of Most Frequent (>10% Dose 1 of IPI-504 Onward) Drug Related Treatment Emergent Adverse Events (TEAEs) by MedDRA Preferred Term (PT) (ITT Population)
Table 14.3.1.10:	Treatment Emergent Serious Adverse Events (SAEs) by MedDRA System Organ Class (SOC) and Preferred Term (PT) (ITT Population)
Table 14.3.1.11:	Treatment Emergent Serious Adverse Events (SAEs) by MedDRA System Organ Class (SOC) Preferred Term (PT), and Maximum Severity While on Double Blind Portion of the Study (ITT Population)
Table 14.3.1.12:	Treatment Emergent Serious Adverse Events (SAEs) by MedDRA System Organ Class (SOC), Preferred Term (PT), and Maximum Severity While on IPI-504 (ITT Population)

Table 14.3.1.13:	Summary of Most Frequent (>10% Dose 1 of IPI-504 Onward) Treatment Emergent Serious Adverse Events (SAEs) by MedDRA Preferred Term (PT) (ITT Population)
Table 14.3.1.14:	Drug Related Treatment-Emergent Serious Adverse Events (SAEs) by MedDRA System Organ Class (SOC) and Preferred Term (PT) (ITT Population)

14.3.2. Listings of Deaths, Other Serious and Significant Adverse Events

The following statistical tables are included in this section:

Table 14.3.2.1:	Listing of Adverse Events Resulting in Study Discontinuation (ITT Population)
Table 14.3.2.2:	Listing of Adverse Events Resulting in Dose Reduction (ITT Population)
Table 14.3.2.3:	Listing of Adverse Events Resulting in Dose Held or Modified (ITT Population)
Table 14.3.2.4:	Listing of Adverse Events Resulting in Death (ITT Population)
Table 14.3.2.5:	Listing of Serious Adverse Events (ITT Population)

14.3.3. Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

The information provided in this section is excerpted from CIOMS forms for the specified patient deaths and serious adverse events as detailed in the following table:

Patient ID	Randomized Treatment	Death	SAE	DC
001-004	Placebo[1]		√	√
001-008	IPI-504		√	
001-011	Placebo[1]		√	
001-014	IPI-504		√	√
001-015	IPI-504		√	
001-016	IPI-504		√	
005-001	NA[2]	√		
005-002	Placebo		√	√
005-003	IPI-504		√	
006-001	IPI-504	√	√	√
006-002	IPI-504		√	
009-001	IPI-504	√	√	√
011-001	IPI-504		√	√
020-001	Placebo		√	
020-002	IPI-504		√	√
024-001	Placebo[1]	√	√	
028-001	Placebo	√	√	
040-001	IPI-504	√	√	√
051-002	Placebo		√	
053-004	IPI-504		√	
056-001	NA[2]	√		
066-001	IPI-504	√	√	√

1 Events were reported during open-label treatment with IPI-504

2 Patients died during the screening period.

Patient #: 001-004 **Gender: Male** **Age: 50 years** **Treatment Assignment: Placebo & Open-label IPI-504**					
SAE term	**Treatment assignment**	**Intensity**	**Relationship**	**Outcome**	**Resulted in study discontinuation**
Renal failure acute	IPI-504	Grade 3	Not related	Resolved	No
Aspartate aminotransferase increased	IPI-504	Grade 3	Definite	Resolved	No
Nausea	IPI-504	Grade 3	Definite	Resolved	No
Vomiting	IPI-504	Grade 3	Definite	Resolved	No
Diarrhoea	IPI-504	Grade 3	Definite	Resolved	No
Lower gastrointestinal haemorrhage	IPI-504	Grade 3	Possible	Resolved	No
Renal failure acute	IPI-504	Grade 3	Not related		No
Diarrhoea	IPI-504	Grade 2	Probable	Resolved with sequelae	No
Vomiting	IPI-504	Grade 2	Possible	Resolved	No
Alanine aminotransferase increased	IPI-504	Grade 3	Definite	Resolved	No
Aspartate aminotransferase increased	IPI-504	Grade 4	Definite	Resolved	Yes
Blood alkaline phosphatase increased	IPI-504	Grade 2	Definite	Ongoing	No
Dehydration	IPI-504	Grade 3	Not related	Resolved	No

Patient number 001-004 was a 50-year-old Asian man diagnosed with GIST in August 2002, with initial presentation in the small bowel. Prior therapies included imatinib, sunitinib, and nilotinib. Cancer surgical history included surgical resection of the primary tumor, nephrectomy for bulky disease, and a radical debulking procedure with pancreaticoduodenectomy. Relevant medical history included hepatitis while on nilotinib, epigastric pain, satiety, indigestion, constipation, and diarrhea. Concomitant medications ferrous sulfate, warfarin sodium, folic acid, diphenhydramine, calcium + vitamin D, fish oil capsules, multivitamins, vitamin B12, vitamin C, vitamin E, loratadine, omeprazole, furosemide, pancrelipase, enoxaparin, metoclopramide, morphine, morphine sulfate controlled-release, simethicone, dronabinol, spironolactone, ondansetron, esomeprazole, atenolol, hydroxyzine, potassium chloride, clonazepam, and tamsulosin.

The patient enrolled in the study on 23-Oct-2008, and was subsequently randomized to placebo. On 23-Oct-2008, baseline spiral computed tomography (CT) revealed the following target lesion measurements: a 29 mm left liver lesion, right liver lesions of 32 mm and 23 mm, multiple mesenteric lesions, and a left lingular nodule. Non-target lesions included multiple liver lesions, mesenteric lesions, and pulmonary nodules. The patient had an Eastern Cooperative Oncology Group (ECOG) performance status level of 1. He started treatment with placebo on 28-Oct-2008 (study Day 1). On 03-Nov-2008 (study Day 7), the patient experienced Grade 1 nausea. On 07-Nov-2008 (study Day 11), Week 2 CT scans revealed:

no change in the size of the target left liver lesion; the right liver lesions had increased from 32 to 35 mm and from 23 to 26 mm, respectively; the target mesenteric lesions and left lingular nodule had increased in size. On 18-Nov-2008 (study Day 22), significant laboratory values were creatinine 1.30 mg/dL (normal range 0.7-1.3), sodium 131 mmol/L (Grade 1), lactate dehydrogenase (LDH) 359 U/L (normal range 107-231), and carbon dioxide (CO2) 22 mmol/L (normal range 23-32), chloride 97 mmol/L (normal range 98-108), and white blood cell count (WBC) 11.3 (normal range 3.8-9.2). Blood urea nitrogen (BUN), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and alkaline phosphatase were within normal limits. The patient had progressed rapidly on study, and on 19-Nov-2008 (study Day 23), he entered the open-label phase of the study due to disease progression. On 20-Nov-2008 (study Day 24), AST, ALT, alkaline phosphatase, total bilirubin, and BUN were within normal limits. Significant laboratory results included creatinine 1.40 mg/dL (Grade 1), sodium 131 mmol/L (Grade 1), LDH 296 U/L (reference range 107-231), CO_2 22 mmol/L (reference range 23-32), chloride 98 mmol/L (reference range 98-108), and WBC 15.6 K/UL (reference range 3.8-9.2). ECOG performance status level was 2. On 21-Nov-2008 (study Day 25), before receiving the first dose of open-label IPI-504, laboratory test results revealed normal AST, ALT, alkaline phosphatase, and BUN. Other laboratory test results included LDH 356 U/L (reference range 107-231), creatinine 1.40 mg/dL (Grade 1), chloride 97 mmol/L , sodium 130 mmol/L (Grade 1), and CO2 22 mmol/L. On 21-Nov-2008 (study Day 25), he received one dose of open-label IPI-504. On the same day (study Day 25), the patient experienced nausea, vomiting, abdominal pain, and diarrhea some time after IPI-504 dosing. He had not experienced any vomiting or diarrhea prior to the 21-Nov-2008 (study Day 25) episode. On 23-Nov-2008 (2 days after initiation of IPI-504), 48 hours after his first open-label dose of IPI-504, he was hospitalized for Grade 3 nausea, Grade 3 vomiting, Grade 3 diarrhea, Grade 3 elevated AST, Grade 3 dehydration, and Grade 2 acute renal failure. Diarrhea was severe and constant on Day 1 of hospitalization, and a rectal tube was inserted. Laboratory results at 11:20 AM revealed a white blood cell (WBC) count of 18.13 K/uL, hemoglobin 12.1 (Grade 1), platelet count 688 K/uL (normal range 155-410), creatinine 2.04 mg/dL (Grade 2), BUN 32 mg/dL (normal range 9-25), AST 489 U/L (Grade 3), ALT 128 U/L (Grade 1), alkaline phosphatase 189 U/L (Grade 1), sodium 134 mmol/L (Grade 1), chloride 99 mmol/L , and CO2 16 mmol/L. Stool samples collected were negative for clostridium difficile, salmonella, shigella, Aeromonas, Plesiomonas, campylobacter, and fecal leukocytes. Prerenal azotemia was diagnosed and treated with intravenous (IV) fluids, with improvement. By 20:08, laboratory results were: WBC 15.53 K/uL, hemoglobin 10.6 g/dL, creatinine 1.63 mg/dL (Grade 2), BUN 28 mg/dL (normal range 9-25), AST 291 U/L (Grade 3), ALT 103 U/L (Grade 1), alkaline phosphatase 173 U/L (Grade 1), LDH 2322 U/L (reference range 107-231),ferritin 27850 ug/L (reference range 20-400), sodium 33 mmol/L (Grade 1), chloride 102 mmol/L and CO2 16 mmol/L. At 20:45, 9000 mg of acetylcysteine were administered orally. At 12:35 AM on 24-Nov-2008 (3 days after initiation of IPI-504), the patient received 5000 mg of oral acetylcysteine, which was repeated every three to five hours, with the last dose given 19:01 on 26-Nov-2008 (5 days after initiation of IPI-504). Laboratory test results later on 24-Nov-2008 (3 days after initiation of IPI-504) included BUN 24 mg/dL, creatinine 1.32 mg/dL (Grade 1, AST 175 U/L (Grade 3), ALT 95 U/L (Grade 1), and alkaline phosphatase 182 U/L (Grade 1). A renal ultrasound (date not provided) was normal for the patient's remaining kidney (prior nephrectomy). By 17:48 on 24-Nov-2008 (3 days after initiation of IPI-504), laboratory test results revealed AST 93 U/L (Grade 2), ALT 75 U/L (Grade 1), alkaline phosphatase 184 U/L (Grade 1), and LDH 1530 U/L (normal range 107-231). On 25-Nov-2008 (4 days after initiation of IPI-504), laboratory test results revealed: BUN and creatinine normal; AST, ALT, and alkaline phosphatase values 56 U/L, 65 U/L, and 185 U/L respectively (all Grade 1); WBC count 21.36 K/uL; , hemoglobin 9.3 g/dL (Grade 2); CO2 21 mmol/L; LDH was 1312 U/L. On 26-Nov-2008 (5 days after initiation of IPI-504), AST was 53 (Grade 1), ALT was 57 U/L (Grade 1, normal range 7-52), LDH was 845 U/L, and alkaline phosphatase was 173 U/L (Grade 1). Testing for other hepatitis etiologies was negative and

included the following: hepatic serologies (with only Hep A being IgG positive), ceruloplasmin, anti-alpha 1 antitrypsin. Infectious disease workup was negative. His WBC was trending upward, yet he was afebrile with stable vital signs throughout his hospitalization. It was noted that the patient had a large tumor burden. Tumor lysis laboratory test results were elevated on admission, and he responded well to allopurinol and IV fluids, with uric acid decreasing from 12.8 to 5.2, and LDH decreasing from 2322 to 845. Treatment was to continue with oral fluids and allopurinol. On 24-Nov-2008 (3 days after initiation of IPI-504), the adverse event of Grade 3 elevated AST resolved, and on 26-Nov-2008 (5 days after initiation of IPI-504), the adverse events of Grade 3 nausea, Grade 3 vomiting, Grade 3 diarrhea, and Grade 3 acute renal failure resolved. On 26-Nov-2008 (5 days after initiation of IPI-504), the patient chose to be discharged from the hospital against medical advice. On 28-Nov-2008 (7 days after initiation of IPI-504), AST was 74 (Grade 1), ALT 80 (Grade 1), LDH 667 U/L, and alkaline phosphatase 220 (Grade 1). On the morning of 02-Dec-2008 (11 days after initiation of IPI-504), laboratory values revealed WBC 15.2K/UL, sodium 133 mmol/L (Grade 1), CO_2 22 mmol/L, LDH 511 U/L, and alkaline phosphatase 215 U/L (Grade 1); chloride, creatinine, AST, ALT were within normal limits. Computed tomography (CT) scans revealed stable disease or slight improvement. IPI-504 was held and reduced in response to the adverse events.

The Investigator assessed the adverse events of elevated AST, nausea, vomiting, and diarrhea as definitely related to IPI-504, and the adverse event of acute renal failure as not related to IPI-504.

On 08-Dec-2008 (17 days after initiation of IPI-504), Dose 2 of open label IPI-504 was administered at 225 mg/m^2. Laboratory results that day included white blood cell count (WBC) 18.1 K/UL, prothrombin time (PT) 23.4 seconds, international normalized ratio (INR) 2.0, creatinine 1.10 mg/dL, uric acid 4.8 mg/dL (within normal range), AST 19 U/L, ALT 22 U/L, alkaline phosphatase 186 U/L (Grade 1), LDH 251 U/L (normal range 107-231), phosphorus 3.7 mg/dL (within normal range), and potassium 4.4 mmol/L (within normal range). On 09-Dec-2008 (18 days after initiation of IPI-504), laboratory results included creatinine 1.7 mg/dL (Grade 1), AST 153 U/L (Grade 1), ALT 51 U/L, and alkaline phosphatase 231 U/L (Grade 1). On 10-Dec-2008 (19 days after initiation of IPI-504), the patient presented to the oncology clinic for planned IV fluids. He reported experiencing diarrhea that day and he was urinating in small amounts only when having a bowel movement. Oxygen saturation was decreased to 85% on room air, which increased to 97% after receiving 6L oxygen via face mask. Laboratory results included: WBC 15.4 K/UL, creatinine 2.10 mg/dL (Grade 2), AST 901 U/L (Grade 4), ALT 269 U/L (Grade 2), and alkaline phosphatase 416 U/L (Grade 2). The patient began vomiting, and was admitted to the Emergency Department (ED) with fever, diarrhea, transaminitis and acute renal failure. Lower extremities were increasingly edematous with elevated jugular venous pressure, abdomen was distended, and slight wheezing in the lungs was noted; however no crackles were heard. Systolic blood pressure was low at admission due to intravascular depletion. Increased creatinine was considered secondary to dehydration from diarrhea "as well as chemotherapy effect". The patient's fever was considered secondary to malignancy. Pneumonia was suspected due to pulmonary lesions, labile blood pressure, leukocytosis, and 10-Dec-2008 (19 days after initiation of IPI-504) chest x-ray results; however, the investigator confirmed that the patient did not have pneumonia. Broad-spectrum antibiotics (vancomycin, ceftazidime, and azithromycin) were started for possible pneumonia or risk of sepsis. At 11:01 PM, 9.5 g of IV acetylcysteine were administered for increased liver function tests, and the patient was rehydrated. Acetylcysteine administration was repeated as a 5 g IV dose approximately every three to five hours. Early morning laboratory results on 11-Dec-2008 (20 days after initiation of IPI-504) included PT 24.5 seconds, INR 2.1, and LDH 2355 U/L. Further laboratory results on 11-Dec-2008 (20 days after initiation of IPI-504) included WBC 13.92 K/uL, PT 26.7 seconds, INR 2.3, ALT 212 U/L (Grade 2), AST 497 U/L (Grade 3), alkaline phosphatase 526 U/L (Grade 2), uric acid 9.3 mg/dL (Grade

1), phosphate 5.1 mg/dL (normal range 2.4-5.0) and LDH 2355 U/L (normal range 107-231). In the evening on 11-Dec-2008 (20 days after initiation of IPI-504), laboratory results included PO_2 104 mmHg, pH 7.23, pCO_2 28 mmHg, WBC 16.03 K/uL, PT 33.5 seconds, INR 3.2, creatinine 2.16 mg/dL (Grade 2), ALT 198 U/L (Grade 2), AST 352 U/L (Grade 3), alkaline phosphatase 494 U/L (Grade 2), uric acid 8.1 mg/dL (Grade 1), phosphate 6.2 mg/dL (normal range 2.4-5.0), potassium 4.2 mmol/L (within normal range) and LDH 1950 U/L (normal range 107-231). On 12-Dec-2008 (21 days after initiation of IPI-504), laboratory results included WBC 18.64 K/uL, PT 19.2 seconds, INR 1.6, creatinine 1.94 mg/dL (Grade 1), ALT 166 U/L (Grade 1), AST 182 (Grade 2), alkaline phosphatase 473 U/L (Grade 2), uric acid 7.8 mg/dL (within normal range), potassium 3.6 mmol/L (within normal range), phosphate 5.0 mg/dL (within normal range), and LDH 1670. The same day, a 5 g dose of acetylcysteine was administered every three to five hours until 12:34 PM, and was then administered again at 8:10 PM. On 13-Dec-2008 (22 days after initiation of IPI-504), two doses of acetylcysteine were given, with one at 9:22 AM, and one at 12:55 PM. Laboratory results included creatinine 1.35 mg/dL (Grade 1) and potassium 2.6 mmol/L (Grade 3). The last doses of acetylcysteine were administered at 12:48 AM and 12:39 PM on 14-Dec-2008 (23 days after initiation of IPI-504). On 14-Dec-2008 (23 days after initiation of IPI-504), laboratory results included creatinine 1.3 mg/dL (within normal range), potassium 3.0 mmol/L (Grade 1), ALT 86 U/L (Grade 1), AST 37 U/L (Grade 1), and alkaline phosphatase 486 U/L (Grade 2). At 20:37 that same day, a repeat potassium result was 3.5 mmol/L (within normal range). Blood and urine cultures were negative on an unspecified date; antibiotics were discontinued on 15-Dec-2008 (24 days after initiation of IPI-504). The patient continued to receive fluids for pressure support. The patient also experienced a "massive lower gastrointestinal bleed" (date not reported), considered likely due to mucosal injury secondary to chemotherapy agent in the setting of anticoagulation. Anticoagulation was reversed with fresh frozen plasma and vitamin K. Once pressures were stabilized and the patient's condition improved, the patient was diuresed with furosemide. On 15-Dec-2008 (24 days after initiation of IPI-504), laboratory results included WBC 12.52 K/uL, PT 15.6 seconds, INR 1.2, creatinine 1.14 mg/dL, ALT 68 U/L (Grade 1), AST 41 (Grade 1), and alkaline phosphatase 472 U/L (Grade 2). On 16-Dec-2008 (25 days after initiation of IPI-504), the patient was ambulating minimally with assistance, was afebrile and was hemodynamically stable with bilateral pitting edema in the lower extremities. Laboratory results included WBC 12.31 K/uL, PT 15.3 seconds, INR 1.2, creatinine 1.08 mg/dL, ALT 71 U/L (Grade 1), AST 91 (Grade 2), and alkaline phosphatase 463 U/L. The investigator reported the patient's exams suggested impressive tumor response, and that that the patient's dehydration had been caused mainly by vomiting and diarrhea, which subsequently led to acute renal failure and hypoxia. The etiology of elevated uric acid levels was never determined and it was deemed not clinically significant by the investigator. On 11-Dec-2008 (20 days after initiation of IPI-504), the adverse events of Grade 4 elevated AST and Grade 3 elevated ALT had resolved, on 16-Dec-2008 (25 days after initiation of IPI-504), the adverse events of Grade 3 lower GI bleed, Grade 2 vomiting, Grade 2 dehydration, and Grade 3 acute renal failure resolved; on 16-Dec-2008 (25 days after initiation of IPI-504), the event of Grade 2 diarrhea resolved with sequelae; and, the event of Grade 2 elevated alkaline phosphatase was ongoing. Study participation was discontinued on 19-Dec-2008 due to Grade 4 elevated AST.

The Investigator assessed the adverse events of elevated AST, elevated ALT, and elevated alkaline phosphatase as definitely related to IPI-504; the adverse event of diarrhea as probably related to IPI-504; the adverse events of lower GI bleed, and vomiting as possibly related to IPI-504; and, the adverse events of renal failure acute and dehydration as not related to IPI-504.

Patient #: 001-008
Gender: Male

Age: 60 years **Treatment Assignment: IPI-504**					
SAE term	**Treatment assignment**	**Intensity**	**Relationship**	**Outcome**	**Resulted in study discontinuation**
Acute pre-renal failure	IPI-504	Grade 2	Probable	Resolved	No
Diarrhoea	IPI-504	Grade 3	Probable	Resolved	No
Diarrhoea	IPI-504	Grade 3	Probable	Resolved	No
Cerebrovascular accident	IPI-504	Grade 2	Not related	Resolved with sequelae	No

Patient number 001-008 was a 60-year-old Asian man diagnosed with GIST on 14-Nov-2003. Prior therapies included imatinib and sunitinib. Cancer surgical history included exploratory laparotomy with resection, partial gastrectomy, and transverse colectomy, with complete surgical resection of GIST. Concurrent medical conditions included abdominal pain, fatigue, and diarrhea. Significant medical history included hematemesis, nausea, left upper quadrant abscess, cough, pleuritic chest pain, dyspnea, hand and foot syndrome, abdominal bloating, excess gas, right upper quadrant pain, mild upper quadrant discomfort, lightheadedness on standing, progressive lower extremity weakness, progressive lower extremity pain, right neck pain, gout, and chest pain. Relevant social history includes travel to Cambodia immediately prior to enrollment in the study. Concomitant medications included amlodipine, clonazepam, lorazepam, colchicine, sucralfate, omeprazole, allopurinol, lisinopril/hydrochlorothiazide, diphenoxylate with atropine, metoclopramide, morphine, oxycodone, and palliative chemotherapy (agent not provided).

The patient enrolled in the study on 19-Dec-2008, and was subsequently randomized to receive IPI-504. On 05-Jan-2009 (study Day 1), he started treatment with study drug and received 2 doses before dosing was temporarily held due to joint pain. On 27-Jan-2009 (study Day 23), dosing resumed, at reduced dose 300 mg/m2 due to Grade 3 arthralgias and myalgias. Pre-therapeutic labs drawn on 27-Jan-2009 (study Day 23) showed baseline creatinine 1.3 mg/dL (normal range 0.7 - 1.3), white blood cell count (WBC) 7.5 K/uL (normal range 3.8 - 9.2), and serum total protein 8.5 g/dL (normal range 6.0 - 8.0). The patient received a total of 3 doses of IPI-504 (2 doses at 400 mg/m2 and 1 dose at 300 mg/m2). On 28-Jan-2009 (study Day 24), the patient developed diarrhea. On 29-Jan-2009 (study Day 25), the patient was hospitalized for Grade 2 diarrhea and Grade 2 pre-renal azotemia with a blood urea nitrogen (BUN) of 43 mg/dL (normal range 9-25 mg/dL) and creatinine 3.20 mg/dL (Grade 2). Symptoms included abdominal distension, more than 10 watery stools per day with occasional spots of dark material or red blood, diffuse lower abdominal tenderness without tap tenderness, and positional upper abdominal pain thought to be secondary to reflux. Vitals on admission included a temperature of 99.4 degrees Fahrenheit, pulse of 90 beats per minute, blood pressure of 90/60 mmHg, respiratory rate of 20 breaths per minute and oxygen saturation of 96% on room air. Other laboratory results on 29-Jan-2009 included white blood cell count (WBC) 21.0 K/uL (normal range 3.8-9.2), lactate dehydrogenase (LDH) 254 U/L (normal range 107-231), phosphorus 4.2 mg/dL (within normal range), potassium 4.0 (within normal range) and uric acid 15.2 (Grade 4). Liver function tests were within normal range. Stool culture captured on 29-Jan-2009 (study Day 25) was negative for aerobic cultures (salmonella, shigella, Aeromonas or Plesiomonas) and campylobacter. Urine culture resulted in growth with mixed flora. Treatment included levofloxacin, metronidazole, normal saline, and lorazepam/diphenoxylate with atropine. On 30-Jan-2009 (study Day 26), laboratory results included WBC 14.82 K/uL, BUN 16 mg/dL, potassium 5.1 mmol/L (Grade 1), and creatinine 1.16 mg/dL (within normal range). Grade 2 pre-

renal azotemia was considered resolved. Abdominal computed tomography (CT) showed no changes in soft tissue nodules and masses compared to previous study on 15-Jan-2009 (study Day 11). No bowel obstruction or evidence of colitis was seen. On 31-Jan-2009 (study Day 27), laboratory results included WBC 11.73 K/uL, BUN 9 mg/dL, and potassium 3.7 mmol/L (within normal range), creatinine 0.89 mg/dL. Laboratory results included creatinine 0.80 mg/dL (within normal range), and potassium 3.5 mmol/L (within normal range). Patient had a positive serology for cytomegalovirus (CMV) IgG, and a negative CMV IgM. Additional stool studies showed a positive Guaiac test, a negative screening for ova and parasites, and negative microbiology results for Clostridium difficile, Yersinia pestis, and Escherichia coli 0157:H7. On 02-Feb-2009 (study Day 29), laboratory results included creatinine 0.87 mg/dL (within normal range) and potassium 3.8 mmol/L (within normal range). On 03-Feb-2009 (study Day 30), the events of Grade 2 diarrhea and Grade 2 pre-renal azotemia were resolved without sequelae, relevant laboratory results were within normal range, and the patient was discharged from the hospital. Treatment with IPI-504 was held. On 17-Feb-2009 (study Day 44), IPI-504 was restarted at reduced dose 225 mg//m^2.

The Investigator assessed the adverse events of pre-renal azotemia and diarrhea as probably related to blinded study drug (IPI-504).

On 23-Feb-2009 (study Day 50), the patient's laboratory results were significant for creatinine 1.7 mg/dL (Grade 1), lactate dehydrogenase (LDH) 209 U/L (within normal range), phosphorus 3.1 mg/dL (within normal range), potassium 3.8 mmol/L and uric acid 11.0 mg/dL (Grade 4). The patient experienced asymptomatic hypotension during infusion of study drug with blood pressure readings in the 80s/50s mmHg range (systolic/diastolic). He received intravenous fluids, and lisinopril was discontinued. On 24-Feb-2009 (study Day 51), the patient developed diarrhea and reported ten episodes of watery, grey, non-bloody stools, as well as night sweats, numbness and tingling in hands and feet, sore throat without cough, chest pain, shortness of breath, and poor oral intake. He was hospitalized on 25-Feb-2009 (study Day 52) for dehydration, after receiving a total of 6 doses of IPI-504. Vital signs in the emergency department included afebrile temperature, pulse 100 beats per minute decreasing to 70 beats per minute after administration of intravenous fluids, and blood pressure 120/80 mmHg. Vital signs on admission included pulse 85 beats per minute, blood pressure 124/73 mmHg, and oxygen saturation 96% on room air. On 25-Feb-2009 (study Day 52), physical exam was remarkable for mild left upper quarter and left lower quarter abdominal tenderness, mild erythematous macular flush over sternum, throat without exudates or focal lesions, and decreased sensation in hands/feet. Laboratory results were remarkable for uric acid 12.0 mg/dL (Grade 4), creatinine 1.16 mg/dL (within normal range), phosphate 3.7 mg/dL (within normal range), and potassium 4.3 mmol/L (within normal range). A chest x-ray revealed no acute cardiopulmonary process. Computed tomography of the chest, abdomen and pelvis was remarkable for new areas of ground glass appearance as well as consolidation, predominantly along the bronchovascular bundles involving both lower lobes (right more than left) and posterior upper lobe segments, possibly representative of atypical infectious process like mycoplasma pneumonia, and no significant change in overall intra-abdominal tumor burden. The patient was noted to be mildly dehydrated. While hospitalized, the patient did not experience diarrhea, shortness of breath, or chest pain and his renal laboratory results were normal. Treatment included diet modification, intravenous (IV) fluids, enoxaparin, and holding lisinopril. Symptoms improved dramatically with IV fluids. On 26-Feb-2009 (study Day 53), the adverse event of diarrhea resolved, and the patient was discharged from the hospital. Laboratory results included uric acid 10.1 mg/dL (Grade 4), LDH 274 U/L (normal range 107-231), phosphate 3.5 mg/dL (within normal range), and potassium 3.9 mmol/L (within normal range) on the day of discharge. Study drug dosing was held due to the adverse event.

The Investigator assessed the second adverse event of diarrhea as probably related to blinded study drug (IPI-504).

Imaging revealed disease progression, and on 09-Mar-2009 (study Day 64), the patient was withdrawn from study. On approximately 12-Mar-2009 (study Day 67), the patient developed left-sided weakness of his arm and leg, along with gait difficulty. History of this event was remarkable for trembling on the left side, and neck and back pain without clarification over whether the former and latter were acute or chronic symptoms. Symptoms waxed and waned but never resolved completely, and worsened when the patient attempted to perform a function with his affected arm. A generalized seizure was reported as unlikely; however, a motor seizure could not be excluded. On 16-Mar-2009 (study Day 71), physical exam was remarkable for left-sided arm ataxia and left leg weakness, including upgoing left-sided plantar reflex. It was unclear whether his vague plantar flexion weakness was old or new; however, power and sensation appeared to be normal. Vital signs, laboratory results and imaging studies were unremarkable, including a computed tomography scan of the head, and a chest and lumbar spine x-ray. The patient was treated for chronic abdominal pain in the emergency department. He was hospitalized on 16-Mar-2009 (study Day 71) for evaluation of left side weakness to rule out a transient ischemic attack, with the only risk factor cited as hypertension. On 16-Mar-2009 (study Day 71), laboratory results included phosphorus 3.8 mg/ dL (within normal range), potassium 3.7 Meq/ L (within normal range), and creatinine 0.8 mg/dL (within normal range). On 17-Mar-2009 (study Day 72), laboratory results included potassium 3.8 Meq/ L (within normal range), and creatinine 0.9 mg/dL (within normal range). On 19-Mar-2009 (study Day 74), laboratory results included uric acid 5.7 mg/dL (within normal range), potassium 3.5 Meq/ L (Grade 1), and creatinine 1.1 mg/dL (within normal range) and lactate dehydrogenase (LDH) 128 IU/L (within normal range). On 20-Mar-2009 (study Day 75), the event of Grade 2 possible stroke resolved with the sequel of mild (Grade 1) continued left-sided weakness, and the patient was discharged from the hospital.

The Investigator assessed the adverse event of possible stroke as not related to blinded study drug (IPI-504).

Patient #: 001-011
Gender: Female
Age: 21 years
Treatment assignment: Placebo and open-label IPI-504

SAE term	Treatment assignment	Intensity	Relationship	Outcome	Resulted in study discontinuation
Anaemia	Pre-treatment	Grade 2	Not related	Resolved	No
Haemturia	Placebo	Grade 3	Not related	Resolved	No
Deep vein thrombosis	IPI-504	Grade 3	Not related	Ongoing	No
Haematoma infection	IPI-504	Grade 3	Not related	Resolved	No
Operative haemorrhage	IPI-504	Grade 3	Not related	Resolved	No

Patient number 001-011 was a 21-year-old Caucasian woman diagnosed with GIST on 08-Apr-2005, with metastases to the small bowel, omentum/mesentery, lungs, and liver. Prior therapies included imatinib, sunitinib, nilotinib, OSI-936, sorafenib, and dasatinib. Cancer surgical history included

exploratory laparotomy with removal of two peritoneal tumors, gastric/duodenal resection with gastric tube placement; resection of pelvic tumor, small bowel, and bilateral salpingo-oophorectomy/ileostomy closure; exploratory laparotomy with debulking of intra-abdominal tumor and resection of right lower quadrant tumor, small bowel resection, and appendectomy; laparotomy with diverting ileostomy. Relevant medical history included right hydroureter, cystoscopy with right ureteral stent placement, perforation of the colon, bowel necrosis, and peritonitis. Relevant concurrent medical conditions included right hydronephrosis, anorexia, and multiple drug allergies. Concomitant medications included scopolamine, estradiol, ibuprofen, dronabinol, methadone, pantoprazole, epinephrine, methylphenidate, nystatin, loratadine, gabapentin, oxybutynin, multivitamin, folic acid, ferrous sulfate, granisetron, sennosides, docusate, polyethylene glycol, lorazepam, and ondansetron.

On 26-Jan-2009, the patient enrolled in the study. During screening on 06-Feb-2009, hematocrit was 25.7% (reference range 24.8-43.6) and hemoglobin 8.6 mg/dL (Grade 2). No evidence of bleeding was discovered based on obvious signs, on computed tomography (CT) scans of chest and abdomen, or in the patient's stool. The patient had difficulty taking iron supplements due to increased nausea from recent chemotherapy. She was diagnosed with Grade 2 microcytic anemia with low iron and total binding capacity, considered likely caused by chronic blood loss, poor oral intake, and chronic disease. Hemolysis was considered unlikely, as bilirubin was low at 0.3 (unit and normal range not provided). The patient was transfused with transfused with one packet of packed red blood cells and instructed to continue iron supplementation. Follow-up hematocrit increased from 17% to 30%. On 07-Feb-2009, hemoglobin was 10.5 mg/dL (Grade 1) and hematocrit was 30.7% (normal range 36-48), and the adverse event was considered resolved. The need for ureteral stent replacement was reported as an alternative etiology for the hematuria.

The Investigator assessed the adverse event of anemia as not related to blinded study drug (placebo).

The patient continued on study, and was randomized to receive placebo. On 09-Feb-2009 (study Day 1) prior to dosing, hemoglobin was 10.7 gm/dL (Grade 1) and hematocrit was 31.1% (normal range 34.8-43.6). The patient began study treatment and received 4 doses of placebo without incident. On 13-Feb-2009 (study Day 5), non-serious symptoms of hematuria began and included pink urine and passing of small blood clots. Urine culture obtained on 21-Feb-2009 (study Day 13) showed mixed flora with a total colony count of 1,000. On 27- Feb-2009 (study Day 19), the patient was hospitalized for Grade 3 gross hematuria. Symptoms included: cranberry-colored urine with 3-4 cm clots, urinary urgency with intense bladder pressure, and urinary frequency, with urination every 15-20 minutes producing 50-100cc of urine at a time. Her heart rate initially was noted as 118 beats per minute, which improved to 90 beats per minute with intravenous (IV) fluids. Physical exam was unremarkable. Lab results included: red blood cells 3.70, hemoglobin 9.7, hematocrit 28.4, platelets 276, creatinine 0.83, blood urea nitrogen 15 (units and normal ranges were not provided). Urinalysis was positive for hematuria and bacteruria and was consistent with a urinary tract infection. Urine culture from 27-Feb-2009 (study Day 19) showed no growth as of 01-Mar-2009 (study Day 21). A seven day course of ciprofloxacin was started. . On 28-Feb-2009 (study Day 20), abdominal CT scan results were consistent with blood clots, and unchanged moderate right hydronephrosis despite a satisfactorily positioned double J catheter, along with a mild unchanged hydronephrosis of the left kidney, due to ureteral obstruction by numerous retroperitoneal metastatic implants. A Foley catheter was placed for hand irrigation in order to extract clots from the bladder. On 02-Mar-2009 (study Day 22), cystoscopy was negative for tumor invasion into the bladder. On 02-Mar-2009 (study Day 22), the ureteral stent was replaced. Laboratory results showed: red blood cells 3.73, hemoglobin 10.0, hematocrit 28.9, platelets 189, creatinine 0.81, blood urea nitrogen 11 (units and normal ranges not provided). The patient's hematuria and discomfort improved during

hospitalization. On 03-Mar-2009 (study Day 23), the adverse event resolved and the patient was discharged on medications oxybutynin and ciprofloxacin, in addition to her admission medications. Study drug was interrupted due to the adverse event.

The Investigator assessed the adverse event of hematuria as not related to blinded study drug (placebo).

On 12-Mar-2009 (study Day 32), after receiving a total of 7 doses of blinded study drug, the patient was noted to have disease progression. On 23-Mar-2009 (study Day 43), she began treatment with open-label IPI-504, and received 4 doses of IPI-504. On 09-Apr-2009 (17 days after initiation of IPI-504), the patient was hospitalized for elective tumor debulking surgery of tumors located in the anterior abdominal wall and pelvis. Her intraoperative course was complicated by hypotension from Grade 3 gross hemorrhage requiring 25 units of packed red blood cells, 20 units fresh frozen plasma, 3 units of platelets, 1 bag of cryoprecipitate, 7 L of normal saline, and vasopressors with resolution of the intraoperative gross hemorrhage. Potassium level during surgery was 7.2 mmol/L (Grade 4) and resolved after treatment with insulin and 50% dextrose solution. On 10-Apr-2009 (18 days after initiation of IPI-504), the patient was transfused with 1 unit of packed red blood cells and laboratory test results included WBC 5.36 K/UL, hematocrit 25% (normal range 36-48), hemoglobin 8.5 g/dL (Grade 2), INR 1.2 (normal range 0.9-1.1), fibrinogen 308 mg/dL (within normal range), PTT 33.5 seconds (within normal range), platelet count 88 (Grade 1), PT 14.9 seconds (normal range 11.9-14.5), and oxygen saturation 99.9% On 12-Apr-2009 (20 days after initiation of IPI-504), the patient was hemodynamically stable. She had adequate pain control with an epidural, methadone patient-controlled analgesic, and a fentanyl drip. Laboratory results were significant for creatinine 1.5 mg/dL (Grade 1), and a subsequent ultrasound showed unstable, moderate to severe right hydronephrosis and moderate left hydronephrosis. She was advanced to a regular diet by 14-Apr-2009 (22 days after initiation of IPI-504but had minimal oral intake. On 17-Apr-2009 (25 days after initiation of IPI-504), she had a fever of 102.8 degrees Fahrenheit and was diagnosed with an intraabdominal infected hematoma. The patient underwent surgery for Grade 3 intraabdominal infected hematoma evacuation and right ureteral stent change. Cultures obtained from hematoma evacuation grew coagulase-negative Staphylococcus and Corynebacteria. Additional laboratory results were significant for WBC 15.77 K/UL, hematocrit 27 % (normal range 36-48), hemoglobin 8.7 g/dL (Grade 2), platelet count 249 (within normal range), and oxygen saturation 99.9% (within normal range). The event was considered resolved. On 24-Apr-2009 (32 days after initiation of IPI-504), an ultrasound due to peripheral edema revealed Grade 3 bilateral common femoral vein deep vein thrombosis (DVTs). The patient was treated with IV heparin and then enoxaparin sodium. On 28-Apr-2009 (36 days after initiation of IPI-504), she was discharged from the hospital without evidence of hematoma collection or infection. Complications of the patient's surgery were reported to be an alternative etiology for the adverse events of deep vein thrombosis, haematoma infection, and operative haemorrhage. Laboratory results were significant for WBC 14.60 K/UL (normal range 4-10), hematocrit 26.2 % (normal range 36-48), hemoglobin 8.2 g/dL (Grade 2), platelet count 403 (within normal range), PT 15.5 seconds (within normal range), PTT 47.6 seconds (normal range 23.8-36.6) and INR 1.2 (normal range 0.9-1.1). The adverse event of bilateral common femoral vein DVTs was ongoing.

The Investigator assessed the adverse events of intraoperative gross hemorrhage, infected hematoma, and bilateral common femoral vein DVTs as not related to IPI-504.

Patient #: 001-014 **Gender: Male** **Age: 57 years** **Treatment Assignment: IPI-504**					
SAE term	**Treatment assignment**	**Intensity**	**Relationship**	**Outcome**	**Resulted in study discontinuation**
Hyperglycaemia	IPI-504	Grade 3	Definite	Resolved	No
Asthenia	IPI-504	Grade 3	Definite	Resolved	No
Nausea	IPI-504	Grade 3	Definite	Resolved	No
Vomiting	IPI-504	Grade 3	Definite	Resolved	No
Atrial fibrillation	IPI-504	Grade 2	Not related	Resolved	No
Aspartate aminotransferase increased	IPI-504	Grade 3	Definite	Resolved	No
Alanine aminotransferase increased	IPI-504	Grade 2	Definite	Resolved	No
Blood alkaline phosphatase increased	IPI-504	Grade 3	Definite	Ongoing	No
Small intestinal obstruction	IPI-504	Grade 3	Not related	Resolved	No
Diarrhoea	IPI-504	Grade 3	Definite	Resolved	No
Atrial fibrillation	IPI-504	Grade 2	Possible	Resolved	No
Lipase increased	IPI-504	Grade 3	Definite	Resolved	No
Diarrhoea	IPI-504	Grade 3	Definite	Resolved	No
Alanine aminotransferase increased	IPI-504	Grade 3	Definite	Ongoing	No
Aspartate aminotransferase increased	IPI-504	Grade 4	Definite	Resolved	Yes

Patient number 001-014 was a 57-year-old Caucasian man diagnosed with GIST on 10-Dec-2004, with initial presentation in the esophagus. Prior therapies included imatinib, sunitinib, and sorafenib, and radiation therapy to the tumor near the remaining part of the liver. Cancer surgical history included resection of GIST liver metastasis and laparoscopic cholecystectomy.

Relevant medical history included abdominal discomfort, intermittent abdominal distress, constipation, postprandial bloating, increased edema, nausea, ileus, post-operative liver function test abnormalities. The patient had no previous history of diabetes mellitus, hyperglycemia, hyperthyroidism, or atrial fibrillation. Concurrent medical conditions include gastroesophageal reflux disease (GERD), and gastroesophagitis. Concomitant medications included diclofenac/misoprostol, docusate, bisacodyl, polyethylene glycol, pantoprazole, metoclopramide, senna, lorazepam, guaifenesin/codeine, benzonatate, and misoprostol.

The patient enrolled in the study on 17-Feb-2009, and was subsequently randomized to receive IPI-504. On 03-Mar-2009 (study Day 1), the patient started treatment with study drug. Following his first dose, he developed right shoulder pain. He presented to the emergency room a few days later, where computed tomography was negative for pulmonary embolism, and he was discharged home.

On 08-Mar-2009 (study Day 6), the patient presented to the emergency room with complaints of nausea, vomiting, abdominal pain, shortness of breath, palpitations, and delirium. He had experienced several episodes of paroxysmal nocturnal dyspnea overnight. He was found to be in atrial fibrillation; heart rate was 220 beats per minute. Thyroid function tests suggested hyperthyroidism, attributed to prior sorafenib use, and there was concern for associated pulmonary edema. On 08-Mar-2009 (study Day 6), an electrocardiogram (ECG) showed atrial fibrillation with rapid ventricular response (heart rate 208 beats per minute). Repeat ECGs on 08-Mar-2009 (study Day 6) also showed atrial fibrillation with rapid ventricular response (heart rate from 118-149). A chest x-ray at 21:35 showed low lung volumes, atelectasis at both bases and ruled out pleural effusions and pulmonary vasculature engorgement. A subsequent chest x-ray was compared to the previous study and showed markedly reduced lung volume with subsegmental atelectasis and ruled out large pleural effusion, pneumothorax, focal consolidation and florid pulmonary edema. The patient was found to have a malignant small bowel obstruction and hyperglycemia on admission. Laboratory results on 08-Mar-2009 (study Day 6) included white blood cell count (WBC) 24.36 (normal range 4-10), hemoglobin 12.4 g/dL (Grade 1), hematocrit 38.7 % (normal range 40-54), cardiac Troponin-I (cTn-I) 0.04 ng/mL (normal range 0.00-0.04), glucose 320 mg/dL (Grade 3), aspartate aminotransferase (AST) 544 U/L (Grade 3), alanine aminotransferase (ALT) 185 U/L (Grade 2), alkaline phosphatase 579 U/L (Grade 2), potassium 5.1 mmol/L (Grade 1), sodium 131 mmol/L (Grade 1), P02 49 mmHg (normal range 65-95), PC02 28 mmHg (normal range 36-47), base excess -6 mEq/L (normal range -3 to 3) and lactic acid 3.6 mmol/L (normal range 0.5-2.2). The patient was treated with intravenous (IV) fluids as well as diltiazem, verapamil and digoxin. His heart rate remained elevated and he required six liters of oxygen to maintain an oxygen saturation above 90%. Endocrinology workup, performed for concern of chemo-induced thyrotoxicosis, was negative. A follow up ECG on 09-Mar-2009 (study Day 7) showed atrial fibrillation with rapid ventricular response (rate of 169 beats per minute), and an anterior myocardial infarction could not be ruled out. On 09-Mar-2009 (study Day 7), an echocardiogram showed normal ventricular function with an estimated ejection fraction of 60-65%, and no pericardial effusion or other significant abnormalities. He was treated with IV amiodarone, IV esmolol, insulin, and antibiotics for presumed pneumonia. An abdominal ultrasound on 09-Mar-2009 (study Day 7) revealed no biliary dilatation in the common bile duct. On 09-Mar-2009 (study Day 7), laboratory results included WBC 26.89 K/uL (normal range 4-10), hemoglobin 11.8 g/dL (Grade 1), hematocrit 36.1% (normal range 40-54), cTn-I <0.04 ng/mL (within normal limits), brain natriuretic peptide (BNP) 52 pg/mL (within normal limits), glucose 426 mg/dL (Grade 3), AST 522 U/L (Grade 3), ALT 179 U/L (Grade 2), alkaline phosphatase 694 U/L (Grade 3), thyroid stimulating hormone (TSH) 0.050 mIU/L (normal range 0.5-5.0), triiodothyronine (T3) 263 ng/dL (reference range 70-170), free thyroxine (T4) 2.0 ng/dL (reference range 0.8-1.8), potassium 4.4 mmol/L (within normal limits), sodium 132 mmol/L (Grade 1), P02 110mmHg (normal range 65-95), PC02 27 mmHg (normal range 36-47), base excess -3 mEq/L (normal range -3 to 3), and total bilirubin of 1.1 mg/dL (normal range of 0.2-1.2). Results from an acetaminophen assay on 09-Mar-2009 (study Day 7) revealed a value of less than 4 ug/mL, which was below the assay range (normal range 10-25). The patient experienced increased abdominal distension with the absence of flatus. A nasogastric tube was inserted and 1.5 liters of fluid was evacuated. A chest x-ray on 10-Mar-2009 (study Day 8) demonstrated continued basilar atelectases with mild interstitial pulmonary edema with associated small bilateral pleural effusions. A radiograph of the kidneys, ureters and bladder (KUB) showed multiple dilated small bowel loops likely indicating an early or partial small bowel obstruction. On 10-Mar-2009 (study Day 8), laboratories

included AST 241 U/L (Grade 3), ALT 161 U/L (Grade 2), alkaline phosphatase 715 U/L (Grade 3), potassium 3.5 mmol/L (within normal values), sodium 131 mmol/L (Grade 1), P02 90mmHg (normal range 65-95), PC02 29 mmHg (normal range 36-47), base excess -2 mEq/L (normal range -3 to 3), and glucose values ranging from 176-242 mg/dL (Grade 2). On 11-Mar-2009 (study Day 9), laboratory results revealed AST 133 U/L (Grade 2), ALT 119 U/L (Grade 1), alkaline phosphatase 606 U/L (Grade 3), potassium 3.8 mmol/L (within normal limits), sodium 137 mmol/L (within normal limits), P02 105mmHg (normal range 65-95), PC02 35 mmHg (normal range 36-47), and base excess of -4 mEq/L (normal range -3 to 3). Glucose values on 11-Mar-2009 (study Day 9) ranged from 146-208 mg/dL (Grade 1-Grade 2), and glycosylated hemoglobin (Hgb A1C) was 7.1% (normal range 4.2-5.8). Blood cultures obtained on 09-Mar-2009 (study Day 7) and 11-Mar-2009 (study Day 9) showed no growth for both specimens. A urine culture obtained on 11-Mar-2009 (study Day 9) showed no growth as of 13-Mar-2009 (study Day 11). On 11-Mar-2009 (study Day 9), a computed tomography (CT) scan of the abdomen and pelvis showed a small bowel obstruction with a left lower quadrant transition point, bowel wall thickening in the distal transverse, descending, and rectosigmoid colon, which could not exclude ischemia or infection, extensive, unchanged metastases of known GIST, central, ground glass opacities that were consistent with pulmonary edema and lingular and right lower lobe consolidations. A chest x-ray revealed no changes from the previous study. On 12-Mar-2009 (study Day 10), an ECG still showed atrial fibrillation with rapid ventricular response (rate of 152 beats per minute), and anterior myocardial infarction could not be ruled out. Laboratory results on 12-Mar-2009 (study Day 10) revealed AST 67 U/L (Grade 1), ALT 81 U/L (Grade 1), alkaline phosphatase 535 (Grade 2), potassium 3.2 mmol/L (within normal limits), and sodium 140 mmol/L (within normal limits). Atrial fibrillation was attributed to transient sorafenib-induced hyperthyroidism. Amiodarone and esmolol were discontinued on 12-Mar-2009 (study Day 10) as the patient was in sinus rhythm and asymptomatic, and his thyroid tests had returned to normal (values not provided). On 12-Mar-2009 (study Day 10), a repeat KUB showed a gas-distended cecum without dilated small bowel loops to suggest obstruction. A chest x-ray showed bilateral perihilar opacities. On 13-Mar-2009 (study Day 11), AST was 42 U/L (Grade 1), ALT was 61 U/L (Grade 1), and alkaline phosphatase was 450 U/L (Grade 2). A chest x-ray revealed small lung volumes, continued patchy opacities in both lower lobes indicating atelectasis but without pneumothorax. Vancomycin was discontinued on 13-Mar-2009 (study Day 11). The patient also received metoprolol, which was discontinued on 16-Mar-2009 (study Day14) as his heart rate and blood pressure stabilized. His delirium resolved during hospitalization, and he was to avoid medications such as zolpidem and lorazepam in the future. The patient's small bowel obstruction was managed medically with steroids, metoclopramide, octreotide, docusate, senna, and polyethylene glycol, and resolved over his hospital stay. Retrospective review of the patient's history indicated that all three episodes of reversible, partial to complete, small bowel obstruction occurred following administration of oral contrast. Additionally, he experienced severe abdominal pain associated with his malignancy, which was treated with opioids and subsequently resolved. Additional treatment during hospitalization included NPH insulin on a sliding scale, prophylactic enoxaparin, which was decreased with his increased ambulation, as well as trazodone for insomnia, and Thorazine. On 15-Mar-2009 (study Day 13), laboratory results revealed AST 66 U/L (Grade 1), ALT 50 U/L (within normal limits), and alkaline phosphatase 529 U/L (Grade 2). On 18-Mar-2009 (study Day 16), AST was 28 U/L (within normal limits), ALT was 29 U/L (within normal limits), and alkaline phosphatase was 389 U/L (Grade 2). His labs continued to stabilize, and discharge labs on 21-Mar-2009 (study Day 19) revealed AST 18 U/L (within normal limits), ALT 18 U/L (within normal limits), alkaline phosphatase 270 U/L (Grade 1), total bilirubin 0.5 mg/dL (within normal limits), potassium 3.9 mmol/L (within normal limits), sodium 136 mmol/L (within normal limits), glucose 107 mg/dL (within normal limits), and WBC 19.46 K/UL (reference range 4-10). His glucose ranged from 53-113 mg/dL (Grade 1) on the day of discharge, and his insulin was discontinued; however, he was instructed to continue monitoring his glucose levels post-

discharge. On 10-Mar-2009 (study Day 8), the adverse event of Grade 3 hyperglycemia resolved, on 11-Mar-2009 (study Day 9), the adverse events of Grade 3 elevated AST, Grade 3 elevated ALT, Grade 3 nausea, Grade 3 vomiting, Grade 3 diarrhea, and Grade 3 generalized weakness resolved; on 12-Mar-2009 (study Day 10), the adverse event of Grade 2 atrial fibrillation resolved; and, on 21-Mar-2009 (study Day 19), the adverse event of Grade 3 malignant small bowel obstruction resolved. On 21-Mar-2009 (study Day 19), the patient was discharged from the hospital. Study drug dose was reduced in response to the adverse events.

The Investigator assessed the adverse events of hyperglycemia, asthenia, nausea, vomiting, elevated AST, elevated ALT, elevated alkaline phosphatase, and diarrhea as definitely related to blinded study drug (IPI-504), and the adverse events of atrial fibrillation and malignant small bowel obstruction as not related to blinded study drug (IPI-504).

Study drug was resumed at a dose of 225 mg/m_2. On 03-Apr-2009 (study Day 32), the patient received the fourth dose of study drug. He felt well until the morning of 04-Apr-2009 (study Day 33), when he developed nausea, vomiting and diarrhea. He presented to the clinic for rehydration and laboratory assessment, where he experienced severe diarrhea with four liquid bowel movements. Laboratory results showed development of transaminitis: AST increased from 25 U/L (within normal limits) to 557 U/L (Grade 4) within 24 hours and ALT increased from 30 (within normal limits) to 167 U/L (Grade 3). Other laboratory results included albumin 3.3 g/dL (Grade 1), alkaline phosphatase 232 U/L (Grade 1), total bilirubin 0.3 mg/dL (within normal limits), amylase 89 U/L (Grade 1), and lipase 193 U/L (Grade 3). Acetylcysteine was started (10 gram dose), and the patient was admitted to the hospital for management of elevated liver function tests and diarrhea. Upon presentation at the hospital, he was noted to have Grade 1 anorexia and grade 1 malaise. Eastern Cooperative Oncology Group (ECOG) status was 2. IV fluids were given for rehydration, and acetylcysteine was continued for elevated liver function tests. Ondansetron, lorazepam and prochlorperazine were given as needed for nausea and vomiting. Repeat laboratory tests at 8:22 pm included AST 869 U/L (Grade 4), ALT 356 U/L (Grade 3), alkaline phosphatase 259 U/L (Grade 1), total bilirubin 0.3 mg/dL, and albumin 3.0 g/dL. Liver function test pattern was reported as consistent with hepatocellular injury. Diarrhea worsened on acetylcysteine and was later controlled with diphenoxylate/atropine and deodorized tincture of opium (DTO). On 05-Apr-2009 (study Day 34), the patient experienced atrial fibrillation with rapid ventricular response (heart rate 170 beats per minute), which persisted in spite of metoprolol and diltiazem boluses, as well as diltiazem drip. The patient was started on an amiodarone infusion, and subsequently converted back to sinus rhythm. The patient remained hemodynamically stable while in atrial fibrillation. The event of atrial fibrillation resolved on 05-Apr-2009 (study Day 34). Laboratory results at 01:33 included ALT 419 U/L (Grade 3), AST 855 U/L (Grade 4), alkaline phosphatase 290 U/L (Grade 1), total bilirubin 0.3 mg/dL (within normal range), and white blood cell count of 15.32 K/UL (normal range 4-10). Repeat laboratory tests at 10:39 showed ALT 337 U/L (Grade 3), AST 433 U/L (Grade 3), alkaline phosphatase 245 U/L (Grade 1), and total bilirubin 0.4 mg/dL (within normal range). On 06-Apr-2009 (study Day 35), laboratory results showed ALT 207 U/L (Grade 2), AST 136 U/L (Grade 2), alkaline phosphatase 232 U/L (Grade 1), and total bilirubin 0.4 mg/dL (within normal range). On 06-Apr-2009 (study Day 35), the adverse events of Grade 4 elevated AST and Grade 3 diarrhea resolved, and patient was discharged from the hospital. On 07-Apr-2009 (study Day 36), the patient's repeat liver function test results were AST 47 U/L (Grade 1) and ALT 129 U/L (Grade 1), alkaline phosphatase 347 U/L (Grade 2). The adverse event of Grade 3 elevated ALT was reported as ongoing. Coagulation parameters remained stable, and the patient was reported to have no signs of hepatic failure. The patient was discharged from the hospital on 06-Apr-2009 (study Day 35). On 10-Apr-2009 (study Day 39), laboratory results showed lipase 49 U/L (within normal range) and amylase 42 U/L (within

normal range). Study participation was discontinued on 10-Apr-2009 (study Day 39) due to the adverse event of Grade 4 elevated AST.

The Investigator assessed the adverse events of lipase increased, diarrhea, elevated AST, and elevated ALT as definitely related to blinded study drug (IPI-504), and the adverse event of atrial fibrillation as possibly related to blinded study drug (IPI-504).

Patient #: 001-015 **Gender: Male** **Age: 48 years** **Treatment Assignment: IPI-504**					
SAE term	**Treatment assignment**	**Intensity**	**Relationship**	**Outcome**	**Resulted in study discontinuation**
Atrioventricular block second degree	IPI-504	Grade 1	Probable	Resolved	No

Patient number 001-015 was a 48-year-old Caucasian man diagnosed with GIST on 26-Jun-2006, with initial presentation in the stomach, colon, and omentum/mesentery. Metastatic disease included gastroesophageal mass, perihepatic lesions, and disease in the anterior mesenteric region. Prior therapies included imatinib, gemcitabine/docetaxel, and sunitinib. Cancer surgical history included tumor resection and failed resection of a portal hepatic lesion. Relevant medical history included sunitinib-related toxicities (hypertension, diarrhea, hand-foot syndrome, stomatitis, fatigue, muscle cramps, and abdominal cramping), rash from imatinib, hypothyroidism, and lower extremity edema. Concomitant medications included levothyroxine, furosemide, and amlodipine besylate.

The patient enrolled in the study on 27-Feb-2009, and was subsequently randomized to receive IPI-504. On 16-Mar-2009 (study Day 1), the patient started treatment with study drug, and received 1 dose. Before dosing, liver and renal function tests were normal, and thyroid stimulating hormone (TSH) level was 0.09 (reference range 0.5-50). At the end of the infusion at 15:20, electrocardiogram (ECG) revealed first degree AV block. Subsequent ECG showed Grade 1 second degree AV block (Mobitz Type 1). The progression from first degree AV block to second degree AV block prompted transfer to the Emergency Department (ED) for observation. Vital signs were stable and physical exam was not significant. ECG at 17:22, 2 hours post-infusion, showed sinus rhythm with first degree AV block and incomplete right bundle branch block; P-R interval was 220 ms. Creatine kinase (CK) was 86 U/L (reference range 41-266), and CKMB <0.2 (reference range 0-5.0). Levothyroxine dose was decreased due to low TSH. Repeat ECG showed normal sinus rhythm with P-R interval 204 ms. Repeat ECG approximately 3 hours later showed normal sinus rhythm with incomplete right bundle branch block; P-R interval was 190 ms. Amlodipine besylate was discontinued, as it was considered to have potentially contributed to the AV block. The patient's P-R interval met the criteria for discharge, and he was released from the ED. The event resolved without sequelae on 16-Mar-2009. Study drug IPI-504 was dose reduced to 300 mg/m2 and the second dose of study drug was administered at this reduced dose on 20-Mar-2009 (study Day 5), 27-Mar-2009 (study Day 12), 06-Apr-2009 (study Day 22) , and 13-Apr-2009 (study Day 29). Subsequent AV block first degree was intermittent Grade 1 post-treatment, and re-appeared after each IPI-504 infusion from 20-Mar-2009 (Day 5) through 13-Apr-2009 (study Day 29).

The Investigator assessed the adverse event of atrioventricular block second degree as probably related to blinded study drug (IPI-504).

Patient #: 001-016 **Gender: Female** **Age: 47 years** **Treatment assignment: IPI-504**					
SAE term	**Treatment assignment**	**Intensity**	**Relationship**	**Outcome**	**Resulted in study discontinuation**
Hypokalaemia	Pre-treatment	Grade 3	Not related	Resolved	No
Vomiting	Pre-treatment	Grade 2	Not related	Resolved	No
Nausea	Pre-treatment	Grade 2	Not related	Resolved	No
Diabetic ketoacidosis	IPI-504	Grade 4	Definite	Resolved	No
Diarrhoea	IPI-504	Grade 3	Definite	Resolved	No
Aspartate aminotransferase increased	IPI-504	Grade 3	Definite	Resolved	No
Blood alkaline phosphatase increased	IPI-504	Grade 2	Definite	Ongoing	No

Patient number 001-016 was a 47-year-old African American woman diagnosed with GIST in March 1998, with initial presentation in the small bowel and omentum/mesentery and subsequent metastases to the liver, peritoneum, and spleen. Prior therapies included imatinib and sunitinib. Cancer surgical history included cryotherapy of hepatic lesion, partial hepatectomy, liver biopsy, and numerous laparotomies and resections. Relevant medical history includes small bowel obstruction, malignant hypertension, pleural effusion, hypotension, hematuria, abdominal wound infection, and Cesarean section. Relevant concurrent medical conditions included decreased appetite, dizziness, nausea, vomiting, hemoptysis, shortness of breath, gout, constipation, abdominal pain, and gastroesophageal reflux disease. The patient had no history of diabetes. Concomitant medications included simethicone, senna, hydromorphone, oxycodone, esomeprazole, magnesium, cimetidine, acetaminophen/ aspirin/caffeine, amlodipine, clonidine, hydroxyzine, hydrochlorothiazide, potassium, temazepam, and allopurinol. Current social history was significant for smoking.

The patient enrolled in the study on 02-Mar-2009, and was subsequently randomized to receive IPI-504. At her 27-Mar-2009 screening visit, she reported acute onset of incessant nausea and vomiting associated with increased abdominal pain concerning for small bowel obstruction. She also had ongoing constipation with last bowel movement three days prior, but with continued flatus. Symptoms included weakness, numbness, dizziness, occasional double vision, blurry vision, trouble walking, insomnia, minor hemoptysis, shortness of breath secondary to abdominal pain, decreased appetite, reflux, nocturia, night sweats, fatigue and minor neck, back and joint pain. Physical exam was remarkable for soft, mildly distended abdomen with positive bowel sounds and significant tenderness in the right upper quadrant. This abdominal tenderness precluded deep palpitation and assessment of hepatosplenomegaly. Lab results included potassium 2.8 mmol/L (Grade 3), lactate dehydrogenase (LDH) 353 U/L (normal range 107-231), alanine transaminase 48 U/L (within normal range), aspartate transaminase 46 U/L (Grade 1) and alkaline phosphatase 291 U/L (Grade 1), and glucose 147 mg/dL (Grade 1). Computed

tomography (CT) of the abdomen showed multiple pulmonary nodules worrisome for metastatic disease and bulky, hepatic and mesentery metastases. The impression was that possible extrinsic compression of the duodenum and stomach from metastases could lead to a low-grade intermittent obstruction. Nausea and vomiting were attributed to compression and the patient was admitted to the hospital for symptom management and electrolyte abnormality. She was treated with intravenous fluids and ondansetron, oxycodone was changed to Dilaudid, and she was started on a low residue diet and potassium/magnesium scales. She also continued to receive her proton-pump inhibitor and deep venous thrombosis prophylaxis, enoxaparin sodium. Abdominal pain was well-controlled on Dilaudid. Nausea and vomiting resolved and the patient was able to eat without discomfort. On 28-Mar-2009, the adverse events of Grade 2 nausea, Grade 2 vomiting, and Grade 3 hypokalemia were resolved, and the patient was discharged from the hospital. No action was taken with IPI-504, as the patient had not yet been dosed with study drug. Laboratory results on discharge showed potassium at 3.4 mmol/L (Grade 2) and osmolality within normal range.

The investigator assessed the events of hypokalemia, vomiting, and nausea as not related to study drug.

The patient continued on study, and was scheduled to start treatment with study drug IPI-504 on 31-Mar-2009 (study Day 1). Pre-dose laboratory results at 10:25 showed glucose 218 mg/dL (Grade 2), potassium 3.5 mmol/dL (within normal range), LDH 633 U/L (normal range 107-231), AST 49 U/L (Grade 1), ALT 50 U/L (within normal range) and AlkP 276 U/L (Grade 1). Repeat glucose laboratory result from 13:09 was 154 mg/dL (Grade 1). The patient received her first dose of IPI-504. On 03-Apr-2009 (study Day 4), pre-dosing laboratory results included glucose 220 mg/dL (Grade 2), LDH 919 U/L (normal range 107-231), AST 99 U/L (Grade 2), ALT 72 U/L (Grade 1), and AlkP 373 U/L (Grade 2). The patient received her second dose of IPI-504. On 04-Apr-2009 (study Day 5), as the patient returned to the clinic for laboratory testing to identify any potential sequelae secondary to diarrhea she had experienced earlier in the week. She was subsequently hospitalized due to hyperglycemia, Grade 3 diarrhea, and nausea. Vital signs at admission included temperature 97.3 degrees F, heart rate 90 beats per minute, blood pressure 160/90 mmHg and respiratory rate 20 breaths per minute. Physical exam was unremarkable. Blood glucose was over 400 mg/dL and bicarbonate was 18 mmol/L, with anion gap of 18 mmol/L. Other laboratory results included AST 105 U/L (Grade 1), ALT 231 U/L (Grade 3), and alkaline phosphatase 463 U/L (Grade 2). Intravenous fluids, potassium, and subcutaneous insulin were administered. Glucose levels began to decrease; however, bicarbonate remained decreased, with an anion gap of 18 mmol/L and a beta-hydroxy butyrate of 3 mmol/L. The patient was diagnosed with diabetic ketoacidosis. Long-acting insulin was started, while fluids and potassium were continued. On 05-Apr-2009 (study Day 6), bicarbonate was 21 mmol/L, b-hydroxybutyrate was 1.89 mmol/L, anion gap was 12mmol/L, and glucose was 179 mg/dL. Insulin and fluids continued and on 06-Apr-2009 (study Day 7), glyburide was started. Nausea, vomiting and diarrhea were considered secondary to chemotherapy. Intravenous fluids were administered, diphenoxylate/atropine was administered for diarrhea and ondansetron was given for nausea. On 06-Apr-2009 (study Day 7), the adverse events of Grade 3 diarrhea and Grade 4 diabetic ketoacidosis were resolved, and the patient was discharged from the hospital. On 10-Apr-2009 (study Day 11), glucose was 227 mg/dL, ALT 127 U/L (Grade 1), AST 146 U/L (Grade 2), and alkaline phosphatase 1025 U/L (Grade 3); the adverse event of Grade 3 elevated AST was considered resolved. On 24-Apr-2009 (study Day 25), glucose was 94 mg/dL, ALT 41 U/L, AST 68 U/L, and alkaline phosphatase 646 U/L (Grade 2). On 08-May-2009 (study Day 39), alkaline phosphatase was 480 U/L (Grade 2). On 22-May-2009 (study Day 53), alkaline phosphatase was 400 U/L (Grade 2). On 05-Jun-2009 (study Day 67), alkaline phosphatase was 657 U/L (Grade 2). The event of elevated Grade 2 alkaline phosphatase was reported as ongoing, as this was a chronic laboratory finding.

The investigator assessed the events of diabetic ketoacidosis, diarrhea, elevated AST, and elevated alkaline phosphatase as definitely related to study drug.

Patient #: 005-001 **Gender: Male** **Age: 40 years** **Treatment assignment: N/A (Screen failure)**					
SAE term	**Treatment assignment**	**Intensity**	**Relationship**	**Outcome**	**Resulted in study discontinuation**
Disease progression	Pre-treatment	Grade 5	Not related	Fatal	No

Patient number 005-001 was a 40-year-old Caucasian man with GIST, diagnosed in February 2007. Prior therapies included imatinib and sunitinib. Medical history and concomitant medications were unknown for this screen failure patient.

The patient enrolled in the study on 29-Jan-2009 and failed screening due to out-of-range bilirubin results and Eastern Cooperative Oncology Group (ECOG) performance status. On 08-Feb-2009, the patient was noted to have symptoms of disease progression. On 09-Feb-2009, the patient was hospitalized with sudden deterioration, and was diagnosed with life-threatening, rapidly progressing disease. Symptoms included gradual increase in drowsiness and confusion, as well as significant abdominal distension. The family opted for palliative care. On 10-Feb-2009, the adverse event of disease progression was fatal (Grade 5). No autopsy was performed. The cause of death was reported as rapidly progressing disease.

The Investigator assessed the adverse event of rapidly progressing disease as not related to study drug.

Patient #: 005-002 **Gender: Man** **Age: 49 years** **Treatment Assignment: Placebo**					
SAE term	**Treatment assignment**	**Intensity**	**Relationship**	**Outcome**	**Resulted in study discontinuation**
Peripheral oedema	Placebo	Grade 3	Not related	Ongoing	Yes
Lethargy	Placebo	Grade 3	Not related	Ongoing	No

Patient number 005-002 was a 49-year-old Caucasian man diagnosed with GIST on 20-Jan-2006, with initial presentation in the omentum/mesentery. Prior therapies included imatinib and sunitinib. Prior surgical history included umbilical lumpectomy. The patient's medical history was significant for hypercalcemia and anemia. Relevant concurrent medical conditions included low phosphate, bilateral leg oedema, cachexia, fatigue, and intermittent dizziness. Concomitant medications were spironolactone, granisetron, esomeprazole, metoclopramide, phosphate, loperamide, and furosemide.

The patient enrolled in the study on 09-Feb-20009, and was subsequently randomized to receive placebo. On 24-Feb-2009 (study Day 1), he started treatment with study drug, and received 7 doses. On 16-Mar-2009 (study Day 21), the patient developed lethargy. On 27-Mar-2009 (study Day 32), the patient was hospitalized for Grade 3 lethargy and Grade 3 peripheral oedema. He also reported nausea and intermittent diarrhea. The adverse events were assessed as interfering with the patient's ability to perform activities of daily living. Disease progression was not detected radiologically. However, the investigator stated that clinical evidence of disease progression was present due to increased size in some lesions, as well as peripheral oedema attributed to extensive pelvic tumor. The patient was discontinued from study on 27-Mar-2009 (study Day 32) due to clinical progression. The patient experienced the onset of deep depression and suicidal thoughts upon notification of his progressive disease. Treatment included mirtazapine, psychiatric support and monitoring. On 31-Mar-2009 (study Day 36), the patient was discharged from the hospital to hospice. The adverse events remained ongoing. Study participation was discontinued due to the adverse event of peripheral edema; no action was taken with study drug in response to the adverse event of lethargy.

The Investigator assessed the adverse events of peripheral edema and lethargy as not related to blinded study drug (placebo).

Patient #: 005-003 **Gender: Female** **Age: 29 years** **Treatment Assignment: IPI-504**					
SAE term	**Treatment assignment**	**Intensity**	**Relationship**	**Outcome**	**Resulted in study discontinuation**
Abdominal pain	IPI-504	Grade 3	Not related	Resolved with sequelae	No
Deep vein thrombosis	IPI-504	Grade 2	Not related	Ongoing	No
Anaemia	IPI-504	Grade 2	Not related	Resolved with sequelae	No

Patient number 005-003 was a 29-year-old Caucasian woman, diagnosed with GIST on 16-Dec-2005, with initial presentation in the small bowel. Prior therapies included imatinib, sunitinib, nilotinib, and investigational product R1507. Cancer surgical history included laparotomy and small bowel resection. The patient's medical history is significant for abdominal pain on 06-Feb-2009, requiring hospitalization. On 06-Feb-2009, the patient's total bilirubin was elevated to 60 micromol/L (normal range 0-17). On 10-Feb-2009, the patient's total bilirubin was 39 micromol/L, and a liver ultrasound was negative for obstruction. Relevant concurrent medical conditions included neurofibromatosis with known benign gliomas to the brain (unrelated to GIST), nausea, and constipation. Concomitant medications included prochlorperazine, metoclopramide, docusate/senna, lactulose, fentanyl, paroxetine, and granisetron.

The patient enrolled in the study on 16-Mar-2009, and was subsequently randomized to receive IPI-504. On 24-Mar-2009 (study Day 1), she started treatment with study drug, and received 4 doses. On 06-Apr-2009 (study Day 14), symptoms included abdominal pain and fullness, nausea, anorexia, and lower limb edema. On 08-Apr-2009 (study Day 16) the patient was hospitalized for symptom management and for the serious adverse event of Grade 3 abdominal pain. Treatment included fentanyl patches and ibuprofen. On 09-Apr-2009 (study Day 17) she experienced Grade 2 deep vein thrombosis (DVT).

Doppler ultrasound of the leg revealed moderate non-occlusive DVT involving the left common and superficial femoral veins, occupying approximately 70% of the transverse luminal diameter at the left femoral vein, with an estimated longitudinal extent of approximately 10 centimeters. The patient was treated with enoxaparin. On12-Apr-2009 (study Day 20) laboratory results revealed hemoglobin 83 g/L (normal range 115-165) and hematocrit 0.27 (normal range 0.37-0.47). On 13-Apr-2009 (study Day 21), hemoglobin was 82 g/L and hematocrit was 0.26. The patient was diagnosed with anemia and was treated with 2 units of packed cells. Her international normalized ratio (INR) was elevated to 1.6, and her activated partial thromboplastin time (APTT) was elevated to 69. This was assessed as likely having a nutritional component, and improved with vitamin K administration. Specialized coagulation screening revealed an isolated Factor XII level of 32% (reference range 50-140). The patient had no known medical conditions related to her Factor XII abnormality. On 15-Apr-2009 (study Day 23), hemoglobin was 92 g/L (reference range 115-165), and hematocrit was 0.28 (reference range 0.37-0.47). Nausea and vomiting with poor oral intake were treated with metoclopramide and levomepromazine. The sensation of fullness in the abdomen was assessed as likely secondary to tumor bulk in the abdomen. Abdominal and thoracic ultrasound showed insufficient ascites or pleural fluid to enable a therapeutic paracentesis or thoracentesis. On 16-Apr-2009 (study Day 24), the adverse event of Grade 3 abdominal pain resolved with the sequela of Grade 2 abdominal pain. The patient was discharged home with home nursing care for enoxaparin administration. On 19-Apr-2009 (study Day 27), the adverse event of Grade 2 anemia resolved with the sequela of Grade 1 anemia. The adverse event of deep vein thrombosis was ongoing.

The Investigator assessed the adverse events of pain-abdomen, left DVT, and anemia as not related to blinded study drug (IPI-504).

Patient #: 006-001
Gender: Male
Age: 72 years
Treatment Assignment: IPI-504

SAE term	Treatment assignment	Intensity	Relationship	Outcome	Resulted in study discontinuation
Renal failure	IPI-504	Grade 5	Remote	Fatal	Yes
Sepsis	IPI-504	Grade 4	Remote	Ongoing	No
Diarrhoea	IPI-504	Grade 3	Probable	Resolved	No

Patient number 006-001 was a 72-year- old Caucasian man diagnosed with GIST on 10-May-2004, with initial presentation in the small bowel. Prior therapies included imatinib and sunitinib. Relevant medical history included hypertension and cardiopathy, and no history of diarrhea. Concomitant medications include perindopril, atorvastatin, acetylsalicylate lysine/ acetylsalicylic acid, esomeprazole, prednisolone, and loperamide. On 05-Mar-2009 and 19-Mar-2009, the patient was administered imaging contrast agent (agent not specified).

The patient enrolled in the study on 17-Mar-2009, and was subsequently randomized to receive IPI-504. On 25-Mar-2009 (study Day 1), the patient started treatment with study drug, and received 1 dose. Significant baseline labs on 25-Mar-2009 (study Day 1) included aspartate aminotransferase (AST) 78 IU/L (Grade 1), alanine aminotransferase (ALT) 61 IU/L (Grade 1), alkaline phosphatase 218 IU/L, lactate dehydrogenase (LDH) 412 IU/L (reference value less than 250 IU/L), uric acid 5.7 mg/ dL (337

umol/L; Grade 1), white blood cell count 4600 (units not provided), polymorphonuclear cells 3900, hemoglobin 9.4, and calcium 2.18. Blood urea nitrogen (BUN), total bilirubin, creatinine, sodium 140, and potassium values were within normal range. On the same day, the patient developed melena. On 26-Mar-2009 (study Day 2), the patient experienced diarrhea from 2:00 am through the afternoon, and presented to the emergency department (ED), where he reported diffuse abdominal pain and continuing melena. Vital signs were described as good. Abdominal examination revealed a distended abdomen with diffuse pain, no defense reactions, and palpable peritoneal nodules. Physical examination revealed no hematemesis, and unchanged, previous, significant upper and lower extremity edemas. On 26-Mar-2009 (study Day 2), laboratory results demonstrated BUN 7.4 mg/dL (21 mmol/L), AST 148 (Grade 2), ALT 73 (Grade 1), alkaline phosphatase 199 IU/L, total bilirubin 1.1 mg/ dL (18 umol/L; Grade 1), creatinine 1.3 mg/dL (114 umol/L; within normal range), LDH 857 IU/L (normal value less than 250 IU/L), sodium 141 mmol/L (within normal range), and potassium 3.5 mmol/L (within normal range) . In the ED, the patient was noted to be dehydrated and the following treatment medications were prescribed: intravenous fluids, suprofen, trimethylphloroglucinol, and omeprazole. On 27-Mar-2009, (study Day 3) a thoraco-abdomino-pelvic computed tomography (CT) scan revealed bilateral, posterior, basal pulmonary atelectasis at the thoracic level, possibly in connection with the sub-diaphragmatic effusion and masses, though possible superinfection at this level was not excluded. At the abdomino-pelvic level, the CT scan revealed no pneumoperitoneum, but revealed possible tumor infiltration of the digestive tract in the duodenal region, first jejunal loops, and the left flexure of the colon. The origin of the melena could not be detected, but visible perforation or hemorrhage was ruled out. A gastro-duodenal endoscopy showed diffuse gastric polyps without evidence of gastrointestinal bleeding. The diarrhea lasted a total of 24 hours and resolved after hospitalization; however, study drug was held on 27-Mar-2009 (study Day 3) due to renal insufficiency when laboratory results showed BUN 18 mg/dL (6.6 mmol/L; reference 3.0 -7.5), AST 198 IU/L (Grade 2), ALT 84 IU/L (Grade 1), alkaline phosphatase 178 IU/L, total bilirubin 1.2 mg/ dL (20 umol/L; Grade 1), creatinine 1.5 mg/dL (115 umol/L ; Grade 3). Additionally, patient developed oligo-anuria followed by anuria, despite placement of a pediatric catheter. A renal ultrasound with contrast ruled out obstructions in the urinary tract and patient was transferred to the intensive care unit. Vital signs included temperature 35.8 degrees Celsius and blood pressure 155/78 mmHg. His weight was 75 kg on admission compared to his usual weight of 65 kg, due to fluid burden. On 28-Mar-2009 (study Day 4), laboratory results showed BUN 21 mg/dL (7.5 mmol/L), AST 257 IU/L (Grade 3), ALT 106 IU/L (Grade 1), alkaline phosphatase 169 IU/L, (reference value less than 135 IU/L), total bilirubin 1.3 mg/dL (23 umol/L; Grade 1), LDH 1156 IU/L (normal range less than 250 IU/L). On 31-Mar-2009 (study Day 7), kidney size was normal on renal ultrasound. Laboratory tests revealed BUN 53 mg/ dL (18.9 mmol/L; normal range 3.0- 7.5), AST 229 IU/L (Grade 3), ALT 153 IU/L (Grade 2), alkaline phosphatase 358 IU/L (normal range <135), total bilirubin 1.4 mg/ dL (Grade 1), creatinine 4.5 mg/dL (402 umol/L; Grade 3), LDH 1092 IU/L (normal range < 250), uric acid 11.1 mg/dL (661 umol/L; Grade 4), potassium 5.6 mmol/ L (Grade 2), and sodium 136 mmol/L (within normal range). On 01-Apr-2009 (study Day 8), laboratory results revealed BUN 59 mg/dL (21 mmol/L), AST 148 IU/L (Grade 2), ALT 126 (Grade 2), alkaline phosphatase 328 IU/L (normal range < 135), total bilirubin 1.4 mg/dL (24 umol/L; Grade 1), creatinine 5.1 mg/dL (450 umol/L ; Grade 3), LDH 1010 IU/L (normal range < 250 IU/L), uric acid 11.1 mg/dL (663 umol/L; Grade 4), potassium 5.3 mmol/L (Grade 1), and sodium 139 mmol/L (within normal range). The patient was treated with intravenous fluids and anticoagulation therapy. On 02-Apr-2009 (study Day 9), lab results included BUN 61 mg/dL (21.9 mmol/L), AST 112 IU/L (Grade 1), ALT 107 IU/L (Grade 1), alkaline phosphatase 327 IU/L (normal range <135), total bilirubin 1.4 mg/dL (24 umol/L; Grade 1), creatinine 5.4 mg/ dL (473 umol/L; Grade 2), LDH 960 IU/L (normal range < 250 IU/L), uric acid 11.1 mg/dL (661 umol/L; Grade 4) potassium 5.0 mmol/L (Grade 1), sodium 141 mmol/L (within normal range). Renal insufficiency was attributed to multiple factors: injection of iodine contrast, dehydration, and intra-

abdominal vesicle pressure of 18, not alleviated by attempts to evacuate ascites. The patient was started on dialysis when he was found to have pulmonary burden and hyperkalemia. Hypothermia and positive blood cultures supported the patient's diagnosis of Enterobacter aerogenes septicemia, which the investigator considered to be life-threatening. Rapid increase of creatinine over 24 hours, of LDH, and of all values associated with acute renal failure was indicative of tumor lysis syndrome. Dialysis was poorly tolerated and orders were changed to comfort measures only, including administration of oxycodone and midazolam. On 03-Apr-2009 (study Day 10), lab results showed BUN 57 mg/dL (21.9 mmol/L), creatinine 4.8 mg/dL (424 umol/L; Grade 3) and LDH 1022 (normal range <250). The event of Grade 3 diarrhea resolved on 26-Mar-2009, and the event of Grade 5 renal failure was fatal on 05-Apr-2009 (study Day 12). Grade 4 sepsis was ongoing at the time of death.
The Investigator assessed the adverse event of diarrhea as probably related to blinded study drug (IPI-504), and the adverse events of sepsis and renal failure as remotely related to blinded study drug (IPI-504). The sponsor assessed the events of sepsis and renal failure as possibly related to treatment with IPI-504.

Patient #: 006-002
Gender: Male
Age: 66 years
Treatment assignment: IPI-504

SAE term	Treatment assignment	Intensity	Relationship	Outcome	Resulted in study discontinuation
Abdominal pain	IPI-504	Grade 3	Not related	Resolved	No

Patient number 006-002 was a 66-year-old year old Caucasian man diagnosed with GIST on 26-May-2005, with initial presentation in the omentum/mesentery. Cancer surgical history included complete surgical resection of GIST, which included resection of the first 3 intestinal loops. Prior therapies included imatinib, sunitinib, and cyclophosphamide. Relevant concurrent medical conditions included prostate adenocarcinoma. Concomitant medications included perindopril, furosemide, tamsulosin, lactulose, rabeprazole, omeprazole, and imatinib (stopped 8 days prior to initiation of GIST).

The patient enrolled in the study on 23-Mar-2009, and was subsequently randomized to receive IPI-504. On 14-Apr-2009 (study Day 1), he started treatment with study drug, and received 1 dose prior to the study being terminated. On 19-Apr-2009 (study Day 6), the patient began to experience abdominal pain in the absence of vomiting, bowel obstruction, or gas. Symptoms continued and on 22-Apr-2009 (study day 9), the patient presented to the emergency department and was hospitalized for Grade 2 abdominal pain. Upon presentation at the hospital, vital signs were unremarkable. White blood cell count (WBC) on an unspecified date was 8,300/mm3. On 22-Apr-2009 (study day 9), significant laboratory results included glucose 5.2 mmol/L (within normal limits), bicarbonate 22 mmol/L (Grade 1), aspartate aminotransferase (AST) 41 UI/L (Grade 1), alanine aminotransferase (ALT) 27 UI/L (within normal limits), alkaline phosphatase 143 UI/L (Grade 1), total bilirubin 18 umol/L (Grade 1), lactate dehydrogenase (LDH) 301 UI/L (normal range <250), total protein 61 g/L (normal range 66-74), C-reactive protein (CRP) 12 mg/L (normal range <6), and international normalized ratio (INR) 1.1. Abdomen was depressible, and exhibited poor sensitivity throughout. Abdominal echography showed no biliary dilatation and was otherwise unremarkable. On 23-Apr-2009 (study Day 10), abdominal computed tomography (CT) showed rapid tumor progression, with a 23% increase in tumor in 15 days.

Significant laboratory results included bicarbonate 23 mmol/L (Grade 1), alkaline phosphatase 132 UI/L (within normal limits), AST 36 UI/L (Grade 1), ALT 22 UI/L (within normal limits), total bilirubin 17 umol/L (Grade 1), LDH 279 UI/L (normal range <250), total protein 59 g/L (normal range 66-74), and CRP 39 mg/L (normal range <6). Amylase and lipase were within normal limits. On 26-Apr-2009 (study Day 13), laboratory results were as follows: glucose 6.3 mmol/L (Grade 1), calcium 2.05 mmol/L (Grade 1), bicarbonate 24 mmol/L (within normal limits), alkaline phosphatase 45 UI/L (within normal limits), total bilirubin 10 umol/L (within normal limits), LDH 338 UI/L (normal range <250), total protein 54 g/L (normal range 66-74), CRP 56 mg/L (normal range <6); remaining chemistry results were within normal limits. On 28-Apr-2009 (study Day 15), the patient experienced fever associated with episodes of diarrhea. Peripheral blood cultures drawn 27-Apr-2009 (study Day 14) and 28-Apr-2009 (study Day 15) were negative. Treatment included analgesics inefopam hydrochloride, phloroglucinol/ trimethylphloroglucinol, paracetamol, tramadol hydrochloride, trimebutine, metoclopramide, and fentanyl; other treatments included morphine, as well as bromazepam and zolpidem for insomnia. Fever and diarrhea rapidly resolved without bacteriological documentation. Abdominal pain resolved with morphine and was considered secondary to acute disease progression. On 29-Apr-2009 (study Day 16), significant laboratory results included calcium 2.08 mmol/L (Grade 1), bicarbonate 26 mmol/L (24-28), AST 41 UI/L (within normal limits), LDH 367 UI/L (normal range <250), total protein 52 g/L (normal range 66-74), CRP 107 mg/L (normal range <6), and INR 1.2. On 30-Apr-2009 (study Day 17), imatinib was restarted. On 04-May-2009 (study Day 21), laboratory results showed bicarbonate, AST, and ALT were within normal limits. Significant laboratory results included creatinine 76 umol/L (normal range 80-125), alkaline phosphatase 142 IU/L (normal range <135), LDH 342 UI/L (normal range <250), total protein 50 g/L (normal range 66-74), and INR 1.2. On 06-May-2009 (study Day 23), cyclophosphamide was started. Acute disease progression was reported to be an alternative etiology for the adverse event. On 07-May-2009 (study Day 24), the adverse event of Grade 3 abdominal pain resolved and the patient was discharged from the hospital. Continued care included palliative care.

The Investigator assessed the adverse event of abdominal pain as not related to blinded study drug (IPI-504).

Patient #: 009-001
Gender: Male
Age: 74 years
Treatment Assignment: IPI-504

SAE term	Treatment assignment	Intensity	Relationship	Outcome	Resulted in study discontinuation
Cardio-respiratory arrest	IPI-504	Grade 5	Possible	Fatal	Yes

Patient number 009-001 was a 74-year-old Caucasian man diagnosed with GIST on 16-Nov-1999, with initial presentation in the stomach and metastases to the liver. Prior therapies included imatinib, sunitinib, dasatinib, and nilotinib. Prior cancer surgical history included biopsy, hemigastrectomy, splenectomy, distal pancreatectomy, needle biopsy of the liver, and an exploratory laparotomy with resection of liver segments 5 & 6. Medical history included gastrointestinal bleeding, anemia, a port-related clot, manic depression, grand mal seizures, and cholecystectomy. Relevant concurrent medical

conditions included anorexia, hypertension, gastric polyps, diverticulosis, and urinary frequency. Concomitant medications were simethicone, lisinopril, tamsulosin, and divalproex.

The patient enrolled in the study on 30-Oct-2008. Laboratory results 30-Oct-2008 included total bilirubin 0.7 mg/dL, alkaline phosphatase 293 U/L (grade 1), aspartate aminotransferase (AST) 55 U/L, alanine aminotransferase (ALT) 73 U/L (grade 1), and lactic dehydrogenase (LDH) 891 U/L. Electrocardiogram (ECG) from 03-Nov-2008 revealed normal sinus rhythm, with a ventricular rate of 71-73 beats per minute (bpm).

The patient was randomized to receive IPI-504. On10-Nov-2008 (study Day 1), he started treatment with study drug. Pre-dose laboratories on 10-Nov-2008 (study Day 1) included total bilirubin 0.3 mg/dL, alkaline phosphatase 271 U/L (grade 1), AST 42 U/L, ALT 30 U/L, and LDH 968 U/L. Pre-dose electrocardiograms (ECGs) showed clinically insignificant sinus bradycardia, in the opinion of the reviewer, with heart rate 54 to 55 bpm. After the first dose of study drug, vital signs included heart rate 56 and blood pressure 152 / 67 mmHg. ECG performed at the end of treatment on 10-Nov-2008 (study Day 1) revealed sinus bradycardia (heart rate 44-47 bpm) and 1st degree atrioventricular block, which were noted to be clinically insignificant by the ECG reviewer. ECGs performed 30 minutes post-dosing showed bradycardia (heart rate 44-48 bpm), 1st degree atrioventricular block and occasional premature ventricular complexes, which were assessed as clinically insignificant by the reviewer. The investigator confirmed the bradycardia was asymptomatic. Vital signs on 11-Nov-2008 (study Day 2) were unremarkable. The patient complained of mild nausea, which was managed with simethicone. On 13-Nov-2008 (study Day 4), prior to the second dose of study drug, laboratory results included total bilirubin 0.5 mg/dL, alkaline phosphatase 269 U/L (grade 1), AST 139 U/L (grade 1), ALT 68 U/L, and LDH 2168 U/L. Pre-dose vital signs included temperature 99.2 degrees F, heart rate 102 bpm, respiration rate 16 and blood pressure 149/70 mmHg. Vital signs after the start of study drug administration (time not specified) were temperature 99.4 degrees F, pulse 64 bpm, respiration rate 20, and blood pressure 156/58 mmHg. On 14-Nov-2008 (study Day 5), one day after his second dose of study medication, the patient reported worsening nausea by telephone, as well as mild diarrhea since his second dose of study medication. Prochlorperazine and ondansetron were prescribed for nausea. According to the patient's wife, the patient was weak on 14-Nov-2008 (study Day 5), and was restless throughout that day and evening. That evening he had labored breathing and complained of liver pain. His wife left him alone at around 9 PM and went to bed. At 10:30 PM, she found him unresponsive on the bathroom floor. Emergency services administered cardiopulmonary resuscitation and intubated the patient. Atropine, epinephrine and bicarbonate were given. The patient was transported to the emergency room (ER), where he arrived on 15-Nov-2008 at 12:19 am in cardiac and respiratory arrest. The patient had no vital signs and was unreactive upon arrival at the ER. At 12:26 am, defibrillation was attempted; however heart rhythm after defibrillation was asystole. The patient was pronounced dead on 15-Nov-2008 (study Day 6) at 12:27 am. The cause of death was reported as cardiopulmonary arrest. No autopsy was performed. Study participation was discontinued due to the adverse event of Grade 5 cardiopulmonary arrest.

The Investigator assessed the adverse event of cardiopulmonary arrest as possibly related to blinded study drug (IPI-504).

Patient #: 011-001 **Gender: Male** **Age: 58 years** **Treatment Assignment: IPI-504**					
SAE term	**Treatment assignment**	**Intensity**	**Relationship**	**Outcome**	**Resulted in study discontinuation**
Myocardial infarction	IPI-504	Grade 4	Probable	Resolved	Yes
Renal failure	IPI-504	Grade 4	Probable	Resolved	Yes
Vomiting	IPI-504	Grade 4	Probable	Resolved	Yes

Patient number 011-001 was a 58-year-old Caucasian man diagnosed with GIST on 21-Feb-2008, with initial presentation in the stomach. Prior therapies included imatinib, sunitinib, and nilotinib. Cancer surgical history included tumor debulking surgery with partial stomach resection. Relevant concurrent medical conditions included peptic esophagitis, chronic obstructive pulmonary disease, and peritoneal carcinosis. Social history was significant for nicotine abuse. Concomitant medications included pantoprazole, spironolactone, and hydrochlorothiazide.

The patient enrolled in the study on 31-Mar-2009, and was subsequently randomized to receive IPI-504. On 01-Apr-2009 (study Day 1), the patient started treatment with study drug, and received 4 doses. On 16-Apr-2009 (study Day 16), the patient presented with a history of extensive diarrhea and vomiting over several days, soft stool, and pressure pain in the left abdomen, with tension and percussion pain over the left renal bed, but with no other current abdominal complaints. His nutritional state and overall condition were diminished, and he was dehydrated. Tachycardia was observed, with a maximum heart rate of 120 beats per minute and hypotension. Vital signs included blood pressure 75/40 mmHg and pulse 88 beats per minute. Physical examination was unremarkable. The patient's dehydration led to renal impairment, resulting in elevated creatinine and urea levels. The patient was hospitalized for Grade 4 emesis, Grade 4 renal failure, and Grade 4 myocardial ischemia. At 17:15, admission laboratory results revealed white blood cell count (WBC) 19.2 g/l (normal range 4.0-11.0), hemoglobin 13.5 g/dl (Grade 1), platelet count 556 g/l (normal range 150-440), sodium 126 mmol/l (Grade 3), potassium 5.4 mmol/l (Grade 1), creatinine 3.0 mg/dl (Grade 2), urea 105 mg/dl (normal range 9-50), glucose 153 mg/dl (Grade 1), aspartate aminotransferase (AST) 25 U/l (within normal limits), alanine aminotransferase 45 U/l (normal range <45), total bilirubin 0.5 mg/dl (normal range <0.5), troponin-I 1.22 ng/ml (normal range <0.05), total creatine kinase (CK) 45 U/l (within normal limits), CK-MB 0.9 ng/ml (normal range <5.0), myoglobin 172 ng/ml (normal range <70), lactate dehydrogenase (LDH) 396 U/L (normal range <250), uric acid 9.9 mg/dL (Grade 1), C-reactive protein (CRP) 22.7 (normal range <0.5), thyroid stimulating hormone (TSH) 5.02 microunits/ml (normal range 0.44-3.80), and coagulation parameters within normal limits. Due to increasing inflammation, antibiotic treatment was initiated with tazobactam/ piperacillin, which was changed to meropenem and tobramycin. At 21:50, repeat laboratories revealed WBC 15.5 g/l (normal range 4.0-11.0), hemoglobin 11.3 g/dl (Grade 1), sodium 126 mmol/L (Grade 3), potassium 4.7 mmol/l (within normal limits), creatinine 2.6 mg/dl (Grade 2), urea 107 mg/dl (normal range 9-50), uric acid 9.7 mg/dl (Grade 1), total CK 34 U/l (within normal limits), CK-MB 34 U/L, Troponin-I 1.08 ng/ml (normal range <0.05), myoglobin 125 ng/ml (normal range <70), CRP 19.1 mg/dl (normal range <0.5), and activated partial prothrombin time (aPTT) 90 seconds (normal range 23-35). On 16-Apr-2009, abdominal x-ray was negative for ileus or perforation. Urological consult found the abdomen slightly tense with pressure pain in the left lower abdomen. Sonography

revealed peripheral free fluid with pronounced ascites, and no lesion in the kidneys on either side. The bladder appeared to be empty, suggesting absence of a postrenal outflow disorder. Urine diagnostics, antibiotics, nephrology consultation, and placement of an indwelling catheter were recommended. The patient's systolic blood pressure reached 85 mmHg and his heart rate was more than 110 beats per minute. On 17-Apr-2009 (study Day 17) at 08:00, laboratory results included WBC 11.7 g/dl (normal range 4.0-11.0), hemoglobin 11.1 g/dl (Grade 1), total CK 50 U/l, CK-MB 1.0 ng/ml (within normal limits), troponin-I 0.80 ng/ml (normal <0.05), myoglobin 176 ng/ml (normal <70), aPTT 32 seconds (within normal limits), and international normalized ratio within normal limits. At 12:00, sodium was 128 mmol/L (Grade 3), creatinine 1.9 mg/dL (Grade 2), BUN 89 mg/dL (normal range 9-50), total CK 46 U/L (normal <180), CK-MB 1.3 ng/ml (normal <5.0), calcium 1.91 mmol/L (Grade 2), GFR 39 ml/minute (normal >60), white blood cells 11.7 G/L (normal range 4.0-11.0). Thoracic x-ray revealed normal heart size, signs of pulmonary venous congestion, and a striped opacity at the left lung base consistent with a small dystelectasis; x-ray was negative for pneumothorax and pleural effusion. An electrocardiogram (ECG) revealed sinus rhythm, heart rate 89 beats per minute, T-wave negativity in lead III, and no ST changes. A thoracic echocardiogram performed under poor acoustic conditions revealed no high level defects; results were as follows: normal-sized left ventricle, end diastolic pressure of 45 mmHg, moderately limited pump function with an ejection fraction of 40%, hypokinesia of the basal septum, narrow right ventricle, no regional wall movement defects, pericardial margin at the most 7 mm above the heart base, noted to be of no hemodynamic relevance, ascites, and suspicion of pleural effusion. A preliminary diagnosis of myocardial ischemia was based on elevated troponin laboratory results and ECG analysis; non-ST myocardial infarction (NSTEMI) was suspected, as no significant ST-changes were observed on the ECG. Diagnosis of NSTEMI was later confirmed. On 17-Apr-2009, the patient's laboratory values had noticeably improved, he was hemodynamically stable, and his respiratory condition was stable. Heparin infusion was started, which was later changed to oral acetylsalicylic acid. Diuretic therapy was initiated with spironolactone 100 mg daily. On 18-Apr-2009 (study Day 18), WBC was 9.0 G/L (within normal limits), sodium was 134 mmol/L (Grade 1), potassium 4.7 mmol/l (within normal limits), creatinine 1.1 mg/dL (within normal limits), CRP 16.3 mg/dL (normal range <0.5), interleukin-6 48.8 pg/mL (normal <5.9), alkaline phosphatase 135 U/L (Grade 1; normal <135), total CK 57 U/L (within normal limits), troponin-I 0.46 ng/mL (normal < 0.05), myoglobin 66 ng/mL (within normal limits), AST 17 U/L (within normal limits) and ALT 20 U/L (within normal limits). On 19-Apr-2009 (study Day 19), laboratory results included potassium 5.3 mmol/L (Grade 1), creatinine and sodium within normal limits, LDH 260 U/L, CRP 12.1 mg/dL. On 22-Apr-2009 (study Day 22), ECG results included sinus tachycardia, heart rate 113 beats per minute, normal heart type, QRS-duration 19 msec, QTC 430 msec, and non-specific T-wave changes; anterior infarction could not be ruled out. Laboratory results included normal BUN, creatinine and troponin-I; CRP 1.8 mg/dL (normal <0.5), and LDH 202 U/L. On 24-Apr-2009 (study Day 24), a transthoracic echocardiogram revealed minimal pericardial effusion of at most 0.7 cm with no hemodynamic relevance, and was otherwise unremarkable. Laboratory results included WBC 7.9 G/L, sodium 134 mmol/L (Grade 1), potassium 5.3 mmol/L (Grade 1 elevation), creatinine and BUN within normal limits, CRP 0.9 mg/dL (normal <0.5) and LDH 155 U/L. The feeling of abdominal tension increased, and more than six liters of fluid were aspirated from the patient's ascites. The investigator felt that the adverse events were life-threatening; emesis and renal failure were noted to be life-threatening because the patient's exsiccosis, anuria, and probable renal failure with pre-renal etiology required a period of vital sign monitoring in the intensive care unit (ICU). Rationale for causality assessment of probably related to study drug included the three-day interval between dosing and onset of the adverse events. The patient was started on sorafenib. On 25-Apr-2009 (study Day 25), the patient was discharged from the hospital. The adverse events resolved on 25-Apr-2009 (study Day 25). The patient discontinued study participation on 25-Apr-2009 (study Day 25) due

to the serious adverse events of Grade 4 myocardial infarction, Grade 4 renal failure, and Grade 4 emesis.

The Investigator assessed the adverse events of myocardial infarction, renal failure, and vomiting as probably related to blinded study drug (IPI-504).

Patient #: 020-001 **Gender: Female** **Age: 45 years** **Treatment Assignment: Placebo**					
SAE term	**Treatment assignment**	**Intensity**	**Relationship**	**Outcome**	**Resulted in study discontinuation**
Hypercalcaemia	Pre-treatment	Grade 3	Not related	Resolved	No
Hypercalcaemia	Pre-treatment	Grade 3	Not related	Resolved with sequelae	No
Hyperglycaemia	Placebo	Grade 3	Not related	Resolved	No
Hypernatraemia	Placebo	Grade 3	Not related	Ongoing	No

Patient number 020-001 was a 45-year-old African American woman diagnosed with GIST on 29-Jul-2003, with initial presentation in the small bowel and metastases to the liver. Prior therapies included imatinib and sunitinib. Cancer surgical history included liver needle biopsy, resection of small bowel tumor in proximal jejunum, and upper endoscopy biopsy. Relevant medical history included recurrent hypercalcemia secondary to malignancy, hypothyroidism, and relevant concurrent medical conditions included uncontrolled type II diabetes mellitus. Concomitant medications included insulin, metformin, duloxetine, meloxicam, Glucophage, omeprazole, ondansetron, metoclopramide, fentanyl, and hydromorphone.

The patient enrolled in the study on 29-Jan-2009. On 02-Feb-2009, during the screening period, the patient presented to the emergency room with a 3-day history of vomiting and decreased oral intake. Serum calcium was 13.3 mg/dL (Grade 3) and the patient was hospitalized for Grade 3 hypercalcemia. Treatment included intravenous (IV) fluids and pamidronate. On 04-Feb-2009, the adverse event resolved. On 05-Feb-2009, serum calcium was 10.6 mg/dL (Grade 1), and review of systems was remarkable for joint pain; the patient was discharged from the hospital.

The Investigator assessed the adverse event of hypercalcemia as not related to blinded study drug.

The patient continued on study and was randomized to receive placebo. She was scheduled to begin study treatment on 16-Feb-2009. Pre-treatment laboratory tests were significant for calcium 13.1 mg/dL (Grade 3), uric acid 14.0 mg/dL (Grade 4), sodium 152 mEq/L (Grade 2), creatinine 1.75 mg/dL (Grade 2), blood urea nitrogen (BUN) 30 mg/dL (normal range 8-20), glucose 196 mg/dL (Grade 2), alkaline phosphatase 228 U/L (Grade 1), and aspartate aminotransferase (AST) 65 U/L (Grade 1). The patient's first study drug treatment was held and the patient was sent to the emergency department, where her family reported occasional confusion and lethargy. She was hospitalized for Grade 3 hypercalcemia, and received intravenous fluids and pamidronate. During hospitalization, the patient's indwelling port could not be accessed. The patient declined a new port placement due to a scheduled chemotherapy infusion on 19-Feb-2009. On 18-Feb-2009, calcium was 10.9 mg/dL (Grade 1), and she was discharged from the

hospital. She was started on nightly infusions of home IV fluids to prevent recurrent hypercalcemia. The event was considered resolved with the sequel of Grade 1 hypercalcemia on 18-Feb-2009.

The Investigator assessed the adverse event of hypercalcemia as not related to blinded study drug (placebo).

On 19-Feb-2009 (study Day 1), the patient started treatment with study drug, and received 2 doses. On 26-Feb-2009 (study Day 8), pre-dose testing was significant for glucose 418 mg/dL (Grade 3) and calcium 11.5 mg/dL (Grade 1). The patient's third dose of study drug was held. The patient's husband reported that she was lethargic and nauseated. Endocrinologist reported glucose was above 500 (unit not provided; normal range 70-140), secondary to poorly-controlled diabetes mellitus. She was admitted to the hospital for Grade 3 hyperglycemia, where treatment included isophane and fast-acting insulin, calcitonin, and IV fluids. Blood glucose and calcium levels stabilized. Computed tomography showed no change in metastatic liver lesions from a previous scan. On 03-Mar-2009 (study Day 13), the patient underwent surgical port-a-cath revision. Thyroid-stimulating hormone was noted to be high, and levothyroxine was restarted. On 03-Mar-2009 (study Day 13), the adverse event of hyperglycemia resolved and the patient was discharged home. IV fluid treatments were to be continued at home via port-a-cath. Study drug dose was reduced in response to the event.

The Investigator assessed the adverse event of hyperglycemia as not related to blinded study drug (placebo).

The patient received her last dose of study drug on 09-Apr-2009 (study Day 49), and stopped treatment on 15-Apr-2009 (study Day 55) when the study was closed. On an unknown date, the patient began palliative care. She was receiving bisphosphonates and IV home hydration. On 06-May-2009 (study Day77), she experienced dehydration, and on 07-May-2009 (study Day 78), she experienced acute on chronic renal failure. In May 2009, the patient was admitted to the hospital for Grade 3 hypernatremia. On 12-May-2009 (study Day 83), laboratory results revealed sodium 153, chloride 129, potassium 4.1, carbon dioxide 20, blood urea nitrogen (BUN) 12 and creatinine 1.8 (no units or normal ranges provided). On 14-May-2009, laboratory results included sodium 156, potassium 4.0, chloride 131, carbon dioxide 18, BUN 13, and creatinine 1.5. A Grade 1 rise in creatinine, and hypernatremia were noted. The patient was sent to the emergency department for correction of electrolyte abnormalities. On 15-May-2009 (study Day 86), laboratory results included sodium 152, potassium 3.0, carbon dioxide 21, BUN 11, creatinine 1.7, and glucose 195. Calcium values were not provided. Bisphosphonates were discontinued, and treatment included percutaneous endoscopic gastrostomy tube, potassium chloride, insulin, and supportive measures. On 15-May-2009 (study Day 86), physical exam was unremarkable and dehydration was noted to be improving. The patient was discharged from the hospital with plans to resume palliative care. The adverse event was ongoing. No action was taken with study drug in response to the event of hypernatremia.

The Investigator assessed the adverse event of hypernatremia as not related to blinded study drug (placebo).

Patient #: 020-002 **Gender: Male** **Age: 59 years** **Treatment Assignment: IPI-504**					
SAE term	**Treatment assignment**	**Intensity**	**Relationship**	**Outcome**	**Resulted in study discontinuation**
Gastrointestinal fistula	IPI-504	Grade 3	Remote	Resolved with sequelae	Yes

Patient number 020-002 was a 59-year-old Caucasian man diagnosed with GIST on 24-Sep-2004. Prior therapies included imatinib and sunitinib. Cancer surgical history included a subtotal gastrectomy. Relevant medical history included migraine headaches and lithotripsy. Concomitant medications included fentanyl, fiber supplement, rizatriptan, multivitamin, and omeprazole.

The patient enrolled in the study on 23-Feb-2009, and was subsequently randomized to IPI-504. On 10-Mar-2009 (study Day 1), the patient started treatment with study drug, and received 3 doses. On 19-Mar-2009 (study Day 10), he experienced a gastrointestinal fistula of the small bowel and was hospitalized for a surgical consult. Computed tomography (CT) revealed increased size of a left liver mass since 06-Mar-2009, which now contained air. Vital signs and physical exam were unremarkable. On 26-Mar-2009 (study Day 17), the patient was discharged from the hospital on intravenous antibiotics and total parenteral nutrition (TPN) to improve his nutritional status before surgery. He was to return for surgery in ten days for consideration of a small bowel segmentectomy and hepatectomy. On 06-Apr-2009 (study Day 28), the patient underwent exploratory laparotomy, extensive lysis of adhesions, right hemicolectomy, and end ileostomy to divert any enteric contents of the transverse colon from his large liver metastasis. On 07-Apr-2009 (study Day 29), his nasogastric tube was removed. Output was noted in his ileostomy almost immediately after the operation. His incision showed no signs of infection. He was ambulating and tolerating a stable diet. Hemoglobin was stable. Due to decreased appetite, TPN was administered nightly. On 10-Apr-2009 (study Day 32), the patient was discharged from the hospital with nightly supplemental TPN for home use. The adverse event resolved on 06-Apr-2009 (study Day 28) with the sequelae of TPN and ileostomy. The patient discontinued study participation on 06-Apr-2009 due to the adverse event of Grade 3 gastrointestinal fistula small bowel.

The Investigator assessed the adverse event of gastrointestinal fistula small bowel as not related to blinded study drug (IPI-504).

Patient #: 024-001 **Gender: Male** **Age: 57 years** **Treatment Assignment: Placebo and Open-label IPI-504**					
SAE term	**Treatment assignment**	**Intensity**	**Relationship**	**Outcome**	**Resulted in study discontinuation**
Ascites	IPI-504	Grade 3	Not related	Resolved with sequelae	No
Dyspnoea	IPI-504	Grade 3	Not related	Resolved	No
Abdominal pain	IPI-504	Grade 3	Not related	Resolved with sequelae	No
Renal failure acute	IPI-504	Grade 3	Not related	Resolved	No
Disease progression	IPI-504	Grade 5	Possible	Fatal	No

Patient number 024-001 was a 57-year-old Hispanic man diagnosed with GIST on 27-Jan-2001, with initial presentation in the stomach, and metastases to the pancreas and liver. Prior therapies included imatinib, sunitinib, and investigational product EZN-2968-02. Cancer surgical history included partial gastrectomy, excision of retroperitoneal tumors, partial colectomy, resection of splenic flexure of colon, partial excision of the pancreas, biopsy guided by computed tomography, and splenectomy. Relevant medical history included dyspnea and pancreatic fistula,. Relevant concurrent medical conditions included constipation, fatigue, and hypertension. leukocytosis, constipation, taste alteration, fatigue, hypertension, and heartburn. Concomitant medications included esomeprazole, amlodipine/benazepril, prochlorperazine, propoxyphene/acetaminophen, hydrocodone, hydromorphone, lorazepam, promethazine, and zolpidem.

The patient enrolled in the study on 10-Feb-2009, and was subsequently randomized to receive placebo. On 02-Mar-2009 (study Day 1), the patient started treatment with placebo; he received 4 doses. On 23-Mar-2009 (study Day 22), the patient started treatment with open-label IPI-504; he received 4 doses of open-label IPI-504. On 03-Apr-2009 (11 days after initiation of IPI-504), the patient experienced shortness of breath and abdominal tenseness. On 06-Apr-2009 (14 days after initiation of IPI-504), he presented to the emergency department and was hospitalized for Grade 3 ascites and possible pulmonary embolism. Symptoms included baseline decreased appetite, nausea, and vomiting, with new onset of multiple episodes of non-bloody, loose stools; worsening shortness of breath and abdominal distension over 3-4 days; with no fever or chills. Vital signs included temperature 37.2 degrees Celsius, blood pressure 105/62 mmHg, pulse 137 beats per minute, respiration 20 breaths per minute and oxygen saturation 97% on 2 liters of oxygen. The patient appeared malnourished on admission and physical exam was remarkable for a soft, distended abdomen with positive bowel sounds as well as mild, diffuse tenderness but without costovertebral angle tenderness. Laboratory results at 12:00 included creatinine kinase MB enzyme (CKMB) 2.1 ng/ml (normal range 0.0-5.0) and Troponin T less than 0.01 ng/ml (within normal range). A chest x-ray showed no acute infiltrate. A pulmonary ventilation and perfusion scan revealed an intermediate probability for pulmonary embolism with indication for further evaluation for deep venous thrombosis and/or pulmonary embolism. Subsequent computed tomography (CT) of the chest and Doppler ultrasound of the lower extremities ruled out pulmonary embolism and deep vein thrombosis. An echocardiogram was remarkable for mild hyperkinesias of the intraventricular septum, mild mitral regurgitation, but with an ejection fraction of 55-60%. Repeat laboratory results at 20:30

included showed CKMB and Troponin T still within normal limits. On 07-Apr-2009 (15 days after initiation of IPI-504), an abdominal CT showed no bowel obstruction; however, it was remarkable for metastases at the gastroesophageal junction which were mildly distended and fluid-filled; extensive, bulky, low-attenuated cystic adenopathy throughout abdominal mesentery, extending from the gastroesophageal junction to the celiac axis; venous attenuation by metastases to the right hepatic vein and right portal vein; and, leftward displacement of the superior mesenteric vein and artery due to bulky adenopathy. Additionally, moderate nodularity was noted in the peritoneal lining throughout the pelvis, likely representing carcinomatosis, and a moderate amount of ascites was located mostly posterior to the liver in both paracolic gutters and the pelvis. An ultrasound-guided paracentesis was performed without complication and 3300 ml of serosanguineous fluid were evacuated from the ascites, with improvement in shortness of breath. Blood cultures obtained on 06-Apr-2009 (14 days after initiation of IPI-504) showed no growth after five days. Pathology of the ascites fluid was unremarkable and microbiology cultures showed no growth after two days. On 08-Apr-2009 (16 days after initiation of IPI-504), the patient was discharged from the hospital. The adverse event of Grade 3 dyspnea was considered resolved, and the adverse event of Grade 3 ascites was considered resolved with the sequel of mild ascites. No action was taken with IPI-504. On 15-Apr-2009, study drug was discontinued due to sponsor terminating the study.

The Investigator assessed the adverse events of ascites and dyspnea as not related to IPI-504.

On 19-Apr-2009 (27 days after initiation of IPI-504), the patient was hospitalized for Grade 3 abdominal pain and grade 3 acute renal failure. Symptoms included poor appetite, nausea, vomiting, worsening abdominal pain (with some improvement after a recent paracentesis for acsites), constipation (without a bowel movement for 3 days and little to no flatus), fatigue, and decreased activity. Laboratory results were remarkable for white blood cell count (WBC) 17.4 (up from 12 1 week prior), sodium 129, creatinine 2.4, chloride 101, potassium 5.7, and glucose 105 (units and normal range not provided). On 20-Apr-2009 (28 days after initiation of IPI-504), vital signs included temperature 36.7 degrees Celsius, blood pressure 113/81 mmHg, heart rate 102 beats per minute, respiratory rate 16 breaths per minute and oxygen saturation 94%. Glasgow coma scale was 15. Physical exam was remarkable for a slightly tachycardiac heart rate with normal rhythm; soft, distended abdomen with hypoactive bowel sounds, occasional high-pitched sounds; mild, diffuse abdominal tenderness to palpitation, and dullness to percussion. The abdominal pain was assessed by the physician as multifactorial, with etiology including the patient's cancer, ileus, and abdominal ascites. A kidney ureter bladder (KUB) scan showed preliminary findings consistent with a colonic ileus without evidence of small bowel obstruction. The patient was treated with baclofen, bisacodyl, docusate/senna, renally-dosed enoxaparin, proton pump inhibitor, and was continued on fentanyl, despite indication that narcotic analgesic use might have caused the ileus. He was diagnosed with acute renal failure (assessed by the investigator as secondary to nausea and dehydration), hyperkalemia (thought to be secondary to acute renal failure), and leucocytosis. On 21-Apr-2009 (29 days after initiation of IPI-504), the subject's vital signs included a temperature of 35.4 degrees Celsius, blood pressure 114/74 mmHg, heart rate 118 beats per minute, respiratory rate 16 breaths per minute and oxygen saturation 94%. The patient's total fluid intake (normal saline) for 24 hours was 3,435 ml and urine output was 825 ml, and he had two bowel movements. Laboratory blood work was significant for sodium 134, BUN 51, potassium 5.3, carbon dioxide 16, and creatinine 1.86 mg/dL. Abdominal pain was likely secondary to GIST and colonic ileus. Acute renal failure was likely due to a pre-renal etiology since fractional excretion of both sodium and urea was noted in the setting of dehydration. A urinalysis was negative. The plan was to obtain a renal ultrasound and bladder scan to rule out obstruction, continue hydration, avoid nephrotoxins, and monitor strict input and output. A repeat KUB scan showed improvement in stool burden. Leukocytosis improved to WBC 15 without

antibiotic treatment, and both blood and urine cultures were negative at 24 hours. With scans showing increasingly significant tumor burden, the patient was offered comfort care and treated with patient-controlled analgesic, metoclopramide, stool softeners and oxygen as needed. On 23-Apr-2009 (31 days after initiation of IPI-504), the adverse event of acute renal failure resolved, and the adverse event of abdominal pain resolved with unspecified sequelae. The patient was discharged to home hospice, where he opted for comfort measures only. He experienced periodic hallucinations and increasing edema. At 12:15 on 06-May-2009 (44 days after initiation of IPI-504), his vital signs included blood pressure 96/58 mmHg, bounding pulse 132 beats per minute; shallow, non-labored respirations at 32 breaths per minute and temperature 97.0 degrees Fahrenheit. At 19:00, the patient died from disease progression. The patient was reported to have stable disease on study drug and progressive disease after discontinuation; therefore, disease progression was reported as possibly related to stopping of study drug. No action was taken with IPI-504.

The Investigator assessed the adverse events of abdominal pain and acute renal failure as not related to IPI-504, and the adverse event of disease progression as possibly related to IPI-504.

The relationship between IPI-504 and the adverse events of ascites, dyspnea, abdominal pain, and acute renal failure was reported as not related, per the investigator, and the relationship between IPI-504 and the adverse event of disease progression was reported as possibly related, per the investigator.

Patient #: 028-001 **Gender: Male** **Age: 86 years** **Treatment Assignment: Placebo**					
SAE term	**Treatment assignment**	**Intensity**	**Relationship**	**Outcome**	**Resulted in study discontinuation**
Disease progression	Placebo	Grade 5	Not related	Fatal	No

Patient number 028-001 was an 86-year-old Caucasian man diagnosed with GIST on 17-Apr-2001, with initial presentation in the esophagus and metastases to the liver and mediastinum. Prior therapies included imatinib, sunitinib, and XL820. Cancer surgical history included tumor resection, esophageal mass biopsies, and esophageal stenting. Relevant medical history included stage 3 chronic kidney disease and basal cell carcinoma of the nose. Concurrent medical conditions included Type 2 diabetes mellitus, actinic keratosis of the right ear, dehydration, pulmonary embolism, weakness, cardiac chest pain, fatigue, shortness of breath, loss of appetite, diarrhea, and malnutrition. Concomitant medications included hydrocodone/acetaminophen, megestrol, ondansetron, and bisacodyl.

The patient enrolled in the study on 09-Dec-2008, and was subsequently randomized to receive placebo. On 20-Jan-2009 (study Day 1), the patient started treatment with study drug, and received 14 doses. On 15-Apr-2009, the patient discontinued study due to sponsor termination of the trial. On 28-Apr-2009 (study Day 99), his final study visit occurred. At that time, Eastern Cooperative Oncology Group (ECOG) performance status score was 3, noted to be a significant deterioration. He had poor oral intake and was receiving intravenous normal saline, 500 ml daily. He had lost weight, had no appetite, and was barely walking. Active treatment for GIST was not recommended due to the patient's significant decline. Additionally, the patient had squamous cell cancer of the ear with increasing lesion size, for which no

treatment was being provided. On 03-May-2009 (study Day 104), the patient died at home of disease progression. The intensity of the adverse event was reported as Grade 5. No autopsy was performed. The cause of death was reported to be progression of disease.

The Investigator assessed the adverse event of disease progression GIST as not related to blinded study drug (placebo).

Patient #: 040-001 **Gender: Male** **Age: 64 years** **Treatment assignment: IPI-504**					
SAE term	**Treatment assignment**	**Intensity**	**Relationship**	**Outcome**	**Resulted in study discontinuation**
Hepatic failure	IPI-504	Grade 5	Probable	Fatal	Yes

Patient number 040-001 was a 64year-old Caucasian man diagnosed with GIST on 09-Apr-2003, with initial site of presentation not specified. Sites of disease included the liver and pancreas. Prior therapies included lengthy courses of imatinib and sunitinib. Cancer surgical history included Whipple procedure with a double bypass, cholecystectomy, and gastrojejunostomy. Relevant medical history included hypertension, hypothyroidism, stomach disorders, and peptic ulcer disease. Concomitant medications included prochlorperazine, omeprazole, hydrochlorothiazide, quinapril, levothyroxine, iron supplement, multivitamin, acetylsalicylic acid, magnesium, glucosamine, hydrocodone/acetaminophen, and oxycodone.

The patient enrolled in the study on 24-Mar-2009, and was randomized to receive IPI-504. On 24-Mar-2009 (study Day 1), the patient started treatment with study drug, and received 4 doses of study drug before onset of the adverse event. On 27-Mar-2009 (study Day 4), laboratory results were significant for alkaline phosphatase 230 Units/ L (Grade 1) and ALT 66 Units/L (Grade 1); AST, total bilirubin, and LDH were within normal limits. On 30-Mar-2009 (study Day 7), the patient was prescribed hydrocodone/acetaminophen 7.5 mg every four hours as needed. On 31-Mar-2009, laboratory results showed alkaline phosphatase 302 Units/L (Grade 1), AST 61 Units/L (Grade 1), ALT 81 Units/L (Grade 1), total bilirubin 0.7 mg/dL (within normal range), and LDH 309 Units/L (normal range 100-250 Units/L). On 03-Apr-2009 (study Day 11), the patient received his fourth dose of blinded study drug. At the time, laboratory results were significant for alkaline phosphatase 474 Units/L (Grade 2), AST 582 Units/L (Grade 3), ALT 431 Units/L (Grade 3), bilirubin 1.3 mg/dL (Grade 1) and LDH 652 Units/L (normal range 100-250 Units/L). Hydrocodone/acetaminophen was discontinued, with increase in chronic back pain.

On 05-Apr-2009 (study Day 13), the patient presented to the Emergency Department (ED) at 6:00 a.m. with a ten hour history of nausea and vomiting with "purple" emesis. Concomitant medications included prochlorperazine, omeprazole, hydrochlorothiazide, quinapril, levothyroxine, acetylsalicylic acid, hydrocodone/acetaminophen, and oxycodone. Fever was reported as 100 degrees Fahrenheit since starting study drug therapy and was 102.8 degrees Fahrenheit in the ED. The patient reported having chills and diaphoresis, was intolerant to oral fluids, and had diffuse crampy like abdominal pain. He also reported minor upper respiratory infection symptoms with congestion. He denied diarrhea, cough, chest

pain, shortness of breath, urinary tract symptoms or rash. Vital signs upon presentation in the ED were: temperature 102.8 degrees Fahrenheit, pulse 107 beats per minute (bpm), respirations 28 breaths per minute, blood pressure 223/111 mmHg and oxygen saturation 98%. Physical exam was significant for bilateral coarse breath sounds at bases and hyperactive bowel sounds. Abdomen was non-distended with diffuse abdominal tenderness to palpation, without rebound or guarding. Laboratory results at 6:55 a.m. included: WBC 6.5 thou/mcL (within normal range), sodium 124 mmol/L (Grade 1), chloride 89 mmol/L (Grade 1), carbon dioxide 18 mmol/L (Grade 1), anion gap 21.6 mmol/L, blood urea nitrogen (BUN) 18 mg/dL (within normal range), creatinine 1.8 mg/dL (Grade 1), glucose 468 mg/dL (Grade 3) and positive serum acetone. Liver function tests included: alkaline phosphatase 829 Units/L (Grade 3), ALT 357 Units/L (Grade 3), AST 1257 Units/L (Grade 4), and total bilirubin 0.8 mg/dL (within normal range). Coagulation parameters showed prothrombin time (PT) 16.1 sec (normal range 11.5-14.0 sec), international normalized ratio (INR) 1.3 (Grade 1) and partial thromboplastin time (PTT) 47.3 seconds (Grade 1). Amylase and lipase were within normal ranges. Blood cultures were drawn and showed no growth at the time of the report. The patient was diagnosed with sepsis and diabetic ketoacidosis. Medications administered in the ED included normal saline, metoclopramide, cefepime, ondansetron, hydromorphone, ibuprofen and insulin. Vital signs at 08:37 a.m. included: temperature 98.7 degrees Fahrenheit, pulse 118 beats per minute, respirations 18 breaths per minute, blood pressure 139/81 mmHg, and oxygen saturation 94%. Chest x-ray at 10:34 a.m. showed small lung volumes with no evidence of acute cardiopulmonary disease. At 10:45 a.m., the patient was transferred to a hospital. Vital signs at this time included temperature 98.7 degrees Fahrenheit, blood pressure 170/130 mmHg, pulse 120 beats per minute, respiration rate 20 breaths per minute, and 96% oxygen saturation on room air. Physical exam was unremarkable. He had been without urine output since the night before this admission, thought to be secondary to poor oral intake and/or a possible obstruction, the cause of which was possibly in the prostate. A Foley catheter was placed and the patient was started on intravenous fluids for rehydration as well as empiric vancomycin and cefepime; parallel blood, urine, and stool cultures were obtained. Laboratory results showed diabetic ketoacidosis (DKA) with no known history of type 1 diabetes but with a pancreatic surgical history. The patient's DKA was thought secondary to increased lactic acid (due either to sepsis or adverse chemotherapy reaction), or an organic acid build-up secondary to renal failure. Fifteen units of insulin did not significantly decrease his blood glucose, and an insulin drip was started. Five percent dextrose was withheld from the intravenous fluids until the patient's glucose level reached 250 mg/dL or below. The patient experienced hyponatremia, partly noted as pseudohyponatremia due to hyperglycemia. Even corrected for hyperglycemia, an actual hyponatremia secondary to true volume depletion (with an increase in the release of antidiuretic hormone) was noted. Hypertension was treated by withholding the patient's hypertensive regimen and changing to a beta-blocker and calcium channel-blocker therapy. Levothyroxine, a proton-pump inhibitor, and subcutaneous heparin were continued. Repeat laboratory tests performed at 12:00 p.m. included: WBC 13.9 k/cumm (normal range 3.8 - 9.8 k/cumm), carbon dioxide 13 mmol/L (Grade 2), BUN 21 mg/dL (within normal range), creatinine 2.41 mg/dL (Grade 2), and glucose 435 mg/dL (Grade 3). Liver function tests included: alkaline phosphatase 885 Units/L (Grade 3), ALT 583 Units/L (Grade 3), AST 1804 Units/L (Grade 4), total bilirubin 1.1 mg/dL (within normal range), direct bilirubin 0.6 mg/dL (normal range 0.0-0.3 mg/dL), and lactate dehydrogenase (LDH) 2415 Units/L (normal range 100-250 Units/L). Urinalysis at 1:20 p.m. was significant for 3+ protein, 4+ glucose, 1+ ketones, 1+ bilirubin, and 2+ blood. At 5:25 p.m., laboratory results included: WBC 23.0 k/cumm (normal range 3.8-9.8 k/cumm), 132 mmol/L (Grade 1), chloride 103 mmol/L (within normal range), carbon dioxide 9 mmol/L (Grade 3), anion gap 20 mmol/L (normal range 0-16 mmol/L), BUN 25 mg/dL (within normal range), creatinine 2.76 mg/dL (Grade 2), and glucose 289 mg/dL (Grade 3). Liver function tests at that time were: alkaline phosphatase 840 Units/L (Grade 3), ALT 661 Units/L (Grade 3), AST 2326 U/L (Grade 4); bilirubin was unchanged. Troponin was 3.93 (range 0.00 - 0.24 ng/ml). Coagulation tests

were: PT 22.9 sec (normal range 11.0-15.0), PTT 75.3 seconds (Grade 2) and INR 2.00 (Grade 2). Magnetic resonance imaging of the pelvis showed multiple cystic and solid hepatic lesions with one new lesion and a noted decrease in size of several established lesions along with an isointense T1 signal, concerning for prostate cancer. An electrocardiogram showed sinus tachycardia without ST-T changes. Chest x-ray at 17:38 performed for respiratory distress showed multifocal air space opacities, concerning for pneumonia and/or edema. Repeat chest x-ray at 19:26 showed placement of an endotracheal tube and no other changes from previous x-ray. On 05-Apr-2009 (study Day 13) at 20:43, the patient died; cause of death was reported as liver failure. The expiration summary attributed the patient's death to cardiac arrest due to severe metabolic acidosis due to multi-organ failure.

The Investigator assessed the adverse events of hepatic failure as probably related to blinded study drug (IPI-504).

Patient #: 051-002
Gender: Male
Age: 71 years
Treatment Assignment: Placebo

SAE term	Treatment assignment	Intensity	Relationship	Outcome	Resulted in study discontinuation
Eastern cooperative oncology group performance status worsened	Placebo	Grade 3	Not related	Resolved	No

Patient number 051-002 was a 71-year-old Caucasian man diagnosed with GIST on 17-Nov-2003, with initial presentation in the stomach. Prior therapies included imatinib and sunitinib. Cancer surgical history included gastrectomy, splenectomy with left pancreas resection, metastasectomy and omentectomy; transurethral bladder resection, and explorative laparotomy with tumor resection and jejunal segment resection. Relevant concurrent medical conditions included coronary artery disease, triple coronary artery bypass graft reactive thrombocytosis, dyspnea on exertion, reactive depression, and abdominal pain. Concomitant medications were metamizole sodium, propranolol hydrochloride, and triamterene.

The patient enrolled in the study on 27-Mar-2009, and was subsequently randomized to receive placebo. On 31-Mar-2009 (study Day 1), the patient started treatment with study drug, and received 4 doses before onset of the adverse event. On 21-Apr-2009 (study Day 22), the patient experienced ECOG reduction (Eastern Cooperative Oncology Group reduction), and was hospitalized. The patient's ECOG score was 2, compared with a baseline score of zero. Symptoms included loss of appetite, weight loss, and fever. Laboratory results included: hemoglobin 8.6 g/dl (Grade 2), hematocrit 0.262 l/l (normal range 0.4-0.5), neutrophils 90.6% (normal range 39-71), sodium 137 mmol/l (within normal limits, WNL), potassium 5.2 mmol/l (Grade 1), chloride 100 mmol/l (WNL), calcium 2.23 mmol/l (WNL), magnesium 1.11 mmol/l (Grade 1), serum creatinine 1.11 mg/dL (within normal limits), blood urea nitrogen 47.0 mg/dL (reference range 6-19.8), uric acid 10.3 mg/dL (Grade 4), aspartate aminotransferase (AST) 28 U/L (WNL), alanine aminotransferase (ALT) 10 U/L (WNL), alkaline

phosphatase 117 U/L (within normal limits), lactate dehydrogenase (LDH) 413 U/L (reference range 100-247), amylase 21 U/L(WNL), lipase 8.0 U/L(WNL), C reactive protein 23.3 mg/dl (normal range <0.5), glucose 128 mg/dl (Grade 1). The origin of the patient's fever was not determined. The patient was treated with parenteral nutrition, pantoprazole, and intravenous electrolytes, vitamins, and minerals. His general condition improved. Disease progression was reported to be an alternative etiology for the adverse event. On 30-Apr-2009 (study Day 31), the patient was discharged from the hospital. The event resolved on 30-Apr-2009 (study Day 31). No action was taken with study drug.

The Investigator assessed the adverse event of ECOG reduction as not related to blinded study drug (placebo).

Patient #: 053-004
Gender: Female
Age: 54 years
Treatment Assignment: IPI-504

SAE term	Treatment assignment	Intensity	Relationship	Outcome	Resulted in study discontinuation
Renal failure acute	IPI-504	Grade 3	Possible	Resolved	No
Diarrhoea	IPI-504	Grade 3	Possible	Resolved	No

Patient number 053-004 was a 54-year-old Asian woman with gastrointestinal stromal tumor, diagnosed on 26-Oct-2001 with initial presentation in the bowel. Prior therapies included imatinib, sunitinib, and nilotinib. Cancer surgical history included small bowel resection. Concurrent conditions included abdominal distension. Concomitant medications included granisetron.

The patient enrolled in the study on 11-Mar-2009, and was subsequently randomized to receive IPI-504. On 24-Mar-2009 (study Day 1), the patient started treatment with study drug, and received 2 doses. On 28-Mar-2009 (study Day 5), she experienced Grade 3 diarrhea, which the investigator considered medically significant. By 29-Mar-2009 (study Day 6), the event resolved without treatment to mild (Grade 1) diarrhea. On 30-Mar-2009 (study Day 7), urine output had decreased, and on 31-Mar-2009 (study Day 8), the patient was hospitalized for azotemia. Admission laboratory values included white blood cell count (WBC) 19.5 x103 /mm3 (reference range 4-10), phosphorus 6.3 mg/dL (reference range 2.5-4.5), glucose 130 mg/dL (Grade 1), creatinine 1.7 mg/dL (Grade 1), blood urea nitrogen (BUN) 59 mg/dL (reference range 10-26), glomerular filtration rate (GFR) 33 (normal >= 60), aspartate aminotransferase (AST) 125 IU/L (Grade 2), alanine aminotransferase (ALT) 53 IU/L (Grade 1), alkaline phosphatase 823 IU/L (Grade 3), total bilirubin 1.4 mg/dL (Grade 1), total carbon dioxide 18.9 mmol/L (reference range 24-31), and lactate dehydrogenase 975 U/L (reference range 120-250). Urinalysis was positive for occult blood and bilirubin. Treatment included normal saline and cefotaxime for suspected acute renal failure secondary to diarrhea. On 02-Apr-2009 (study Day 10), laboratory results were significant for creatinine 1.1 mg/dL, BUN 43 mg/dL (normal range 10-26), GFR 55 (normal >= 60), AST 70 (Grade 1), ALT 50 (Grade 1), and alkaline phosphatase 907 IU/L (Grade 3). On 03-Apr-2009 (study Day 11), computed tomography scans showed stable disease. On 07-Apr-2009 (study Day 15), the patient's creatinine level was 1.1 mg/dL. Laboratory results on 08-Apr-2009 (study Day 16) were significant for creatinine 0.6 mg/dL, BUN 47 mg/dL (reference range 10-26), GFR >= 90 (within reference range), and alkaline phosphatase 656 IU/L (Grade 3). The patient remained stable for 48

hours. The adverse event of Grade 3 diarrhea resolved on 28-Mar-2009 (study Day 5). On 09-Apr-2009 (study Day 17), the adverse event of Grade 3 acute renal failure resolved and the patient was discharged from the hospital. IPI-504 was held and reduced due to the adverse events.

The investigator assessed the adverse events of acute renal failure and diarrhea as possibly related to blinded study drug (IPI-504).

Patient #: 056-001 **Gender: Male** **Age: 57 years** **Treatment Assignment: N/A**					
SAE term	**Treatment assignment**	**Intensity**	**Relationship**	**Outcome**	**Resulted in study discontinuation**
Disease progression	Pre-treatment	Grade 5	Not related	Fatal	No
Abdominal pain	Pre-treatment	Grade 4	Not related	Ongoing	No

Patient number 056-001 was a 57-year-old Caucasian man diagnosed with GIST on an unknown date. Information regarding prior therapies, surgical history, and medical history was not provided. Concomitant medications were metopimazine, chlorpromazine, acetaminophen, phloroglucinol, esomeprazole, trimebutine maleate, and ondansetron.

The patient enrolled in the study on 23-Mar-2009. He did not start study treatment due to worsening performance status. On 24-Mar-2009, the patient was hospitalized for vomiting and Grade 4 abdominal pain. He was treated with morphine and intravenous steroids. On 26-Mar-2009, his condition worsened. On 01-Apr-2009, the adverse event of disease progression was fatal (Grade 5). No autopsy was performed. The event of abdominal pain was ongoing at the time of death.

The Investigator assessed the adverse events of disease progression and abdominal pain as not related to study drug.

Patient #: 066-001 **Gender: Female** **Age: 71 years** **Treatment Assignment: IPI-504**					
SAE term	**Treatment assignment**	**Intensity**	**Relationship**	**Outcome**	**Resulted in study discontinuation**
Metabolic acidosis	IPI-504	Grade 5	Possible	Fatal	Yes
Disseminated intravascular coagulation	IPI-504	Grade 5	Possible	Fatal	Yes
Nausea	IPI-504	Grade 3	Possible	Ongoing	No
Vomiting	IPI-504	Grade 3	Possible	Ongoing	No
Diarrhoea	IPI-504	Grade 3	Possible	Ongoing	No

Patient number 066-001 was a 71-year-old Hispanic woman diagnosed with GIST on 08-Feb-1999, with initial presentation in the small bowel and recurrences to the liver. Prior therapies included imatinib and sunitinib. Cancer surgical history included small bowel resection, left hepatectomy, and cholecystectomy. Medical history includes pancreatitis. Relevant concurrent medical conditions include hypertension, diabetes, chronic kidney disease (Grade 1), and anemia. Concomitant medications included pioglitazone until 2007 and sitagliptin starting March 2009 for diabetes control; clonidine, atenolol, allopurinol, lisinopril, valsartan/hydrochlorothiazide, ondansetron, megestrol, escitalopram, magnesium, and pravastatin.

The patient enrolled in the study on 10-Mar-2009, and was subsequently randomized to receive IPI-504. Laboratory results prior to entering the study included: white blood cell count (WBC) 19.3 x 10e3/uL (reference range 4.8-10.8 x 10e3/uL), creatinine 1.4 mg/dL (Grade 1), blood urea nitrogen (BUN) 32 (reference range 7-17 mg/dL), glucose 182 mg/dL (Grade 2), aspartate aminotransferase 67 U/L (Grade 1), alanine aminotransferase (ALT) 8 U/L (within normal range), alkaline phosphatase 88 U/L (within normal range), total bilirubin 0.3 mg/dL (Grade 1), lactate dehydrogenase (LDH) 4929 U/L (reference range 313-618 U/L). Coagulation parameters were within reference range, and other laboratory results were unremarkable.

On 31-Mar-2009 (study Day 1), the patient started treatment with study drug, and received 2 doses. On 03-Apr-2009 (study Day 4), she had no complaints and was described as looking quite well. Laboratory results on that date included: WBC 12.0 x10e3/uL (reference range 4.8-10.9 x10e3/uL), potassium 5.5 mEq/L (Grade 1), glucose 146 mg/dL (Grade 1), BUN 45 mg/dL (reference range 7-17 mg/dL), and creatinine 1.7 mg/dL (Grade 1). Liver function tests were: AST 42 U/L (Grade 1), ALT 16 U/L (within normal range), alkaline phosphatase 90 U/L (within normal range), total bilirubin 0.2 mg/dL (within normal range), and lactate dehydrogenase (LDH) 2745 U/L (reference range 313-617 U/L). On 04-Apr-2009 (study Day 5), the patient phoned the physician with complaints of nausea, vomiting (fourteen episodes), diarrhea (ten episodes), and subsequent abdominal pain. She reported to the emergency department (ED) as instructed, and was hypertensive upon arrival, with a blood pressure of 170/100 mmHg. ED notes indicated the patient had a one day history of black stools and bloody diarrhea. Other symptoms at presentation included chills, headache, nonproductive cough, and overall generalized pain. Physical exam was significant for tensing upon abdominal palpation. Renal function studies were worsening in the setting of dehydration and the patient was given 250 cc of normal saline. On 05-Apr-

2009 (study Day 6) at 2:30 am, vital signs included: temperature 97 degrees Fahrenheit, pulse 99 beats per minute (bpm) in sinus rhythm, respirations 18 per minute, and blood pressure 170/110 mmHg. At 2:36am, abdominal x-ray showed no intra-abdominal free air, no evidence of obstruction, mild elevation of the left hemidiaphragm with atelectasis at the left lung base, and underlying infiltrate at the left lung base. At 2:40 a.m., laboratory results included: white blood cell count (WBC) 14.93 10^3/uL (reference range 4.80-10.80), prothrombin time (PT) 15.9 seconds (reference range 12.4-15.2), international normalized ratio (INR) 1.21 (Grade 1), activated partial thromboplastin time (PTT) 45.3 seconds (reference range 24.7-39.8), sodium 139 mmol/L (within normal range), chloride 101 mmol/L (within normal range), potassium 5.1 mmol/L (within normal limits), carbon dioxide 19.6 mmol/L (Grade 1), blood urea nitrogen (BUN) 43.0 mg/dL (reference range 7.0-18.0), creatinine 2.22 mg/dL (Grade 2), glucose 168 mg/dL (Grade 2), aspartate aminotransferase (AST) 420.0 (Grade 3), alanine aminotransferase (ALT) 72.0 (Grade 1), alkaline phosphatase 178 U/L (Grade 1), total bilirubin 0.14 mg/dL (within normal range), amylase 207 U/L (Grade 2), lipase 726 U/L (Grade 3), and lactic acid 5.0 mmol/L (reference range 0.4-2.0). On the morning of 05-Apr-2009 (study Day 6), the patient was admitted to the hospital. She was noted to be hypertensive, for which enalapril was given. Vital signs at 7:00 am included: pulse 106 bpm, respirations 18 per minute, and blood pressure 148/101 mmHg. Laboratory results included positive guaiac. The patient was noted to have lactic acidosis and acute kidney injury, assessed as probably secondary to vomiting. At 7:30 am, blood pressure was 155/105 mmHg and aliskiren was added to medications for uncontrolled blood pressure. At 8:50 am, arterial blood gas (ABG) results included pH 7.24 (reference range 7.35-7.45), pCO_2 20.0 mmHg (reference range 35.0-45.0), pO_2 61.0 mmHg (reference range 75.0-100), and bicarbonate (HCO_3) 8.6 mmol/L (reference range 22.0-26.0). At 9:58 a.m., laboratory results included: carbon dioxide 11.7 mmol/L, glucose 67 mg/dL (Grade 1), BUN 46.0 mg/dL (reference range 7.0-18.0 mg/dL), creatinine 2.53 mg/dL (Grade 2), anion gap 28.3 mmol/L (reference range 10.0-20.0 mmol/L), and lactic acid 12.9 mmol/L (reference range 0.4-2.0 mmol/L). At approximately 10:40 am, the patient had a bowel movement that consisted of bloody and mucous-filled diarrhea. Subsequently, she became hypotensive (blood pressure 70/49 mmHg) and unresponsive. Shortly thereafter, she was noted to be in respiratory distress and was intubated. The drop in blood pressure was determined to be secondary to volume depletion, and fluid replacement was continued. At approximately 12:00 pm, vital signs were stable. Physical exam revealed non-icteric sclera. Lungs were clear upon auscultation bilaterally. Heart rate was regular. Abdomen was soft, nontender and nondistended. Extremities were negative for edema. The patient was diagnosed with lactic acidosis and the anion gap was determined to be of concern. Pressors were not administered as blood pressure responded immediately to fluids. The assessing physician was uncertain if her lactic acidosis and anion gap were attributable to progression of disease, blinded study drug treatment, or dehydration in the setting of nausea, vomiting, and diarrhea. Chest x-ray showed alveolar disease within the right hemithorax, which represented pneumonia. At 1:29 pm, the patient's heart rate dropped to 37 beats per minute which progressed to asystole. Atropine was given and cardiopulmonary resuscitation (CPR) was started. By 2:00 pm, the patient was noted to be resuscitated, and vital signs included: pulse 120 bpm, respiratory rate 20 per minute, and blood pressure 106/88 mmHg. The patient was noted to be actively bleeding from her arms, for which dressings were applied. At 2:00 pm, laboratory results included: WBC 17.38 10^3/uL (reference range 4.80-10.80), troponin-I 14.93 ng/mL (reference range 0.04-0.05), creatine kinase-MB (CKMB) 16.2 ng/mL (reference range 0.5-3.6), PT 36.6 seconds (reference range 12.4-15.2), INR 3.35 (Grade 3), PTT >200 seconds (Grade 3), sodium 147 mmol/L (Grade 1), potassium 6.8 mmol/L (Grade 2), chloride 110 mmol/L (Grade 1), carbon dioxide 7.5 mmol/L (Grade 3), anion gap 29.5 mmol/L (reference range 10.0 to 20.0 mmol/L), BUN 42.0 mg/dL (reference range 7.0-18.0), creatinine 2.42 mg/dL (Grade 2), AST 4340 U/L (Grade 4), ALT 2292 U/L (Grade 4), total bilirubin 0.24 mg/dL (within normal range), and alkaline phosphatase 194 U/L (Grade 3). Serum phosphorus was 13.3 mg/dL. ABG results were: pH 6.80 (reference range 7.35-7.45), pCO2

42.0 mmHg (within normal limits), and pO2 160 mmHg (reference range 75.0-100.0). Chest x-ray showed no definitive evidence of a pneumothorax. Persistent alveolar disease within the right hemithorax was noted and presumed to represent pneumonia. Computed tomography of the abdomen and pelvis with oral contrast revealed small bilateral pleural effusions and bibasilar infiltrates, a stable gastric mass measuring 14 cm, and no evidence of bowel obstruction or focal inflammation. At 3:35 pm, the patient became bradycardic and then pulseless. Resuscitation measures were performed, bicarbonate was administered, and the patient stabilized. Subsequent evaluation noted the patient was experiencing disseminated intravascular coagulation (DIC), and was critically ill due to ischemic bowel or rapid turnover in necrosis of the large gastrointestinal mass. At 4:45 PM, ABG showed pH 6.85 (Grade 3), pCO_2 60.0 mmHg (35.0-45.0) and pO_2 106.0 mmHg (reference range 75.0-100.0). At 4:55 PM, laboratory results included fibrinogen <60 mg/dL (Grade 2), PT 60.1 seconds (reference range 12.4-15.2), INR 6.13 (Grade 3), PTT >200 seconds (Grade 3), D-Dimer >20.0 ug/mL FEUs (normal range 0.22-0.50), BUN 46.0 mg/dL (normal range 7.0-18.0), creatinine 2.62 mg/dL (Grade 2), carbon dioxide 14.6 mmol/L (Grade 2), and anion gap 25.4 mmol/L (normal range 10.0-20.0). At 7:55 PM, ABG results revealed pH 7.18 (normal range 7.35-7.45), pCO_2 32.0 mmHg (normal range 35.0-45.0), and pO_2 105.0 mmHg (normal range 75.0-100.0). Vitamin K, fresh frozen plasma and cryoprecipitate were administered. Chest x-ray at 6:53 pm showed a presumed layering of a right pleural effusion and mild coronary congestion. At 8:00 PM, troponin-I was 28.51 ng/mL (normal range 0.04-0.05) and CK-MB 69.0 ng/mL (normal range 0.5-3.6). At 5:45 pm, consult noted that surgical intervention was not an option, and the patient's family opted for no further resuscitative measures. At 11:30 pm, the patient was noted to be in critical status with poor prognosis. The family requested that vasopressors be discontinued, and comfort measures be continued only. Morphine (2 mg) was given for comfort. The patient died at 11:43 pm; the probable cause of death was reported as metabolic acidosis. No autopsy was performed. The adverse events of Grade 5 metabolic acidosis and Grade 5 disseminated intravascular coagulation were fatal on 05-Apr-2009 (study Day 6). The adverse events of Grade 3 nausea, Grade 3 vomiting, and Grade 3 diarrhea were ongoing at the time of death. The cause of death was reported as metabolic acidosis. Study participation was discontinued as a result of the adverse events of metabolic acidosis and disseminated intravascular coagulation.

The Investigator assessed the adverse events of metabolic acidosis, DIC, nausea, vomiting, and diarrhea as possibly related to blinded study drug (IPI-504).

14.3.4. Abnormal Laboratory Value Listing (Each Patient)

The following statistical tables are included in this section:

Table 14.3.4.1:	Listing of Hematology Results with CTCAE Grade 3 or Above- (ITT Population)
Table 14.3.4.2:	Listing of Chemistry Results with CTCAE Grade 3 or Above- (ITT Population)
Table 14.3.4.3:	Listing of Liver Function Test (LFT) Values > ULN - (ITT Population)

14.3.5. Other Safety Tabulations

The following statistical tables are included in this section:

Table 14.3.5.1:	Summary of Heart Rate over time for the Double Blind Portion of the Study (ITT Population)
Table 14.3.5.2:	Summary of Heart Rate While on IPI-504 (ITT Population)
Table 14.3.6.1:	Summary and Change from Baseline for Laboratory Parameters by Time Point for the Double Blind Portion of the Study: Hematology (ITT Population)
Table 14.3.6.2:	Summary and Change from Baseline for Laboratory Parameters by Time Point for the Double Blind Portion of the Study: Chemistry (ITT Population)
Table 14.3.6.3:	Summary and Change from Baseline for Laboratory Parameters by Time point While on IPI-504: Hematology (ITT Population)
Table 14.3.6.4:	Summary and Change from Baseline for Laboratory Parameters by Time point While on IPI-504: Chemistry (ITT Population)
Table 14.3.6.5:	Laboratory Tables of CTCAE Grades for Hematology Parameters (ITT Population)
Table 14.3.6.6:	Laboratory Tables of CTCAE Grades for Chemistry Parameters (ITT Population)
Table 14.3.6.7	Laboratory Shift Tables of CTCAE Grades for Hematology Parameters (ITT Population)
Table 14.3.6.8:	Laboratory Shift Tables of CTCAE Grades for Chemistry Parameters (ITT Population)
Table 14.3.6.9:	Summary of Liver Function Test (LFT) Abnormalities Over Time (ITT Population)
Table 14.3.6.10:	Summary of Worst Grade of Liver Function Test (LFT) Abnormalities (ITT Population)

14.3.6. Figures

The following statistical figures are included in this section:

15. REFERENCE LIST

1 Hirota S, Isozaki K, Moriyama Y, Hashimoto K, Nishida T, Ishiguro S, Kawano K, Hanada M, Kurata A, Takeda M, Tunio GM, Matsuzawa Y, Kanakura Y, Shinomura Y, Kitamura Y. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science (1998) 279:577-580.

2 Lux ML, Rubin BP, Biase TL, Chen C-J, Maclure T, Demetri G, Xiao S, Singer S, Fletcher CDM, Fletcher JA. KIT extracellular and kinase domain mutations in gastrointestinal stromal tumors. American Journal of Pathology (2000) 156:791-795.

3 Rubin BP, Singer S, Tsao C, Duensing A, Lux ML, Ruiz R, Hibbard MK, Chen C-J, Xiao S, Tuveson DA, Demetri GD, Fletcher CDM, Fletcher JA. KIT activation is a ubiquitous feature of gastrointestinal stromal tumors. Cancer Research (2001) 61:8118-8121.

4 Sihto H, Sarlomo-Rikala M, Tynninen O, Tanner M, Andersson LC, Franssila K, Nupponen NN, Joensuu H. KIT and platelet-derived growth factor receptor alpha tyrosine kinase gene mutations and KIT amplifications in human solid tumors. J Clin Oncology (2005) 23:49-57.

5 Heinrich MC, Shoemaker JS, Corless CL, Hollis D, Demetri GD, Bertagnolli MM, Fletcher JA. Correlation of target kinase genotype with clinical activity of imatinib mesylate (IM) in patients with metastatic GI stromal tumors (GISTs) expressing KIT (KIT+). ASCO (2005): Abstract #7.

6 Dematteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. Ann Surg (2000) 231:51-58.

7 Pratt WB, Toft DO. Regulation of signaling protein function and trafficking by the hsp90/hsp70-based chaperone machinery. Exp Biol Med (2003) 228:111-133.

8 Maloney A, Workman P. HSP90 as a new therapeutic target for cancer therapy: the story unfolds. Expert Opin Biol Ther (2002) 2:3-24.

9 Nathan DF, Lindquist S. Mutational analysis of HSP90 function: interactions with a steroid receptor and a protein kinase. Mol Cell Biol (1995) 15:3917-3925.

10 Rutherford SL, Lindquist S. Hsp90 as a capacitor for morphological evolution. Nature (1998) 396:336-342.

11 Queitsch C, Sangster TA, Lindquist S. Hsp90 as a capacitor of phenotypic variation. Nature (2002) 417:618-624.

12 DeBoer C, Dietz A. The description and antibiotic production of Streptomyces hygroscopicus var. geldanus. J Antibiotics (1976) 29:1182-1188.

13 Uehara Y, Hori M, Takeuchi T, Umezawa H. Phenotypic change from transformed to normal induced by benzoquinoid ansamycins accompanies inactivation of p60src in rat kidney cells infected with Rous sarcoma virus. Mol Cell Biol (1986) 6:2198-2206.

14 Schulte TW, Neckers LM. The benzoquinone ansamycin 17-allylamino-17-demethoxygeldanamycin binds to Hsp90 and shares important biologic activities with geldanamycin. Cancer Chemother Pharmacol (1998) 42:273-279.

15 Sydor JR, Normant E, Pien CS, et al. Development of 17-allylamino-17-demethoxygeldanamycin hydroquinone hydrochloride (IPI-504), an anti-cancer agent directed against Hsp90. Proc Natl Acad Sci USA. 2006; 103(46):17408-13.

16 Heinrich MC, Corless CL, Duensing A, McGreevey L, Chen C-J, Joseph N, Singer S, Griffith DJ, Haley A, Town A, Demetri GD, Fletcher CDM, Fletcher JA. PDGFRA activating mutations in gastrointestinal stromal tumors. Science (2003) 299:708-710.

17 Kang HJ, Nam SW, Kim H, Rhee H, Kim N-G, Kim H, Hyung WJ, Noh SH, Kim J-H, Yun C-O, Liu ET, Kim H. Correlation of KIT and platelet-derived growth factor receptor α mutations with gene activation and expression profiles in gastrointestinal stromal tumors. Oncogene (2005) 24:1066–1074.

18 Matei D, Satpathy M, Cao L, Lai Y-C, Nakshatri H, Donner DB. The platelet-derived growth factor receptor α is destabilized by geldanamycins in cancer cells. J Biol Chem (2007) 282: 445-453.

19 Antoch G, Kanja J, Bauer S, Kuehl H, Renzing-Koehler K, Schuette J, Bockisch A, Debatin JF, Freudenberg LS. Comparison of PET, CT and dual-modality PET/CT imaging for monitoring of imatinib (STI571) therapy in patients with gastrointestinal stromal tumors. J Nuclear Medicine (2004) 45: 357-365.

20 van den Abbeele AD, Badawi RD, Cliché JP, Janicek MJ, Tetrault R, Spangler T, Potter A, Merriam P, Silberman S, Dimitrijevic S, Demetri GD. 18-FDG-PET predicts response to imatinib mesylate (Gleevec) in patients with advanced gastrointestinal stromal tumors (GIST). ASCO Annual Meeting (2002): Abstract 1610.

21 Young H, Baum R, Cremerius U, Herholz K, Hoekstra O, Lammertsma AA, Pruim J, Price R. Measurement of clinical and subclinical tumour response using [18F]-fluorodeoxyglucose and positron emission tomography: review and 1999 EORTC recommendations. Eur J Cancer (1999) 35:1773-1782.

16. APPENDICES

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

The following protocols and protocol amendments are included in this appendix:

Protocol IPI-504-06

- Original Protocol IPI-504-06 (May 19, 2008)

Protocol IPI-504-06 Amendment 1

- Protocol IPI-504-06 Amendment 1 (July 16, 2008)
- Protocol IPI-504-06Amendment 1 Summary of Changes (July 16, 2008)

Protocol IPI-504-06 Amendment 2

- Protocol IPI-504-06 Amendment 2 (September 15, 2008)
- Protocol IPI-504-06Amendment 2 Summary of Changes (September 15, 2008)

Protocol IPI-504-06 Amendment 3

- Protocol IPI-504-06 Amendment 3 (February 20, 2009)
- Protocol IPI-504-06Amendment 3 Summary of Changes (February 20, 2009)

16.1.2 Sample Case Report Form

A sample case report form is provided in this appendix.

16.1.3 List of IECs or IRBs – Representative Written Information for Patient and Sample Consent Forms

The following list of IECs and IRBs contains initiated sites only.

Country	Principal Investigator	IRB/IEC	Chairman
Australia	Paul Eliadis	Bellberry Limited 1st Floor 71 Anzac highway Ashford South Australia, Australia 5035	Yvette L Winter
	David Goldstein	Cancer Institute NSW Clinical Research Ethics Committee Lev 1 Biomedical building Australian Technology Park Eveleigh New South Wales, Australia 2015	Prof. William Walters
	Chris Karapetis	Flinders Clinical Research Ethics Committee Flinders Medical Centre, Flinders Drive Bedford Park South Australia, Australia 5042	Member list is not published. Office of Human Research Protections (OHRP) IRB #: IRB00001792, FWA00001785
	Dusan Kotasek	Bellberry Limited 1st Floor 71 Anzac highway Ashford South Australia, Australia 5035	Yvette L Winter
	Grant McArthur	Peter MacCallum Cancer Centre HREC Locked bag 1 A'Beckett St East Melbourne, Australia 8006	Prof Peter Sheldrake
Belgium	Luc Dirix	UCL Saint-Luc Commission d' Ethique Biomedicale Avenue Hippocrate 55-14 Brussels, Belgium 1200	Jean-Marie Maloteaux, MD
	Yves Humblet	UCL Saint-Luc Commission d' Ethique Biomedicale Avenue Hippocrate 55-14 Brussels, Belgium 1200	Jean-Marie Maloteaux, MD
Canada	Karen Mulder	Alberta Cancer Board REB 10123 99 Street Suite 1500 Edmonton, Alberta, Canada T5J 3H1	Scott North, MD

Country	Principal Investigator	IRB/IEC	Chairman
France	Antoine Adenis	CPP Ile de France VII CHU de Bicêtre - Cour de Sibérie 78 rue du Général Leclerc LE KREMLIN BICETRE CEDEX, France 94 275	Marc Pucheault, MD
	Emmanuelle Bompas	CPP Ile de France VII CHU de Bicêtre - Cour de Sibérie 78 rue du Général Leclerc LE KREMLIN BICETRE CEDEX, France 94 275	Marc Pucheault, MD
	Axel Le Cesne	CPP Ile de France VII CHU de Bicêtre - Cour de Sibérie 78 rue du Général Leclerc LE KREMLIN BICETRE CEDEX 94 275	Marc Pucheault, MD
Germany	Sebastian Bauer	LÄK Brandenburg Dreifertstr. 12 Cottbus, Germany 03044	Prof. Dr. med. Michael Matthias, MD
	Viktor Gruenwald	LÄK Brandenburg Dreifertstr. 12 Cottbus, Germany 03044	Prof. Dr. med. Michael Matthias, MD
	Peter Hohenberger	LÄK Brandenburg Dreifertstr. 12 Cottbus 03044	Prof. Dr. med. Michael Matthias, MD
	Peter Reichardt	LÄK Brandenburg Dreifertstr. 12 Cottbus, Germany 03044	Prof. Dr. med. Michael Matthias, MD
	Markus Schlemmer	LÄK Brandenburg Dreifertstr. 12 Cottbus, Germany 03044	Prof. Dr. med. Michael Matthias, MD
Israel	Baruch Brenner	Rabin MC EC Zabotinsky 39 Peta-Tikva, Israel 49100	Meir Lahav, MD
	Ephraim Idelevich	Kaplan MC EC Rehovot, Israel 76100	Lidya Arkavi, MD
	Einat Shacham-Shmueli	Sourasky MC EC Weizmann 6 Tel-Aviv, Israel 64239	Prof. Marcel Topilski, MD

Country	Principal Investigator	IRB/IEC	Chairman
Italy	Paolo Casali	Comitato Etico Istituto Nazionale per la Cura dei Tumori Via Venezian 1 Milano, Italy 20133	Roberto Satolli, MD
South Korea	Yoon-Koo Kang	Asan Medical Center IRB 388-1, Pungnap-2-dong, Songpa-gu Seoul 138-736	Myung-Soo Joo
	Joon Oh Park	Samsung Medical Center IRB 50, Irwon-dong, Gangnam-gu Seoul, South Korea 135-710	Won Yong Lee, MD, Ph.D
Sweden	Mikael Eriksson	Regionala Etikprövningsnämnden i Lund Box 133 Lund, Sweden SE-221 00	Anna Tansjö
	Martin Erlanson	Regionala Etikprövningsnämnden i Lund Box 133 Lund, Sweden SE-221 00	Anna Tansjö
USA	Lei Chen	University of Utah IRB 75 South 2000 East Salt Lake City, UT 84112	Gerald Treiman, MD
	Elena Chiorean	Indiana University/Clarian IRB 620 Union Drive Room 618 Indianapolis, Indiana, USA 46202-5167	Member list is not published. Office of Human Research Protections (OHRP) IRB #: IRB00000222.
	Warren Chow	City of Hope IRB 1500 East Duarte Road Duarte, California, USA 91010-3000	Member list is not published. Office of Human Research Protections (OHRP) IRB #: IRB00000060, FWA00000692
	Bartosz Chmielowski	Office for Protection of Research Subjects (OPRS) 11000 Kinross Avenue Suite 102 Los Angeles, California, USA 90095	Daniel Clemens, MD, Ph.D.
	George Demetri	Dana-Farber Cancer Institute IRB Massachusetts USA	Member list is not published. Federal Wide Assurance #: FWA00001121

Country	Principal Investigator	IRB/IEC	Chairman
USA (continued)	Anthony Elias	Western IRB (WIRB) 3535 Seventh Avenue, SW Olympia, Washington, USA 98508-2029	Theodore D. Schultz, J.D.
	Charles Forscher	Research Compliance (IRB) Cedars-Sinai Medical Center 8383 Wilshire Blvd Suite 742 Beverly Hills, California, USA 90211	Stephen Lim, MD
	Richard Gorman	Copernicus Group IRB (CGIRB) 1 Triangle Drive Suite 100 RTP, NC, USA 27709	Glenn C. Veit, JD, CIP
	Michael Heinrich	OHSU IRB Mailcode: L106-RI 2525 SW First Avenue Portland Oregon 97201	Susan B. Bankowski, MS, JD
	Pamela Kaiser	Copernicus Group IRB (CGIRB) 1 Triangle Drive Suite 100 RTP, NC, USA 27709	Glenn C. Veit, JD, CIP
	Hedy Kindler	Office of Review Services McGiffert Hall, 2nd Fl 5751 S Woodlawn Ave Chicago, Illinois, USA 60637	Elizabeth McNally, MD, Ph.D.
	Joel Picus	WUSM Human Research Protection Office (IRB) 660 S. Euclid Ave, Box 8089 St. Louis, Missouri, USA 63110-1093	Philip A. Ludbrook, MD
	Joseph Pizzolato	Mount Sinai Medical Center IRB 4300 Alton Road Miami Beach, Florida, USA 33140	Member list is not published. Office of Human Research Protections (OHRP) IRB #: IRB00000168
	Dennis Priebat	Medstar Research Institute - Georgetown University IRB 3900 Reservoir Rd NW, MedDent SW104 Washington, DC 20057	Member list is not published. Office of Human Research Protections (OHRP) IRB #: IRB00002119
	Gerald Rosen	St. Vincent's Medical Center IRB 170 West 12th Street Staff House New York, New York, USA	Mark Astiz, MD

Country	Principal Investigator	IRB/IEC	Chairman
		10011	
USA (continued)	Brian Samuels	Kootenai Medical Center IRB 2003 Lincoln Way Coeur d'Alene, Idaho, USA 83814	Susan Herbst, RN, MS
	Keith Skubitz	Research Subjects' Protection Programs Univ. of Minnesota 420 Delaware Street SE D-528 Mayo Memorial Building, MMC 820 Minneapolis, Minnesota, USA 55455	Member list is not published. Federal Wide Assurance #: FWA00000312
	Katherine Thornton	Johns Hopkins Medicine IRB Office of Human Subjects Research 1620 McElderry St., Reed Hall, Suite B-130 Baltimore, MD 21205	Howard Lederman, MD, Ph.D.
	Margaret von Mehren	Fox Chase Cancer Center IRB 50 Huntingdon Pike Rockledge, Pennsylvania, USA 19046	Clifford Perlis, MD

Sample consent forms are provided for:

- Sample Informed Consent Form – EU only
- Sample Informed Consent Form – US only
- Sample Genetic Consent Form

16.1.4 List and Description of Investigators and Other Important Participants in the Study Including Brief CVs

The curriculum vitae for the Principal Investigators who participated in the study are provided in this appendix:

Country	Site No.	Investigator	Organization	City, State
Australia	72*	Eliadis, Paul	Hematology and Oncology Clinics of Australasia	Auchenflower
	16	Goldstein, David	Prince of Wales Hospital	Randwick
	23	Kotasek, Dusan	Adelaide Cancer Centre	Ashford
	39	Karapetis, Christos	Flinders Medical Centre	Adelaide
	5*	McArthur, Grant	Peter MacCallum Cancer Institute	Melbourne, Victoria
Belgium	60	Dirix, Luc	Sint - Augustinus Hopital	Wilrijk
	38*	Humblet, Yves	Universitaires S. Luc Ucl	Brussels
Canada	49	Mulder, Karen	Cross Cancer Institute, University of Alberta	Edmonton
France	92	Adenis, Antoine	Centre Oscar Lambret	Lille
	56	Bompas, Emmanuelle	Centre Rene Gauducheau	Nantes
	6*	Le Cesne, Axel	Institut Gustave Roussy	Villejuif Cedex
Germany	51*	Bauer, Sebastian	West German Cancer Center	Essen
	50	Gruenwald, Viktor	Medical School Hannover	Hannover
	10	Hohenberger, Peter	Klinikum der Stadt Mannheim	Mannheim
	8*	Reichardt, Peter	HELIOS Klinikum	Bad Saarow
	11*	Schlemmer, Markus	Klinikum der Universitaet Muenchen-Grosshadern	Muenchen
Israel	58	Brenner, Baruch	Oncology Institute - Rabin Medical Center	Petach Tikva
	61	Idelevitch, Efraim	Kaplan Medical Center	Rehovot
	44	Shacham-Shmueli, Einat	Sourasky Medical Center	Tel Aviv
Italy	3	Casali, Paolo	Istituto Nazionale Tumori	Milano
South Korea	53*	Kang, Yoon-Koo	Asian Medical Center	Seoul
	55	Park, Joon Oh	Samsung Medical Center	Seoul
Sweden	12	Eriksson, Mikael	Lund University Onkologiska Klinken	Lund
	83	Erlanson, Martin	Kirurgiska Kliniken, Norrlands Universitetssjukhus	Umeå

Country	Site No.	Investigator	Organization	City, State
USA	70	Chen, Lei L.	University of Utah Huntsman Cancer Institute	Salt Lake City, UT
	24*	Chiorean, Elena	Indiana University Cancer Center	Indianapolis, IN
	28*	Chmielowski, Bartosz	UCLA	Los Angeles, CA
	20*	Chow, Warren	City of Hope Medical Center	Duarte, CA
	1*	Demetri, George	Dana-Farber Cancer Institute	Boston, MA
	25*	Elias, Anthony	University of Colorado	Aurora, CO
	29*	Forscher, Charles A.	Cedars-Sinai Medical Center	Los Angeles, CA
	41*	Gorman, Richard	New Bern Cancer Care	New Bern, NC
	64	Heinrich, Michael	Oregon Health and Science University	Portland, OR
	21	Kaiser, Pamela	Lutheran General Hospital	Park Ridge, IL
	22	Kindler, Hedy L.	University of Chicago Medical Center	Chicago, IL
	40*	Picus, Joel	Washington University	St. Louis, MO
	66*	Pizzolato, Joseph	Mount Sinai Hospital	Miami Beach, FL
	27*	Priebat, Dennis	Washington Hospital Center	Washington, DC
	71	Rosen, Gerald	St. Vincent's Cancer Center	New York, NY
	33	Samuels, Brian	Kootenai Cancer Center	Coeur d'Alene, ID
	34	Skubitz, Keith	University of Minnesota	Minneapolis, MN
	65	Thornton, Katherine	Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins	Baltimore, MD
	9*	von Mehren, Margaret	Fox Chase Cancer Center	Philadelphia, PA

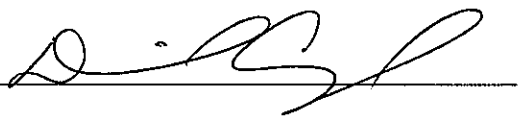
*Study sites that enrolled and treated at least one patient prior to study termination.

16.1.5 Signatures of Principal or Coordinating Investigator(s) or Sponsor's Responsible Medical Officer

STUDY TITLE: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study Evaluating the Efficacy and Safety of IPI-504 in Patients with Metastatic and/or Unresectable Gastrointestinal Stromal Tumors Following Failure of at Least Imatinib and Sunitinib

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

MEDICAL OFFICER/SIGNATORY:

SIGNATURE: 

AFFILIATION: Infinity Pharmaceuticals, Inc.
780 Memorial Drive
Cambridge, MA 02139

DATE: April 1st, 2010

16.1.6 Listing of Patients Receiving Test Drug(s)/Investigational Products from Specific Batches Where More Than One Batch Was Used

Listing 16.2.5.2 provides a by-patient listing of test drug, including the kit numbers for IPI-504 and placebo.

16.1.7 Randomization Scheme and Codes

The following document is included in this appendix:

IPI-504-06 Randomization Scheme

16.1.8 Audit Certificates

Audits of clinical sites were not conducted as the study was terminated early.

The audit certificate for the database quality review is available upon request.

16.1.9 Documentation of Statistical Methods

The following documents are included in this appendix:

Final Statistical Analysis Plan (Amendment 2), March 19, 2010

16.1.10 Documentation of Inter-Laboratory Standardization Methods and Quality Assurance Procedures if Used

Local laboratories were utilized during this study. Normal ranges from each clinical trial site were taken into account when calculating out-of-range laboratory values. CLIA certification and normal ranges for all clinical trial sites are on file in the Trial Master File and are available from the Sponsor upon request.

16.1.11 Publications Based on the Study

Demetri GD, LeCesne A, Von Mehren M. Chmielowski B, Bauer S, Chow WA, et al. Final results from a phase III study of IPI-504 (retaspimycin hydrochloride) versus placebo in patients with gastrointestinal

stromal tumors (GIST) following failure of kinase inhibitor therapies. Gastrointestinal Cancers Symposium. Orlando, FL. January 22-24, 2010. Abstract #64.

16.1.12 Important Publications Referenced in the Report

All references are listed in Section 15 of this report, and are available upon request.

16.2 Patient Listings

16.2.1 Discontinued Patients

The following listings are included in this section:

Listing 16.2.1_1: Discontinued Patients

16.2.2 Protocol Deviations

The following listings are included in this section:

Listing 16.2.2_1: Protocol Deviations - ITT Population

16.2.3 Patients Excluded from the Efficacy Analysis

The following listings are included in this section:

Listing 16.2.3_1: Patients Excluded from the Efficacy Analysis

Listing 16.2.3_2: Adverse Events that Occurred in Patients Who were Screened and Never Randomized

16.2.4 Demographic Data

The following listings are included in this section:

Listing 16.2.4.1: Eligibility - All Screened Patients

Listing 16.2.4.2: Enrollment - ITT Population

Listing 16.2.4.3: Stratification Factors - ITT Population

Listing 16.2.4.4: Demographics - ITT Population

Listing 16.2.4.5: Medical History by MedDRA System Organ Class (SOC) and Preferred Term (PT) - ITT Population

Listing 16.2.4.6: GIST Tumor History - ITT Population

Listing 16.2.4.7: Cancer Surgical History - ITT Population

Listing 16.2.4.8: Prior Radiation History - ITT Population

Listing 16.2.4.9: Prior Treatment of GIST Tumor - ITT Population

Listing 16.2.4.10: RECIST/WHO Responses from Prior Treatments - ITT Population

Listing 16.2.4.11: Prior Treatment Intolerance to Imatinib or Sunitinib - ITT Population

Listing 16.2.4.12: Tumor Mutational Status Results - ITT Population

Listing 16.2.4.13: Open Label (OL) - ITT Population

16.2.5 Compliance and/or Drug Concentration Data

The following listings are included in this section:

Listing 16.2.5.1: Study Drug Exposure - ITT Population

Listing 16.2.5.2: Study Drug Administration - ITT Population

16.2.6 Individual Efficacy Response Data

The following listings are included in this section:

Listing 16.2.6.1.1: Recorded RECIST Response Assessment- Central Reads (ITT Population)

Listing 16.2.6.1.2: Recorded RECIST Response Assessment- Investigator Reads (ITT Population)

Listing 16.2.6.1.3: Calculated RECIST- Central Reads (ITT Population)

Listing 16.2.6.1.4: Calculated RECIST- Investigator Reads (ITT Population)

Listing 16.2.6.1.5: Recorded RECIST Details- Central Reads (ITT Population)

Listing 16.2.6.1.6: Recorded RECIST Details- Investigator Reads (ITT Population)

Listing 16.2.6.2.1: Patients with a Disease Control Rate or Progression defined from Recorded RECIST Central Reads or Death - ITT Population

Listing 16.2.6.2.2: Patients with a Disease Control Rate or Progression defined from Recorded RECIST Investigator Reads or Death - ITT Population

Listing 16.2.6.3.1: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-Core 30) Outcome Scales (ITT Population)

Listing 16.2.6.3.2: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-Core 30) Results (ITT Population)

Listing 16.2.6.3.3: Brief Pain Inventory Composite Outcomes (ITT Population)

Listing 16.2.6.3.4: Brief Pain Inventory (BPI) Scores (ITT Population)

Listing 16.2.6.3: Follow up for Deaths -ITT Population

16.2.7 Adverse Event Listings (Each Patient)

The following listings are included in this section:

Listing 16.2.7.1:	Adverse Events Sorted by Treatment Group, Subject, and Start Date (ITT Population)
Listing 16.2.7.2:	Adverse Events with Grade ≥ 3 (ITT Population)

16.2.8 Listings of Individual Laboratory Measurements by Patient

The following listings are included in this section:

Listing 16.2.8.1:	Hematology Laboratory Evaluations -ITT Population
Listing 16.2.8.2:	Clinical Chemistry Laboratory Evaluations- ITT Population
Listing 16.2.8.3:	Other Laboratory Tests Collected but not Required Per the Protocol - ITT Population

16.2.9 Other Safety Listings

The following listings are included in this section:

Listing 16.2.9.1:	Vital Signs (ITT Population)
Listing 16.2.9.2:	Mean ECG Assessment- ITT Population
Listing 16.2.9.3:	ECG Individual Assessments (ITT Population)
Listing 16.2.9.4:	Patients with Mean QTCF > 450 ms- ITT Population
Listing 16.2.9.5:	Patients with Mean QTCB > 450 ms -ITT Population
Listing 16.2.9.6:	Patients with Mean Heart Rate < 50 bpm (Sinus Bradycardia)- ITT Population
Listing 16.2.9.7:	Patients with Mean PR > 200 ms- (ITT Population)
Listing 16.2.9.8:	ECOG Performance Status (ITT Population)
Listing 16.2.9.9:	Concomitant Medications (ITT Population)
Listing 16.2.9.10:	Concomitant Procedures (ITT Population)
Listing 16.2.9.11:	Subsequent Cancer Therapies Post Treatment (ITT Population)

16.3 Case Report Forms

16.3.1 CRFs for Deaths, Other Serious Adverse Events and Withdrawals for Adverse Event

The following CRFs are included in this appendix:

Patient ID	Randomized Treatment	Death	SAE	DC
001-004	Placebo[1]		√	√
001-008	IPI-504		√	
001-011	Placebo[1]		√	
001-014	IPI-504		√	√
001-015	IPI-504		√	
001-016	IPI-504		√	
005-001	NA[2]	√		
005-002	Placebo		√	√
005-003	IPI-504		√	
006-001	IPI-504	√	√	√
006-002	IPI-504		√	
009-001	IPI-504	√	√	√
011-001	IPI-504		√	√
020-001	Placebo		√	
020-002	IPI-504		√	√
024-001	Placebo[1]	√	√	
028-001	Placebo	√	√	
040-001	IPI-504	√	√	√
051-002	Placebo		√	
053-004	IPI-504		√	
056-001	NA[2]	√		
066-001	IPI-504	√	√	√

1 Events were reported during open-label treatment with IPI-504

2 Patients died during the screening period.

16.3.2 Other CRFs Submitted

Not applicable.

16.4 Individual Patient Listings (U.S. Archival Listings)

All by-patient data listings are included in Appendix 16.2.

16.5 Bioanalytical Report

The Study IPI-504-06 Bioanalytical Report is included in this appendix.