Polaris Group

CLINICAL STUDY REPORT

A Randomized, Double-Blind, Multi-Center Phase 3 Study of ADI-PEG 20 Plus Best Supportive Care (BSC) Versus Placebo Plus BSC in Subjects With Advanced Hepatocellular Carcinoma (HCC) Who Have Failed Prior Systemic Therapy

Protocol Number:	POLARIS2009-001
Name of Drug:	ADI-PEG 20
Indication:	Hepatocellular carcinoma
ClinicalTrials.gov Identifier:	NCT01287585
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Drug Development Phase:	3
Study Initiation Date:	15Jul2011: screening date of first subject
Study Completion Date:	23Jul2015: date of last study-related procedure
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Report Date:	10Apr2016

The study was conducted according to the International Conference on Harmonisation harmonised tripartite guideline E6(R1): Good Clinical Practice.

CLINICAL STUDY REPORT APPROVAL

Approved by the following:

John S. Bomalaski

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13 May 2016

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4 List of Abbreviations

Abbreviation	Definition
ADI	arginine deiminase
AE	adverse event
AESI	adverse events of special interest
AFP	alpha-fetoprotein
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
ASS	argininosuccinate synthetase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BODC	best overall disease control
BODCR	best overall disease control rate
BOOR	best overall objective response
BOTR	best overall tumor response
CFR	Code of Federal Regulations
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CR	complete response
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTM	clinical trial material
DesigneRx	DesigneRx Pharmaceuticals, Inc
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	end-of-treatment
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factors

Abbreviation	Definition
GI	gastrointestinal
HCC	hepatocellular carcinoma
HCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IHC	immunohistochemistry
IM	intramuscular
INR	international normalized ratio
IRB	institutional review board
ITT	intent to treat
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NA	North America
NASH	nonalcoholic steatohepatitis
NCI	National Cancer Institute
OS	overall survival
PD	progressive disease
PEG	polyethylene glycol
PFS	progression-free survival
PPD	Pharmaceutical Product Development, LLC
PR	partial response
PS	performance status
PT	prothrombin time
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SOC	system organ class
Std Dev	standard deviation

Abbreviation	Definition
TBD	to be determined
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
TMF	trial master file
TTP	time to tumor progression

5 Ethics

5.1 Independent Ethics Committee or Institutional Review Board

The investigator ensured that the protocol and consent form were reviewed and approved by the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) (Section 16.1.3) prior to the start of any study procedures. The IRB/IEC was appropriately constituted and performed its functions in accordance with Food and Drug Administration (FDA) regulations, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and local requirements, as applicable.

In addition, the IRB/IEC approved all protocol amendments (except for logistical or administrative changes), written informed consent documents, subject recruitment procedures, written information to be provided to the subjects, available safety information, information about payment and compensation available to subjects, the investigator's curriculum vitae and/or other evidence of qualifications, and any other documents requested by the IRB/IEC and regulatory authority, as applicable.

The final protocol (Amendment 4) and comprehensive summary of changes for each of 4 protocol amendments (a version for all study centers except for Italy, and another version for Italian study centers) are presented in Section 16.1.1.

5.2 Ethical Conduct of the Study

This study was conducted in accordance with the Declaration of Helsinki and GCP according to ICH guidelines. Specifically, this study was based on adequately performed laboratory and animal experimentation; the study was conducted under a protocol reviewed by an IRB or IEC; the study was conducted by scientifically and medically qualified persons; the benefits of the study were in proportion to the risks; the rights and welfare of the subjects were respected; the physicians conducting the study did not find the hazards to outweigh the potential benefits; and each subject gave his or her written, informed consent before any protocol-driven tests or evaluations were performed.

5.3 Subject Information and Consent

The nature and purpose of the study was fully explained to each subject. Written informed consent was obtained from each subject prior to any study procedures being performed. The consent documents used for the study included all the required elements of informed consent per regulatory requirements and were reviewed and approved by the appropriate IRB/IEC (Section 16.1.3) before use.

6 Investigators and Study Administrative Structure

A total of 74 study centers (68 of which enrolled subjects) were initiated for this study in: China (17 study centers), Italy (10 study centers), Republic of Korea (5 study centers), Taiwan (11 study centers), United Kingdom (10 study centers), and the United States (21 study centers). A list of investigators who enrolled subjects is provided in Section 16.1.4.

The study was conducted under the sponsorship of Polaris Group. Clinical monitoring, data management, and statistical analyses were performed under contract with PPD, the contract research organization (CRO), in collaboration with Polaris Group. The IRB/IEC services were provided by local and central IRBs/IECs (Section 16.1.3). The central laboratories, bioanalytical laboratory, drug depots, and other individuals involved in either the coordination of the study or the analysis and reporting of the results are presented in Table 6-1.

Table 6-1 Study Administration Structure

Name	Address	Role
Polaris Group	**9373 Towne Centre Drive, Suite 150 San Diego, CA 92121 United States**	**Sponsor**
John S. Bomalaski, MD	9373 Towne Centre Drive, Suite 150 San Diego, CA 92121 United States	Sponsor Representative
Ghassan Abou-Alfa, MD	Memorial Sloan-Kettering Cancer Center 1275 York Avenue New York, NY 10021 United States	Lead Investigator and Lead Clinical Study Center
PPD	**929 North Front Street Wilmington, NC 28401 United States**	**Contract Research Organization**
Kent Buhler	PPD 929 North Front Street Wilmington, NC 28401 United States	Director, Project Management
Elizabeth Williams	PPD 9330 Scranton Rd #200 San Diego, CA 92121 United States	Senior Project Manager, Global Project Management
Cynthia Gonzales	PPD 929 North Front Street Wilmington, NC 28401 United States	Medical Director

Name	Address	Role
Christy Ros	PPD 3900 Paramount Parkway Morrisville, NC 27560 United States	Principal Clinical Data Manager
Aaron Camp	PPD 7551 Metro Center Drive, Suite 300 Austin, TX 78744 United States	Senior Manager Biostatistics
Pharmacovigilance Group	PPD Fleming House Phoenix Crescent Strathclyde Business Park Bellshill, Lanarkshire ML4 3NJ United Kingdom	SAE Reporting
	PPD 929 North Front Street Wilmington, NC 28401 United States	**Interactive Web Response System**
DesigneRx Pharmaceuticals, Inc	DesigneRx Pharmaceuticals, Inc. 4941 Allison Pkwy, Vacaville, CA 95688 United States	**Clinical Supplies**
Michael G. Baker, PhD	Samorn Biosciences, Inc. 4156 Couts Street San Diego, CA 92103 United States	**Medical Writer**
NRES Committee London - City and East	Lewins Mead BS1 2NT Bristol United Kingdom	**Central Ethics Committee (United Kingdom)**
Comitato Etico IRCCS Istituto Nazionale per lo Studio e la Cura Dei Tumori Fondaz. G. Pascale	Via Mariano Semmola 80131 Napoli Italy	**Central Ethics Committee (Italy)**
Covance Central Laboratory Services – Indianapolis	8211 SciCor Drive Indianapolis, IN 46214 United States	**Global Central Laboratory - United States**
Covance Central Laboratory Services – Geneva	Rue Moise-Marcinhes 7 1217 Geneva Meryin-Geneva Switzerland	**Global Central Laboratory - European Union**
Protech Pharmaservices Corporation (PPC)	4th Floor, No. 360 Rueiguang Road Neihu Chiu Taipei, Taiwan	**Global Central Laboratory - Taiwan**

Name	Address	Role
Covance Pharmaceutical R&D – Shanghai	Shanghai Branch Building #3, No. 3377 Kangxin Road SIMZ Pundong Shanghai 201318 China	**Bioanalytical Laboratory**
Catalent Pharma Solutions (formerly Aptuit)	10245 Hickman Mills Drive Kansas City, MO 64137 United States	**Drug Depot – United States**
Catalent Pharma Solutions (formerly Aptuit)	Unit 107, Tenth Avenue, Deeside Industrial Park, Deeside CH5 2UA, Wales	**Drug Depot – European Union**
Zuellig Pharma	No. 1-2, Jiou Chu Zi, Heping Village 1st Neighborhood, Dayuan Township Taoyuan County 337, Taiwan, R.O.C	**Drug Depot – Taiwan**
TNT Korea	#8-1 Magok-Dong, Gangseo-Gu, Seoul, Korea	**Drug Depot – Korea**
Cardinal Health	418 Ban Ting Road, Jiu Ting, Shanghai, China 201615	**Drug Depot – China**

7 Introduction

Primary liver cancer (hepatocellular carcinoma [HCC]) is one of the most common malignancies in the world (El-Serag 2012; Gomaa 2008, Roberts 2008; Altekruse 2009). It is the fifth most common cancer worldwide and the third most common cause of death from cancer, as reflected by approximately 600,000 deaths per year. The international incidence is approximately 1 million cases. In the United States, approximately 19,000 new cases are diagnosed annually, with approximately 18,000 deaths annually. Despite all forms of current treatment, most patients are dead 1 year after diagnosis.

Systemic chemotherapy with standard agents has a poor response rate; none have shown encouraging results (Ryder 2003; Llovet 2005; El-Serag 2012; Yau 2008). However, the oral agent sorafenib, a multi-kinase inhibitor of the vascular endothelial growth factor receptor, the platelet-derived growth factor and *Raf*, showed promising results in Phase 2 and 3 studies in the United States, Europe, and Asia. Sorafenib has been approved in the United States and European Union for treatment of advanced HCC, based on a median survival of 10.7 months in subjects receiving sorafenib compared with 7.9 months in subjects receiving placebo (Llovet 2008b). Despite these encouraging results, there remains a substantial need for effective, safe systemic therapies for advanced HCC patients, including those who have already failed systemic chemotherapy (O'Neil 2007; Abou-Alfa 2008 and 2009; Llovet 2008a; Kelley 2008; Roberts 2008; Yau 2008; Zhu 2008; Flaherty 2009; Kane 2009; Keating 2009).

Based on the potential anti-cancer activity of arginine depletion (Section 2.1.3 of the Protocol [Section 16.1.1]), interest has been focused on the development of arginine deiminase (ADI), an arginine degrading enzyme, as a drug. The resulting investigational drug product, ADI-PEG 20, is a sterile solution of ADI conjugated with polyethylene glycol (PEG) of 20 kilodaltons in sodium phosphate (pH 6.6 to 7.0) and 130 mM sodium chloride buffer. Arginine deiminase is a recombinant protein cloned from *Mycoplasma hominis* and produced in *Escherichia coli*. In producing ADI-PEG 20, the conjugation of ADI with PEG 20 is achieved using a succinimidyl succinate linker.

The results obtained from global Phase 1 and 2 studies with HCC (Section 2.3.1 of the Protocol [Section 16.1.1]) indicate that the study drug appeared to be safe and effective, and was associated with an apparent improvement in survival in subjects in 3 different geographic regions. Prolonged treatment (>12 months) appears safe. Treatment for 6 months may have resulted in stable disease (SD) on computed tomography (CT) scan, but these lesions may have contained significant necrotic tissue on histopathological examination.

The toxicities expected from the use of ADI-PEG 20 are relatively mild, based on the clinical experience to date. The most frequently reported physical symptom was mild, temporary tenderness at the injection site beginning 24 hours after the injection and lasting 1 to 2 days. The most common laboratory toxicities, even at doses higher than the dose used for this study, were mild (grade 1 to 2) and asymptomatic elevations of various serum chemistry values: uric acid, lipase, amylase, transaminases. Significantly elevated serum uric acid levels (hyperuricemia) were treated with intravenous urate oxidase (rasburicase, Elitek®; Sanofi, Paris, France) or allopurinol. Although 1 subject with relapsed/refractory acute myeloid leukemia (AML) reported tumor lysis syndrome (TLS) that was believed by the Sponsor to be disease-related, no other subject developed other manifestations of TLS. Also noted were elevated levels of fibrinogen, which were not accompanied by evidence of coagulopathy.

In the sorafenib Phase 3 studies as first line chemotherapy in advanced HCC, a 2% objective response rate was observed in Europe-Americas and 3.3% in Asia-Pacific (Llovet 2008b; Roberts 2008; Kelley 2008; Cheng 2009). A similar low response rate has been noted in subjects treated with ADI-PEG 20 in the United States, Taiwan, and Italy. The effect of ADI-PEG 20 is expected to be an initial nutritional deprivation of tumor cells, and not a decrease in tumor size; tumor cells may be necrotic, yet the size of the lesion in cirrhotic tissue was expected to remain unchanged. Also, some subjects treated with ADI-PEG 20 have had progressive disease (PD) by Response Evaluation Criteria in Solid Tumors (RECIST) guideline version 1.1, yet tolerated the drug well, and went on to demonstrate an objective response and/or prolonged survival. Therefore, the primary efficacy endpoint in this study was overall survival (OS), instead of objective responses on CT scans, which are recommended for this cancer and more typically observed with traditional cytotoxic agents (Llovet 2008a). This study included subjects who had already received prior treatment with sorafenib or another systemic chemotherapeutic agent(s).

This Phase 3 study was designed to confirm the preliminary findings on ADI-PEG 20 and to further establish its clinical benefit and safety in HCC. There is currently no standard systemic therapeutic treatment for subjects with advanced HCC that have failed first line systemic therapy. Thus, a placebo control was used to determine the safety and effectiveness of ADI-PEG 20.

8 Study Objectives

8.1.1 Primary Objective

The primary objective of this study was to assess overall survival.

8.1.2 Secondary Objectives

The secondary objectives of this study were as follows:

- Assessment of safety and tolerability
- Assessment of progression-free survival (PFS), tumor response rate by RECIST (1.1), and time to tumor progression (TTP)

9 Investigational Plan

9.1 Overall Study Design and Plan

This was a multi-center, multi-national, Phase 3, double-blind (subject, caregiver, investigator, and outcomes assessor), placebo-controlled study of ADI-PEG 20 in subjects with advanced HCC who had failed prior systemic therapy. Failure was defined as having progressed radiographically on, or been intolerant to, prior systemic therapy. Intolerance was defined as discontinuation due to an AE(s) on prior systemic therapy that was unacceptable to the treating physician and/or subject, with or without dose interruption and modification. For sorafenib or any other systemic antineoplastic agent, failure generally required at least 14 days of treatment for the agent that defined failure. Thus, ADI-PEG 20 was being evaluated as second line, and in some cases third line or later systemic chemotherapy.

Eligible subjects received ADI-PEG 20 at 18 mg/m^2 or placebo by intramuscular (IM) injection (1 cycle = 4 weekly treatments). Subjects in both groups continued to receive best supportive care. Computed tomography or magnetic resonance imaging (MRI) scans were performed at baseline and at the end of every 12 weeks (3 cycles) for assessment of tumor response according to RECIST 1.1 criteria.

As diet was a potiential source of arginine, dietary restrictions for arginine-rich foods were also strongly recommended (see informed consent [Section 16.1.3]).

A complete schedule of assessments can be found in Section 1.4 of the Protocol (Section 16.1.1).

9.1.1 Duration of Study

Subjects were screened within 28 days of potential participation in the study by CT or MRI scans and within 14 days for other screening related procedures including history, physical examination, and baseline laboratory tests. Subjects could continue to receive treatments unless one of the following occurred at any time during the course of therapy: unacceptable AEs, death, or PD. Subjects with a CR may have received 1 more cycle (4 weekly treatments).

The anticipated enrollment period was 52 weeks, and the anticipated follow-up period was 24 weeks.

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

Phase 3 studies of sorafenib used a multi-center, multi-national, double-blind, placebo-controlled study design for first line systemic therapy in advanced HCC

(Llovet 2008b; Cheng 2009). In the Asian study, the randomization for sorafenib to placebo was 2:1, and in the European-Americas study it was 1:1. This study used 2:1 randomization.

This study stratified subjects before randomization according to: (1) geographical region - Asian versus North America (NA) and Europe, and (2) prior failed treatment with sorafenib (sorafenib failures) versus prior failed treatment with another systemic antineoplastic agent (other antineoplastic failures). The sorafenib Phase 3 studies only enrolled subjects with Child-Pugh grade A cirrhosis. This study enrolled subjects with Child-Pugh grades A and B7 cirrhosis. The inclusion of B7 subjects (as of Protocol Version 003, dated 16Nov2012) was consistent with the recently completed second line, Phase 3 HCC study of brivanib (ClinicalTrials.gov identifier: NCT00825955). Subjects with Child-Pugh grade B cirrhosis have a worse prognosis than subjects with grade A cirrhosis, and those with grade C cirrhosis have an even worse prognosis compared to grade B subjects, especially in the setting of coexistent HCC (Bruix 2005; Cammà 2009; Tandon 2009; Huitzil-Melendez 2010). Thus, to limit the number of subjects who could die from their underlying cirrhosis and not HCC, this study was restricted to Child-Pugh grade A and B7 subjects only. There is no standard systemic therapeutic treatment for subjects with advanced HCC that had failed first line systemic therapy. Thus, a placebo control was used to determine the safety and effectiveness of ADI-PEG 20.

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

A subject was eligible for study participation if he/she met the following criteria:

1. Prior diagnosis of HCC confirmed histologically or cytologically.
2. Prior treatment with at least 1 systemic agent, with documented PD after systemic agent(s), or AEs associated with prior systemic agent(s) that resulted in discontinuance of that agent(s). Failure was defined as having progressed radiographically on, or been intolerant to, prior systemic therapy. Intolerance was defined as discontinuation due to an AE(s) on prior systemic therapy that was unacceptable to the treating physician and/or patient, with or without dose interruption and modification. For sorafenib or any other systemic antineoplastic agent, failure required at least 14 days of treatment for the agent that defined failure, except for a subject who had a severe allergic reaction to the prior systemic agent at any time, even less than 14 days of treatment of that agent and thus it would have been imprudent to rechallenge them with that agent.

3. Measurable disease using RECIST 1.1 criteria (Appendix A of the Protocol, [Section 16.1.1]). The presence of at least 1 measurable lesion was required. Subjects who had received local-regional therapy such as (but not limited to) chemoembolization, embolization, cryoablation, hepatic artery therapy, percutaneous ethanol injection, radiation therapy, radiofrequency ablation, or surgery were eligible, provided that they had either a target lesion which had not been treated with local therapy and/or the target lesion(s) within the field of the local-regional therapy had shown an increase of ≥20% in size. Local-regional therapy must have been completed at least 4 weeks prior to the baseline CT scan. Local therapies including chemoembolization did not count as prior systemic therapy.
4. Cirrhotic status of Child-Pugh grade A and B7. Child-Pugh status was determined based on clinical findings and laboratory data during the screening period (Appendix C of the Protocol [Section 16.1.1]). Subjects on anticoagulants received only 1 point for their INR status.
5. Expected survival of at least 3 months.
6. Age ≥18 years.
7. No prior systemic treatment for HCC in the last 2 weeks prior to first dose of study drug or placebo.
8. Fully recovered from prior major surgery and none within 2 weeks prior to first dose of study drug or placebo. Liver biopsy for HCC confirmation was allowed.
9. Female subjects of childbearing age and male subjects were asked to use appropriate contraception for both the male and female for the duration of the study. Subjects agreed to use 2 forms of contraception or agreed to refrain from intercourse for the duration of the study. Females could not be pregnant at the start of the study, and a negative serum human chorionic gonadotropin (HCG) pregnancy test was required before entry into the study.
10. Informed consent was obtained prior to study initiation.
11. No concurrent investigational studies were allowed.
12. Total bilirubin <3.0 mg/dL and no evidence of bile obstruction.
13. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤5 × upper limit of normal range.
14. Absolute neutrophil count (ANC) >1500/µL.
15. Platelets >50,000/µL.

16. Serum uric acid ≤8 mg/dL (with or without medication control).
17. Serum creatinine ≤1.5 × the upper limit of normal range, or, if serum creatinine >1.5 × the upper limit of normal range, then creatinine clearance ≥60 mL/min was required.
18. Serum albumin level ≥2.8 g/dL.
19. Prothrombin time (PT)-international normalized ratio (INR): PT <6 seconds above control or INR <1.7.
20. Subjects with active hepatitis B or C on antiviremic compounds could remain on such treatment, except for interferon.
21. Brain metastases were allowed if well controlled and without seizures.
22. Encephalopathy – none or mild (grade 1 or 2, by Child-Pugh classification); lactulose or other supportive care was allowed.
23. Ascites – absent or slight (by Child-Pugh classification); diuretic therapy was allowed.

9.3.2 Exclusion Criteria

A subject was not eligible for study participation if he/she met any of the exclusion criteria:

1. Candidate for potential curative therapies (ie, resection or transplantation) or local-regional approaches (ie, ablation, embolization).
2. Prior allograft transplantation including liver transplantation.
3. Significant cardiac disease (New York Heart Association Class III or IV; Appendix D of the Protocol [Section 16.1.1]).
4. Serious infection requiring treatment with systemically administered antibiotics.
5. Pregnancy or lactation.
6. Expected noncompliance.
7. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure (New York Heart Association Class III or IV), unstable angina pectoris, cardiac arrhythmia, or psychiatric illness or social situations that would limit compliance with study requirements.
8. Subjects who received any anticancer treatment within 2 weeks prior to first dose of study drug or placebo.

9. Subjects not fully recovered from toxicities associated with previous HCC local-regional or systemic therapies.
10. Subjects with history of another primary cancer, with the exception of: a) curatively resected nonmelanoma skin cancer; b) curatively treated cervical carcinoma in situ; or c) other primary solid tumor with no known active disease present that in the opinion of the investigator would not have affected subject outcome in the setting of current HCC diagnosis.
11. Subjects treated with ADI-PEG 20 previously.
12. Allergy to pegylated products.
13. History of seizure disorder.
14. Bleeding esophageal or gastric varices within the prior 3 months, except if banded or treated.
15. Subjects known to be HIV positive.
16. Uncontrolled ascites (defined as not easily controlled with diuretic treatment).
17. Had received any blood transfusion, blood component preparation, erythropoietin, albumin preparation, or granulocyte-colony stimulating factors (G-CSF) within 7 days prior to screening laboratories or after screening laboratories were obtained until first dose of study drug or placebo.
18. Use of traditional medicines approved by local authorities, including but not limited to Chinese herbs, within 2 weeks prior to the first dose of study drug or placebo.
19. Eastern Cooperative Oncology Group (ECOG) performance status >2.

9.3.3 Removal of Subjects from Therapy or Assessment

Subjects were free to discontinue the study at any time, for any reason, and without prejudice to further treatment. The investigator could remove a subject if, in his/her judgment, continued participation would have posed unacceptable risk to the subject or to the integrity of the study data.

A subject experiencing any of the following was to be withdrawn from the treatment:

1. Progressive disease.
2. Significant noncompliance on the part of the subject.
3. Refusal of the subject to continue treatment or observations.

4. Unacceptable toxicity, including a drug-related grade 4 adverse event, except for laboratory abnormalities that could have been corrected with interventions (eg, hyperuricemia treated with allopurinol).
5. Decision by the investigator that termination was in the subject's best medical interest.
6. Unrelated medical illness or complication.
7. Death.
8. Lost to follow-up.
9. At the request of Polaris.
10. At the request of the Data Safety Monitoring Board.

9.3.4 Withdrawal Procedures

In the event of a subject's withdrawal, the investigator promptly notified the medical monitor and made every effort to complete the end-of-study assessments (Section 6.2.11 of the Protocol [Section 16.1.1]). After discontinuation/withdrawal from the study, a subject was entered into the follow-up period, and contacted regularly (every month) for survival status until death or study closure.

If a subject died during the study or within 30 days of stopping treatment, the investigator was to inform Polaris' representative. The cause of death was to be reported in detail, within 24 hours, on a Serious Adverse Event (SAE) form and reported to Polaris' representative (Section 9 of the Protocol [Section 16.1.1]). Subjects who signed informed consent and underwent at least some of the screening procedures, but not randomly assigned, were considered screening failures. The reason for withdrawal was noted. A record of such subjects was to be maintained in the Trial Master File (TMF) at the study site and retained for the required period of time in compliance with the Code of Federal Regulations (CFR) 21 §312.57(c) and GCP. All withdrawn subjects were to be followed until resolution of any AEs, or until the unresolved AEs were judged by the investigator to have stabilized.

9.4 Treatments

9.4.1 Treatments Administered

The study drug, ADI-PEG 20, as well as placebo, were to be administered intramuscularly to subjects once weekly by a study nurse. The dosage of ADI-PEG 20 was 18 mg/m^2.
A comparable volume of placebo, based on body surface area, was to be administered to subjects randomly assigned to placebo. Subjects were to remain in the treatment area for

1 hour (± 15 minutes) after the injection, followed by assessments for safety and tolerability, including obtaining vital signs.

9.4.2 Identity of Investigational Product

The investigational drug product was a sterile solution of ADI-PEG 20 in sodium phosphate (pH 6.6 to 7.0) and 130 mM sodium chloride buffer. Arginine deiminase is a recombinant protein cloned from *M. hominis* and produced in *E. coli*. In producing ADI-PEG 20, the conjugation of ADI with PEG 20 is achieved using a succinimidyl succinate linker. Thus, ADI-PEG 20 is an arginine degrading enzyme, ADI, coupled to PEG 20. The dose of ADI-PEG 20 was 18 mg/m^2.

The placebo formulation was a sterile solution of sodium phosphate buffer containing low viscosity sodium carboxymethylcellulose, PEG 3350, propylene glycol, and Tween 80. The placebo did not contain ADI, PEG 20, or succinimidyl linker.

To preserve blinding, the ADI-PEG 20 drug product and its matching placebo were identical in appearance and labeled with a unique medication number assigned to subjects by an interactive web response system (IWRS).

9.4.2.1 Packaging and Labeling

Label text was approved according to Polaris or its designees. The drug product and placebo labels complied with local legal and regulatory requirements and were multi-language, where appropriate. The proper storage conditions of the study drug and placebo were described on the medication labels.

The following clinical trial materials (CTM) were used:

- ADI-PEG 20 for IM injection
- Placebo for IM injection

ADI-PEG 20 was produced by DesigneRx Pharmaceuticals, Inc (DesigneRx), a subsidiary of Polaris. Placebo was identical in appearance to the active study drug, and also supplied by DesigneRx.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects were randomly assigned on a 2:1 basis in a blinded fashion to ADI-PEG 20 or matching placebo given IM on a weekly basis. To accomplish this, a computer-generated randomization schedule was prepared by the selected CRO. Subjects were assigned to study drug or placebo and further stratified into 4 groups using the 2 levels of geographic region

(Asia vs NA and Europe) and sorafenib treatment status (non-sorafenib failure and sorafenib failure):

1. Asia and non-sorafenib failure
2. Asia and sorafenib failure
3. NA and Europe and non-sorafenib failure
4. NA and Europe and sorafenib failure

A subject was classified as a "sorafenib failure" if sorafenib was a treatment for at least 14 days and the criteria for failure were met. For this classification, sorafenib was not required to be the last or only prior systemic antineoplastic treatment taken before randomization. A subject was classified as a "non-sorafenib failure" if they were sorafenib naïve, or had been treated with sorafenib for less than 14 days (except for a subject who had a severe allergic reaction to sorafenib), and had been treated with another systemic antineoplastic agent. All analyses incorporating stratification factors were conducted using the stratification factors as entered into the IWRS rather than the electronic case report form (eCRF). A sensitivity analysis identical to the primary analysis was conducted using the stratification factors as entered into the eCRF.

The randomization schedule was not stratified by study site.

9.4.4 Selection of Doses in the Study

The dose of ADI-PEG 20 was 18 mg/m^2 administered IM. Subjects received 1 injection weekly of ADI-PEG 20 or placebo into the deltoid, gluteal, or quadriceps muscles (note: this totaled approximately 2.5 to 4 mL; if this volume was problematic from an institutional nursing perspective, it could be given as 2 injections in different IM locations once weekly). The injections could be given ±3 days from the assigned study visit. Subjects were to be observed in the clinic for 1 hour ±15 minutes following each ADI-PEG 20 administration (1-2 injections). Treatments were not to be interrupted due to either scheduling for CT (or MRI) scans or delays in the assessment of CT (or MRI) scan results.

9.4.5 Selection and Timing of Dose for Each Subject

The dose of ADI-PEG 20 used in this study was based on the results from completed Phase 1 and 2 studies in HCC.

9.4.5.1 Dose Adjustments

Treatment could be held for up to 2 weeks for any subject who demonstrated grade 3 nonhematologic toxicity or hematologic toxicity, as defined by the National Cancer Institute

(NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.02, at the time of the scheduled dose. Once the toxicity resolved to grade <3, treatment could resume and not wait for the next scheduled dose visit. Use of hematopoietic growth factors was allowed to treat hematologic toxicity at the discretion of the investigator. Thus, the dose could be delayed for up to 2 weeks, but not adjusted. Grade 3 or 4 laboratory abnormalities (eg, hyperuricemia) that were corrected with interventions did not require cessation of therapy.

9.4.6 Blinding

Subjects were randomly assigned to receive ADI-PEG 20 drug product or matching placebo in a double-blind fashion. Thus, neither the investigator nor the subject knew which study treatment was being administered. The randomization number was assigned based on information obtained from an IWRS.

To preserve blinding, the ADI-PEG 20 drug product and its matching placebo were identical in appearance and labeled with a unique medication number assigned to subjects by an IWRS.

SAS programming could occur as study data accumulated to allow analysis programs to be ready at the time the study finished. In such an event, arbitrary treatment group assignments were to be randomly linked to subjects, effectively rendering any output of programs meaningless.

The complete randomization lists were archived with the IWRS. If a medical emergency arose requiring identification of the study medication administered, the blind could be broken to manage the acute situation of the subject. The investigator was to make every effort to contact the medical monitor for discussion prior to unblinding of the study medication. Unblinding was allowed for emergency purposes only and was to be conducted by the investigator via the IWRS. Investigators were instructed that the occurrence of an SAE should not routinely precipitate the immediate unblinding of the label. If unblinding was necessary for the treatment of a subject for an SAE, every effort was to be made to contact Polaris, or its designee, prior to unblinding. If this was not feasible, then contact was to occur within 24 hours of unblinding, including prompt notification to the medical monitor.

Had unblinding occurred, the study medication (ADI-PEG 20 or placebo) was to be discontinued. Subjects who discontinued study drug/placebo could not restart treatment.

Subjects ongoing at study end (once the 487 events were observed for the final analysis) could continue to receive weekly treatment on either ADI-PEG 20 or placebo until the study

was unblinded. Once the study treatment assignments were known, the subjects receiving ADI-PEG 20 could continue to receive weekly treatment until one of the following occurred at any time during the course of therapy: unacceptable AEs, death, PD, or decision by the Sponsor. Subjects with a CR could receive 1 additional cycle (4 weekly treatments). Subjects receiving placebo were to be consulted regarding alternative treatment options.

Subjects wishing to continue study treatment followed the Schedule of Assessments in Table 9-4.

9.4.7 Prior and Concomitant Therapy

All medications (prescription and over-the-counter), vitamin and mineral supplements, and/or herbs taken by the participant were to be documented on the concomitant medication CRF and include: start and stop date, dose and route of administration, and indication. Medications taken for a procedure were also to be included.

9.4.7.1 Nonpermitted Concomitant Therapies

Subjects could not receive chemotherapy, radiation therapy, or immunotherapy during the study. Subjects could not receive interferon.

9.4.7.2 Permitted Concomitant Therapies

At the discretion of the investigator, any drug or non-drug therapy necessary to treat any condition arising during the study, except another systemic therapy (chemotherapy) and/or radiation therapy, and/or immunotherapy for HCC was permitted. Treatment with antihistamines or corticosteroids was not recommended, but could be instituted at the discretion of the treating physician if clinically necessary. Investigators could prescribe all other concomitant medications or treatments deemed necessary to provide adequate subject care.

For management of hyperuricemia (CTCAE grade ≥3), allopurinol therapy was to be administered to subjects until serum uric acid levels normalized and symptoms resolved. If the hyperuricemia did not respond to allopurinol, uricase (rasburicase) therapy could be administered. All prescription and non-prescription drugs were to be recorded in the concomitant medications section of the eCRF, listing generic (preferably) or brand name, indication, dose, route, and dates of administration. All non-drug therapies were to be recorded in the respective sections of the eCRF.

9.4.8 Treatment Compliance

The investigators or appropriate designee maintained a record of all study medications received and dispensed and also source documents for each subject in the study, consisting of case and visit notes.

Skipped doses were not made up. Subjects followed the same weekly regimen as if no doses were missed or not given.

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and Safety Measurements Assessed and Schedule of Events

The following section describes in detail all study procedures. Table 9-1 provides the schedule of visits and assessments for Screening and Weeks 1 to 12 of the study. Table 9-2 provides the schedule of visits and assessments for Weeks 13 to 36 of the study, including the end of treatment (EOT) visit. Table 9-3 provides the assessments and procedures for follow up after the last treatment.

Table 9-4 provides the schedule of visits and assessments for subjects ongoing at study end (once the 487 events were observed for the final analysis).

Table 9-1 Study Assessments and Procedures: Pre-Study (Screening) and Weeks 1 to 12

	Study Week												
Study Procedure	**Screening[a]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Review of inclusion and exclusion criteria	X												
Informed consent	X												
Comprehensive history and physical examination[b]	X												
Brief history and physical examination[c]			X		X		X		X		X		X
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X												
Body weight	X	X	X		X		X		X		X		X
ECOG PS	X	X	X		X		X		X		X		X
AE assessment[e]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Dietary recommendation compliance		X	X	X	X	X	X	X	X	X	X	X	X
Surgical resection candidate?		X	X	X	X	X	X	X	X	X	X	X	X

Study Procedure	Study Week												
	Screening[a]	1	2	3	4	5	6	7	8	9	10	11	12
CT (or MRI) scan and tumor response status[f]	X												X
ECG	X	X[m]			X[n]								X[n]
Pregnancy test[g]	X												
Clinical laboratory tests													
Hematology[h]	X		X		X		X		X		X		X
Chemistryi	X		X		X		X		X		X		X
Uric acid	X		X	X	X	X	X	X	X		X		X
AFP	X				X				X				X
Hepatitis B and C[j]	X				X				X				X
Randomization	X												
Special blood tests[k]													
Arginine + citrulline	X		X		X				X				X
Anti-ADI-PEG 20 antibodies	X		X		X				X				X
ADI-PEG 20 levels	X		X		X				X				X
Study drug/placebo administration		X	X	X	X	X	X	X	X	X	X	X	X
HCC tissue for IHC[l]	X												

Abbreviations: ADI-PEG 20, arginine deiminase-polyethylene glycol of 20,000 molecular weight; AE, adverse event; AFP, alpha-fetoprotein; ASS, argininosuccinate synthetase; CT, computed tomography; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; IHC, immunohistochemistry; MRI, magnetic resonance imaging.

Note: All study evaluations and related procedures were to occur ±3 days of the planned date except for CT (or MRI) scan, which was to occur ±7 days of the planned date (with the exception of the screening visit). See Appendices for more specific information on revised RECIST 1.1 criteria (Appendix A of the Protocol [Section 16.1.1]), Child-Pugh classification (Appendix B of the Protocol [Section 16.1.1]), ECOG performance status (Appendix C of the Protocol [Section 16.1.1]), New York Heart Association Functional Capacity (Appendix D of the Protocol [Section 16.1.1]), and Tumor-Node-Metastases Classification (Appendix E of the Protocol [Section 16.1.1]).

[a] Screening assessments, except for informed consent and CT (or MRI) scan were to be conducted within 14 days prior to receiving the first dose of study drug or placebo, including day of first dosing within the 14 days. See Section 6.1 of the Protocol [Section 16.1.1] for details.

[b] Comprehensive history and physical examination: comprehensive medical history included etiology of HCC, tumor node metastases staging (American Joint Commission on Cancer grading) including presence or absence of vascular invasion, portal vein thrombosis and extrahepatic spread, Child-Pugh classification, demographics, prior surgery, prior chemotherapy/radiation therapy, review of systems and allergy; comprehensive physical examination includes vital sign measurements, height, weight, and physical examination of all organ systems.

[c] Brief history and physical examination: included vital sign measurements, brief review of systems, and physical examination of pertinent organ systems.

[d] Blood pressure, heart rate, temperature and respiration rate. On dosing days, vital sign measurements were to be taken prior to receiving study drug or placebo and 1 hour ±15 minutes after dose.

[e] Adverse events, including serious adverse events and toxicities were to be assessed. Baseline toxicities/symptoms were to be recorded starting with the date of signing of informed consent. These were to be recorded until 30 days after last drug administration. Adverse events that were still ongoing at End-of-Treatment visit were to be followed up until resolution or stabilization.

[f] Computed tomography scans of the chest/abdomen/pelvis with contrast and triphasic liver were to be conducted within 28 days prior to subject receiving the first ADI-PEG 20 or placebo treatment. If a subject was allergic to intravenous contrast despite use of diphenhydramine and corticosteroids, then MRI of the abdomen and pelvis with

gadolinium and CT of the chest without contrast was to be obtained within 28 days prior to subject receiving the first ADI-PEG 20 or placebo treatment. Tumor measurements were to be noted and tumor response status by investigator calculated.

[g] Female subjects only, serum based.

[h] Complete blood count, differential count, platelet count, prothrombin time or international normalized ratio, and partial thromboplastin time - drawn before ADI-PEG 20 or placebo treatment on the specified study weeks.

[i] Comprehensive chemistry (AFP, albumin, alkaline phosphatase, blood urea nitrogen, calcium, carbon dioxide, chloride, creatinine, direct bilirubin, glucose [non fasting], hepatitis B and C studies [continued studies only if baseline positive], indirect bilirubin, lactose dehydrogenase, phosphate, potassium, aspartate transaminase, alanine transaminase, sodium, total bilirubin, total cholesterol, total protein, and uric acid) - drawn before ADI-PEG 20 or placebo treatment on the specified study weeks.

[j] If anti-hepatitis C virus antibody was positive, hepatitis C virus titer was to be performed before first treatment and at every 4 weeks on study, and once off study. If hepatitis B surface antigen and/or hepatitis B core antibody were positive, the relevant hepatitis B test(s) (hepatitis B antigen and/or hepatitis B core antibody and/or hepatitis B virus titer) were to be performed every 4 weeks on study, and at the end of the treatment. Hepatitis B virus titer could be performed before first treatment and at these times at a local laboratory in addition to or as alternate to the hepatitis B tests listed above.

[k] Blood samples were to be collected before ADI-PEG 20 or placebo treatment on the specified study weeks.

[l] Archived HCC tissue of sufficient amount and quality were to be available, if possible, for IHC determination of ASS status, and other biomarkers. Archived HCC tissue and determination of argininosuccinate synthetase status were not required for study entry.

[m] ECG after 1st dose was to be performed within 1 – 2 hours after dosing.

[n] ECG was to be performed before dosing.

Table 9-2 Study Assessments and Procedures: Weeks 13 to 24, and Weeks 25 to 36 and Subsequent 12-Week Cycles, Including End-of-Treatment Visit

Study Procedure	Study Week												
	13 25	**14 26**	**15 27**	**16 28**	**17 29**	**18 30**	**19 31**	**20 32**	**21 33**	**22 34**	**23 35**	**24 36[a]**	**EOT[b]**
Brief history and physical examination[c]		X		X		X		X		X		X	X
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight		X		X		X		X		X		X	X
ECOG PS		X		X		X		X		X		X	X
AE assessment[e]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Dietary recommendation compliance	X	X	X	X	X	X	X	X	X	X	X	X	
Surgical resection candidate?	X	X	X	X	X	X	X	X	X	X	X	X	X
CT (or MRI) scan and tumor response status[f]												X	
ECG													X
Clinical laboratory tests													
Hematology[g]		X		X		X		X		X		X	X
Chemistry[h]		X		X		X		X		X		X	X
Uric acid		X		X		X		X		X		X	X
AFP				X				X				X	X
Hepatitis B and C[i]				X				X				X	X
Special blood tests[j]													
Arginine + citrulline				X				X				X	
Anti-ADI-PEG 20 antibodies				X				X				X	
ADI-PEG 20 levels				X				X				X	
Study drug/placebo administration	X	X	X	X	X	X	X	X	X	X	X	X	

Abbreviations: ADI-PEG 20, arginine deiminase-polyethylene glycol of 20,000 molecular weight; AE, adverse event; AFP, alpha-fetoprotein; CT, computed tomography; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance status; MRI, magnetic resonance imaging.

Note: All study evaluations and related procedures could occur ±3 days of the planned date except for CT (or MRI) scan which could occur +7 days of the planned date.

[a] Subjects who remained on treatment after 24 weeks continued following the schedule in Table 9-4. Thus, for example, Week 25 (of Weeks 25-36) followed the schedule for Week 13. Therefore, CT scans were obtained every 12 weeks (ie, at 36, 48, 60 weeks, etc) for those still on treatment.

[b] End-of-Treatment visit occurred 30-35 days after last study drug/placebo administration.

[c] Brief history and physical examination: included vital signs, brief review of systems, and physical examination of pertinent organ systems.

[d] Blood pressure, heart rate, body temperature, and respiratory rate.

[e] Adverse events, including serious AEs and toxicities were to be assessed. Baseline toxicities/symptoms were to be recorded starting with the date of signing of informed consent. These were to be recorded until 30 days after last drug administration. Adverse events that were still ongoing at End-of-Treatment visit were to be followed up until resolution of any AEs, or until the unresolved AEs were judged by the investigator to have stabilized.

[f] Computed tomography scans of the chest/abdomen/pelvis with contrast and triphasic liver were conducted. If a subject was allergic to intravenous contrast despite use of diphenhydramine and corticosteroids, then MRI of the abdomen and pelvis with gadolinium and CT of the chest without contrast were to be obtained within 28 days prior to subject receiving the first ADI-PEG 20 or placebo treatment. Tumor measurements were noted and tumor response status by investigator was calculated.

[g] Complete blood count, differential count, platelet count, prothrombin time or international normalized ratio, and partial prothrombin time - drawn before ADI-PEG 20 or placebo treatment on the specified study weeks.

[h] Comprehensive chemistry (AFP, albumin, alkaline phosphatase, blood urea nitrogen, calcium, carbon dioxide, chloride, creatinine, direct bilirubin, glucose [non fasting], human chorionic gonadotropin, hepatitis B and C studies, indirect bilirubin, lactose dehydrogenase, phosphate, potassium, aspartate transaminase, alanine transaminase, sodium, total bilirubin, total cholesterol, total protein, and uric acid) - drawn before ADI-PEG 20 or placebo treatment on the specified study weeks.

[i] If anti-hepatitis C virus antibody was positive, hepatitis C virus titer was performed before first treatment and at every 4 weeks on study, and once off study. If hepatitis B surface antigen and/or hepatitis B core antibody were positive, the relevant hepatitis B test(s) (hepatitis B antigen and/or hepatitis B core antibody and/or hepatitis B virus titer) were to be performed every 4 weeks on study, and at the end of the treatment. Hepatitis B virus titer could be performed before first treatment and at these times at a local laboratory in addition to or as alternate to the hepatitis B tests listed above.

[j] Blood samples were collected before ADI-PEG 20 or placebo treatment on the specified study weeks.

Table 9-3 Study Assessments and Procedures: Follow-Up After Last Treatment

Study Procedure	Every 1 Month (± 7 days)
Survival status	X
Adverse event assessment	X
New procedures or therapy[a]	X

[a] If the subject had received any diagnostic or therapeutic procedures or subsequent antitumor/anticancer therapy, the type of procedure and name of the drug(s) in the treatment regimen were to be collected and the date of the new anticancer treatment noted.

Table 9-4 Study Assessments and Procedures – Open-Label Extension

	Study Week												
Study Procedure	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**EOT**
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	
AE assessment[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug administration[b]	X	X	X	X	X	X	X	X	X	X	X	X	

Abbreviations: AE, adverse event, EOT, end of treatment.

Note: All study evaluations and related procedures were to occurr ±3 days of the planned date.

Subjects who remained on treatment after 12 weeks continued to follow the schedule in this table. For example, Week 13 followed the schedule for Week 1, Week 14 followed the schedule for Week 2, etc.

[a] Adverse events, including serious AEs were to be assessed at each visit. Ongoing AEs were to be followed until resolution. New AEs were to be recorded until 30 days after last drug administration. Adverse events were to be reported to Polaris monthly. Serious AEs were to be reported within 24 hours of awareness to Polaris (safety@polarispharma.com).

[b] During blinded extension, visits were registered in the Interactive Web Response System. During Open-Label Extension, Polaris provided a list of vial numbers to be pulled from inventory and given to subjects at each visit.

9.5.1.1 Study Drug Dosing

The study drug dosing consisted of the number of doses administered and the duration of exposure.

9.5.1.2 Demographics and Baseline Characteristics

The demographics and baseline characteristics consisted of the following:

- Gender
- Age
- Race
- Ethnicity
- Prior medications

- Geographic region
- Prior failed systemic antineoplastic agent (sorafenib vs non-sorafenib)
- Prior surgery, radiotherapy, and other therapy
- ECOG performance status
- Child-Pugh classification parameters (encephalopathy, ascites, bilirubin, albumin, and prothrombin time)
- Presence or absence of macroscopic vascular invasion (portal vein or branches)
- Presence or absence of extrahepatic spread
- Etiology of HCC
- Weight
- Height
- Body surface area

9.5.1.3 Primary Efficacy Variable

The primary efficacy variable was OS (time from randomization until death from any cause).

9.5.1.4 Secondary Efficacy Variables

The secondary efficacy variables were as follows:

- PFS
- Objective response rate and best overall objective response rate (if applicable)
- Duration of objective response
- Tumor response rate at each visit and best overall tumor response
- TTP
- Disease control rate at each visit and best overall disease control rate
- Surgical resection
- Change in alpha-fetoprotein (AFP)

9.5.1.5 Immunogenicity, Pharmacodynamic, and Pharmacokinetic Assessments

9.5.1.5.1 Immunogenicity Parameters

Immunogenicity was assessed by measurement of peripheral blood antibodies to ADI-PEG 20.

9.5.1.5.2 Pharmacodynamic Parameters

Pharmacodynamics was assessed by measurement of peripheral blood levels of arginine and citrulline by liquid chromatography-mass spectrometry.

9.5.1.5.3 Pharmacokinetic Parameters

Pharmacokinetics was also assessed by measurement of peripheral blood levels of ADI-PEG 20.

9.5.1.6 Safety Assessments

Laboratory tests, vital sign measurements, physical examinations, and subject medical history were performed to detect new abnormalities and any deterioration in preexisting conditions. All clinically significant abnormalities and deteriorations were to be recorded in the eCRFs as AEs and graded according to the NCI CTCAE v4.02.

9.5.1.6.1 Adverse Events

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product that did not necessarily have a causal relationship with the treatment. Therefore, an AE could have been any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

9.5.1.6.1.1 Recording of Adverse Events

The severity of all AEs was assessed according to the NCI CTCAE v4.02.

Preplanned hospitalizations were excluded from the definition of SAEs (Section 9.5.1.6.1.7).

Action taken regarding study drug was categorized as no action taken, permanently discontinued, or stopped temporarily. Any further treatment required for the event was recorded.

Event outcome at resolution or time of last follow-up was recorded as event recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, or unknown.

9.5.1.6.1.2 Assessment of Adverse Events – Relationship to Study Drug

The relationship of all serious and non-serious AEs to the investigational agent(s) was determined by the investigator on the basis of his or her clinical judgment, using one of the following terms (in accordance with NCI Guideline "Expedited Adverse Event Reporting Requirements for NCI Investigational Agents," NCI Cancer Therapy Evaluation Program, January 2001):

- Definitely related (The AE was clearly related to the investigational agent)
- Probably related (The AE was likely related to the investigational agent)

- Possibly related (The AE may have been related to the investigational agent)
- Unlikely related (The AE was doubtfully related to the investigational agent)
- Not related (The AE was clearly not related to the investigational agent)

Note: Adverse event information provided in the investigator's brochure was available to support assessments of AE relationship to investigational treatment.

9.5.1.6.1.3 Following Adverse Events

All AEs were to be followed until they were resolved or stabilized, or until all attempts to determine resolution of the event had been exhausted. The investigator was to use his/her discretion in ordering additional tests as necessary to monitor the resolution of such events.

Note: All follow-up information pertaining to SAEs was to be forwarded to Polaris or its designee within 24 hours of awareness.

9.5.1.6.1.4 Discontinuation Due to Adverse Events

Subjects could be withdrawn from the study at any time. Subjects withdrawn from the study due to an AE, whether serious or non-serious, were to be followed by the investigator until the clinical outcome from the AE was determined. Any subject who experienced an AE could be withdrawn at any time from the study at the discretion of the investigator. The AE(s) was to be noted in the appropriate eCRFs, and the subject's progress followed until the AE was resolved, and the medical monitor was notified.

9.5.1.6.1.5 Pregnancy

A subject who became pregnant was to be discontinued from the study and followed up until partum.

9.5.1.6.1.6 Post-study Adverse Events

Adverse events that were identified at the last assessment visit (or the early termination visit) were to be recorded on the AE eCRF with the status of the AE noted and followed until resolution or deemed stable by the investigator. All events that were ongoing at that time were to be recorded as ongoing in the eCRF. Serious AEs were to follow the SAE reporting procedures specified in Section 9.5.8 of the Protocol (Section 16.1.1). Thus, AEs were to be recorded until 30 days after the last drug administration.

9.5.1.6.1.7 Serious Adverse Events

Subjects were monitored throughout the study for AEs.

An SAE was any untoward medical occurrence that:

- Resulted in death,
- Was life-threatening*,
- Required inpatient hospitalization or prolongation of existing hospitalization,
- Resulted in persistent or significant disability or incapacity,
- Was a congenital anomaly/birth defect, or
- Was another medically important condition**.

* The term "life-threatening" in the definition of "serious" referred to an event in which the subject was at risk of death at the time of the event; it did not refer to an event that hypothetically might have caused death if it were more severe.

** Medically important conditions that may not have resulted in death, were not immediately life-threatening, or did not require hospitalization could be considered as SAEs when, based upon appropriate medical judgment, they may have jeopardized the subject or may have required intervention to prevent one of the outcomes listed in the definition in this section. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Note: The term "severe" is often used to describe the intensity (severity) of an event (such as: mild, moderate, or severe, eg, pain). The event itself may have been of relatively minor medical significance (such as a severe headache). This was not the same as "serious", which was based on subject/event outcome or action criteria usually associated with events that posed a threat to the subject's life or vital functions. Seriousness (not severity) served as a guide for defining regulatory reporting obligations.

9.5.1.6.2 Vital Signs

The following vital sign measurements were to be performed:

- Systolic and diastolic blood pressure in the sitting position using an appropriate size of cuff
- Respiratory rate
- Heart rate
- Body temperature

9.5.1.6.3 Laboratory Tests

Samples were to be obtained for the clinical laboratory tests listed in Table 9-5 according to the assessment schedule described in Table 9-1 and Table 9-2 (with further details in Section 6.2 of the Protocol [Section 16.1.1]). Certified central laboratories (details are

provided in Section 16.1.10) were utilized to process and provide results for the clinical laboratory tests (hematology, chemistry, uric acid, AFP, and hepatitis B and C studies). The baseline laboratory test results for clinical assessment for a particular test were defined as the last measurement prior to the initial dose of study drug. A certified laboratory affiliated with the study site could be utilized in case of eligibility confirmation or analyte retesting, but was not to be used for routine laboratory testing without prior approval of the sponsor.

A central laboratory was utilized to process and provide results of blood sampling for special tests (pharmacodynamics [peripheral blood arginine and citrulline levels], immunogenicity [anti-ADI-PEG 20 antibodies] and pharmacokinetics [peripheral blood ADI-PEG 20 levels]).

Table 9-5 Clinical Laboratory Tests

Hematology	Serum Chemistry
Hematocrit	Alpha-fetoprotein
Hemoglobin	Albumin
Red blood cell count	Alkaline phosphatase
White blood cell count	Blood urea nitrogen
Neutrophils (%)	Calcium
Bands (%)	Carbon dioxide
Lymphocytes (%)	Chloride
Monocytes (%)	Creatinine
Basophils (%)	Direct bilirubin
Eosinophils (%)	Glucose
Platelet count (estimate not acceptable)	Human chorionic gonadotropin
Prothrombin time or international normalized ratio	Hepatitis B and C studies
Activated partial thromboplastin time	Indirect bilirubin
	Lactate dehydrogenase
	Phosphate
	Potassium
	Serum aspartate aminotransferase
	Serum alanine aminotransferase
	Sodium
	Total bilirubin
	Total cholesterol
	Total protein
	Uric acid

For any laboratory test value outside the reference range that the investigator considered clinically significant:

- The investigator could repeat the test to verify the out-of-range value.
- The investigator was to follow the out-of-range value to a satisfactory clinical resolution or stabilization.

- A laboratory test value that required a subject to be discontinued from the study or receive treatment was to be recorded as an AE.

9.5.1.6.4 Physical Examination

A comprehensive physical examination, including height and weight, was to be performed at the screening visit. A brief history and physical examination appropriate to the subject's clinical condition were to be performed at every other visit (Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24, and every 2 weeks thereafter) and at other times as clinically indicated. Any findings or absence of findings relative to each subject's physical examination were to be carefully documented in the subject's eCRF.

9.5.1.6.5 Electrocardiogram

An electrocardiogram (ECG) was to be performed at baseline, after the 1st treatment (within 1-2 hours of dosing), before the 4th and 12th treatments, and at the EOT visit.

9.5.2 Appropriateness of Measurements

The measures of efficacy used in this study reflect accepted standard of care (ie, are widely used and generally recognized as reliable, accurate, relevant, and able to discriminate between effective and ineffective treatment agents).

Safety evaluations selected for this study are typical of those for this subject population and are widely utilized and accepted measures.

9.5.3 Drug Concentration Measurements

The blood concentration measurements include the blood levels of ADI-PEG 20 (including relationship with arginine and citrulline levels).

9.6 Data Quality Assurance

Polaris and its designees implemented and maintained quality control and quality assurance procedures with written standard operating procedures to ensure that the study was conducted and data were generated, documented, and reported in compliance with the protocol, GCP, and applicable regulatory requirements. This study was conducted in accordance with the provisions of the Declaration of Helsinki and all revisions thereof (Brazil 2013), and in accordance with FDA CFR (CFR §312.50 and §312.56) and ICH E6(R1) Guidelines on GCP (CPMP/ICH/135/95) and the provisions of the European Union (EU) Clinical Trial Directives 2001/20/EC and 2002/20/EC.

9.7 Statistical Methods Planned

9.7.1 Statistical and Analytical Plans

The statistical analysis plan (SAP) is provided in Section 16.1.9.

9.7.1.1 Analysis Populations

There were 2 analysis populations defined for this study:

1. The "Intent-to-treat (ITT) Population" comprised all subjects who were randomly assigned into the study. Subjects were analyzed as randomly assigned.
2. The "Safety Population" comprised all subjects who were randomly assigned into the study and who received at least 1 dose (or any portion of a dose) of study medication. Subjects were analyzed based on the actual treatment received.

9.7.1.2 Analysis of the Study

Unless otherwise noted, all statistical tests are 2-sided and a difference resulting in a *P* value of less than or equal to 0.05 was considered statistically significant. All *P* values are rounded to and displayed in 4 decimals. If a *P* value less than 0.0001 occurred, it is shown in tables as <0.0001.

Descriptive summaries of variables are provided where appropriate. For continuous variables, the number of non-missing values (n) and the median, mean, standard deviation (Std Dev), minimum, and maximum were tabulated by treatment. For categorical variables, the counts and proportions of each value were tabulated by treatment. Expansion of descriptive table categories within each treatment may occur if such elaborations were thought to be useful.

All collected data are presented in listings. Data not subject to analysis according to this plan do not appear in any tables or graphs but are included in the data listings.

Post-hoc exploratory analyses not identified in the SAP were performed to further examine the study data. These analyses are included in:

- Table 14.3.1.9.1 Drug Related Treatment Emergent Adverse Events Causing Discontinuation of Study Drug (Safety Population)
- Listing 16.2.4.5.1 Qualifying Agents (Safety Population)

As a sensitivity analysis, the primary analysis of OS was repeated including deaths occurring after the date of the 487th event.

All safety analyses include data through the date of the 487th death observed and all additional data entered until database lock. The only data that were required to be collected after the date of the 487th event were deaths and SAEs.

9.7.2 Data Handling Procedures

Unscheduled or repeated laboratory results were not analyzed for the summary of continuous values but are included in the laboratory shift tables (Section 6.1.10.2 of the SAP [Section 16.1.9]). Unscheduled tests were included with the time of the nearest regularly scheduled test. If there was a scheduled, and 1 or more unscheduled tests assigned to the same time point, the most conservative test (ie, a test with low or high results) was used. Repeated tests were included only if they reflected abnormal (low or high) results and the corresponding original results were normal.

9.7.3 Handling of Early Termination Visits

Early termination visit data for safety variables were analyzed at the closest scheduled visit. If the closest visit had valid data, the early termination data were assigned to the next available visit.

Note that RECIST 1.1 criteria were not assessed at early termination. If there were no data, RECIST 1.1 could not be assessed.

9.7.3.1 Pooling of Investigator Centers

For various efficacy analyses described in the SAP (Section 16.1.9), centers were pooled together by geographic region (Asia vs NA and Europe).

9.7.3.2 Baseline Values

Baseline values were the values obtained prior to the first dose of study drug at Week 1. If the baseline value was missing prior to the first dose of study drug at Week 1, or was not measured at that time, the value at screening was treated as the baseline.

9.7.4 Statistical Analysis Methods

9.7.4.1 Subject Disposition and Dosing Summary

The tabulation of number of subjects in each treatment group and overall are displayed for all subjects who were screened, and for those who were randomly assigned to treatment, in the Safety and ITT Populations, respectively.

The number and percentage of subjects who completed or discontinued the study are displayed for each treatment group and overall together with reasons for early termination,

where the percentage is based on the total number of randomly assigned subjects in that treatment group.

The number of doses administered is summarized by treatment group for both the Safety and ITT Populations.

9.7.4.2 Demographics and Baseline Characteristics

Subject demographic data and baseline characteristics are summarized descriptively by treatment group and overall. The demographic data and baseline characteristics were summarized for the ITT Population.

9.7.4.3 Prior and Concomitant Medications

The number and percentage of subjects who took prior medications are summarized descriptively by the Anatomical Therapeutic Chemical (ATC) classification and preferred term as coded in the WHO Drug Dictionary 01 March 2014 for each treatment group. Concomitant medications are summarized similarly. Prior and concomitant medications are summarized for the Safety Population.

9.7.4.4 Efficacy Endpoints

All efficacy analyses were conducted on the ITT Population.

9.7.4.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint was OS (time from randomization until death from any cause).

Overall survival is summarized using the Kaplan-Meier method. Point estimates (25th, 50th, and 75th percentiles) along with 95% confidence intervals are provided by treatment group. Survival estimates are also shown graphically for each treatment group.

Treatments were compared using a stratified log-rank test (stratified by the 4 levels of the region, sorafenib treatment status variable).

9.7.4.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints were PFS, objective response rate, duration of objective response, tumor response at each visit, time to tumor progression, disease control rate at each visit, and the occurrence of surgical resections.

Progression-free survival and the best overall objective response (BOOR) rate were tested sequentially. Progression-free survival between the treatment groups was first assessed at the

$\alpha = 0.05$ level. If this test was significant then the BOOR rate between the treatment groups was to be assessed at the $\alpha = 0.05$ level. The BOOR rate was only assessed if the test between treatment groups for PFS was significant (at the $\alpha = 0.05$ level). Ordering the tests in this manner controls the type I error for both tests. Specifics on the analyses for these variables are discussed.

Progression-free survival was analyzed using the same methods as used for OS described in Section 9.7.4.4.1.

The number and percentage of subjects who exhibited objective response (Yes, No, or missing) at each radiology testing visit, and BOOR are presented by treatment group. A Cochran-Mantel-Haenszel (CMH) general association test was used to compare the objective response rates between the 2 treatment groups, stratified by the 4 levels of the region and sorafenib treatment status variable at each visit and for BOOR.

Duration of objective response was analyzed using the same methods as used for OS described in Section 9.7.4.4.1. Only subjects who had an objective response were included in the analysis.

The number and percentage of subjects who exhibited each level of tumor response (CR, partial response [PR], SD, PD, or missing) at each radiology testing visit, and best overall tumor response (BOTR) are presented by treatment group. A CMH mean scores test was used to compare the tumor response rates between the 2 treatment groups, stratified by the 4 levels of the region and sorafenib treatment status variable at each visit and for BOTR.

Time to tumor progression was analyzed using the same methods as used for OS described in Section 9.7.4.4.1).

The number and percentage of subjects who exhibited disease control (Yes, No, or missing) are presented at each radiology testing visit, and best overall disease control (BODC) by treatment group. A CMH general association test was used to compare the disease control rates between the 2 treatment groups, stratified by the 4 levels of the region and sorafenib treatment status variable at each visit and for BODC.

The number and percentage of subjects who had a surgical resection during the study (yes/no) are displayed for each treatment group.

Changes in AFP levels were assessed.

9.7.4.4.3 Additional Efficacy Analyses

The primary efficacy analysis of OS was repeated as a sensitivity analysis using all deaths through the time of data cut-off.

Overall survival was analyzed using additional stratified log-rank tests along with log-rank tests for different subgroups. These tests assessed the sensitivity of the results obtained in the primary efficacy analysis as described in Section 9.7.4.4.1.

Separate stratified log-rank tests were used to compare OS across treatment groups using each of the following stratification factors:

- Geographical region (Asia vs NA and Europe)
- Sorafenib treatment status (non-sorafenib failure and sorafenib failure)
- ECOG performance status at screening (0 vs 1 and 2)
- Presence or absence of macroscopic vascular invasion (portal vein or branches)
- Presence or absence of extrahepatic spread
- Etiology of HCC (hepatitis C, hepatitis B, alcohol, nonalcoholic steatohepatitis [NASH], and other)
- Antiviral therapy use (yes or no)

Separate log-rank tests (stratified by the 4 levels of the region – sorafenib treatment status variable) were used to compare OS across treatment groups within each level of the following subgroups:

- Region – sorafenib treatment status (Asia and non-sorafenib failure, Asia and sorafenib failure, NA and Europe and non-sorafenib failure, and NA and Europe and sorafenib failure)
- Geographical region (Asia vs NA and Europe)
- Sorafenib treatment status (non-sorafenib failure and sorafenib failure)
- ECOG performance status at screening (0 vs 1 and 2)
- Presence or absence of macroscopic vascular invasion (portal vein or branches)
- Presence or absence of extrahepatic spread
- Etiology of HCC (hepatitis C, hepatitis B, alcohol, nonalcoholic steatohepatitis [NASH], and other)
- Antiviral therapy use (yes or no)

9.7.4.5 Immunogenicity Analyses

Blood levels of antibodies to ADI-PEG 20 are summarized descriptively for each treatment group by visit for the observed value as well as for the change from baseline value.

For the ADI-PEG 20 treatment group, the relationship between the antibody levels, both actual and change from baseline, and OS were assessed by using the estimated hazard ratio obtained from a Cox proportional hazards model that included the antibody level as a covariate.

Also within the ADI-PEG 20 treatment group, the correlation between the antibody levels and arginine blood levels was calculated using Pearson's correlation coefficient. The same analysis was performed with the citrulline levels.

9.7.4.6 Pharmacodynamic Analyses

Blood levels of arginine and citrulline are summarized descriptively for each treatment group by visit for the observed value.

Subjects were considered to have arginine depletion if there was a negative change from baseline and a level at or below 10 μM for arginine blood levels. Similarly, subjects wereconsidered to have citrulline increase if there was at least a 50% increase from baseline for citrulline blood levels. Numbers of subjects with arginine depletion and numbers of subjects with citrulline increase were displayed by time point.

For the ADI-PEG 20 treatment group, the relationship between the duration of arginine depletion (for ≤3 weeks, >3 weeks and ≤7 weeks, and >7 weeks) and OS was assessed by using the estimated hazard ratio obtained from a Cox proportional hazards model, after adjusting for treatment duration. The relationship between arginine depletion levels and safety variables (eg, most frequently reported drug-related AEs [such as hyperuricemia, pruritus, and rash], and laboratory abnormalities) was assessed (using appropriate nonparametric tests and logistic regression). The same analyses were performed with the citrulline increase levels.

9.7.4.7 Pharmacokinetic Analysis

Pharmacokinetic data (peripheral blood ADI-PEG 20 levels) are summarized descriptively and correlated with OS, pharmacodynamics, and safety variables using methods similar to those described in Sections 9.7.4.5 and 9.7.4.6.

9.7.4.8 Safety Analyses

All safety analyses were conducted on the Safety Population.

9.7.4.8.1 Adverse Events

Adverse events were codified using the NCI CTCAE v4.02, which provides a mechanism for grading the severity of the AE. These events were mapped to the Medical Dictionary for

Regulatory Activities (MedDRA) Version 18.0 system for reporting (preferred term and body system).

The number and percentage of subjects with any treatment-emergent adverse events (TEAEs) are displayed by system organ class and preferred term for each treatment group.

Within each preferred term, subjects were counted only once if they had more than 1 event reported during the treatment period. The same summary was performed for all serious TEAEs and all TEAEs causing discontinuation of study drug.

The TEAEs are also summarized by greatest reported severity grade (grades 1-5) for each event preferred term. Counts indicate subjects reporting 1 or more TEAEs that mapped to the severity grade classification for each preferred term. At each level of summarization (system organ class or event preferred term), subjects were only counted once. The TEAEs are summarized by greatest reported relationship in a similar manner and were also summarized by concomitant antiviral therapy use (yes/no).

A listing was produced for all subjects who reported serious TEAEs or who discontinued study medication due to TEAEs.

All TEAEs are listed individually by subject. In addition, a separate listing was produced for AEs that were not treatment-emergent.

9.7.4.8.2 Laboratory Parameters

Laboratory results are summarized descriptively for each treatment group by visit for the observed value as well as for the change from baseline value. In addition, laboratory shift tables are provided for all laboratory parameters where low/normal/high or abnormal/normal status was ascertained. Shift tables are also provided by concomitant antiviral therapy use (yes/no).

9.7.4.8.3 Vital Signs

Vital signs are summarized descriptively for each treatment group by visit for the observed value as well as for the change from baseline value.

9.7.4.8.4 Other Safety Analyses

Physical examination results are summarized descriptively for each treatment group by visit.

The number and percentage of subjects in each ECOG group (0 vs 1 and 2) are summarized categorically for each treatment group by visit.

The number and percentage of subjects in each AFP change category (decrease, stable, rise) were summarized for each treatment group. Treatments were compared using a CMH mean scores test.

Electrocardiogram parameters are summarized descriptively for each treatment group by visit for the observed continuous values as well as for the change from baseline value. Overall interpretation (normal/abnormal and QTc >450 ms) is summarized descriptively.

The number and percentage of subjects who used any antiviral therapy (yes/no) are displayed for each treatment group.

In some cases, inferential statistical comparisons may have been requested by the medical report writer (eg, analysis of variance comparing vital signs or laboratory values between treatment groups). All such requests were carried out by the statistician. In such instances, *P* values served as measures of distance to facilitate the clinical review and screening of these numerous variables.

9.7.5 Determination of Sample Size

Information on sorafenib phase 3 studies in HCC provided respectively by Llovet, et al (Llovet et al 2008b) and Cheng et al (Cheng et al 2009) was used to estimate treatment and control post progression survival for Asian and Pacific (A/P) subjects as well as for North American and European (NA/EU) subjects. The initial sample size estimation for this study based on these studies provided an expected difference between control and treatment subjects of 1.6 months (5.6 – 4.0 months).

Using this projected effect size (Section 6.2 of the SAP [Section 16.1.9], the following assumptions were used to estimate the starting sample size for the study:

The study was conducted as a group-sequential design with a single interim analysis planned at the 50% information time point where the primary efficacy endpoint (OS) was to be tested using a 1-sided log-rank test. Due to slower than expected enrollment during the study, and after discussion with the FDA, the interim analysis was removed. The sample size remained as originally planned.

- An overall 1-sided type I error rate (α) of 0.025 was assumed.
- An overall type II error rate (β) of 0.07 was assumed (ie, power = 0.93).
- As noted, the recruitment and randomization of 2 AP subjects for every 1 NA/EU subject and 2 active subjects per control subject was assumed.

- It was assumed that recruitment would take place over 12 months with each month evidencing approximately the same recruitment percentage of the total sample (8.33%) in both groups.
- A total study time of 18 months was assumed (a 12-month recruitment period and a 6-month follow-up period).
- It was assumed that each subject was monitored for death from the time of recruitment to the end of the 18-month study period and that censoring occurred at the end of the 18-month study period.
- It was assumed that in a given year 5% of treatment and control subjects would be lost to follow-up. Using the relationship $P_{yearly} = 1 - (1 - P_{monthly})^{12}$, the monthly loss proportion was assumed to be 0.0043.
- It was assumed that no treatment subject was switched in the 18-month study period to a treatment regimen equivalent in outcome to control. It further was assumed that no control subject was switched in the 18-month period to a treatment regimen equivalent in outcome to ADI-PEG 20.
- Following calculations for a fixed sample size, adjustments were made to allow for the group sequential design in order to maintain the overall α-level and power. In this study the boundaries were constructed using the O'Brien-Fleming method.
  The corresponding maximum information percentage relative to a fixed sample design is 102.525. As such, the number of needed subjects and events were both increased by 2.525%. Note that the interim analysis was removed while the study was still blinded. See Section 6.3 of the SAP (Section 16.1.9) for more details.

Using these assumptions and rounding up to whole subjects, the following estimated sample size (subjects and events) was obtained (Table 9-6).

Table 9-6 Sample Size Estimation

Population Proportion		Assumed Median Survival		Estimated Subject Requirement (N)			Estimated Event Requirement (E)			
%AP	%NA/EU	Control Median Survival	Treatment Median Survival	N Control	N Treatment	N Total	E Control	E Treatment	E Total	Hazard Ratio
0.67	0.33	4	5.6	211	422	633	176	311	487	0.7143

Abbreviations: AP, Asia Pacific; EU, European Union; NA, North America.

Notes: α = 0.05; Power = 0.93; Percent Treatment Improvement = 40%; Two-tailed Log Rank Test; Recruitment Period 12 Months; Follow-up Period 6 Months; 5% Yearly Lost to Follow-up; Treatment to Control Ratio 2:1; No Placebo-to-Treatment or Treatment-to-Placebo Switching. Estimates for this and other tables acquired with PASS 2008 (Version 08.0.6, Released May 13, 2008) relying on the methods of Lakatos, Edward (1988), Biometrics, Volume 44, March, p 229-241.

Source: Statistical Analysis Plan, Section 6.2 (Section 16.1.9).

9.8 Changes in the Conduct of the Study or Planned Analyses

9.8.1 Changes in the Conduct of the Study

The protocol was amended 4 times. In addition, an Italian-specific amendment was also implemented. The only difference between the Italian-specific protocol amendments and the comprehensive protocol amendments was the following:

- The Italian-specific protocol stated that prior treatment with standard therapy for advanced HCC had to include sorafenib (unless contraindicated), for inclusion criterion #2.

Complete details of the changes implemented in each amendment are provided in Section 16.1.1.

Protocol Version 001, dated 30Jun2011, was not implemented, and the following changes were also carried forward to the next version:

- The number of days allowed for an injection from the planned injection date was tightened.
- HCC tissue was allowed to be used for determination of additional biomarkers.
- Hepatitis B PCR quantification was added as na option in addition to hepatitis B antigen and/or antibody for following hepatitis B infection.
- The length that subjects were observed following an injection before vital signs were repeated was clarified.
- Cytological confirmation of HCC was added to the inclusion criteria.
- Populations to be assessed were clarified in the statistical portion of the protocol.

The following is a summary of the major changes implemented with Protocol Version 002, dated 17Oct2011:

- The number of sites was updated from “to be determined” (TBD) to approximately 50-60.
- It was clarified that the screening assessments were to occur within 14 days of starting treatment, with the day of treatment included within the 14 days.
- It was clarified that height was to be collected only at screening.
- Body weight and ECOG performance status collections were changed from every visit to even numbered visits plus Weeks 1 and EOT.
- Dietary compliance was clarified.
- Clarified information regarding candidates for surgical resection.
- The window of time to obtain vital signs after dosing was clarified.

- Times to obtain baseline hepatitis C viral titer were clarified.
- Potential use of hepatitis B virus titer was clarified.
- It was clarified that EOT visit should be 30-35 days instead of 30 (±5) days after the last study drug/placebo administration.
- It was clarified that the IWRS was used instead of Interactive Voice Response System.
- It was clarified that 2 melanoma studies that were ongoing at the time of initial protocol submission were now closed.
- The wording in Section 4.1 was changed to be consistent with the inclusion criterion #2.
- It was clarified that failure of a prior chemotherapy agent included a severe allergic reaction occurring before having received 14 days of that treatment.
- Inclusion criterion #7 and #8 and exclusion criterion #7 and #17 were clarified regarding the timing of systemic treatment for HCC in the previous 2 weeks prior to first dose of study drug or placebo.
- Inclusion criterion #18, serum albumin level, was corrected to reflect Child-Pugh criteria.
- Obtaining data on body height, body weight, and testing for hepatitis viral load during clinic visits was clarified.
- Obtaining information on whether the subject was a candidate for surgical resection was clarified.
- Obtaining follow-up information on subjects was clarified, including blood for pharmacodynamics, immunology, and pharmacokinetics.
- The amount of blood to be drawn was clarified.
- A section was added on managing skipped doses.

The following is a summary of the major changes implemented with Protocol Version 003, dated 16Nov2012:

- Informed Consent Form screening window was extended to 28 days.
- The AE assessment study procedure footnote was clarified to distinguish between baseline toxicities and weekly visit assessments.
- End-of-treatment dietary recommendation compliance was removed from visit procedure requirement as a subject would have ceased treatment by the time this visit occurred.
- The follow-up visit window was added.
- Study citations were updated to reflect current information.

- Inclusion criterion #4 was revised to include cirrhotic status of Child-Pugh B7.
- Inclusion criterion #8 was clarified to better define recovery from surgery.
- An exclusion criterion was added to disallow liver transplantation.
- Blood drawing for special studies was added to Week 2.
- Thawed investigational drug storage condition was clarified.
- Dose adjustment rationale was revised to include unrelated grade 3 toxicities.
- It was clarified that the study monitor was not required to collect original study drug dispensing records at the end of the study (ie, copies allowed).
- Treatment of hyperuricemia was clarified.
- Independent radiology review for subjects presenting with partial or complete response was added.
- The use of local laboratories for routine testing was clarified.
- Mandatory repeat of out-of-range laboratory test value was removed to emphasize freedom of investigator decision.
- The timing and content of SAE reporting was clarified.

The following is a summary of the major changes implemented with Protocol Version 004, dated 05Dec2014:

- Blinded and Open-Label Extension was added.
- Interim analysis was deleted.
- MedDRA version was confirmed.
- Additional efficacy analysis was revised to mirror the SAP.
- Pharmacodynamic statistical analysis was revised to mirror the SAP.
- Immunogenicity statistical analysis was revised to mirror the SAP.

9.8.2 Changes in the Planned Analysis

The following planned analyses noted in the SAP version 4.0, dated 02Apr2015, were not performed, or were modified:

Table 9-7 Changes to the Planned Analyses

Planned Table or Listing Number	Planned Table or Listing Title	SAP Sections	Rationale
Table 14.1.2.1	Demographics and Baseline Characteristics (Safety Population)	6.1.4	Judged unnecessary to present these for the Safety Population in addition to the Intent-to-Treat Population
Table 14.1.5.1	Drug Exposure (Safety Population)	5.1, 6.1.3	Judged unnecessary to present these for the Safety Population in addition to the Intent-to-Treat Population
Table 14.2.2.2	Objective Response Rate and Best Overall Objective Response Rate (Intent-to-Treat Population)	6.1.6.2	Judged unnecessary due to the low response rates in both groups
Table 14.2.2.3	Duration of Objective Response (Intent-to-Treat Population)	6.1.6.2	Judged unnecessary due to the low response rates in both groups
Table 14.2.2.8	Percent Change From Baseline in Serum Alpha-Fetoprotein (ng/mL) (Intent-to-Treat Population)	6.1.6.2	Judged unnecessary due to the rates of change in both groups
Table 14.2.3.1	Duration of Overall Survival – Stratified by Geographical Region (Intent-to-Treat Population)	6.1.6.3	Consolidated into Table 14.2.3.
Table 14.2.3.2	Duration of Overall Survival – Stratified by Prior Sorafenib Treatment Status (Intent-to-Treat Population)	6.1.6.3	Consolidated into Table 14.2.3.
Table 14.2.3.3	Duration of Overall Survival – Stratified by Screening ECOG Performance Status (0 vs 1+) (Intent-to-Treat Population)	6.1.6.3	Consolidated into Table 14.2.3.
Table 14.2.3.4	Duration of Overall Survival – Stratified by Macroscopic Vascular Invasion (Intent-to-Treat Population)	6.1.6.3	Consolidated into Table 14.2.3.
Table 14.2.3.5	Duration of Overall Survival – Stratified by Extrahepatic Spread Status (Intent-to-Treat Population)	6.1.6.3	Consolidated into Table 14.2.3.

Planned Table or Listing Number	Planned Table or Listing Title	SAP Sections	Rationale
Table 14.2.3.6	Duration of Overall Survival – Stratified by HCC Etiology (Intent-to-Treat Population)	6.1.6.3	Consolidated into Table 14.2.3.
Table 14.2.3.7	Duration of Overall Survival – Stratified by Antiviral Therapy Use (Intent-to-Treat Population)	6.1.6.3	Consolidated into Table 14.2.3.
Table 14.2.8.1	Overall Survival vs ADI-PEG 20 Antibody Levels for Subjects Receiving ADI-PEG 20 (Intent-to-Treat Population)	6.1.7	Judged unnecessary after review of final data
Table 14.2.8.2	Overall Survival vs ADI-PEG 20 Blood Levels for Subjects Receiving ADI-PEG 20 (Intent-to-Treat Population)	6.1.9	Judged unnecessary after review of final data
Table 14.2.8.4	Overall Survival vs Duration of Arginine Depletion for Subjects Receiving ADI-PEG 20 (Intent-to-Treat Population)	6.1.8	Replaced by *14.2.8.4 - Overall Survival vs Duration of Arginine Depletion for Subjects Receiving ADI-PEG 20 with Adjustment for Treatment Duration* to adjust the Cox model with treatment duration for controlling its effect Changed the brackets of arginine depletion duration to ≤3 weeks, >3 weeks and ≤7 weeks, and >7 weeks.
Table 14.2.8.5	Citrulline Increase (Intent-to-Treat Population)	6.1.8	Changed the definition of citrulline increase from any positive change to >= 50% positive changes to avoid inclusion of measurement errors
Table 14.2.8.6	Overall Survival vs Duration of Citrulline Increase for Subjects Receiving ADI-PEG 20 (Intent-to-Treat Population)	6.1.8	Raplced the table by *14.2.8.6 - Overall Survival vs Duration of Citrulline Increase for Subjects Receiving ADI-PEG 20 with Adjustment for Treatment Duration with Adjustment for Treatment Duration* to adjust the Cox model with treatment duration for controlling its effect Changed the definition of citrulline increase from any positive

Planned Table or Listing Number	Planned Table or Listing Title	SAP Sections	Rationale
			change to >= 50% positive changes to avoid inclusion of measurement errors. Changed the brackets of citrulline increase duration to ≤3 weeks, >3 weeks and ≤7 weeks, and >7 weeks.
Table 14.3.1.9.1	Drug Related Treatment Emergent Adverse Events Causing Discontinuation of Study Drug (Safety Population)	not in SAP	Additional table added for post-hoc analysis
Table 14.3.4.1	Change From Baseline in Hematology (Safety Population)	6.1.10.2	Judged unnecessary because data are presented in shift tables
Table 14.3.4.2	Change From Baseline in Serum Chemistry (Safety Population)	6.1.10.2	Judged unnecessary because data are presented in shift tables
Table 14.3.5.2	Change From Baseline in ECG Parameters (Safety Population)	6.1.10.4	Judged unnecessary because data are presented in shift table instead (Table 14.3.5.3 and 14.3.5.4)
Listing 16.2.4.5.1	Qualifying Agents (Safety Population)	not in SAP	Additional listing added for post-hoc analysis
Listing 16.2.7.2	Non-Treatment-Emergent Adverse Events	6.1.10.1	Judged unnecessary

Abbreviations: SAP, Statistical Analysis Plan.

10 Study Subjects

Tables and figures for demographic, background, and disposition data are located in Section 14.1.

Relevant data listings are located in Section 16.2.

A summary of subject disposition and primary reason for discontinuation from the study is provided in Table 14.1.1.

Randomization and unblinding data are presented by subject in Listing 16.1.7. Subjects not meeting all eligibility criteria are presented by subject in Listing 16.2.2.1. Subjects excluded from the analyses population are presented by subject in Listing 16.2.3.1.

10.1 Disposition of Subjects

Disposition data are presented by subject in Listing 16.2.1. Child-Pugh score at screening is presented by subject in Listing 16.2.4.2.

A total of 854 subjects were assessed for eligibility and 635 unique subjects were randomly assigned to 1 of 2 treatment groups, with 1 subject being randomized twice in error (Table 10-1). The most common reasons for discontinuing treatment were disease progression (77.1%) and AE (9.5%). The percentage of subjects who were followed in the follow-up visits was 85.4% in the ADI-PEG 20 treatment group and 84.8% in the placebo group.

Table 10-1 Disposition (Intent-to-Treat Population)

Number of Subjects	ADI-PEG 20 N = 424 N (%)	Placebo N = 211 N (%)	Total N = 635 N (%)
Included in the Intent-to-Treat Population[a]	424 (100.0)	211 (100.0)	635 (100.0)
Included in the Safety Population[b]	421 (99.3)	209 (99.1)	630 (99.2)
Discontinued treatment	416 (98.1)	204 (96.7)	620 (97.6)
Primary reason[c]			
Adverse event	42 (10.1)	17 (8.3)	59 (9.5)
Death	13 (3.1)	8 (3.9)	21 (3.4)
Disease progression	322 (77.4)	156 (76.5)	478 (77.1)
Withdrew consent	28 (6.7)	16 (7.8)	44 (7.1)
Other	11 (2.6)	7 (3.4)	18 (2.9)
Followed in the Follow-up Visits	362 (85.4)	179 (84.8)	541 (85.2)
Terminated from the protocol	357 (84.2)	181 (85.8)	538 (84.7)
Primary reason[d]			
Death	338 (94.7)	174 (96.1)	512 (95.2)
Lost to follow-up	7 (2.0)	2 (1.1)	9 (1.7)
Voluntary withdrawal	9 (2.5)	2 (1.1)	11 (2.0)
Other	3 (0.8)	3 (1.7)	6 (1.1)

Abbreviation: ADI-PEG 20, arginine deiminase-polyethylene glycol of 20,000 molecular weight.

Note: Unless otherwise noted, the denominator for percentages is the total number of subjects (N) in each treatment arm overall.

[a] The Intent-to-Treat Population was defined as all subjects who were randomly assigned to treatment, either with ADI-PEG 20 or to placebo.

[b] The Safety Population was defined as all subjects who were randomly assigned and received at least 1, or any portion of a dose of study medication.

[c] Denominators for percentages are the total number of subjects who discontinued treatment.

[d] Denominators for percentages are the total number of subjects who terminated from the protocol.

Source: Table 14.1.1.

10.2 Protocol Deviation/Violations

All protocol deviations were captured in Listing 16.2.2.1. Important (ie, major) deviations were grouped into the following categories and summarized by treatment group and overall for the ITT Population in Table 14.1.2.1:

i. Study Treatment Administration/Dispensing
ii. Concomitant Medications
iii. Inclusion Criteria
iv. Exclusion Criteria

v. Informed Consent
vi. Study Treatment Randomization
vii. Study Treatment Unblinding
viii. Withdrawal/Termination Criteria
ix. Other Protocol Deviations

The percentage of subjects who had at least one major protocol deviation was 7.08% in the ADI-PEG 20 treatment group and 9.95% in the placebo group. The most common major deviations were inclusion/exclusion issues, and deviations related to study treatment randomization (Table 10-2).

Table 10-2 Protocol Deviations (Intent-to-Treat Population)

Number of Subjects	ADI-PEG 20 N = 424 N (%)	Placebo N = 211 N (%)	Total N = 635 N (%)
Number of major protocol deviations	34	25	59
Number of Subjects with at least one major protocol deviation	30 (7.08)	21 (9.95)	51 (8.03)
Major deviation[a]			
Study treatment administration/dispensing	1 (2.94)	1 (4.00)	2 (3.39)
Concomitant medications	4 (11.76)	2 (8.00)	6 (10.17)
Informed consent	1 (2.94)	2 (8.00)	3 (5.08)
Inclusion/Exclusion issues	17 (50.00)	14 (56.00)	31 (52.54)
Study treatment randomization	6 (17.65)	4 (16.00)	10 (16.95)
Other protocol deviations	5 (14.71)	2 (8.00)	7 (11.86)

Abbreviation: ADI-PEG 20, arginine deiminase-polyethylene glycol of 20,000 molecular weight.
Note: Unless otherwise noted, the denominator for percentages is the total number of subjects (N) in each treatment arm overall.
[a] Denominators for percentages are the number of subjects with at least one major protocol deviation.
Source: Table 14.1.2.1.

11 Efficacy Evaluation

11.1 Data Sets Analyzed

The ITT Population consisted of 635 unique (100.0%) subjects and the Safety Population consisted of 630 unique (99.2%) subjects.

11.2 Demographic and Other Baseline Characteristics

Subject demographics of the intent-to-treat population are summarized in Table 11-1.

Demographic data are summarized in Table 14.1.2.2 (ITT Population), and presented by subject in Listing 16.2.4.1.

There were 352 (83.0%) males and 72 (17.0%) females in the ADI-PEG 20 treatment group and 168 (79.6%) males and 43 (20.4%) females in the Placebo treatment group. The ADI-PEG treatment group had a mean age of 60.5 ± 12.33 years (range 18 to 85 years), and the Placebo treatment group had a mean age of 60.6 ± 13.30 years (range 21 to 89 years).

Table 11-1 Demographics (Intent-to-Treat Population)

	ADI-PEG 20 N = 424 N (%)	Placebo N = 211 N (%)	Total N = 635 N (%)
Gender			
Male	352 (83.0)	168 (79.6)	520 (81.9)
Female	72 (17.0)	43 (20.4)	115 (18.1)
Age (years)[a]			
n	424	211	635
Mean (Std Dev)	60.5 (12.33)	60.6 (13.30)	60.6 (12.65)
Median	61.0	62.0	61.0
Min, max	18, 85	21, 89	18, 89
Race			
White	145 (34.2)	80 (37.9)	225 (35.4)
Arabic/North African heritage	0	1 (0.5)	1 (0.2)
White/Caucasian/ European heritage	145 (34.2)	79 (37.4)	224 (35.3)
Black or African American	13 (3.1)	5 (2.4)	18 (2.8)
American Indian or Alaska Native	0	0	0
Asian	261 (61.6)	123 (58.3)	384 (60.5)
Mainland China	53 (12.5)	30 (14.2)	83 (13.1)
Taiwan	129 (30.4)	66 (31.3)	195 (30.7)

	ADI-PEG 20 N = 424 N (%)	Placebo N = 211 N (%)	Total N = 635 N (%)
Central/South Asian heritage	0	2 (0.9)	2 (0.3)
Southeast Asian heritage	10 (2.4)	2 (0.9)	12 (1.9)
Japanese heritage	1 (0.2)	0	1 (0.2)
East Asian heritage	2 (0.5)	2 (0.9)	4 (0.6)
North East Asian heritage	52 (12.3)	21 (10.0)	73 (11.5)
Other	11 (2.6)	0	11 (1.7)
Mixed	3 (0.7)	0	3 (0.5)
Native Hawaiian or other Pacific Islander	2 (0.5)	0	2 (0.3)
Other	3 (0.7)	3 (1.4)	6 (0.9)
Ethnicity			
Hispanic or Latino	13 (3.1)	9 (4.3)	22 (3.5)
Not Hispanic or Latino	411 (96.9)	202 (95.7)	613 (96.5)
Weight (kg)			
n	424	211	635
Mean (Std Dev)	69.40 (15.250)	67.94 (14.880)	68.91 (15.132)
Median	66.80	66.20	66.40
Min, max	40.0, 133.8	40.9, 124.6	40.0, 133.8
Height (cm)			
n	424	211	635
Mean (Std Dev)	167.82 (8.371)	166.81 (7.975)	167.48 (8.249)
Median	168.90	167.00	168.00
Min, max	144.0, 190.5	145.0, 186.0	144.0, 190.5
Body surface area (m^2)[b]			
n	423	209	632
Mean (Std Dev)	1.786 (0.2176)	1.759 (0.2019)	1.777 (0.2127)
Median	1.750	1.750	1.750
Min, max	1.32, 2.72	1.33, 2.39	1.32, 2.72

Abbreviations: ADI-PEG 20, arginine deiminase-polyethylene glycol of 20,000 molecular weight; Max, maximum; Min, minimum; Std Dev, standard deviation.

Note: Unless otherwise noted, the denominator for percentages is the total number of subjects (N) in each treatment arm or overall.

[a] Age was calculated to be the integer part of (Date of Informed Consent – Date of Birth + 1)/365.25.

[b] Body Surface Area was calculated as (Height × Weight / 3600)$^{1/2}$.

Source: Table 14.1.2.2.

Baseline characteristics of the intent-to-treat population are summarized in Table 11-2.

Tumor history of HCC is presented by subject in Listing 16.2.4.4. Prior systemic chemotherapy is presented by subject in Listing 16.2.4.5. Prior surgery and prior radiotherapy are presented by subject in Listing 16.2.4.6 and Listing 16.2.4.7, respectively. Other prior therapies are presented by subject in Listing 16.2.4.8, and the first line agent that qualified the subject for the study is presented in Listing 16.2.4.5.1.

Sorafenib treatment status was similar in both treatment groups. Sorafenib failure occurred in 549 (86.5%) subjects overall, while non-sorafenib failure occurred in 86 (13.5%) subjects overall. Serum AFP at baseline was similar in both treatment groups. Baseline serum AFP level ≥200 µg/L occurred in 353 (55.6%) subjects overall, while serum AFP <200 µg/L occurred in 277 (43.6%) subjects overall.

Table 11-2 Baseline Characteristics (Intent-to-Treat Population)

	ADI-PEG 20 N = 424 N (%)	**Placebo N = 211 N (%)**	**Total N = 635 N (%)**
Geographic Region[a]			
Asia	226 (53.3)	112 (53.1)	338 (53.2)
North America and Europe	198 (46.7)	99 (46.9)	297 (46.8)
Sorafenib treatment status[b]			
Sorafenib failure	367 (86.6)	182 (86.3)	549 (86.5)
Progressed	299 (70.5)	146 (69.2)	445 (70.1)
Intolerance	68 (16.0)	36 (17.1)	104 (16.4)
Non-sorafenib failure	57 (13.4)	29 (13.7)	86 (13.5)
Progressed	45 (10.6)	26 (12.3)	71 (11.2)
Intolerance	12 (2.8)	3 (1.4)	15 (2.4)
Name of other qualifying agent			
Angiogenesis inhibitor	17 (4.0)	9 (4.3)	26 (4.1)
Fluorouracil-platinum regimen	21 (5.0)	10 (4.7)	31 (4.9)
Other	13 (5.4)	7 (3.3)	20 (3.1)

	ADI-PEG 20 N = 424 N (%)	Placebo N = 211 N (%)	Total N = 635 N (%)
Geographic region by sorafenib treatment status[b]			
Asia – sorafenib failure	175 (41.3)	87 (41.2)	262 (41.3)
Asia – non-sorafenib failure	51 (12.0)	25 (11.8)	76 (12.0)
North America and Europe – sorafenib failure	192 (45.3)	95 (45.0)	287 (45.2)
North America and Europe – non-sorafenib failure	6 (1.4)	4 (1.9)	10 (1.6)
ECOG Performance Status			
0: Normal activity, asymptomatic	188 (44.3)	97 (46.0)	285 (44.9)
1: Symptomatic, fully ambulatory	226 (53.3)	110 (52.1)	336 (52.9)
2: Symptomatic, in bed <50% of time	10 (2.4)	4 (1.9)	14 (2.2)
Child-Pugh classification			
Grade			
4 points	0	1 (0.5)	1 (0.2)
A: 5-6 points	387 (91.3)	188 (89.1)	575 (90.6)
B: 7 points	37 (8.7)	22 (10.4)	59 (9.3)
Subscores			
Bilirubin (mg/dL)			
1: <2	414 (97.6)	203 (96.2)	617 (97.2)
2: 2-3	10 (2.4)	8 (3.8)	18 (2.8)
Albumin (g/dL)			
1: >3.5	285 (67.2)	134 (63.5)	419 (66.0)
2: 2.8-3.5	138 (32.5)	77 (36.5)	215 (33.9)
3: <2.8	1 (0.2)	0	1 (0.2)
INR (or prothrombin time)[c]			
1: <1.7 (or <4 seconds)	424 (100.0)	209 (99.1)	633 (99.7)
2: 1.7-2.3 (or 4-6 seconds)	0	1 (0.5)	1 (0.2)
Missing	0	1 (0.5)	1 (0.2)
Hepatic encephalopathy			
1: Absent	424 (100.0)	210 (99.5)	634 (99.8)
2: Mild (grade 1-2)	0	1 (0.5)	1 (0.2)

	ADI-PEG 20 N = 424 N (%)	Placebo N = 211 N (%)	Total N = 635 N (%)
Ascites			
1: Absent	357 (84.2)	167 (79.1)	524 (82.5)
2: Mild	67 (15.8)	44 (20.9)	111 (17.5)
Tumor History			
Time since first diagnosis (years)[d]			
n	420	210	630
Mean (Std Dev)	2.7 (2.69)	2.9 (2.58)	2.7 (2.66)
Median	1.8	2.2	1.9
Min, max	0, 18	0, 16	0, 18
Etiology of HCC			
HBV	226 (53.3)	106 (50.2)	332 (52.3)
HCV	112 (26.4)	55 (26.1)	167 (26.3)
Alcohol	51 (12.0)	32 (15.2)	83 (13.1)
NASH	24 (5.7)	12 (5.7)	36 (5.7)
Other	57 (13.4)	29 (13.7)	86 (13.5)
Tumor stage at study entry			
I	2 (0.5)	0	2 (0.3)
II	21 (5.0)	16 (7.6)	37 (5.8)
IIIA	42 (9.9)	24 (11.4)	66 (10.4)
IIIB	16 (3.8)	6 (2.8)	22 (3.5)
IIIC	12 (2.8)	13 (6.2)	25 (3.9)
IV	331 (78.1)	152 (72.0)	483 (76.1)
Vascular invasion			
Absent	298 (70.3)	146 (69.2)	444 (69.9)
Present	126 (29.7)	65 (30.8)	191 (30.1)
Major branch of portal or hepatic vein	114 (90.5)	45 (69.2)	159 (83.2)
Other vasculature	12 (9.5)	20 (30.8)	32 (16.8)
Portal vein thrombosis			
Absent	296 (69.8)	149 (70.6)	445 (70.1)
Present	128 (30.2)	62 (29.4)	190 (29.9)
Extrahepatic spread			
Absent	105 (24.8)	58 (27.5)	163 (25.7)
Present	319 (75.2)	153 (72.5)	472 (74.3)
Lung	108 (33.9)	42 (27.5	150 (2331.8)
Lymph node	49 (15.4)	21 (13.7)	70 (14.8)
Bone	18 (5.6)	10 (6.5)	28 (5.9)
Other	144 (45.1)	80 (52.3)	224 (47.5)

	ADI-PEG 20 N = 424 N (%)	Placebo N = 211 N (%)	Total N = 635 N (%)
Alpha Fetoprotein (µg/L)[e]			
≥200	233 (55.0)	120 (56.9)	353 (55.6)
<200	187 (44.1)	90 (42.7)	277 (43.6)
Missing[d]	4 (0.9)	1 (0.5)	5 (0.8)
Prior therapy/radiotherapy			
Radiotherapy	106 (25.0)	52 (24.6)	158 (24.9)
Surgery related to actual cancer	240 (56.6)	111 (52.6)	351 (55.3)
Transcatheter arterial chemoembolization	243 (57.3)	116 (55.0)	359 (56.5)
Radiofrequency ablation	95 (22.4)	46 (21.8)	141 (22.2)
Percutaneous ethanol	30 (7.1)	17 (8.1)	47 (7.4)
Other therapy	98 (23.1)	39 (18.5)	137 (21.6)
Antiviral therapy use			
Yes	154 (36.3)	77 (36.5)	231 (36.4)
No	270 (63.7)	134 (63.5)	404 (63.6)

Abbreviations: ADI-PEG 20, arginine deiminase-polyethylene glycol of 20,000 molecular weight; AFP, alpha-fetoprotein; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; INR, international normalized ratio; IWRS, Interactive Web Response System; Max, maximum; Min, minimum; NASH, nonalcoholic steatohepatitis; Std Dev, standard deviation.

Note: Unless otherwise noted, the denominator for percentages is the total number of subjects (N) in each treatment arm or overall.

[a] Geographic Region per IWRS and Geographic Region per eCRF were hard-coded based on site location and are therefore identical.

[b] Sorafenib Treatment Status per eCRF are derived from Sorafenib Treatment Status per IWRS and are therefore identical. Ten subjects, 101-0018, 110-0003, 121-0004, 205-0017, 257-0013, 302-0002, 305-0019, 207-0013, 305-0001, and 305-0024 were stratified incorrectly to the non-sorafenib failure group.

[c] No subscore for INR (or prothrombin time) was assigned for subject 108-0003 at baseline.

[d] Time since first diagnosis was calculated as the integer part of (Date of Informed Consent – Date of Initial Diagnosis + 1)/365.25.

[e] Subjects 101-0036, 205-0003, 405-0002, 405-0010, and 510-0002 did not have baseline AFP data.

Source: Table 14.1.2.2.

11.2.1 Prior Medications

Medications used by subjects prior to entering the study are summarized in Table 14.1.3 and provided in Listing 16.2.4.9 by subject.

Concomitant medications are summarized in Table 14.1.4 and presented by subject in Listing 16.2.4.9. New diagnostic or therapeutic procedures are presented by subject in Listing 16.2.4.10. Concomitant medications used by at least 10% of subjects included furosemide (34.0%), paracetamol (31.0%), metoclopramide (22.5%), spironolactone

(21.0%), entecavir (22.0%), omeprazole (16.0%), lorazepam (13.0%), silybum marianum (13.0%), morphine (12.0%), lactulose (12.0% [under the Bile and Liver Therapy class]), amlodipine (12.0%), ursodeoxycholic acid (12%), dexamethasone (11.0%), lansoprazole (11.0%), ultracet (11.0%), lactulose (10.0% [under the Drugs for Constipation class]), and magnesium oxide (10.0% [under the Drugs for Constipation class])).

11.3 Measurements of Treatment Compliance

Study medication details are presented by subject in Listing 16.2.5.1.

11.4 Efficacy Results and Tabulations of Individual Subject Data

11.4.1 Analysis of Efficacy

Tables and figures for the efficacy data are located in Section 14.2.

Relevant data listings are located in Section 16.2.

The ITT Population was used for the analysis of the efficacy data.

11.4.1.1 Primary Efficacy

The primary efficacy variable was OS (time from randomization until death from any cause). Overall survival data are presented by subject in Listing 16.2.6.1a (primary) and Listing 16.2.6.1b (sensitivity analysis). The proportion of subjects in each treatment group who died is summarized in Table 14.2.1.1a (primary) and Table 14.2.1.1b (sensitivity analysis), and illustrated in Figure 14.2.1.1a (primary) and Figure 14.2.1.1b (sensitivity analysis).

For the primary analysis, a total of 487 subjects had died as of the cut-off date (24Mar2015). For the ITT Population (635 subjects), median OS was estimated at 7.8 months (range 0.37 to 41.8+ months) for the ADI-PEG 20 treatment group and 7.4 months (range 0.67 to 47.73+ months) for the Placebo treatment group, which did not reach statistical significance ($P = 0.884$) (Table 11-3 and Figure 11-1).

For the sensitivity analysis, a total of 525 subjects had died as of the date of last study contact. For the ITT Population (635 subjects), median OS was estimated at 7.3 months (range 0.37 to 41.8+ months) for the ADI-PEG 20 treatment group and 7.2 months (range 0.67 to 47.73+ months) for the Placebo treatment group, which did not reach statistical significance ($P = 0.775$) (Table 11-4 and Figure 11-2).

Table 11-3 Duration of Overall Survival (Intent-to-Treat Population)

	ADI-PEG 20 N = 424	Placebo N = 211	Total N = 635
Number (%) of subjects			
Censored	102 (24.1)	45 (21.8)	148 (23.3)
Died	322 (75.9)	165 (78.2)	487 (76.7)
Duration of overall survival (months)[a]			
N	424	211	635
25th Percentile	3.6	4.03	3.73
Median (95% CI)	7.8 (6.77, 8.57)	7.4 (6.37, 9.03)	7.5 (6.87, 8.3)
75th Percentile	14.93	14.93	14.93
Min, max	0.37, 41.8+	0.67, 47.73+	0.37, 47.73+
Chi^2-value[b]			0.02
P value[b]			0.884

Abbreviations: ADI-PEG 20, arginine deiminase-polyethylene glycol of 20,000 molecular weight; CI, confidence interval; Max, maximum; Min, minimum.

Note: Unless otherwise noted, the denominator for percentages is the total number of subjects (N) in each treatment arm overall. Percentiles and confidence intervals were calculated using Kaplan-Meier methods. Censored observations were indicated by "+". The primary analysis includes deaths that occurred before the date of the 487th event.

[a] Duration of Overall Survival was defined as (Date of Death [due to any cause]) – Date of Randomization + 1)/30. For subjects who were alive at the time of data cut-off (24Mar2015), duration of overall survival was censored at the date of last contact or the date of death.

[b] The Chi^2-value and *P* value were obtained using a 2-sided Log-Rank Test stratified by region and sorafenib treatment status. Overall Survival was assessed at the $\alpha = 0.05$ level.

Source: Table 14.2.1.1a.

Table 11-4 Duration of Overall Survival – Sensitivity Analysis (Intent-to-Treat Population)

	ADI-PEG 20 N = 424	Placebo N = 211	Total N = 635
Number (%) of subjects			
Censored	77 (18.2)	33 (15.6)	110 (17.3)
Died	347 (81.8)	178 (84.4)	525 (82.7)
Duration of overall survival (months)[a]			
N	424	211	635
25th Percentile	3.53	3.97	3.6
Median (95% CI)	7.3 (6.33, 8.13)	7.2 (6.33, 8.57)	7.2 (6.53, 8)
75th Percentile	13.47	14.17	13.77
Min, max	0.37, 41.8+	0.67, 47.73+	0.37, 47.73+
Chi^2-value[b]			0.08
P value[b]			0.775

Abbreviations: ADI-PEG 20, arginine deiminase-polyethylene glycol of 20,000 molecular weight; CI, confidence interval; Max, maximum; Min, minimum.

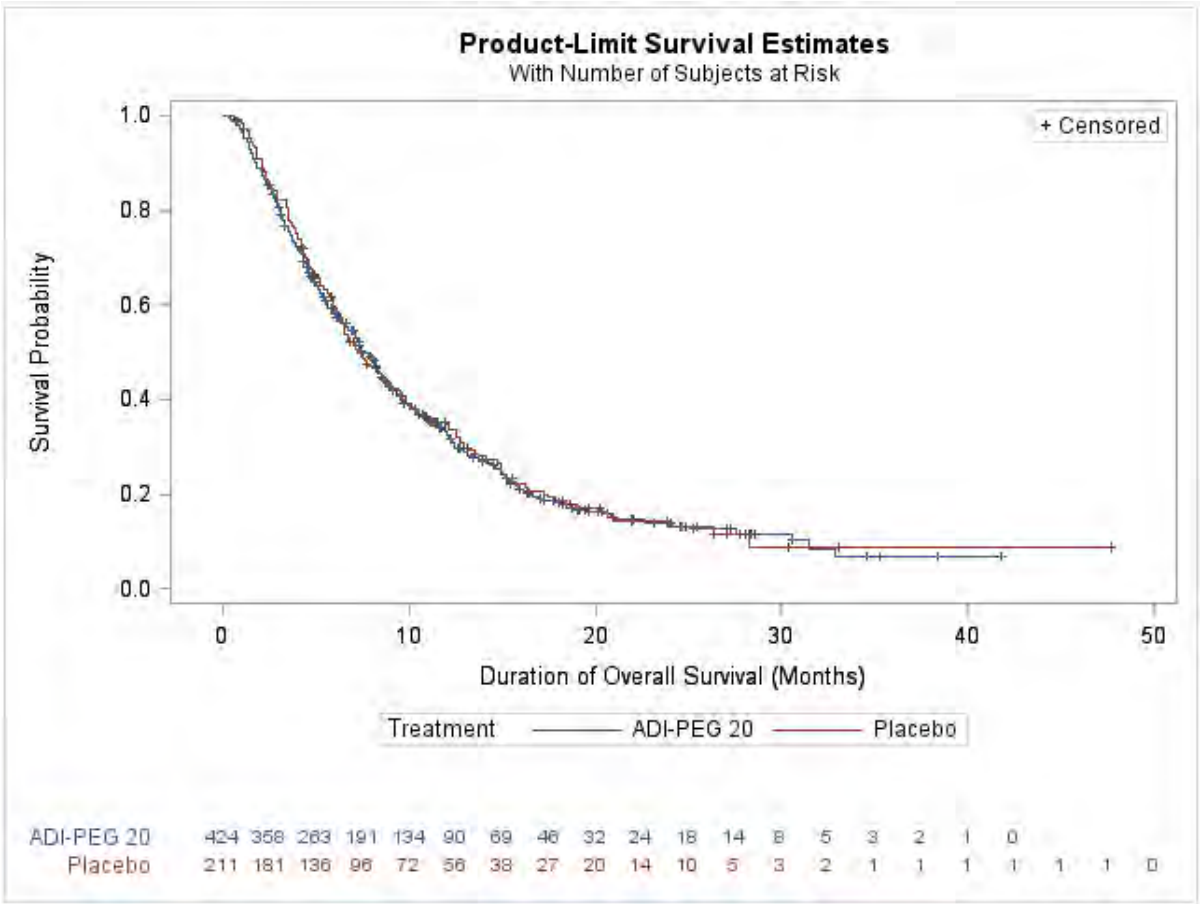
Note: Unless otherwise noted, the denominator for percentages is the total number of subjects (N) in each treatment arm overall. Percentiles and confidence intervals were calculated using Kaplan-Meier methods. Censored observations were indicated by "+". The sensitivity analysis includes all deaths.

[a] Duration of Overall Survival was defined as (Date of Death [due to any cause]) – Date of Randomization + 1)/30. For subjects who were alive at the time of data cut-off (22Jul2015), duration of overall survival was censored at the date of last contact.

[b] The Chi^2-value and *P* value were obtained using a 2-sided Log-Rank Test stratified by region and sorafenib treatment status. Overall Survival was assessed at the $\alpha = 0.05$ level.

Source: Table 14.2.1.1b.

Figure 11-1 Kaplan-Meier Plot of Duration of Overall Survival (Intent-to-Treat Population)

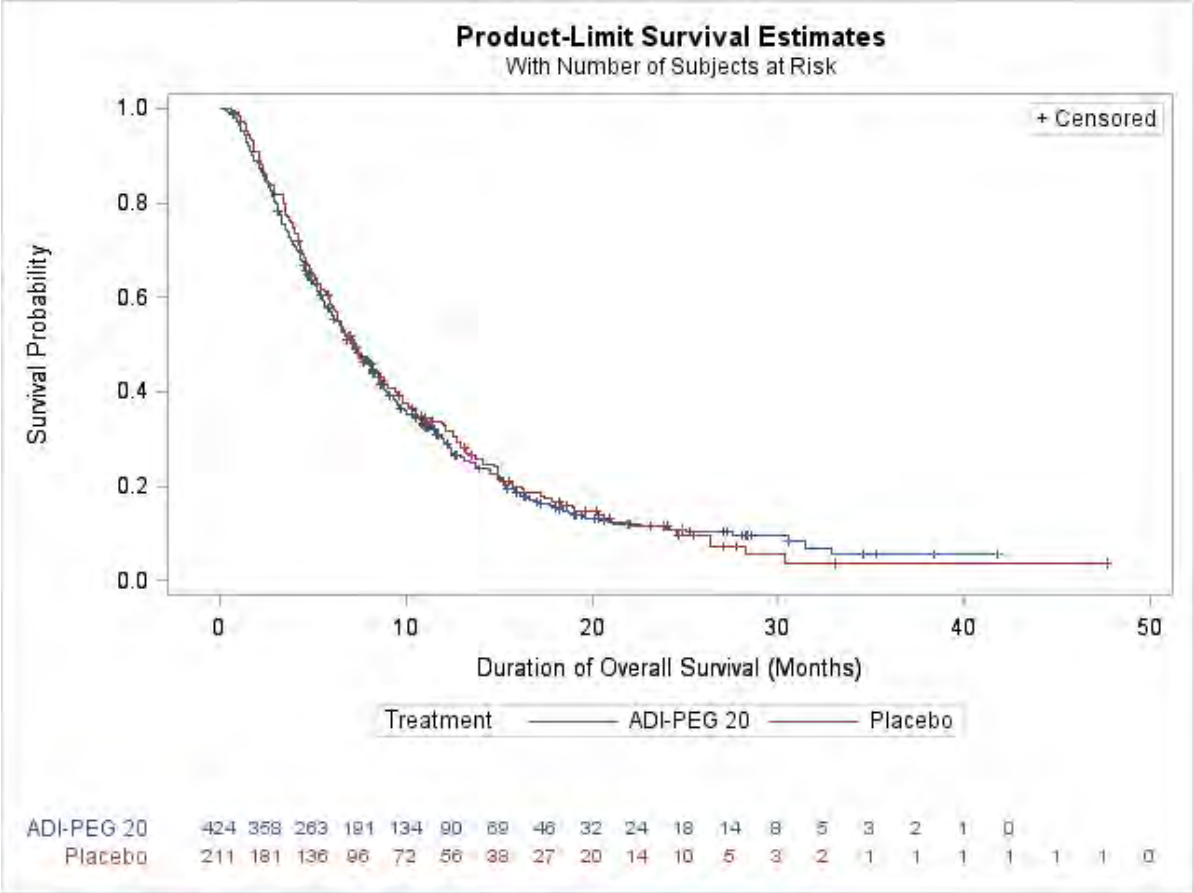


Abbreviation: ADI-PEG 20, arginine deiminase-polyethylene glycol of 20,000 molecular weight.

Note: Duration of Overall Survival was defined as (Date of Death [due to any cause]) or Disease Progression – Date of Randomization + 1)/30. The primary analysis includes deaths that occurred before the date of the 487th event. For subjects who were alive at the time of data cut-off (24Mar2015), duration of overall survival was censored at the date of last contact or the date of death.

Source: Figure 14.2.1.1a.

Figure 11-2 **Kaplan-Meier Plot of Duration of Overall Survival – Sensitivity Analysis (Intent-to-Treat Population)**



Abbreviation: ADI-PEG 20, arginine deiminase-polyethylene glycol of 20,000 molecular weight.

Note: Duration of Overall Survival was defined as (Date of Death [due to any cause]) or Disease Progression – Date of Randomization + 1)/30. For subjects who were event-free at the time of data cut-off (22Jul2015), duration of progression-free survival was censored at the date of last tumor assessment.

Source: Figure 14.2.1.1b.

11.4.1.2 Secondary Efficacy

The secondary efficacy variables data are presented as follows:

- PFS (Table 14.2.2.1, Listing 16.2.6.3, Figure 14.2.2.2)
- Objective response rate and best overall objective response rate (Listing 16.2.6.4)Tumor response at each visit and best overall tumor response (Table 14.2.2.4, Listing 16.2.6.5)
- TTP (Table 14.2.2.5, Figure 14.2.2.6, Listing 16.2.6.6)
- Disease control rate at each visit and best overall disease control rate (Table 14.2.2.7)
- Change in Alpha-fetoprotein (AFP) (Table 14.2.2.9 [by category], Listing 16.2.6.7)

11.4.1.2.1 Progression-Free Survival

Tumor assessment summary data are presented by subject in Listing 16.2.6.2.

The proportion of subjects in each treatment group who progressed, the duration of PFS, and the corresponding statistics are summarized in Table 11-5 and presented graphically in Figure 11-3. The median duration of PFS was 2.6 months (range 0+ to 33.37+ months) for ADI-PEG 20 treatment group and 2.6 months (range 0+ to 24.57+ months) for the Placebo treatment group, which did not reach statistical significance ($P = 0.075$).

Table 11-5 Duration of Progression-Free Survival (Intent-to-Treat Population)

	ADI-PEG 20 N = 424	Placebo N = 211	Total N = 635
Number (%) of subjects			
Censored	125 (29.5)	63 (29.9)	188 (29.6)
Progressed	287 (67.7)	141 (66.8)	428 (67.4)
Died	12 (2.8)	7 (3.3)	19 (3.0)
Duration of progression-free survival (months)[a]			
N	424	211	635
25th Percentile	2.37	2.37	2.37
Median (95% CI)	2.6 (2.6, 2.63)	2.6 (2.6, 2.7)	2.6 (2.6, 2.63)
75th Percentile	5.17	5.43	5.33
Min, max	0+, 33.37+	0+, 24.57+	0+, 33.37+
Chi^2-value[b]			3.17
P value[b]			0.075

Abbreviations: ADI-PEG 20, arginine deiminase-polyethylene glycol of 20,000 molecular weight; CI, confidence interval; Max, maximum; Min, minimum.

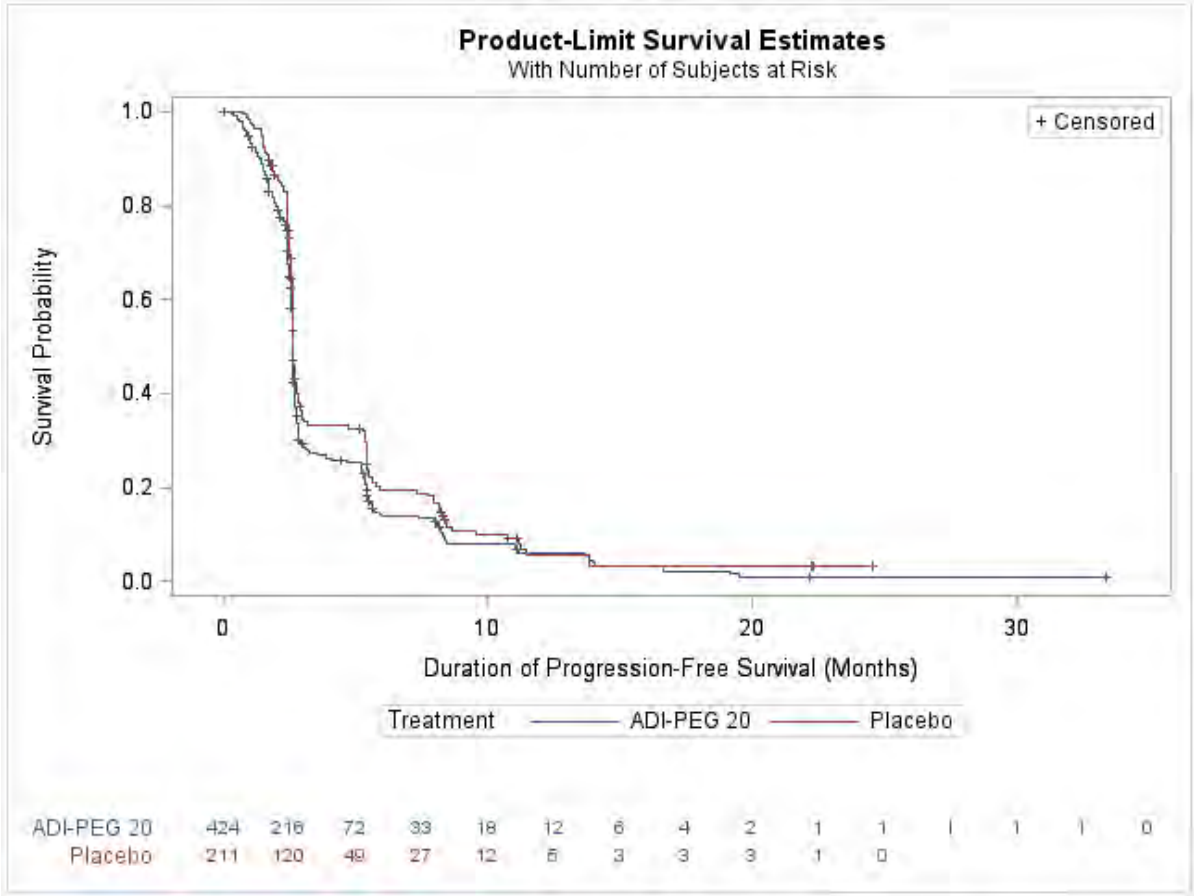
Note: Unless otherwise noted, the denominator for percentages is the total number of subjects (N) in each treatment arm overall. Percentiles and confidence intervals were calculated using Kaplan-Meier methods. Censored observations were indicated by "+".

[a] Duration of Progression-Free Survival was defined as (Date of Death [due to any cause]) or Disease Progression Date of Randomization + 1)/30. For subjects who were event-free at the time of data cut-off, duration of progression-free survival was censored at the date of last tumor assessment.

[b] The Chi^2-value and *P* value were obtained using a 2-sided Log-Rank Test stratified by region and sorafenib treatment status. Progression-Free Survival was assessed at the $\alpha = 0.05$ level.

Source: Table 14.2.2.1.

Figure 11-3 Kaplan-Meier Plot of Duration of Progression-Free Survival (Intent-to-Treat Population)



Abbreviation: ADI-PEG 20, arginine deiminase-polyethylene glycol of 20,000 molecular weight.

Note: Duration of Progression-Free Survival was defined as (Date of Death [due to any cause]) or Disease Progression – Date of Randomization + 1)/30. For subjects who were event-free at the time of data cut-off, duration of progression-free survival was censored at the date of last tumor assessment.

Source: Figure 14.2.2.2.

11.4.1.2.1.1 Tumor Response at Each Visit and Best Overall Tumor Response

The tumor response is summarized for selected time points and the BOTR in Table 11-6. The tumor response rate did not reach statistical significance between the ADI-PEG 20 treatment group and the Placebo treatment group at 12 weeks, 24 weeks, 36 weeks, 48 weeks, or 60 weeks (P = 0.273, 0.693, 0.800, 0.278, 0.655, respectively) or for BOTR (P = 0.273). Note that the tumor response was evaluated incorrectly as PR for subject 208-0001 (ADI-PEG 20 treatment group) at the week 24 visit. The site confirmed that the response should be SD after database lock. The BOTR for this subject should also be SD. Also, the response was not evaluated for subject 209-0013 (ADI-PEG 20 treatment group)

at the Week 24 and Week 36 visits even though the scan results were available. The site confirmed that the response at both Week 24 and Week 36 was PD after database lock. No hardcoding was implemented to change the data.

Table 11-6 Tumor Response and Best Overall Tumor Response (Intent-to-Treat Population)

	ADI-PEG 20 N = 424 N (%)	Placebo N = 211 N (%)	Total N = 635 N (%)	*P* Value[a]
Tumor response at:				
Week 12				
Complete Response	0	0	0	0.273
Partial Response	2 (0.5)	2 (0.9)	4 (0.6)	
Stable Disease	91 (21.5)	56 (26.5)	147 (23.1)	
Progressive Disease	160 (37.7)	83 (39.3)	243 (38.3)	
Unable to Evaluate	1 (0.2)	0	1 (0.2)	
Week 24				
Complete Response	0	0	0	0.693
Partial Response	3 (0.7)	4 (1.9)	7 (1.1)	
Stable Disease	38 (9.0)	25 (11.8)	63 (9.9)	
Progressive Disease	32 (7.5)	20 (9.5)	52 (8.2)	
Unable to Evaluate	0	0	0	
Week 36				
Complete Response	0	0	0	0.800
Partial Response	1 (0.2)	3 (1.4)	4 (0.6)	
Stable Disease	17 (4.0)	12 (5.7)	29 (4.6)	
Progressive Disease	13 (3.1)	13 (6.2)	26 (4.1)	
Unable to Evaluate	0	0	0	
Week 48				
Complete Response	0	0	0	0.278
Partial Response	1 (0.2)	0	1 (0.2)	
Stable Disease	10 (2.4)	6 (2.8)	16 (2.5)	
Progressive Disease	5 (1.2)	6 (2.8)	11 (1.7)	
Unable to Evaluate	0	0	0	
Week 60				
Complete Response	0	0	0	0.655
Partial Response	1 (0.2)	0	1 (0.2)	
Stable Disease	5 (1.2)	3 (1.4)	8 (1.3)	
Progressive Disease	4 (0.9)	1 (0.5)	5 (0.8)	
Unable to Evaluate	0	0	0	

BOTR:				
Complete Response	0	0	0	0.273
Partial Response	3 (0.7)	6 (2.8)	9 (1.4)	
Stable Disease	102 (24.1)	60 (28.4)	162 (25.5)	
Progressive Disease	227 (53.5)	100 (47.4)	327 (51.5)	
Unable to Evaluate	0	0	0	
Missing	92 (21.7)	45 (21.3)	137 (21.6)	

Abbreviation: ADI-PEG 20, arginine deiminase-polyethylene glycol of 20,000 molecular weight; BOTR, best overall tumor response.

Note: Unless otherwise noted, the denominator for percentages is the total number of subjects (N) in each treatment arm overall. Tumor response was assessed per Response Evaluation Criteria In Solid Tumors (RECIST) 1.1. A best overall tumor response (BOTR) variable was also calculated using the tumor response values from all radiology testing visits. If tumor response was missing for all radiology testing visits then the BOTR was missing.

[a] For each timepoint and BOTR, *P* values were obtained using a Cochran-Mantel-Haenszel general association test stratified by region and sorafenib treatment status.

Source: Table 14.2.2.4.

11.4.1.2.2 Time to Tumor Progression

The number of subjects who progressed and the time to tumor progression are summarized in Table 11-7. The median (95% CI) time to tumor progression was 2.6 months (2.6, 2.63) in the ADI-PEG 20 treatment group and 2.6 months (2.6, 2.77) in the Placebo treatment group.

Table 11-7 Time to Tumor Progression (Intent-to-Treat Population)

	ADI-PEG 20 N = 424	Placebo N = 211	Total N = 635
Number (%) of subjects			
Censored	135 (31.8)	70 (33.2)	205 (32.3)
Progressed	289 (68.2)	141 (66.8)	430 (67.7)
Time to tumor progression (months)[a]			
N	424	211	635
25th Percentile	2.37	2.5	2.37
Median (95% CI)	2.6 (2.6, 2.63)	2.6 (2.6, 2.77)	2.6 (2.6, 2.63)
75th Percentile	5.17	5.43	5.37
Min, max	0+, 33.37+	0+, 24.57+	0+, 33.37+
Chi^2-value[b]			3.38
P value[b]			0.066

Abbreviations: ADI-PEG 20, arginine deiminase-polyethylene glycol of 20,000 molecular weight; CI, confidence interval; Max, maximum; Min, minimum.

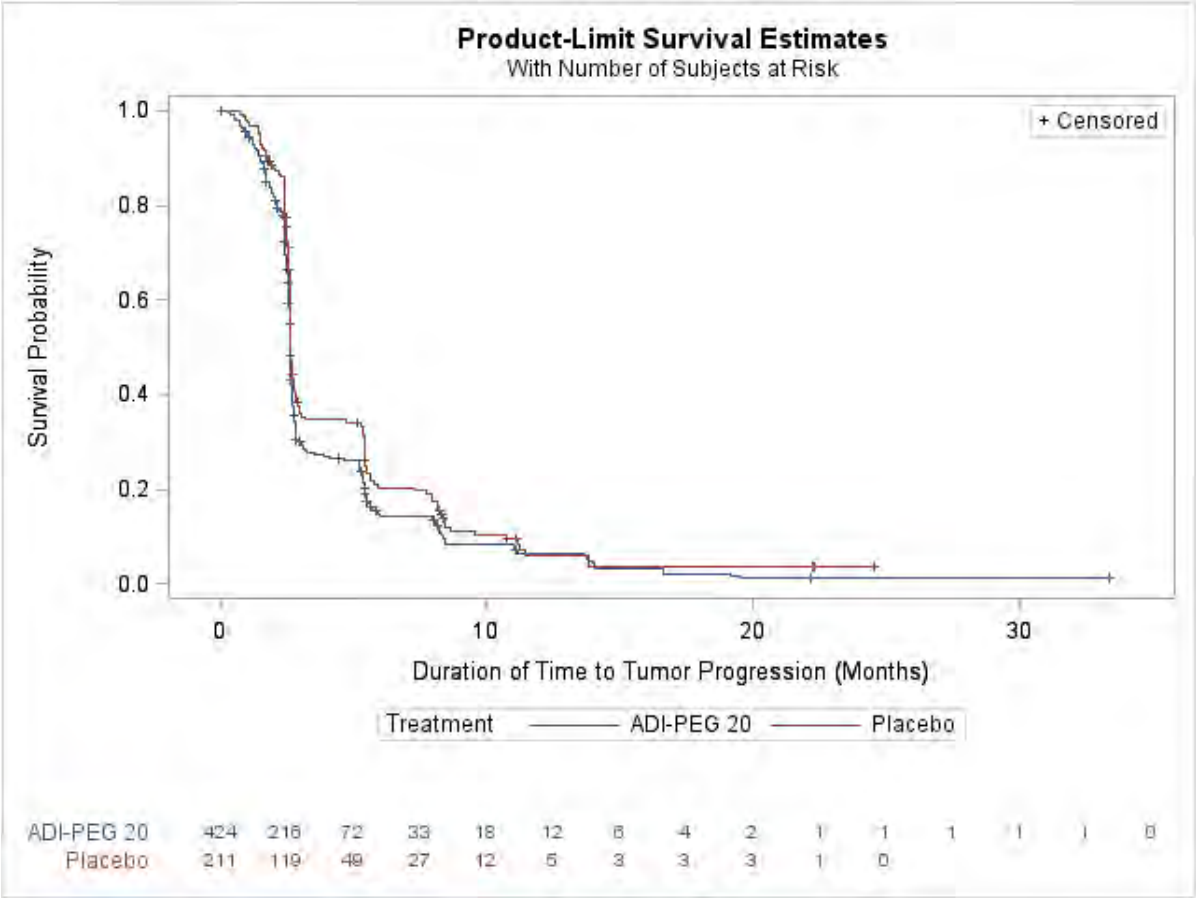
Note: Unless otherwise noted, the denominator for percentages is the total number of subjects (N) in each treatment arm overall. Percentiles and confidence intervals were calculated using Kaplan-Meier methods. Censored observations were indicated by "+".

[a] Time to tumor progression was defined as (Date of Disease Progression – Date of Randomization + 1)/30. For subjects without disease progression at the time of data cut-off, time to tumor progression was censored at the date of last tumor assessment.

[b] The Chi^2-value and *P* value were obtained using a 2-sided Log-Rank Test stratified by region and sorafenib treatment status.

Source: Table 14.2.2.5.

Figure 11-4 **Kaplan-Meier Plot of Time to Tumor Progression (Intent-to-Treat Population)**



Abbreviation: ADI-PEG 20, arginine deiminase-polyethylene glycol of 20,000 molecular weight.

Note: Time to tumor progression was defined as (Date of Disease Progression – Date of Randomization + 1)/30. For subjects without disease progression at the time of data cut-off, time to tumor progression was censored at the date of last tumor assessment.

Source: Figure 14.2.2.6.

11.4.1.2.3 Disease Control Rate at Each Visit and Best Overall Disease Control Rate

The disease control rate at selected time points and BODC are summarized in Table 11-8. The BODC (disease control = Yes) was observed for 105 (24.8%) subjects in the ADI-PEG 20 treatment group and 66 (31.3%) subjects in the Placebo treatment group, which was not statistically significant ($P = 0.190$).

Table 11-8 Disease Control Rate and Best Overall Disease Control Rate (Intent-to-Treat Population)

	ADI-PEG 20 N = 424	Placebo N = 211	Total N = 635	*P* Value[a]
Disease control at:				
Week 12				
Yes	93 (21.9)	58 (27.5)	151 (23.8)	0.302
No	161 (38.0)	83 (39.3)	244 (38.4)	
Week 24				
Yes	41 (9.7)	29 (13.7)	70 (11.0)	0.891
No	32 (7.5)	20 (9.5)	52 (8.2)	
Week 36				
Yes	18 (4.2)	15 (7.1)	33 (5.2)	0.877
No	13 (3.1)	13 (6.2)	26 (4.1)	
Week 48				
Yes	11 (2.6)	6 (2.8)	17 (2.7)	0.298
No	5 (1.2)	6 (2.8)	11 (1.7)	
Week 60				
Yes	6 (1.4)	3 (1.4)	9 (1.4)	0.655
No	4 (0.9)	1 (0.5)	5 (0.8)	
BODC:				
Yes	105 (24.8)	66 (31.3)	171 (26.9)	0.190
No	227 (53.5)	100 (47.4)	327 (51.5)	
Missing	92 (21.7)	45 (21.3)	137 (21.6)	

Abbreviation: ADI-PEG 20, arginine deiminase-polyethylene glycol of 20,000 molecular weight; BODC, best overall disease control.

Note: Unless otherwise noted, the denominator for percentages is the total number of subjects (N) in each treatment arm overall. Disease Control was defined as complete response, partial response, or stable disease per Response Evaluation Criteria In Solid Tumors (RECIST) 1.1. A BODC variable was also calculated using the disease control values from all radiology testing visits. If a subject had disease control (disease control = Yes) at any radiology testing visit then the BODC was Yes. If disease control = No for all radiology testing visits then the BODC was No. If disease control was missing for all radiology testing visits then the BODC was missing.

[a] For each week and overall, *P* values were obtained using a Cochran-Mantel-Haenszel general association test stratified by region and sorafenib treatment status.

Source: Table 14.2.2.7.

11.4.1.2.4 Surgical Resections

Subjects with surgical resections are summarized in Table 11-9. Surgical resections were reported for 24 (5.7%) subjects in the ADI-PEG 20 treatment group and 10 (4.7%) subjects in the Placebo treatment group.

Table 11-9 Surgical Resections (Intent-to-Treat Population)

	ADI-PEG 20 N = 424 N (%)	Placebo N = 211 N (%)	Total N = 635 N (%)
Subjects with Surgical Resection	24 (5.7)	10 (4.7)	34 (5.4)
Resection performed before last dose	9 (2.1)	6 (2.8)	15 (2.4)
Resection performed after last dose	15 (3.5)	4 (1.9)	19 (3)
Patients without Surgical Resection	400 (94.3)	200 (94.8)	600 (94.5)
Missing	0 (0.0)	1 (0.5)	1 (0.2)

Abbreviation: ADI-PEG 20, arginine deiminase-polyethylene glycol of 20,000 molecular weight.

Note: Unless otherwise noted, the denominator for percentages is the total number of subjects (N) in each treatment arm overall. Only procedures that occurred on or after the first dose of study drug were summarized.

Source: Table 14.2.2.8.

11.4.1.2.5 Change in Alpha-Fetoprotein

Serum AFP change categories are categorized as decline, stable, or rise in Table 11-10.
A decline in AFP was observed in 36 subjects (8.49%) in the ADI-PEG 20 treatment group and 18 subjects (8.53%) in the Placebo treatment group. The difference between the treatment groups was not statistically significant ($P = 0.8345$).

Table 11-10 Serum Alpha-Fetoprotein Change Categories (Intent-to-Treat Population)

	ADI-PEG 20 N = 424	Placebo N = 211	Total N = 635
Decline	36 (8.49)	18 (8.53)	54 (8.50)
Stable	150 (35.38)	80 (37.91)	230 (36.22)
Rise	234 (55.19)	112 (53.08)	346 (54.49)
Chi^2-value[a]			0.3619
P value[a]			0.8345

Abbreviation: ADI-PEG 20, arginine deiminase-polyethylene glycol of 20,000 molecular weight.

Note: Unless otherwise noted, the denominator for percentages is the total number of subjects (N) in each treatment arm overall. Serum alpha-fetoprotein change categories were calculated for each subject by deriving the best response from baseline to any postbaseline assessment. Decline = maximum percent change ≤–50%, Stable = –50% <maximum percent change <50%, and Rise = maximum percent change ≥50%. Subjects 101-0036, 205-0003, 405-0002, 405-0010, and 510-0002 did not have baseline AFP data

[a] The Chi^2-value and *P* value were obtained using a Cochran-Mantel-Haenszel mean scores test using modified relative to an identified distribution scores.

Source: Table 14.2.2.9.

11.4.1.3 Additional Efficacy Analyses (Sensitivity Analyses)

Separate stratified log-rank tests were used to compare OS across treatment groups using each of the following stratification factors (Table 14.2.3a for the primary analysis including deaths that occurred through the date of the 487th event, and Table 14.2.3b for the sensitivity analysis including all 525 deaths):

- Geographical region (Asia vs NA and Europe) (primary: $P = 0.813$; sensitivity: $P = 0.796$)
- Sorafenib treatment status (non-sorafenib failure and sorafenib failure) (primary: $P = 0.914$; sensitivity: $P = 0.884$)
- ECOG performance status at screening (0 vs 1 and 2) (primary: $P = 0.823$; sensitivity: $P = 0.830$)
- Presence or absence of macroscopic vascular invasion (portal vein or branches) (primary: $P = 0.622$; sensitivity: $P = 0.570$)
- Presence or absence of extrahepatic spread (primary: $P = 0.840$; sensitivity: $P = 0.814$)
- Etiology of HCC (hepatitis C, hepatitis B, alcohol, NASH, and other) (primary: $P = 0.904$; sensitivity: $P = 0.809$)
- Antiviral therapy use (yes or no) (primary: $P = 0.759$; sensitivity: $P = 0.772$)

Note that ten subjects, 101-0018, 110-0003, 121-0004, 205-0017, 257-0013, 302-0002, 305-0019, 207-0013, 305-0001, and 305-0024 were stratified incorrectly to the non-sorafenib failure group.

None of the *P* values for these sensitivity analyses reached statistical significance.

Separate log-rank tests (stratified by the 4 levels of the region – sorafenib treatment status variable) were used to compare OS across treatment groups within each level of the following subgroups:

- Region – sorafenib treatment status (Asia – non-sorafenib failure, Asia – sorafenib failure, NA and Europe – non-sorafenib failure, and NA and Europe – sorafenib failure) (Table 14.2.4.1) (*P* = 0.110, *P* = 0.072, *P* = 0.588, and *P* = 0.622, respectively)
- Geographical region (Asia vs NA and Europe; Table 14.2.4.2) (*P* = 0.361 and *P* = 0.557, respectively)
- Sorafenib treatment status (non-sorafenib failure and sorafenib failure; Table 14.2.4.3) (*P* = 0.092 and *P* = 0.350, respectively)
- ECOG performance status at screening (0 vs 1 and 2; Table 14.2.4.4) (*P* = 0.166 and *P* = 0.573, respectively)
- Presence versus absence of macroscopic vascular invasion (portal vein or branches; Table 14.2.4.5) (*P* = 0.087 and *P* = 0.538, respectively)
- Presence versus absence of extrahepatic spread (Table 14.2.4.6) (*P* = 0.520 and *P* = 0.759, respectively)
- Etiology of HCC (hepatitis C, hepatitis B, alcohol, NASH, and other; Table 14.2.4.7) (*P* = 0.206, *P* = 0.824, *P* = 0.166, *P* = 0.464, and *P* = 0.819, respectively)
- Antiviral therapy use (yes or no; Table 14.2.4.8) (*P* = 0.494 and *P* = 0.929, respectively)

None of the *P* values for these sensitivity analyses reached statistical significance.

11.4.2 Pharmacodynamic Results

Figure 11-5 and Figure 11-6 show the mean blood levels of Arginine and Citrulline by visit week, respectively. Blood samples for each visit week were collected 7 days post dosing.

Pharmacodynamic results are presented by subject in Listing 16.2.6.9. Tables for pharmacodynamic analysis are located in Section 14.2.

Figure 11-5 **Mean Blood Arginine Levels for Subjects Receiving ADI-PEG 20 by Visit Week (Intent-to-Treat Population)**

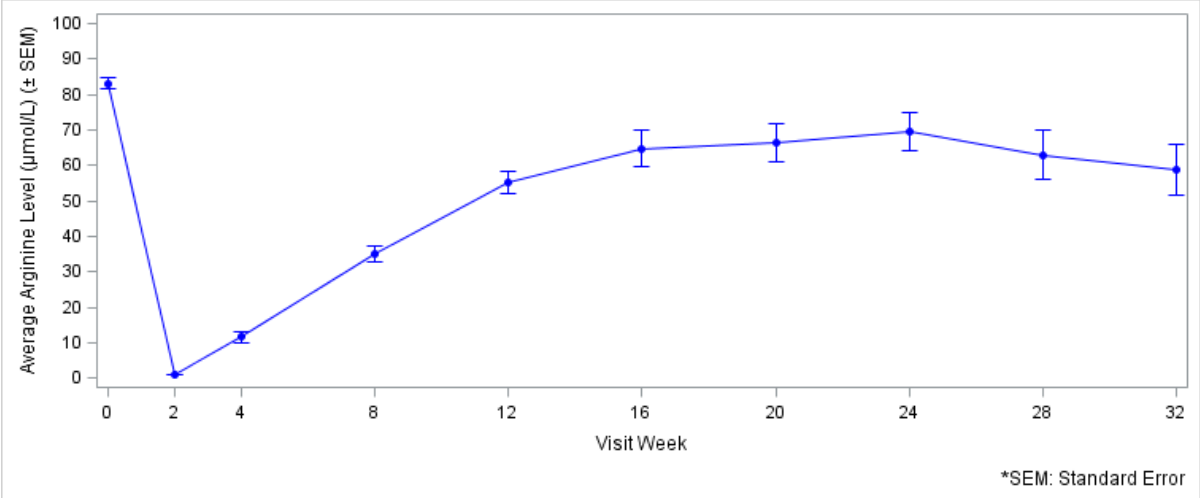
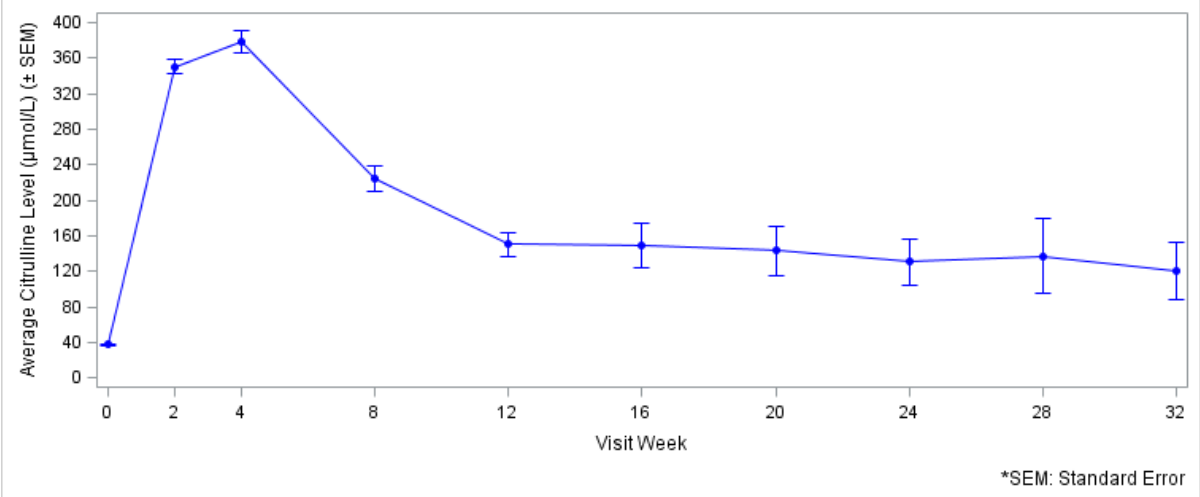


Figure 11-6 **Mean Blood Citrulline Levels for Subjects Receiving ADI-PEG 20 by Visit Week (Intent-to-Treat Population)**



Arginine depletion is summarized in Table 14.2.8.3, and citrulline increase is summarized in Table 14.2.8.5. Subjects were considered to have arginine depletion if there was a negative change from baseline and a level at or below 10 µM for arginine blood levels. Similarly, subjects were considered to have citrulline increase if there was at least a 50% increase from baseline for citrulline blood levels. The relationship between the duration of arginine depletion and OS is summarized in Table 14.2.8.4 and Figure 11-7, and the relationship

between the duration of citrulline increase and OS is summarized in Table 14.2.8.6 and Figure 11-8. Compared to the subjects with arginine depletion for ≤3 weeks (median OS: 5.7 months), subjects who experienced arginine depletion for >3 to ≤7 weeks or for >7 weeks had a longer OS (median: 8.3 months, $P = 0.9603$; median: 12.5 months, $P = 0.0002$, respectively), after adjusting for treatment duration ($P < 0.0001$). Compared to the subjects with citrulline increase for ≤3 weeks (median OS: 5.2 months), subjects with citrulline increase for >3 to ≤7 weeks, or for >7 weeks had a longer OS (median: 6.3 months, $P = 0.955$; median: 13.0 months, $P < 0.0006$, respectively), after adjusting for treatment duration ($P < 0.0001$).

Figure 11-7 **Kaplan-Meier Plot of Overall Survival vs. Duration of Arginine Depletion for Subjects Receiving ADI-PEG 20 (Intent-to-Treat Population)**

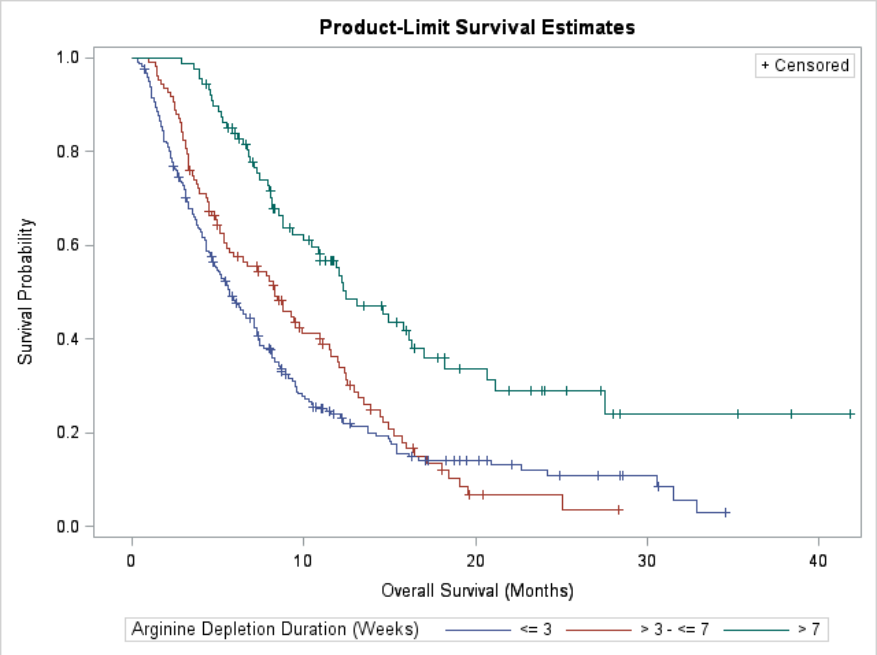
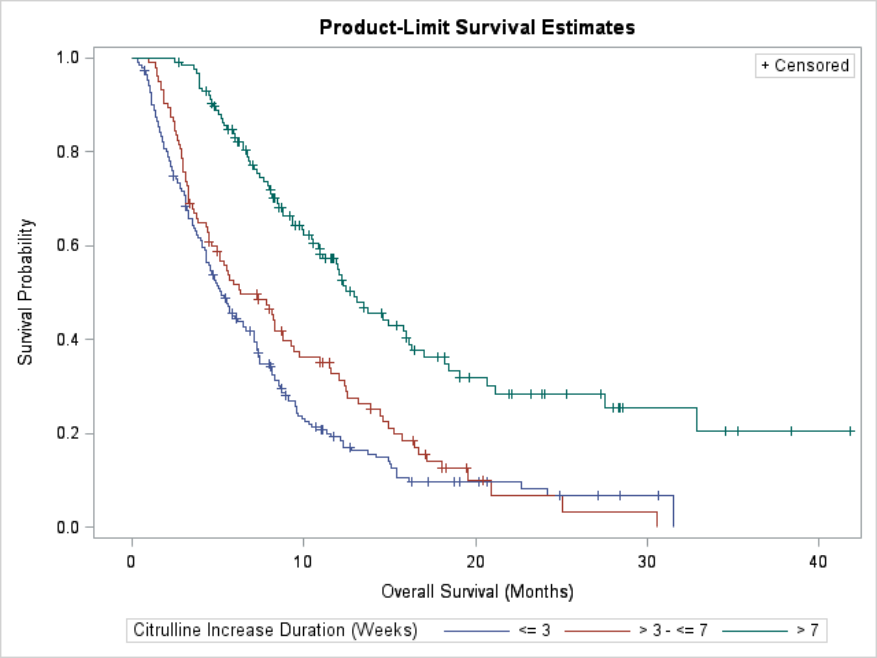


Figure 11-8 **Kaplan-Meier Plot of Overall Survival vs. Duration of Citrulline Increase for Subjects Receiving ADI-PEG 20 (Intent-to-Treat Population)**

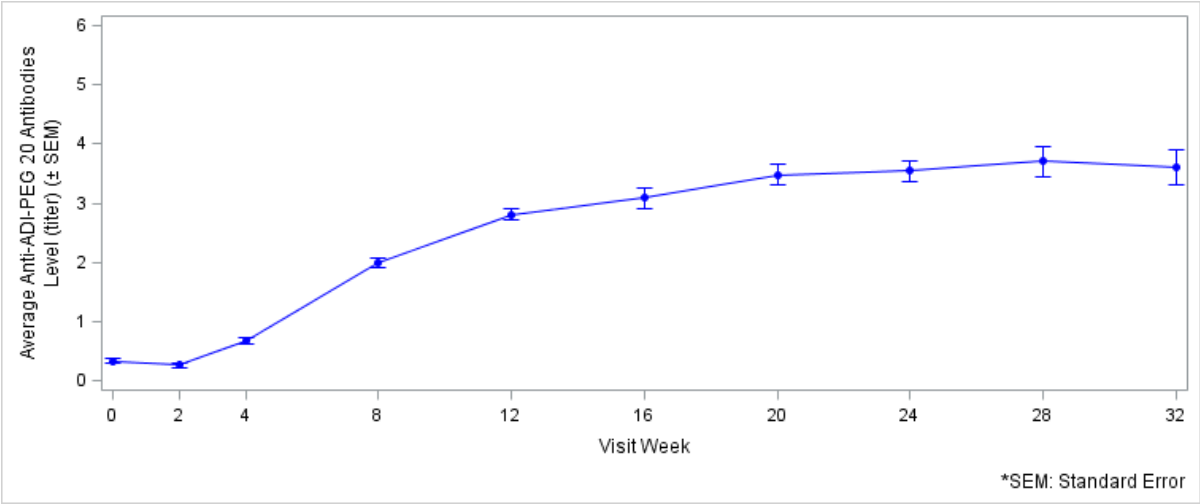


11.4.3 Immunogenicity Results

Anti-ADI-PEG 20 antibody titers are summarized in Figure 11-9 that shows the mean anti-ADI-PEG 20 antibodies titer by visit week. The median baseline anti-ADI-PEG 20 antibodies value was 0 in the ADI-PEG 20 treatment group and 0 in the Placebo treatment group. The maximum median postbaseline change from baseline was 2 in the ADI-PEG 20 treatment group and 0 in the Placebo treatment group.

Immunogenicity results are presented by subject in Listing 16.2.6.8.

Figure 11-9 **Mean Blood Anti-ADI-PEG 20 Antibodies Titer for Subjects Receiving ADI-PEG 20 by Visit Week (Intent-to-Treat Population)**

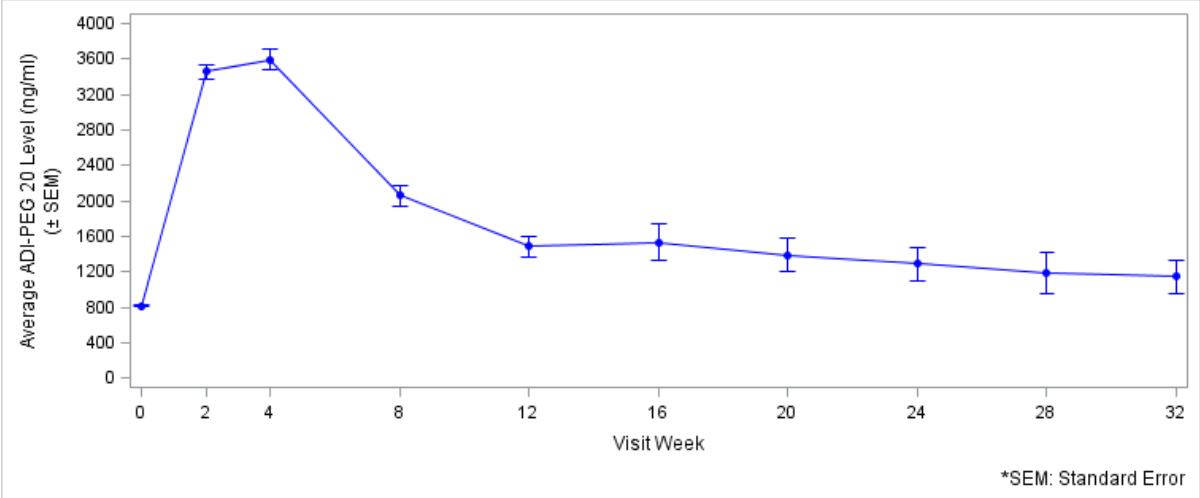


The correlation of anti-ADI-PEG 20 antibody levels to blood arginine levels is summarized in Table 14.2.5.2, and the correlation of anti-ADI-PEG 20 antibody levels to blood citrulline levels is summarized in Table 14.2.5.3. The correlation was statistically significant ($P < 0.0001$) for actual blood arginine levels and change from baseline at Week 4, Week 8, Week 12, and Week 16; and also at Week 2 (same P value) for change from baseline. The correlation was statistically significant ($P < 0.0001$) for actual blood citrulline blood levels and change from baseline at Week 4, Week 8, Week 12 and Week 16; and also at Week 2 ($P = 0.0004$) for actual citrulline blood.

11.4.4 Pharmacokinetic Results

Pharmacokinetic analysis results are presented by subject in Listing 16.2.6.10 and mean ADI-PEG 20 levels are presented by visit week in Figure 11-10.

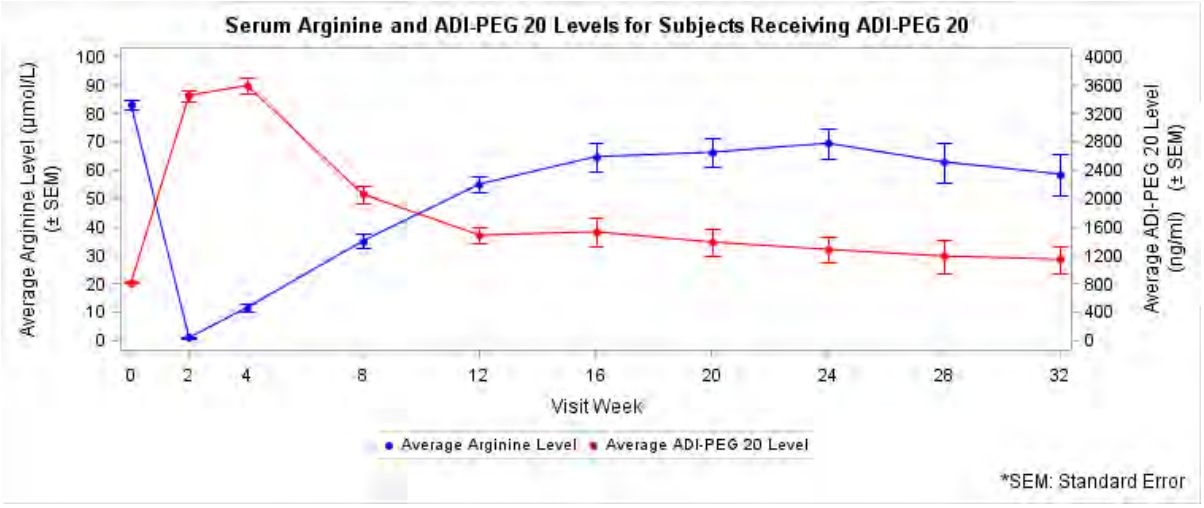
Figure 11-10 **Mean Blood ADI-PEG 20 Levels for Subjects Receiving ADI-PEG 20 by Visit Week (Intent-to-Treat Population)**

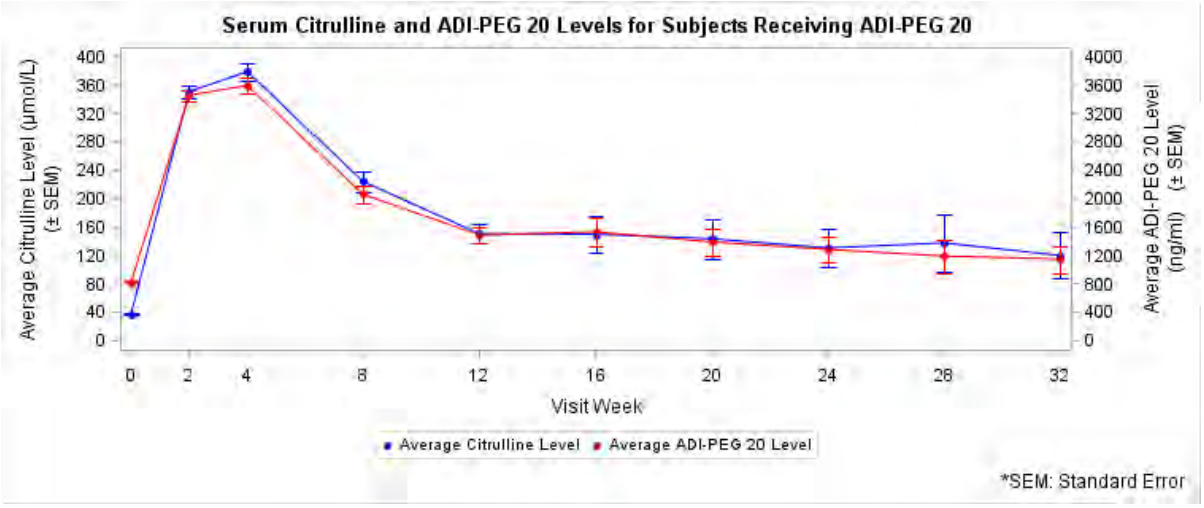


The correlation of ADI-PEG 20 blood levels and arginine blood levels is summarized in Table 14.2.7.1. The null hypothesis that the 2 variables were not correlated was rejected for the following change from baseline time points: Week 4, Week 8, Week 12, and Week 16. Therefore, ADI-PEG 20 and arginine blood levels can be considered as correlated and these measures are shown in Figure 11-11.

The correlation of ADI-PEG 20 blood levels and citrulline blood levels is summarized in Table 14.2.7.2. The null hypothesis that the 2 variables were not correlated was rejected for the following change from baseline time points: Week 2, Week 4, Week 8, Week 12, and Week 16. Therefore, ADI-PEG 20 and citrulline blood levels can be considered as correlated correlated and these measures are shown in Figure 11-11.

Figure 11-11 **Mean Blood Anti-ADI-PEG 20 Antibodies titer for Subjects Receiving ADI-PEG 20 by Visit Week (Intent-to-Treat Population)**





11.4.5 Statistical/Analytical Issues

11.4.5.1 Adjustments for Covariates

The additional efficacy analyses (Section 9.7.4.4.3) were performed using Cox proportional hazards models that included covariates.

11.4.5.2 Handling of Dropouts or Missing Data

Imputations of missing portions of dates for AEs and concomitant medications are described in Section 6.4.5 of the SAP (Section 16.1.9).

No data imputation was performed for efficacy analyses including for date of death. If a date of death was missing (all or portions of dates) the analyses used the date of last contact.

11.4.5.3 Interim Analyses and Data Monitoring

Due to slower than expected enrollment, and after discussion with the FDA, the interim analysis was removed. Note that the sample size remained as originally planned.

11.4.5.4 Multicenter Studies

While this was a multicenter study, treatment-by-center interactions were not explored in the statistical analyses.

11.4.5.5 Multiple Comparison/Multiplicity

No adjustments were made to control for multiple comparisons or multiplicity.

11.4.5.6 Use of an "Efficacy Subset" of Subjects

No efficacy subset was included in this study.

11.4.5.7 Active-Control Studies Intended to Show Equivalence

This study did not include an active control.

11.4.5.8 Examination of Subgroups

The additional efficacy analyses included examinations of subgroups. Overall survival was analyzed using additional stratified log-rank tests along with log-rank tests for different subgroups, as described in Section 9.7.4.4.3.

11.4.6 Tabulation of Individual Response Data

Individual response data are presented in Section 16.2.

11.4.7 Drug Dose, Drug Concentration, and Relationships to Response

Drug dose and relationships to response were not investigated in this study.

11.4.8 Drug-Drug and Drug-Disease Interactions

Drug-drug and drug-disease interactions were not investigated for this study.

11.4.9 By-Subject Displays

Individual response data are presented in Section 16.2.

11.4.10 Efficacy Conclusions

For the primary analysis (at the time of 487 deaths), using the ITT Population (635 subjects), median OS was estimated at 7.8 months (range 0.37 to 41.8+ months) for the ADI-PEG 20 treatment group and 7.4 months (range 0.67 to 47.73+ months) for the Placebo treatment group, which did not reach statistical significance ($P = 0.884$).

For the sensitivity analysis (all 525 deaths), using the ITT Population, median OS was estimated at 7.3 months (range 0.4 to 41.8+ months) for the ADI-PEG 20 treatment group and 7.2 months (range 0.7 to 47.7+ months) for the Placebo treatment group, which did not reach statistical significance ($P = 0.775$).The median duration of PFS was 2.6 months (range 0+ to 33.37+ months) for ADI-PEG 20 treatment group and 2.6 months (range 0+ to 24.57+ months) for the Placebo treatment group, which did not reach statistical significance ($P = 0.075$).

The tumor response rate did not reach statistical significance between the ADI-PEG 20 treatment group and the Placebo treatment group at 12 weeks, 24 weeks, 36 weeks, 48 weeks, or 60 weeks ($P = 0.273$, 0.693, 0.800, 0.278, 0.655, respectively) or for BOTR ($P = 0.273$).

The median (95% CI) time to tumor progression was 2.6 months (2.6, 2.63) in the ADI-PEG 20 treatment group and 2.6 months (2.6, 2.77) in the Placebo treatment group.

The BODC (disease control = Yes) was observed for 105 (24.8%) subjects in the ADI-PEG 20 treatment group and 66 (31.3%) subjects in the Placebo treatment group, which was not statistically significant ($P = 0.190$).

Surgical resections were reported for 24 (5.7%) subjects in the ADI-PEG 20 treatment group and 10 (4.7%) subjects in the Placebo treatment group.

A decline in alpha-fetoprotein was observed in 36 subjects (8.49%) in the ADI-PEG 20 treatment group and 18 subjects (8.53%) in the Placebo treatment group. The difference between the treatment groups was not statistically significant ($P = 0.8345$).

Separate stratified log-rank tests were used to compare OS across treatment groups using each of the following stratification factors:

- Geographical region (Asia vs NA and Europe) (primary: $P = 0.813$; sensitivity: $P = 0.796$)
- Sorafenib treatment status (non-sorafenib failure and sorafenib failure) (primary: $P = 0.914$; sensitivity: $P = 0.884$)
- ECOG performance status at screening (0 vs 1 and 2) (primary: $P = 0.823$; sensitivity: $P = 0.830$)
- Presence or absence of macroscopic vascular invasion (portal vein or branches) (primary: $P = 0.622$; sensitivity: $P = 0.570$)

- Presence or absence of extrahepatic spread (primary: $P = 0.840$; sensitivity: $P = 0.814$)
- Etiology of HCC (hepatitis C, hepatitis B, alcohol, NASH, and other) (primary: $P = 0.904$; sensitivity: $P = 0.809$)
- Antiviral therapy use (yes or no) (primary: $P = 0.759$; sensitivity: $P = 0.772$)

None of the *P* values for these sensitivity analyses reached statistical significance.

Separate log-rank tests (stratified by the 4 levels of the region – sorafenib treatment status variable) were used to compare OS across treatment groups within each level of the following subgroups:

- Region – sorafenib treatment status (Asia – non-sorafenib failure, Asia – sorafenib failure, NA and Europe – non-sorafenib failure, and NA and Europe – sorafenib failure) ($P = 0.110$, $P = 0.072$, $P = 0.588$, and $P = 0.622$, respectively)
- Geographical region (Asia vs NA and Europe) ($P = 0.361$ and $P = 0.557$, respectively)
- Sorafenib treatment status (non-sorafenib failure and sorafenib failure) ($P = 0.092$ and $P = 0.350$, respectively)
- ECOG performance status at screening (0 vs 1 and 2) ($P = 0.166$ and $P = 0.573$, respectively)
- Presence versus absence of macroscopic vascular invasion (portal vein or branches) ($P = 0.087$ and $P = 0.538$, respectively)
- Presence versus absence of extrahepatic spread ($P = 0.520$ and $P = 0.759$, respectively)
- Etiology of HCC (hepatitis C, hepatitis B, alcohol, NASH, and other) ($P = 0.206$, $P = 0.824$, $P = 0.166$, $P = 0.464$, and $P = 0.819$, respectively)
- Antiviral therapy use (yes or no) ($P = 0.494$ and $P = 0.929$, respectively)

None of the *P* values for these sensitivity analyses reached statistical significance.

The null hypothesis that the ADI-PEG 20 blood levels and arginine blood levels were not correlated was rejected for the following change from baseline time points: Week 4, Week 8, Week 12, and Week 16. Therefore, ADI-PEG 20 and arginine blood levels can be considered as correlated. The null hypothesis that the ADI-PEG 20 blood levels and citrulline blood levels were not correlated was rejected for the following change from baseline time points: Week 2, Week 4, Week 8, Week 12, and Week 16. Therefore, ADI-PEG 20 and citrulline blood levels can be considered as correlated. Compared to the subjects with arginine depletion for ≤3 weeks (median OS: 5.7 months), subjects who experienced arginine

depletion for >3 to ≤7 weeks or for >7 weeks had a longer OS (median: 8.3 months, $P = 0.9603$; median: 12.5 months, $P = 0.0002$, respectively), after adjusting for treatment duration. Compared to the subjects with citrulline increase for ≤3 weeks (median OS: 5.2 months), subjects with citrulline increase for >3 to ≤7 weeks, or for >7 weeks had a longer OS (median: 6.3 months, $P = 0.955$; median: 13.0 months, $P < 0.0006$, respectively), after adjusting for treatment duration.

12 Safety Evaluation

Tables and figures for safety data are located in Section 14.3.

Relevant data listings are located in Section 16.2.

12.1 Extent of Exposure

Exposure to ADI-PEG 20 or Placebo is summarized by treatment group in Table 12-1.

Drug exposure is summarized by treatment group in Table 14.1.5.1 (ITT Population). Study drug details are presented by subject in Listing 16.2.5.1.

The mean (Std Dev) number of doses was 13.97 (14.54) and 16.47 (16.58) for the ADI-PEG 20 and Placebo treatment group, respectively. The mean (Std Dev) duration of exposure was 12.7 (14.38) weeks for the ADI-PEG 20 treatment group and 14.98 (16.06) weeks for the Placebo treatment group. The number of subjects with at least one dose delay was 174 (41.0%) in the ADI-PEG 20 treatment group and 72 (34.1%) in the Placebo treatment group. The most common reasons for dose delays were AEs, laboratory abnormalities, and other.

Table 12-1 Drug Exposure (Intent-to-Treat Population)

	ADI-PEG 20 N = 424 N (%)	Placebo N = 211 N (%)	Total N = 635 N (%)
Number of doses administered			
n	424	210	634
Mean (Std Dev)	13.97 (14.54)	16.47 (16.58)	14.8 (15.28)
Inter quartile range	6, 13	7, 21	6, 16
Median	11	11	11
Min, max	0, 145	0, 98	0, 145
Duration of exposure (weeks)[a]			
n	424	210	634
Mean (Std Dev)	12.7 (14.38)	14.98 (16.06)	13.45 (14.98)
Inter quartile range	5.5, 11.3	6.4, 16.1	6, 11.7
Median	10.1	10.8	10.1
Min, max	0, 145.9	0, 108.4	0, 145.9
Number of dose delays	339	125	464
Number of subjects with at least 1 dose Delay	174 (41.0)	72 (34.1)	246 (38.7)
Reason for dose delay			
Adverse event	226 (53.3)	84 (39.8)	310 (48.8)
Laboratory abnormality	41 (9.7)	16 (7.6)	57 (9.0)
Other	72 (17.0)	25 (11.8)	97 (15.3)

Abbreviations: ADI-PEG 20, arginine deiminase-polyethylene glycol of 20,000 molecular weight; Max, maximum; Min, minimum; Std Dev, standard deviation.

Note: Unless otherwise noted, the denominator for percentages is the total number of subjects (N) in each treatment arm overall. Subject 101-0010 is excluded since this subject does not have any dose administration record.

[a] Duration of exposure (weeks) was calculated as (Date of Last Dose – Date of First Dose + 1)/7.

Source: Table 14.1.5.1.

12.2 Adverse Events

12.2.1 Brief Summary of Adverse Events

Treatment-emergent AEs are presented by subject in Listing 16.2.7.1.

The incidence of subjects experiencing an AE was similar among the two treatment groups (Table 12-2).

A total of 406 (96.4%) subjects reported TEAEs in the ADI-PEG 20 treatment group and 201 (96.2%) in the Placebo treatment group. Among the TEAEs, 241 (57.2%) subjects reported drug-related TEAEs in the ADI-PEG 20 treatment group and 110 (52.6%) in the

Placebo treatment group, although it was determined after database lock that the grade 5 gastric hemorrhage experienced by subject 513-0004 was not related to treatment with ADI-PEG 20. A total of 192 (45.6%) subjects reported serious TEAEs in the ADI-PEG 20 treatment group and 79 (37.8%) in the Placebo treatment group.

The incidence of subjects with TEAEs causing discontinuation of study drug was similar in the ADI-PEG 20 treatment group (16.6%) than the Placebo treatment group (14.8%). The incidence of on-study deaths was slightly higher in the ADI-PEG 20 treatment group (15.2%) than the Placebo treatment group (10.5%).

A summary of TEAEs is provided in Table 12-2.

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

	ADI-PEG 20 N = 421 N (%)	Placebo N = 209 N (%)	Total N = 630 N (%)
Any TEAE	406 (96.4)	201 (96.2)	607 (96.3)
Drug-related TEAE[a, b]	241 (57.2)	110 (52.6)	351 (55.7)
Serious TEAE[b]	192 (45.6)	79 (37.8)	271 (43.0)
Drug-related[a, b], serious TEAE	21 (5.0)	3 (1.4)	24 (3.8)
Grade >3 TEAE[b]	88 (20.9)	31 (14.8)	119 (18.9)
Grade >3, serious TEAE[b]	72 (17.1)	25 (12.0)	97 (15.4)
Grade >3, serious, drug-related TEAE[a, b]	4 (1.0)	0	4 (0.6)
TEAE causing discontinuation of study drug	70 (16.6)	31 (14.8)	101 (16.0)
TEAE using concomitant antiviral therapy	154 (36.6)	77 (36.8)	231 (36.7)
TEAE not using concomitant antiviral therapy	267 (63.4)	132 (63.2)	399 (63.3)
On study deaths[c]	64 (15.2)	22 (10.5)	86 (13.7)

Abbreviations: ADI-PEG 20, arginine deiminase-polyethylene glycol of 20,000 molecular weight; TEAE, treatment-emergent adverse event.

Note: Unless otherwise noted, the denominator for percentages is the total number of subjects (N) in each treatment arm overall. Treatment-emergent adverse events included all adverse events that started on or after the first dose date of study drug, or adverse events that were present prior to the first dose of study drug, but their severity or relationship increased after the first dose of study drug, up to and including 30 days after the final study drug dosing date. At each level of summarization subjects were only counted once.

[a] A drug-related TEAE was an event classified as definitely, probably, or possibly related to the study drug.

[b] Subject 513-0004 experienced a grade 5 gastric haemorrhage that was determined after database lock to be not related to treatment with ADI-PEG 20.

[c] On-study deaths are defined as deaths that occur within 30 days of the last dose of study drug. On-study deaths of the following 10 patients were not captured as adverse events and were extracted from Survival Status: 102-0007, 107-0003, 113-0005, 113-0010, 115-0006, 207-0006, 257-0018, 305-0045, 309-0026 and 405-0043. The day of death is unknown for the following four patients: 119-0001, 310-0004, 311-0008 and 503-0003. Based on the information collected, the four patients were not deceased within the time window of on-study deaths.

Source: Table 14.3.1.1.

12.2.2 Display of Adverse Events

12.2.2.1 Treatment-Emergent Adverse Events with a CTCAE Grade >3

The total number of subjects who reported TEAEs with a CTCAE grade >3 was 88 (20.9%) in the ADI-PEG 20 treatment group and 31 (14.8%) in the Placebo treatment group (Table 12-3). The most frequently reported on-therapy grade 4 and 5 TEAEs were under the Neoplasms benign, malignant and unspecified (incl cysts and polyps); Investigations; and Metabolism and nutrition disorders system organ classes (SOCs) in both treatment groups. Malignant neoplasm progression was the most common CTCAE grade >3 TEAE under the Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC and overall, with an event rate higher in the ADI-PEG 20 treatment group than in the Placebo treatment group (5.0% vs 1.9%, respectively). Disease progression was the second most common CTCAE grade >3 TEAE overall, with an event rate equal in the ADI-PEG 20 treatment group and in the Placebo treatment group (1.9% each).

Table 12-3 Treatment-Emergent Adverse Events by CTCAE Grade for Events with Grade >3 (Safety Population)

System Organ Class Preferred Term[a]	ADI-PEG 20 N = 421 N (%)	Placebo N = 209 N (%)	Total N = 630 N (%)
Total number of TEAEs with grade >3	110	47	157
Number of subjects with at least 1 TEAE with grade >3	88 (20.9)	31 (14.8)	119 (18.9)
Grade 4	50 (11.9)	17 (8.1)	67 (10.6)
Grade 5	38 (9.0)	14 (6.7)	52 (8.3)
Blood and lymphatic system disorders	2 (0.5)	0	2 (0.3)
Grade 4	2 (0.5)	0	2 (0.3)
Grade 5	0	0	0
Anaemia	1 (0.2)	0	1 (0.2)
Grade 4	1 (0.2)	0	1 (0.2)
Grade 5	0	0	0
Hypersplenism	1 (0.2)	0	1 (0.2)
Grade 4	1 (0.2)	0	1 (0.2)
Grade 5	0	0	0
Leukopenia	1 (0.2)	0	1 (0.2)
Grade 4	1 (0.2)	0	1 (0.2)
Grade 5	0	0	0
Neutropenia	1 (0.2)	0	1 (0.2)
Grade 4	1 (0.2)	0	1 (0.2)
Grade 5	0	0	0
Cardiac disorders	1 (0.2)	1 (0.5)	2 (0.3)
Grade 4	0	1 (0.5)	1 (0.2)
Grade 5	1 (0.2)	0	1 (0.2)

System Organ Class Preferred Term[a]	ADI-PEG 20 N = 421 N (%)	Placebo N = 209 N (%)	Total N = 630 N (%)
Cardiac arrest	1 (0.2)	0	1 (0.2)
Grade 4	0	0	0
Grade 5	1 (0.2)	0	1 (0.2)
Cardiac failure	0	1 (0.5)	1 (0.2)
Grade 4	0	1 (0.5)	1 (0.2)
Grade 5	0	0	0
Gastrointestinal disorders	10 (2.4)	4 (1.9)	14 (2.2)
Grade 4	5 (1.2)	2 (1.0)	7 (1.1)
Grade 5	5 (1.2)	3 (1.4)	8 (1.3)
Abdominal pain	1 (0.2)	0	1 (0.2)
Grade 4	0	0	0
Grade 5	1 (0.2)	0	1 (0.2)
Diarrhoea	0	1 (0.5)	1 (0.2)
Grade 4	0	1 (0.5)	1 (0.2)
Grade 5	0	0	0
Gastrointestinal haemorrhage	4 (1.0)	1 (0.5)	5 (0.8)
Grade 4	2 (0.5)	0	2 (0.3)
Grade 5	2 (0.5)	1 (0.5)	3 (0.5)
Oseophageal verices haemorrhage	3 (0.7)	0	3 (0.5)
Grade 4	2 (0.5)	0	2 (0.3)
Grade 5	1 (0.2)	0	1 (0.2)
Upper gastrointestinal haemorrhage	2 (0.5)	2 (1.0)	4 (0.6)
Grade 4	1 (0.2)	1 (0.5)	2 (0.3)
Grade 5	1 (0.2)	2 (1.0)	3 (0.5)
General disorders and administration site conditions	9 (2.1)	6 (2.9)	15 (2.4)
Grade 4	1 (0.2)	0	1 (0.2)
Grade 5	8 (1.9)	6 (2.9)	14 (2.2)
Disease progression	8 (1.9)	4 (1.9)	12 (1.9)
Grade 4	1 (0.2)	0	1 (0.2)
Grade 5	7 (1.7)	4 (1.9)	11 (1.7)
General physical health deterioration	1 (0.2)	2 (1.0)	3 (0.5)
Grade 4	0	0	0
Grade 5	1 (0.2)	2 (1.0)	3 (0.5)

System Organ Class Preferred Term[a]	ADI-PEG 20 N = 421 N (%)	Placebo N = 209 N (%)	Total N = 630 N (%)
Hepatobiliary disorders	7 (1.7)	2 (1)	9 (1.4)
Grade 4	5 (1.2)	1 (0.5)	6 (1.0)
Grade 5	2 (0.5)	1 (0.5)	3 (0.5)
Hepatic failure	4 (1.0)	1 (0.5)	5 (0.8)
Grade 4	3 (0.7)	1 (0.5)	4 (0.6)
Grade 5	1 (0.2)	0	1 (0.2)
Hepatic haemorrhage	1 (0.2)	1 (0.5)	2 (0.3)
Grade 4	1 (0.2)	0	1 (0.2)
Grade 5	0	1 (0.5)	1 (0.2)
Hepatitis toxic	1 (0.2)	0	1 (0.2)
Grade 4	1 (0.2)	0	1 (0.2)
Grade 5	0	0	0
Liver injury	1 (0.2)	0	1 (0.2)
Grade 4	0	0	0
Grade 5	1 (0.2)	0	1 (0.2)
Infections and infestations	6 (1.4)	3 (1.4)	9 (1.4)
Grade 4	6 (1.4)	3 (1.4)	9 (1.4)
Grade 5	0	0	0
Escherichia urinary tract infection	1 (0.2)	0	1 (0.2)
Grade 4	1 (0.2)	0	1 (0.2)
Grade 5	0	0	0
Sepsis	4 (1.0)	3 (1.4)	7 (1.1)
Grade 4	4 (1.0)	3 (1.4)	7 (1.1)
Grade 5	0	0	0
Urosepsis	1 (0.2)	1 (0.5)	2 (0.3)
Grade 4	1 (0.2)	1 (0.5)	2 (0.3)
Grade 5	0	0	0
Injury, poisoning and procedural complications	0	1 (0.5)	1 (0.2)
Grade 4	0	0	0
Grade 5	0	1 (0.5)	1 (0.2)
Subdural haematoma	0	1 (0.5)	1 (0.2)
Grade 4	0	0	0
Grade 5	0	1 (0.5)	1 (0.2)

System Organ Class Preferred Term[a]	ADI-PEG 20 N = 421 N (%)	Placebo N = 209 N (%)	Total N = 630 N (%)
Investigations	18 (4.3)	3 (1.4)	21 (3.3)
Grade 4	18 (4.3)	3 (1.4)	21 (3.3)
Grade 5	0	0	0
Aspartate aminotransferase increased	4 (1.0)	2 (1.0)	6 (1.0)
Grade 4	4 (1.0)	2 (1.0)	6 (1.0)
Grade 5	0	0	0
Blood bilirubin increased	8 (1.9)	1 (0.5)	9 (1.4)
Grade 4	8 (1.9)	1 (0.5)	9 (1.4)
Grade 5	0	0	0
Blood cholesterol increased	3 (0.7)	0	3 (0.5)
Grade 4	3 (0.7)	0	3 (0.5)
Grade 5	0	0	0
Blood uric acid increased	1 (0.2)	0	1 (0.2)
Grade 4	1 (0.2)	0	1 (0.2)
Grade 5	0	0	0
Platelet count decreased	2 (0.5)	0	2 (0.3)
Grade 4	2 (0.5)	0	2 (0.3)
Grade 5	0	0	0
White blood cell count decreased	1 (0.2)	0	1 (0.2)
Grade 4	1 (0.2)	0	1 (0.2)
Grade 5	0	0	0
Metabolism and nutrition disorders	10 (2.4)	8 (3.8)	18 (2.9)
Grade 4	10 (2.4)	8 (3.8)	18 (2.9)
Grade 5	0	0	0
Diabetes mellitus	1 (0.2)	0	1 (0.2)
Grade 4	1 (0.2)	0	1 (0.2)
Grade 5	0	0	0
Hypercalcaemia	1 (0.2)	2 (1.0)	3 (0.5)
Grade 4	1 (0.2)	2 (1.0)	3 (0.5)
Grade 5	0	0	0
Hypercholesterolaemia	0	1 (0.5)	1 (0.2)
Grade 4	0	1 (0.5)	1 (0.2)
Grade 5	0	0	0
Hyperkalaemia	0	1 (0.5)	1 (0.2)
Grade 4	0	1 (0.5)	1 (0.2)
Grade 5	0	0	0

System Organ Class Preferred Term[a]	ADI-PEG 20 N = 421 N (%)	Placebo N = 209 N (%)	Total N = 630 N (%)
Hypernatraemia	1 (0.2)	0	1 (0.2)
Grade 4	1 (0.2)	0	1 (0.2)
Grade 5	0	0	0
Hyperuricaemia	5 (1.2)	1 (0.5)	6 (1.0)
Grade 4	5 (1.2)	1 (0.5)	6 (1.0)
Grade 5	0	0	0
Hypoglycaemia	2 (0.5)	1 (0.5)	3 (0.5)
Grade 4	2 (0.5)	1 (0.5)	3 (0.5)
Grade 5	0	0	0
Hypokalaemia	1 (0.2)	0	1 (0.2)
Grade 4	1 (0.2)	0	1 (0.2)
Grade 5	0	0	0
Hyponatraemia	0	1 (0.5)	1 (0.2)
Grade 4	0	1 (0.5)	1 (0.2)
Grade 5	0	0	0
Metabolic acidosis	0	1 (0.5)	1 (0.2)
Grade 4	0	1 (0.5)	1 (0.2)
Grade 5	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	27 (6.4)	6 (2.9)	33 (5.2)
Grade 4	5 (1.2)	3 (1.4)	8 (1.3)
Grade 5	23 (5.5)	4 (1.9)	27 (4.3)
Brain cancer metastatic	1 (0.2)	0	1 (0.2)
Grade 4	0	0	0
Grade 5	1 (0.2)	0	1 (0.2)
Hepatic neoplasm	1 (0.2)	0	1 (0.2)
Grade 4	0	0	0
Grade 5	1 (0.2)	0	1 (0.2)
Malignant neoplasm progression	21 (5.0)	4 (1.9)	25 (4.0)
Grade 4	5 (1.2)	1 (0.5)	6 (1.0)
Grade 5	16 (3.8)	3 (1.4)	19 (3.0)
Metastases to central nervous system	3 (0.7)	1 (0.5)	4 (0.6)
Grade 4	0	1 (0.5)	1 (0.2)
Grade 5	3 (0.7)	1 (0.5)	4 (0.6)
Neoplasm malignant	1 (0.2)	0	1 (0.2)
Grade 4	0	0	0
Grade 5	1 (0.2)	0	1 (0.2)
Neoplasm progression	1 (0.2)	1 (0.5)	2 (0.3)

System Organ Class Preferred Term[a]	ADI-PEG 20 N = 421 N (%)	Placebo N = 209 N (%)	Total N = 630 N (%)
Grade 4	0	1 (0.5)	1 (0.2)
Grade 5	1 (0.2)	0	1 (0.2)
Nervous system disorders	8 (1.9)	3 (1.4)	11 (1.7)
Grade 4	4 (1.0)	2 (1.0)	6 (1.0)
Grade 5	4 (1.0)	1 (0.5)	5 (0.8)
Brain stem infarction	1 (0.2)	0	1 (0.2)
Grade 4	0	0	0
Grade 5	1 (0.2)	0	1 (0.2)
Coma hepatic	1 (0.2)	0	1 (0.2)
Grade 4	0	0	0
Grade 5	1 (0.2)	0	1 (0.2)
Haemorrhage intracranial	1 (0.2)	0	1 (0.2)
Grade 4	1 (0.2)	0	1 (0.2)
Grade 5	0	0	0
Hepatic encephalopathy	5 (1.2)	1 (0.5)	6 (1.0)
Grade 4	3 (0.7)	0	3 (0.5)
Grade 5	2 (0.5)	1 (0.5)	3 (0.5)
Somnolence	0	1 (0.5)	1 (0.2)
Grade 4	0	1 (0.5)	1 (0.2)
Grade 5	0	0	0
Spinal cord compression	0	1 (0.5)	1 (0.2)
Grade 4	0	1 (0.5)	1 (0.2)
Grade 5	0	0	0
Renal and urinary disorders	0	1 (0.5)	1 (0.2)
Grade 4	0	1 (0.5)	1 (0.2)
Grade 5	0	0	0
Acute kidney injury	0	1 (0.5)	1 (0.2)
Grade 4	0	1 (0.5)	1 (0.2)
Grade 5	0	0	0
Respiratory, thoracic and mediastinal disorders	4 (1.0)	4 (1.9)	8 (1.3)
Grade 4	3 (0.7)	2 (1.0)	5 (0.8)
Grade 5	2 (0.5)	2 (1.0)	4 (0.6)

System Organ Class Preferred Term[a]	ADI-PEG 20 N = 421 N (%)	Placebo N = 209 N (%)	Total N = 630 N (%)
Acute respiratory failure	0	1 (0.5)	1 (0.2)
Grade 4	0	1 (0.5)	1 (0.2)
Grade 5	0	0	0
Dyspnoea	3 (0.7)	0	3 (0.5)
Grade 4	2 (0.5)	0	2 (0.3)
Grade 5	1 (0.2)	0	1 (0.2)
Haemoptysis	0	1 (0.5)	1 (0.2)
Grade 4	0	0	0
Grade 5	0	1 (0.5)	1 (0.2)
Respiratory failure	1 (0.2)	2 (1.0)	3 (0.5)
Grade 4	1 (0.2)	1 (0.5)	2 (0.3)
Grade 5	1 (0.2)	1 (0.5)	2 (0.3)
Vascular disorders	0	1 (0.5)	1 (0.2)
Grade 4	0	1 (0.5)	1 (0.2)
Grade 5	0	0	0
Hypotension	0	1 (0.5)	1 (0.2)
Grade 4	0	1 (0.5)	1 (0.2)
Grade 5	0	0	0

Abbreviations: ADI-PEG 20, arginine deiminase-polyethylene glycol of 20,000 molecular weight; CTCAE, Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.

Note: Unless otherwise noted, the denominator for percentages is the total number of subjects (N) in each treatment arm overall. Treatment-emergent adverse events included all adverse events that started on or after the first dose date of study drug, or adverse events that were present prior to the first dose of study drug, but their severity or relationship increased after the first dose of study drug, up to and including 30 days after the final study drug dosing date. At each level of summarization, if more than 1 event was reported, a subject was counted only once under the worst CTCAE grade experienced.

[a] Events were mapped to the Medical Dictionary for Regulatory Activities (MedDRA Version 18.0) system for reporting (preferred term and body system).

Source: Table 14.3.1.6.

12.2.2.2 Drug Related Treatment-Emergent Adverse Events with a CTCAE Grade >3

The number of subjects with at least 1 drug-related TEAE with a grade >3 was low in both groups at 8 (1.9%) in the ADI-PEG 20 treatment group and 1 (0.5%) in the Placebo treatment group (Table 12-4), although it was determined after database lock that the grade 5 gastric hemorrhage experienced by subject 513-0004 was not related to treatment with ADI-PEG 20. On-therapy, drug-related grade 4 and 5 TEAEs were most frequently reported under the Investigations SOC in the ADI-PEG 20 treatment group. Hepatic failure and Blood cholesterol increased were the most common drug-related, CTCAE grade >3 TEAE under the Hepatobiliary disorders and Investigations SOCs, respectively, and overall, with an event

rate that was low but slightly higher in the ADI-PEG 20 treatment group than in the Placebo treatment group (0.5% vs 0.0%, respectively).

Table 12-4 Drug-Related Treatment-Emergent Adverse Events by CTCAE Grade for Events with Grade >3 (Safety Population)

System Organ Class Preferred Term[a]	ADI-PEG 20 N = 421 N (%)	Placebo N = 209 N (%)	Total N = 630 N (%)
Total number of drug-related[b] TEAEs with grade >3 [c]	8	1	9
Number of subjects with at least 1 drug-related TEAE with grade >3[c]	8 (1.9)	1 (0.5)	9 (1.4)
Grade 4	7 (1.7)	1 (0.5)	8 (1.3)
Grade 5[c]	1 (0.2)	0	1 (0.2)
Gastrointestinal disorders[c]	1 (0.2)	0	1 (0.2)
Grade 4	0	0	0
Grade 5[c]	1 (0.2)	0	1 (0.2)
Gastrointestinal haemorrhage[c]	1 (0.2)	0	1 (0.2)
Grade 4	0	0	0
Grade 5[c]	1 (0.2)	0	1 (0.2)
Hepatobiliary disorders	2 (0.5)	0	2 (0.3)
Grade 4	2 (0.5)	0	2 (0.3)
Grade 5	0	0	0
Hepatic failure	2 (0.5)	0	2 (0.3)
Grade 4	2 (0.5)	0	2 (0.3)
Grade 5	0	0	0
Investigations	3 (0.7)	0	3 (0.5)
Grade 4	3 (0.7)	0	3 (0.5)
Grade 5	0	0	0
Aspartate aminotransferase increased	1 (0.2)	0	1 (0.2)
Grade 4	1 (0.2)	0	1 (0.2)
Grade 5	0	0	0
Bood cholesterol increased	2 (0.5)	0	2 (0.3)
Grade 4	2 (0.5)	0	2 (0.3)
Grade 5	0	0	0

System Organ Class Preferred Term[a]	ADI-PEG 20 N = 421 N (%)	Placebo N = 209 N (%)	Total N = 630 N (%)
Metabolism and nutrition disorders	1 (0.2)	1 (0.5)	2 (0.3)
Grade 4	1 (0.2)	1 (0.5)	2 (0.3)
Grade 5	0	0	0
Hypercholesterolaemia	0	1 (0.5)	1 (0.2)
Grade 4	0	1 (0.5)	1 (0.2)
Grade 5	0	0	0
Hyperuricaemia	1 (0.2)	0	1 (0.2)
Grade 4	1 (0.2)	0	1 (0.2)
Grade 5	0	0	0
Nervous system disorders	1 (0.2)	0	1 (0.2)
Grade 4	1 (0.2)	0	1 (0.2)
Grade 5	0	0	0
Hepatic encephalopathy	1 (0.2)	0	1 (0.2)
Grade 4	1 (0.2)	0	1 (0.2)
Grade 5	0	0	0

Abbreviations: ADI-PEG 20, arginine deiminase-polyethylene glycol of 20,000 molecular weight; CTCAE, Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.

Note: Unless otherwise noted, the denominator for percentages is the total number of subjects (N) in each treatment arm overall. Treatment-emergent adverse events included all adverse events that started on or after the first dose date of study drug, or adverse events that were present prior to the first dose of study drug, but their severity or relationship increased after the first dose of study drug, up to and including 30 days after the final study drug dosing date. At each level of summarization, if more than 1 event was reported, a subject was counted only once under the worst CTCAE grade experienced.

[a] Events were mapped to the Medical Dictionary for Regulatory Activities (MedDRA Version 18.0) system for reporting (preferred term and body system).

[b] A drug-related event was an event classified as definitely, probably, or possibly related to the study drug.

[c] Subject 513-0004 experienced a grade 5 gastric haemorrhage that was determined after database lock to be not related to treatment with ADI-PEG 20.

Source: Table 14.3.1.7.

12.2.2.3 Drug-Related, Serious Treatment-Emergent Adverse Events with a CTCAE Grade >3

The number of subjects with at least 1 drug-related, serious TEAE with a grade >3 was 4 (1.0%) in the ADI-PEG 20 treatment group and 0 (0.0%) in the Placebo treatment group (Table 12-5), although it was determined after database lock that the grade 5 gastric hemorrhage experienced by subject 513-0004 was not related to treatment with ADI-PEG 20. On-therapy, drug-related, serious grade 4 and 5 TEAEs were most frequently reported under the Hepatobiliary disorders SOC in the ADI-PEG 20 treatment group. Hepatic failure was the most common drug-related, serious CTCAE grade >3 TEAE under the Hepatobiliary

disorders SOC and overall, with a similar event rate in the ADI-PEG 20 treatment group and in the Placebo treatment group (0.5% and 0.0%, respectively).

Table 12-5 Drug-Related, Serious Treatment-Emergent Adverse Events by CTCAE Grade for Events with Grade >3 (Safety Population)

System Organ Class Preferred Term[a]	ADI-PEG 20 N = 421 N (%)	Placebo N = 209 N (%)	Total N = 630 N (%)
Total number of drug-related[b], serious TEAEs with grade >3	4	0	4
Number of subjects with at least 1 drug-related, serious TEAE with grade >3[c]	4 (1.0)	0	4 (0.6)
Grade 4	3 (0.7)	0	3 (0.5)
Grade 5[c]	1 (0.2)	0	1 (0.2)
Gastrointestinal disorders[c]	1 (0.2)	0	1 (0.2)
Grade 4	0	0	0
Grade 5[c]	1 (0.2)	0	1 (0.2)
Gastrointestinal haemorrhage[c]	1 (0.2)	0	1 (0.2)
Grade 4	0	0	0
Grade 5[c]	1 (0.2)	0	1 (0.2)
Hepatobiliary disorders	2 (0.5)	0	2 (0.3)
Grade 4	2 (0.5)	0	2 (0.3)
Grade 5	0	0	0
Hepatic failure	2 (0.5)	0	2 (0.3)
Grade 4	2 (0.5)	0	2 (0.3)
Grade 5	0	0	0
Nervous system disorders	1 (0.2)	0	1 (0.2)
Grade 4	1 (0.2)	0	1 (0.2)
Grade 5	0	0	0
Hepatic encephalopathy	1 (0.2)	0	1 (0.2)
Grade 4	1 (0.2)	0	1 (0.2)
Grade 5	0	0	0

Abbreviations: ADI-PEG 20, arginine deiminase-polyethylene glycol of 20,000 molecular weight; CTCAE, Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.

Note: Unless otherwise noted, the denominator for percentages is the total number of subjects (N) in each treatment arm overall. Treatment-emergent adverse events included all adverse events that started on or after the first dose date of study drug, or adverse events that were present prior to the first dose of study drug, but their severity or relationship increased after the first dose of study drug, up to and including 30 days after the final study drug dosing date. At each level of summarization, if more than 1 event was reported, a subject was counted only once under the worst CTCAE grade experienced.

[a] Events were mapped to the Medical Dictionary for Regulatory Activities (MedDRA Version 18.0) system for reporting (preferred term and body system).

[b] A drug-related event was an event classified as definitely, probably, or possibly related to the study drug.

[c] Subject 513-0004 experienced a grade 5 gastric haemorrhage that was determined after database lock to be not related to treatment with ADI-PEG 20.

Source: Table 14.3.1.8.

12.2.3 Analysis of Adverse Events

12.2.3.1 Most Common Adverse Events

On-therapy TEAEs were most frequently reported under the gastrointestinal disorders, and General disorders and administration site conditions SOCs in both treatment groups (Table 12-6). Fatigue was the most common TEAE under the General disorders and administration site conditions SOC and overall, with a similar event rate in the ADI-PEG 20 and the Placebo treatment groups (23.3% and 26.8%, respectively). Decreased appetite under the Metabolism and nutrition disorders SOC was the second most common TEAE overall, with a similar event rate in the ADI-PEG 20 and the Placebo treatment groups (22.8% and 19.6%, respectively).

Although the incidence of other commonly occurring TEAEs was generally similar between the treatment groups, an imbalance was observed for the Skin and subcutaneous tissue disorders SOC, where events were more common in the ADI-PEG 20 treatment group (34.9% vs 25.8%, respectively).

The number of subjects reporting at least one TEAE who received antiviral therapy or not (223 and 384, respectively; Table 14.3.1.2) closely mirrors the number of subjects who received antiviral therapy or not (231 [36.4%] vs 404 [63.6%], respectively). The distribution of commonly occurring TEAEs among the SOCs was generally similar between the ADI-PEG 20 and Placebo treatment groups whether or not antiviral therapy was received.

Table 12-6 Treatment-Emergent Adverse Events Reported in ≥7.5% of Total Subjects by Decreasing Frequency (Safety Population)

System Organ Class Preferred Term[a]	ADI-PEG 20 N = 421 N (%)	Placebo N = 209 N (%)	Total N = 630 N (%)
Total number of TEAEs	4252	2089	6341
Number of subjects with at least 1 TEAE	406 (96.4)	201 (96.2)	607 (96.3)
Gastrointestinal disorders	277 (65.8)	140 (67.0)	417 (66.2)
Nausea	80 (19.0)	37 (17.7)	117 (18.6)
Abdominal pain	79 (18.8)	36 (17.2)	115 (18.3)
Abdominal distension	61 (14.5)	35 (16.7)	96 (15.2)
Diarrhoea	58 (13.8)	36 (17.2)	94 (14.9)
Constipation	51 (12.1)	31 (14.8)	82 (13.0)
Ascites	53 (12.6)	27 (12.9)	80 (12.7)
Vomiting	53 (12.6)	26 (12.4)	79 (12.5)
Abdominal pain upper	50 (11.9)	24 (11.5)	74 (11.7)
General disorders and administration site conditions	257 (61.0)	126 (60.3)	383 (60.8)
Fatigue	98 (23.3)	56 (26.8)	154 (24.4)
Oedema peripheral	78 (18.5)	39 (18.7)	117 (18.6)
Pyrexia	77 (18.3)	40 (19.1)	117 (18.6)
Metabolism and nutrition disorders	165 (39.2)	79 (37.8)	244 (38.7)
Decreased appetite	96 (22.8)	41 (19.6)	137 (21.7)
Hypoalbuminaemia	31 (7.4)	16 (7.7)	47 (7.5)
Respiratory, thoracic and mediastinal disorders	152 (36.1)	82 (39.2)	234 (37.1)
Cough	64 (15.2)	37 (17.7)	101 (16.0)
Dyspnoea	50 (11.9)	24 (11.5)	74 (11.7)
Investigations	156 (37.1)	77 (36.8)	233 (37.0)
Aspartate aminotransferase increased	62 (14.7)	29 (13.9)	91 (14.4)
Blood bilirubin increased	41 (9.7)	18 (8.6)	59 (9.4)
Alanine aminotransferase increased	37 (8.8)	17 (8.1)	54 (8.6)
Musculoskeletal and connective tissue disorders	161 (38.2)	65 (31.1)	226 (35.9)
Back pain	45 (10.7)	25 (12.0)	70 (11.1)
Skin and subcutaneous tissue disorders	147 (34.9)	54 (25.8)	201 (31.9)
Pruritus	56 (13.3)	27 (12.9)	83 (13.2)
Rash	43 (10.2)	17 (8.1)	60 (9.5)
Blood and lymphatic system disorders	80 (19.0)	37 (17.7)	117 (18.6)
Anaemia	46 (10.9)	24 (11.5)	70 (11.1)

System Organ Class Preferred Term[a]	ADI-PEG 20 N = 421 N (%)	Placebo N = 209 N (%)	Total N = 630 N (%)
Psychiatric disorders	78 (18.5)	35 (16.7)	113 (17.9)
Insomnia	44 (10.5)	18 (8.6)	62 (9.8)

Abbreviations: ADI-PEG 20, arginine deiminase-polyethylene glycol of 20,000 molecular weight; TEAE, treatment-emergent adverse event.

Note: Unless otherwise noted, the denominator for percentages is the total number of subjects (N) in each treatment arm overall. Treatment-emergent adverse events included all adverse events that started on or after the first dose date of study drug, or adverse events that were present prior to the first dose of study drug, but their severity or relationship increased after the first dose of study drug, up to and including 30 days after the final study drug dosing date. At each level of summarization, subjects were only counted once.

[a] Events were mapped to the Medical Dictionary for Regulatory Activities (MedDRA Version 18.0) system for reporting (preferred term and body system).

Source: Table 14.3.1.2.

12.2.3.2 Adverse Events by Maximum Intensity

Most TEAEs were CTCAE grade 1 (Table 12-7). Other than disease progression and malignant neoplasm progression, no individual TEAE that was grade 5 in intensity was experienced by more than 3 subjects in either treatment group. Two events were experienced by more than 20% of subjects in either treatment group; fatigue (98 [23.3%] subjects in the ADI-PEG 20 treatment group, and 56 [26.8%] subjects in the Placebo treatment group), and decreased appetite (96 [22.8%] subjects in the ADI-PEG 20 treatment group, and 41 [19.6%] subjects in the Placebo treatment group). No events occurred more frequently (at least 10% higher) in one treatment group versus the other.

Table 12-7 Treatment-Emergent Adverse Events by Treatment Group and CTCAE Grade, Reported in ≥7.5% of Total Subjects per Group by Decreasing Frequency (Safety Population)

	ADI-PEG 20 N = 421						
	CTCAE Grade						
System Organ Class Preferred Term[a]	1	2	3	4	5	Total	Missing
Total number of TEAEs	2235	1301	600	65	45	4252	6
Number of subjects with at least 1 TEAE	51 (12.1)	90 (21.4)	177 (42.0)	44 (10.5)	44 (10.5)	406 (96.4)	0
Gastrointestinal disorders	112 (26.6)	94 (22.3)	61 (14.5)	5 (1.2)	5 (1.2)	277 (65.8)	0
Nausea	55 (13.1)	23 (5.5)	2 (0.5)	0	0	80 (19.0)	0
Abdominal pain	30 (7.1)	30 (7.1)	18 (4.3)	0	1 (0.2)	79 (18.8)	0
Abdominal distension	30 (7.1)	26 (6.2)	5 (1.2)	0	0	61 (14.5)	0
Diarrhoea	32 (7.6)	22 (5.2)	4 (1.0)	0	0	58 (13.8)	0
Abdominal pain upper	36 (8.6)	13 (3.1)	1 (0.2)	0	0	50 (11.9)	0
Ascites	23 (5.5)	19 (4.5)	11 (2.6)	0	0	53 (12.6)	0
Vomiting	36 (8.6)	14 (3.3)	3 (0.7)	0	0	53 (12.6)	0
Constipation	32 (7.6)	18 (4.3)	1 (0.2)	0	0	51 (12.1)	0
General disorders and administration site conditions	137 (32.5)	78 (18.5)	33 (7.8)	1 (0.2)	8 (1.9)	257 (61.0)	0
Fatigue	58 (13.8)	32 (7.6)	8 (1.9)	0	0	98 (23.3)	0
Oedema peripheral	39 (9.3)	29 (6.9)	10 (2.4)	0	0	78 (18.5)	0
Pyrexia	67 (15.9)	10 (2.4)	0	0	0	77 (18.3)	0
Metabolism and nutrition disorders	65 (15.4)	57 (13.5)	32 (7.6)	10 (2.4)	0	165 (39.2)	1 (0.2)
Decreased appetite	52 (12.4)	36 (8.6)	8 (1.9)	0	0	96 (22.8)	0

System Organ Class Preferred Term[a]	ADI-PEG 20 N = 421 CTCAE Grade 1	2	3	4	5	Total	Missing
Musculoskeletal and connective tissue disorders	89 (21.1)	59 (14.0)	13 (3.1)	0	0	161 (38.2)	0
Back pain	28 (6.7)	15 (3.6)	2 (0.5)	0	0	45 (10.7)	0
Arthralgia	15 (3.6)	13 (3.1)	6 (1.4)	0	0	34 (8.1)	0
Investigations	26 (6.2)	38 (9.0)	74 (17.6)	18 (4.3)	0	156 (37.1)	0
Aspartate aminotransferase increased	14 (3.3)	6 (1.4)	38 (9.0)	4 (1.0)	0	62 (14.7)	0
Blood bilirubin increased	5 (1.2)	13 (3.1)	15 (3.6)	8 (1.9)	0	41 (9.7)	0
Alanine aminotransferase increased	10 (2.4)	11 (2.6)	16 (3.8)	0	0	37 (8.8)	0
Respiratory, thoracic and mediastinal disorders	72 (17.1)	56 (13.3)	20 (4.8)	2 (0.5)	2 (0.5)	152 (36.1)	0
Cough	33 (7.8)	30 (7.1)	1 (0.2)	0	0	64 (15.2)	0
Dyspnoea	29 (6.9)	11 (2.6)	7 (1.7)	2 (0.5)	1 (0.2)	50 (11.9)	0
Skin and subcutaneous tissue disorders	96 (22.8)	46 (10.9)	5 (1.2)	0	0	147 (34.9)	0
Pruritus	35 (8.3)	20 (4.8)	1 (0.2)	0	0	56 (13.3)	0
Rash	27 (6.4)	16 (3.8)	0	0	0	43 (10.2)	0
Nervous system disorders	56 (13.3)	31 (7.4)	28 (6.7)	4 (1.0)	4 (1.0)	123 (29.2)	0
Hepatic encephalopathy	6 (1.4)	9 (2.1)	12 (2.9)	3 (0.7)	2 (0.5)	32 (7.6)	0
Blood and lymphatic system disorders	13 (3.1)	28 (6.7)	36 (8.6)	2 (0.5)	0	80 (19.0)	1 (0.2)
Anaemia	4 (1.0)	23 (5.5)	18 (4.3)	1 (0.2)	0	46 (10.9)	0
Psychiatric disorders	48 (11.4)	26 (6.2)	4 (1.0)	0	0	78 (18.5)	0
Insomnia	31 (7.4)	12 (2.9)	1 (0.2)	0	0	44 (10.5)	0

System Organ Class Preferred Term[a]	Placebo N = 209 CTCAE Grade 1	2	3	4	5	Total	Missing
Total number of TEAEs	1178	578	282	29	18	2089	4
Number of subjects with at least 1 TEAE	29 (13.9)	59 (28.2)	82 (39.2)	14 (6.7)	17 (8.1)	201 (96.2)	0
Gastrointestinal disorders	61 (29.2)	49 (23.4)	26 (12.4)	1 (0.5)	3 (1.4)	140 (67.0)	0
Nausea	26 (12.4)	10 (4.8)	1 (0.5)	0	0	37 (17.7)	0
Abdominal pain	17 (8.1)	14 (6.7)	5 (2.4)	0	0	36 (17.2)	0
Diarrhoea	28 (13.4)	5 (2.4)	2 (1.0)	1 (0.5)	0	36 (17.2)	0
Abdominal distension	25 (12.0)	9 (4.3)	1 (0.5)	0	0	35 (16.7)	0
Constipation	20 (9.6)	9 (4.3)	2 (1.0)	0	0	31 (14.8)	0
Vomiting	19 (9.1)	7 (3.3)	0	0	0	26 (12.4)	0
Ascites	8 (3.8)	12 (5.7)	7 (3.3)	0	0	27 (12.9)	0
Abdominal pain upper	14 (6.7)	8 (3.8)	2 (1.0)	0	0	24 (11.5)	0
General disorders and administration site conditions	64 (30.6)	39 (18.7)	17 (8.1)	0	6 (2.9)	126 (60.3)	0
Fatigue	33 (15.8)	16 (7.7)	7 (3.3)	0	0	56 (26.8)	0
Pyrexia	34 (16.3)	5 (2.4)	1 (0.5)	0	0	40 (19.1)	0
Oedema peripheral	25 (12.0)	11 (5.3)	3 (1.4)	0	0	39 (18.7)	0
Asthenia	7 (3.3)	8 (3.8)	1 (0.5)	0	0	16 (7.7)	0
Respiratory, thoracic and mediastinal disorders	41 (19.6)	27 (12.9)	10 (4.8)	2 (1.0)	2 (1.0)	82 (39.2)	0
Cough	25 (12.0)	11 (5.3)	1 (0.5)	0	0	37 (17.7)	0
Dyspnoea	12 (5.7)	6 (2.9)	6 (2.9)	0	0	24 (11.5)	0

	Placebo N = 209						
	CTCAE Grade						
System Organ Class Preferred Term[a]	1	2	3	4	5	Total	Missing
Metabolism and nutrition disorders	31 (14.8)	21 (10.0)	19 (9.1)	8 (3.8)	0	79 (37.8)	0
Decreased appetite	25 (12.0)	13 (6.2)	3 (1.4)	0	0	41 (19.6)	0
Hypoalbuminaemia	5 (2.4)	10 (4.8)	1 (0.5)	0	0	16 (7.7)	0
Investigations	18 (8.6)	20 (9.6)	36 (17.2)	3 (1.4)	0	77 (36.8)	0
Aspartate aminotransferase increased	6 (2.9)	5 (2.4)	16 (7.7)	2 (1.0)	0	29 (13.9)	0
Blood bilirubin increased	3 (1.4)	3 (1.4)	11 (5.3)	1 (0.5)	0	18 (8.6)	0
Alanine aminotransferase increased	5 (2.4)	4 (1.9)	8 (3.8)	0	0	17 (8.1)	0
Blood alkaline phosphatase increased	5 (2.4)	6 (2.9)	6 (2.9)	0	0	17 (8.1)	0
Musculoskeletal and connective tissue disorders	30 (14.4)	27 (12.9)	8 (3.8)	0	0	65 (31.1)	0
Back pain	10 (4.8)	9 (4.3)	5 (2.4)	0	0	25 (12.0)	1 (0.5)
Musculoskeletal pain	10 (4.8)	7 (3.3)	0	0	0	17 (8.1)	0
Infections and infestations	13 (6.2)	30 (14.4)	16 (7.7)	3 (1.4)	0	62 (29.7)	0
Upper respiratory tract infection	5 (2.4)	11 (5.3)	0	0	0	16 (7.7)	0
Nervous system disorders	32 (15.3)	15 (7.2)	12 (5.7)	2 (1.0)	1 (0.5)	62 (29.7)	0
Dizziness	18 (8.6)	1 (0.5)	0	0	0	19 (9.1)	0

System Organ Class Preferred Term[a]	Placebo N = 209 CTCAE Grade 1	2	3	4	5	Total	Missing
Skin and subcutaneous tissue disorders	40 (19.1)	12 (5.7)	2 (1.0)	0	0	54 (25.8)	0
Pruritus	24 (11.5)	2 (1.0)	1 (0.5)	0	0	27 (12.9)	0
Rash	13 (6.2)	3 (1.4)	1 (0.5)	0	0	17 (8.1)	0
Blood and lymphatic system disorders	7 (3.3)	14 (6.7)	16 (7.7)	0	0	37 (17.7)	0
Anaemia	6 (2.9)	6 (2.9)	12 (5.7)	0	0	24 (11.5)	0
Psychiatric disorders	26 (12.4)	4 (1.9)	5 (2.4)	0	0	35 (16.7)	0
Insomnia	15 (7.2)	2 (1.0)	1 (0.5)	0	0	18 (8.6)	0

Abbreviations: ADI-PEG 20, arginine deiminase-polyethylene glycol of 20,000 molecular weight; CTCAE, Common Terminology Criteria for Adverse Events; Std Dev, standard deviation; TEAE, treatment-emergent adverse event.

Note: Unless otherwise noted, the denominator for percentages is the total number of subjects (N) in each treatment arm overall. Treatment-emergent adverse events included all adverse events that started on or after the first dose date of study drug, or adverse events that were present prior to the first dose of study drug, but their severity or relationship increased after the first dose of study drug, up to and including 30 days after the final study drug dosing date. At each level of summarization, a subject was only counted once at the greatest reported CTCAE grade if the subject reported 1 or more events. Events were codified using National Cancer Institute CTCAE v4.02.

[a] Events were mapped to the Medical Dictionary for Regulatory Activities (MedDRA Version 18.0) system for reporting (preferred term and body system).

Source: Table 14.3.1.10.

12.2.3.3 Adverse Events by Relationship to Study Drug

The overall incidence of TEAEs considered related to study drug by the investigator was 57.2% in the ADI-PEG 20 treatment group and 52.6% in the Placebo treatment group (Table 12-8), although it was determined after database lock that the grade 5 gastric hemorrhage experienced by subject 513-0004 was not related to treatment with ADI-PEG 20. Most TEAEs considered related to study drug were reported in no more than 7.5% of subjects; those reported in more than 7.5% of subjects in any treatment group are presented in Table 12-8.

No events occurred more frequently (at least 10% higher) in one treatment group versus the other. The overall incidence of serious TEAEs considered related to study drug by the investigator was 5.0% in the ADI-PEG 20 treatment group and 1.4% in the Placebo treatment group (Table 12-9). Most serious TEAEs considered related to study drug were reported in less than 1.0% of subjects, with the exception of hypersensitivity in 1.0% and hepatic encephalopathy in 1.2% of subjects in the ADI-PEG 20 treatment group; those reported in all subjects in any treatment group are presented in Table 12-9.

Table 12-8 Treatment-Emergent Adverse Events by Treatment Group and Relationship to Study Drug, Reported in ≥7.5% of Total Subjects per Group by Decreasing Frequency (Safety Population)

	ADI-PEG 20 N = 421					
System Organ Class	**Unrelated**		**Related**			
Preferred Term[a]	**Not Related**	**Unlikely**	**Possibly**	**Probably**	**Definitely**	**Total**
Total number of TEAEs	2215	1063	703	218	53	4252
Number of subjects with at least 1 TEAE	77 (18.3)	88 (20.9)	125 (29.7)	82 (19.5)	34 (8.1)	406 (96.4)
Gastrointestinal disorders	118 (28.0)	90 (21.4)	54 (12.8)	14 (3.3)	1 (0.2)	277 (65.8)
Nausea	33 (7.8)	21 (5.0)	22 (5.2)	4 (1.0)	0	80 (19.0)
Abdominal pain	49 (11.6)	23 (5.5)	7 (1.7)	0	0	79 (18.8)
Abdominal distension	45 (10.7)	14 (3.3)	1 (0.2)	1 (0.2)	0	61 (14.5)
Diarrhoea	25 (5.9)	15 (3.6)	14 (3.3)	3 (0.7)	1 (0.2)	58 (13.8)
Ascites	36 (8.6)	17 (4.0)	0	0	0	53 (12.6)
Vomiting	20 (4.8)	13 (3.1)	17 (4.0)	3 (0.7)	0	53 (12.6)
Abdominal pain upper	31 (7.4)	16 (3.8)	3 (0.7)	0	0	50 (11.9)
Constipation	24 (5.7)	21 (5.0)	5 (1.2)	1 (0.2)	0	51 (12.1)
General disorders and administration site conditions	99 (23.5)	52 (12.4)	54 (12.8)	33 (7.8)	19 (4.5)	257 (61.0)
Fatigue	31 (7.4)	22 (5.2)	36 (8.6)	9 (2.1)	0	98 (23.3)
Oedema peripheral	56 (13.3)	20 (4.8)	2 (0.5)	0	0	78 (18.5)
Pyrexia	44 (10.5)	20 (4.8)	6 (1.4)	7 (1.7)	0	77 (18.3)
Metabolism and nutrition disorders	74 (17.6)	47 (11.2)	35 (8.3)	8 (1.9)	1 (0.2)	165 (39.2)
Decreased appetite	47 (11.2)	32 (7.6)	15 (3.6)	2 (0.5)	0	96 (22.8)
Musculoskeletal and connective tissue disorders	76 (18.1)	42 (10.0)	28 (6.7)	12 (2.9)	3 (0.7)	161 (38.2)
Back pain	26 (6.2)	15 (3.6)	4 (1.0)	0	0	45 (10.7)
Arthralgia	12 (2.9)	7 (1.7)	11 (2.6)	3 (0.7)	1 (0.2)	34 (8.1)

	ADI-PEG 20 N = 421					
System Organ Class	**Unrelated**		**Related**			
Preferred Term[a]	**Not Related**	**Unlikely**	**Possibly**	**Probably**	**Definitely**	**Total**
Investigations	57 (13.5)	45 (10.7)	46 (10.9)	8 (1.9)	0	156 (37.1)
Aspartate aminotransferase increased	24 (5.7)	19 (4.5)	18 (4.3)	1 (0.2)	0	62 (14.7)
Blood bilirubin increased	26 (6.2)	11 (2.6)	4 (1.0)	0	0	41 (9.7)
Alanine aminotransferase increased	17 (4.0)	8 (1.9)	11 (2.6)	1 (0.2)	0	37 (8.8)
Respiratory, thoracic and mediastinal disorders	92 (21.9)	50 (11.9)	9 (2.1)	1 (0.2)	0	152 (36.1)
Cough	38 (9.0)	21 (5.0)	5 (1.2)	0	0	64 (15.2)
Dyspnoea	32 (7.6)	13 (3.1)	4 (1.0)	1 (0.2)	0	50 (11.9)
Skin and subcutaneous tissue disorders	41 (9.7)	31 (7.4)	39 (9.3)	28 (6.7)	8 (1.9)	147 (34.9)
Pruritus	15 (3.6)	13 (3.1)	16 (3.8)	11 (2.6)	1 (0.2)	56 (13.3)
Rash	7 (1.7)	8 (1.9)	14 (3.3)	12 (2.9)	2 (0.5)	43 (10.2)
Nervous system disorders	56 (13.3)	37 (8.8)	23 (5.5)	6 (1.4)	1 (0.2)	123 (29.2)
Hepatic encephalopathy	15 (3.6)	12 (2.9)	5 (1.2)	0	0	32 (7.6)
Blood and lymphatic system disorders	38 (9.0)	23 (5.5)	11 (2.6)	8 (1.9)	0	80 (19.0)
Anaemia	25 (5.9)	16 (3.8)	5 (1.2)	0	0	46 (10.9)
Psychiatric disorders	53 (12.6)	19 (4.5)	6 (1.4)	0	0	78 (18.5)
Insomnia	32 (7.6)	10 (2.4)	2 (0.5)	0	0	44 (10.5)

	Placebo N = 209					
System Organ Class	**Unrelated**		**Related**			
Preferred Term[a]	**Not Related**	**Unlikely**	**Possibly**	**Probably**	**Definitely**	**Total**
Total number of TEAEs	1249	501	250	49	40	2089
Number of subjects with at least 1 TEAE	53 (25.4)	38 (18.2)	64(30.6)	23 (11.0)	23 (11.0)	201 (96.2)
Gastrointestinal disorders	71 (34.0)	32 (15.2)	28 (13.4)	6 (2.9)	3 (1.4)	140 (67.0)
Nausea	15 (7.2)	5 (2.4)	14 (6.7)	3 (1.4)	0	37 (17.7)
Abdominal pain	21 (10.0)	13 (6.2)	2 (1.0)	0	0	36 (17.2)
Diarrhoea	20 (9.6)	5 (2.4)	10 (4.8)	1 (0.5)	0	36 (17.2)
Abdominal distension	23 (11.0)	11 (5.3)	0	0	1 (0.5)	35 (16.7)
Constipation	17 (8.1)	11 (5.3)	3 (1.4)	0	0	31 (14.8)
Ascites	19 (9.1)	7 (3.3)	1 (0.5)	0	0	27 (12.9)
Vomiting	11 (5.3)	7 (3.3)	7 (3.3)	1 (0.5)	0	26 (12.4)
Abdominal pain upper	16 (7.7)	7 (3.3)	1 (0.5)	0	0	24 (11.5)
General disorders and administration site conditions	45 (21.5)	26 (12.4)	29 (13.9)	9 (4.3)	17 (8.1)	126 (60.3)
Fatigue	17 (8.1)	10 (4.8)	22 (10.5)	6 (2.9)	1 (0.5)	56 (26.8)
Pyrexia	25 (12.0)	6 (2.9)	4 (1.9)	3 (1.4)	2 (1.0)	40 (19.1)
Oedema peripheral	25 (12.0)	11 (5.3)	3 (1.4)	0	0	39 (18.7)
Asthenia	6 (2.9)	6 (2.9)	2 (1.0)	2 (1.0)	0	16 (7.7)
Investigations	39 (18.7)	26 (12.4)	11 (5.3)	1 (0.5)	0	77 (36.8)
Aspartate aminotransferase increased	9 (4.3)	13 (6.2)	6 (2.9)	1 (0.5)	0	29 (13.9)
Blood bilirubin increased	9 (4.3)	8 (3.8)	1 (0.5)	0	0	18 (8.6)
Blood alkaline phosphatase increased	10 (4.8)	5 (2.4)	2 (1.0)	0	0	17 (8.1)
Alanine aminotransferase increased	5 (2.4)	8 (3.8)	3 (1.4)	1 (0.5)	0	17 (8.1)

	Placebo N = 209					
System Organ Class	**Unrelated**		**Related**			
Preferred Term[a]	**Not Related**	**Unlikely**	**Possibly**	**Probably**	**Definitely**	**Total**
Metabolism and nutrition disorders	41 (19.6)	18 (8.6)	12 (5.7)	6 (2.9)	2 (1.0)	79 (37.8)
Decreased appetite	26 (12.4)	7 (3.3)	5 (2.4)	2 (1.0)	1 (0.5)	41 (19.6)
Hypoalbuminaemia	13 (6.2)	1 (0.5)	2 (1.0)	0	0	16 (7.7)
Musculoskeletal and connective tissue disorders	40 (19.1)	16 (7.7)	6 (2.9)	2 (1.0)	1 (0.5)	65 (431.1)
Back pain	20 (9.6)	5 (2.4)	0	0	0	25 (12.0)
Musculoskeletal pain	10 (4.8)	4 (1.9)	0	2 (1.0)	1 (0.5)	17 (8.1)
Respiratory, thoracic and mediastinal disorders	54 (25.8)	21 (10.0)	5 (2.4)	1 (0.5)	1 (0.5)	82 (39.2)
Cough	30 (14.4)	5 (2.4)	2 (1.0)	0	0	37 (17.7)
Dyspnoea	13 (6.2)	7 (3.3)	3 (1.4)	0	1 (0.5)	24 (11.5)
Infections and infestations	38 (18.2)	23 (11.0)	1 (0.5)	0	0	62 (29.7)
Upper respiratory tract infection	12 (5.7)	4 (1.9)	0	0	0	16 (7.7)
Nervous system disorders	28 (13.4)	19 (9.1)	14 (6.7)	0	1 (0.5)	62 (29.7)
Dizziness	7 (3.3)	8 (3.8)	4 (1.9)	0	0	19 (9.1)
Skin and subcutaneous tissue disorders	18 (8.6)	13 (6.2)	17 (8.1)	6 (2.9)	0	54 (25.8)
Pruritus	12 (5.7)	7 (3.3)	6 (2.9)	2 (1.0)	0	27 (12.9)
Rash	2 (1.0)	7 (3.3)	5 (2.4)	3 (1.4)	0	17 (8.1)
Blood and lymphatic system disorders	25 (12.0)	4 (1.9)	5 (2.4)	2 (1.0)	1 (0.5)	37 (17.7)
Anaemia	15 (7.2)	3 (1.4)	4 (1.9)	2 (1.0)	0	24 (11.5)
Psychiatric disorders	23 (11.0)	8 (3.8)	4 (1.9)	0	0	35 (16.7)
Insomnia	11 (5.3)	5 (2.4)	2 (1.0)	0	0	18 (8.6)

	Placebo N = 209					
System Organ Class	**Unrelated**		**Related**			
Preferred Term[a]	**Not Related**	**Unlikely**	**Possibly**	**Probably**	**Definitely**	**Total**

Abbreviations: ADI-PEG 20, arginine deiminase-polyethylene glycol of 20,000 molecular weight; TEAE, treatment-emergent adverse event.

Note: Unless otherwise noted, the denominator for percentages is the total number of subjects (N) in each treatment arm overall. Treatment-emergent adverse events included all adverse events that started on or after the first dose date of study drug, or adverse events that were present prior to the first dose of study drug, but their severity or relationship increased after the first dose of study drug, up to and including 30 days after the final study drug dosing date. At each level of summarization, a subject was only counted once at the greatest reported related event if the subject reported 1 or more events.

[a] Events were mapped to the Medical Dictionary for Regulatory Activities (MedDRA Version 18.0) system for reporting (preferred term and body system).

Source: Table 14.3.1.3.

Table 12-9 Drug-Related, Serious Treatment-Emergent Adverse Events (Safety Population)

System Organ Class Preferred Term[a]	ADI-PEG 20 N = 421 N (%)	Placebo N = 209 N (%)	Total N = 630 N (%)
Total number of drug-related, serious TEAEs[c]	28	3	31
Number of subjects with at least 1 drug-related[b], serious TEAE[c]	21 (5.0)	3 (1.4)	24 (3.8)
Gastrointestinal disorders[c]	4 (1.0)	0	4 (0.6)
Gastrointestinal haemorrhage[c]	1 (0.2)	0	1 (0.2)
Oesophageal varices haemorrhage	1 (0.2)	0	1 (0.2)
Stomatitis	1 (0.2)	0	1 (0.2)
Vomiting	1 (0.2)	0	1 (0.2)
General disorders and administration site conditions	1 (0.2)	1 (0.5)	2 (0.3)
Injection site pain	1 (0.2)	0	1 (0.2)
Malaise	0	1 (0.5)	1 (0.2)
Hepatobiliary disorders	2 (0.5)	0	2 (0.3)
Hepatic failure	2 (0.5)	0	2 (0.3)
Immune system disorders	6 (1.4)	0	6 (1.0)
Anaphylactic reaction	1 (0.2)	0	1 (0.2)
Anaphylactic shock	1 (0.2)	0	1 (0.2)
Hypersensitivity	4 (1.0)	0	4 (0.6)
Investigations	1 (0.2)	0	1 (0.2)
Alanine aminotransferase increased	1 (0.2)	0	1 (0.2)
Aspartate aminotransferase increased	1 (0.2)	0	1 (0.2)
Musculoskeletal and connective tissue disorders	2 (0.5)	1 (0.5)	3 (0.5)
Arthralgia	1 (0.2)	0	1 (0.2)
Muscular weakness	1 (0.2)	1 (0.5)	2 (0.3)
Nervous system disorders	8 (1.9)	0	8 (1.3)
Haemmorrhage intracranial	1 (0.2)	0	1 (0.2)
Headache	1 (0.2)	0	1 (0.2)
Hepatic encephalopathy	5 (1.2)	0	5 (0.8)
Hyperammonaemic encephalopathy	1 (0.2)	0	1 (0.2)

System Organ Class Preferred Term[a]	ADI-PEG 20 N = 421 N (%)	Placebo N = 209 N (%)	Total N = 630 N (%)
Skin and subcutaneous tissue disorders	2 (0.5)	1 (0.5)	3 (0.5)
Dermatitis allergic	1 (0.2)	0	1 (0.2)
Rash	0	1 (0.5)	1 (0.2)
Rash macular	1 (0.2)	0	1 (0.2)

Abbreviations: ADI-PEG 20, arginine deiminase-polyethylene glycol of 20,000 molecular weight; TEAE, treatment-emergent adverse event.

Note: Unless otherwise noted, the denominator for percentages is the total number of subjects (N) in each treatment arm overall. Treatment-emergent adverse events included all adverse events that started on or after the first dose date of study drug, or adverse events that were present prior to the first dose of study drug, but their severity or relationship increased after the first dose of study drug, up to and including 30 days after the final study drug dosing date. At each level of summarization, a subject was only counted once if the subject reported 1 or more events.

[a] Events were mapped to the Medical Dictionary for Regulatory Activities (MedDRA Version 18.0) system for reporting (preferred term and body system).

[b] A drug related event was an event classified as definitely, probably, or possibly related to the study drug.

[c] Subject 513-0004 experienced a grade 5 gastric haemorrhage that was determined after database lock to be not related to treatment with ADI-PEG 20.

Source: Table 14.3.1.5.

12.2.4 Listing of Adverse Events by Subject

All TEAEs are presented by subject in Listing 16.2.7.1.

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

12.3.1 Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1.1 Deaths

In the ADI-PEG 20 treatment group, 64 (15.2%) subjects died during the study (on-study deaths are defined as deaths that occur within 30 days of the last dose of study drug) and 22 (10.5%) in the Placebo treatment group.

The number of subjects who died during the study is presented in Table 14.3.2.1.

12.3.1.2 Other Serious Adverse Events

The number of subjects who experienced serious TEAEs during the study is summarized by treatment group in Table 12-10. In the ADI-PEG 20 treatment group, 192 (45.6%) subjects experienced serious TEAEs during the study compared with 79 (37.8%) subjects in the Placebo treatment group. The most commonly reported preferred term was malignant neoplasm progression, with 28 (6.7%) subjects in the ADI-PEG 20 treatment group, compared with 5 (2.4%) subjects in the Placebo treatment group, and was the most frequent event in the Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC

(which was also the most commonly reported SOC). The next most commonly reported preferred terms were hepatic encephalopathy (21 [5.0%] subjects in the ADI-PEG 20 treatment group compared with 4 [1.9%] subjects in the Placebo treatment group), and disease progression (15 [3.6%] subjects in the ADI-PEG 20 treatment group compared with 10 [4.8%] subjects in the Placebo treatment group), both at 25 (4.0%) subjects overall.

Table 12-10 Serious Treatment-Emergent Adverse Events (Safety Population)

System Organ Class Preferred Term[a]	ADI-PEG 20 N = 421 N (%)	Placebo N = 209 N (%)	Total N = 630 N (%)
Total number of serious TEAEs	307	133	440
Number of subjects with at least 1 serious TEAE	192 (45.6)	79 (37.8)	271 (43.0)
Blood and lymphatic system disorders	5 (1.2)	1 (0.5)	6 (1.0)
Anaemia	5 (1.2)	0	5 (0.8)
Febrile neutropenia	0	1 (0.5)	1 (0.2)
Cardiac disorders	5 (1.2)	2 (1.0)	7 (1.1)
Angina pectoris	1 (0.2)	0	1 (0.2)
Atrial fibrillation	3 (0.7)	0	3 (0.5)
Cardiac arrest	1 (0.2)	0	1 (0.2)
Cardiac failure	0	1 (0.5)	1 (0.2)
Cardiac failure congestive	0	1 (0.5)	1 (0.2)
Left ventricular dysfunction	1 (0.2)	0	1 (0.2)
Mitral valve disease	1 (0.2)	0	1 (0.2)
Eye disorders	1 (0.2)	0	1 (0.2)
Cataract	1 (0.2)	0	1 (0.2)
Gastrointestinal disorders	42 (10.0)	18 (8.6)	60 (9.5)
Abdominal distension	3 (0.7)	0	3 (0.5)
Abdominal pain	6 (1.4)	2 (1)	8 (1.3)
Abdominal pain lower	1 (0.2)	0	1 (0.2)
Ascites	1 (0.2)	4 (1.9)	5 (0.8)
Constipation	0	1 (0.5)	1 (0.2)
Diarrhoea	0	1 (0.5)	1 (0.2)
Duodenal ulcer	1 (0.2)	0	1 (0.2)
Enteritis	1 (0.2)	0	1 (0.2)
Enterocolitis	1 (0.2)	0	1 (0.2)
Gastric varices haemorrhage	2 (0.5)	0	2 (0.3)
Gastritis haemorrhagic	1 (0.2)	0	1 (0.2)
Gastrointestinal haemorrhage	4 (1.0)	3 (1.4)	7 (1.1)
Haematochezia	2 (0.5)	0	2 (0.3)
Lower gastrointestinal haemorrhage	1 (0.2)	0	1 (0.2)
Mouth haemorrhage	1 (0.2)	0	1 (0.2)
Nausea	1 (0.2)	0	1 (0.2)
Oesophageal varices haemorrhage	9 (2.1)	0	9 (1.4)

System Organ Class Preferred Term[a]	ADI-PEG 20 N = 421 N (%)	Placebo N = 209 N (%)	Total N = 630 N (%)
Pancreatitis	1 (0.2)	0	1 (0.2)
Pancreatitis acute	0	1 (0.5)	1 (0.2)
Portal hypertensive gastropathy	1 (0.2)	0	1 (0.2)
Small intestinal haemorrhage	1 (0.2)	0	1 (0.2)
Stomatitis	2 (0.5)	0	2 (0.3)
Upper gastrointestinal haemorrhage	4 (1.0)	5 (2.4)	9 (1.4)
Vomiting	3 (0.7)	1 (0.5)	4 (0.6)
General disorders and administration site conditions	30 (7.1)	19 (9.1)	49 (7.8)
Asthenia	3 (0.7)	1 (0.5)	4 (0.6)
Disease progression	15 (3.6)	10 (4.8)	25 (4.0)
Fatigue	0	2 (1.0)	2 (0.3)
General physical health deterioration	1 (0.2)	2 (1.0)	3 (0.5)
Generalised oedema	1 (0.2)	0	1 (0.2)
Hernia	1 (0.2)	0	1 (0.2)
Injection site pain	1 (0.2)	0	1 (0.2)
Malaise	1 (0.2)	1 (0.5)	2 (0.3)
Non-cardiac chest pain	1 (0.2)	0	1 (0.2)
Oedema peripheral	3 (0.7)	1 (0.5)	4 (0.6)
Performance status decreased	0	1 (0.5)	1 (0.2)
Pyrexia	6 (1.4)	5 (2.4)	11 (1.7)
Hepatobiliary disorders	16 (3.8)	8 (3.8)	24 (3.8)
Bile duct obstruction	0	1 (0.5)	1 (0.2)
Biliary colic	1 (0.2)	0	1 (0.2)
Cholangitis	1 (0.2)	0	1 (0.2)
Cholangitis acute	1 (0.2)	0	1 (0.2)
Cholecystitis acute	1 (0.2)	0	1 (0.2)
Hepatic failure	5 (1.2)	2 (1.0)	7 (1.1)
Hepatic haemorrhage	2 (0.5)	1 (0.5)	3 (0.5)
Hepatic pain	1 (0.2)	1 (0.5)	2 (0.3)
Hepatitis toxic	1 (0.2)	0	1 (0.2)
Hyperbilirubinaemia	1 (0.2)	2 (1.0)	3 (0.5)
Jaundice	1 (0.2)	0	1 (0.2)
Jaundice cholestatic	0	1 (0.5)	1 (0.2)
Liver injury	1 (0.2)	0	1 (0.2)
Immune system disorders	6 (1.4)	0	6 (1.0)

System Organ Class Preferred Term[a]	ADI-PEG 20 N = 421 N (%)	Placebo N = 209 N (%)	Total N = 630 N (%)
Anaphylactic reaction	1 (0.2)	0	1 (0.2)
Anaphylactic shock	1 (0.2)	0	1 (0.2)
Hypersensitivity	4 (1.0)	0	4 (0.6)
Infections and infestations	22 (5.2)	13 (6.2)	35 (5.6)
Abdominal infection	0	1 (0.5)	1 (0.2)
Bacteraemia	0	1 (0.5)	1 (0.2)
Biliary tract infection	3 (0.7)	1 (0.5)	4 (0.6)
Cellulitis	1 (0.2)	0	1 (0.2)
Chest wall abscess	1 (0.2)	0	1 (0.2)
Diarrhoea infectious	1 (0.2)	0	1 (0.2)
Escherichia urinary tract infection	1 (0.2)	0	1 (0.2)
Gastroenteritis	1 (0.2)	0	1 (0.2)
Incision site infection	0	1 (0.5)	1 (0.2)
Infection	4 (1.0)	1 (0.5)	5 (0.8)
Liver abscess	0	1 (0.5)	1 (0.2)
Lobar pneumonia	1 (0.2)	0	1 (0.2)
Localised infection	1 (0.2)	0	1 (0.2)
Lower respiratory tract infection	1 (0.2)	1 (0.5)	2 (0.3)
Lung infection	0	1 (0.5)	1 (0.2)
Orchitis	0	1 (0.5)	1 (0.2)
Pneumonia	2 (0.5)	3 (1.4)	5 (0.8)
Sepsis	3 (0.7)	2 (1.0)	5 (0.8)
Urinary tract infection	1 (0.2)	1 (0.5)	2 (0.3)
Urosepsis	1 (0.2)	0	1 (0.2)
Injury, poisoning and procedural complications	6 (1.4)	3 (1.4)	9 (1.4)
Compression fracture	0	1 (0.5)	1 (0.2)
Fall	0	1 (0.5)	1 (0.2)
Fracture	1 (0.2)	0	1 (0.2)
Humerus fracture	1 (0.2)	0	1 (0.2)
Lower limb fracture	1 (0.2)	0	1 (0.2)
Post procedural haemorrhage	1 (0.2)	0	1 (0.2)
Spinal compression fracture	1 (0.2)	0	1 (0.2)
Stoma site haemorrhage	1 (0.2)	0	1 (0.2)
Subdural haematoma	0	1 (0.5)	1 (0.2)
Wound complication	1 (0.2)	0	1 (0.2)

System Organ Class Preferred Term[a]	ADI-PEG 20 N = 421 N (%)	Placebo N = 209 N (%)	Total N = 630 N (%)
Investigations	15 (3.6)	4 (1.9)	19 (3.0)
Alanine aminotransferase increased	1 (0.2)	0	1 (0.2)
Ammonia increased	1 (0.2)	0	1 (0.2)
Aspartate aminotransferase increased	3 (0.7)	1 (0.5)	4 (0.6)
Blood bilirubin increased	9 (2.1)	1 (0.5)	10 (1.6)
Ejection fraction decreased	1 (0.2)	0	1 (0.2)
Hepatic enzyme increased	0	1 (0.5)	1 (0.2)
International normalised ratio increased	0	1 (0.5)	1 (0.2)
Neutrophil count decreased	1 (0.2)	0	1 (0.2)
Urine output decreased	1 (0.2)	0	1 (0.2)
Metabolism and nutrition disorders	5 (1.2)	11 (5.3)	16 (2.5)
Cachexia	0	1 (0.5)	1 (0.2)
Decreased appetite	1 (0.2)	1 (0.5)	2 (0.3)
Dehydration	2 (0.5)	1 (0.5)	3 (0.5)
Diabetes mellitus	1 (0.2)	1 (0.5)	2 (0.3)
Fluid overload	0	1 (0.5)	1 (0.2)
Hypercalcaemia	0	3 (1.4)	3 (0.5)
Hyperkalaemia	1 (0.2)	1 (0.5)	2 (0.3)
Hypoglycaemia	1 (0.2)	1 (0.5)	2 (0.3)
Hyponatraemia	0	1 (0.5)	1 (0.2)
Metabolic acidosis	0	1 (0.5)	1 (0.2)
Musculoskeletal and connective tissue disorders	7 (1.7)	3 (1.4)	10 (1.6)
Arthralgia	1 (0.2)	1 (0.5)	2 (0.3)
Arthritis	1 (0.2)	0	1 (0.2)
Back pain	2 (0.5)	1 (0.5)	3 (0.5)
Mobility decreased	1 (0.2)	0	1 (0.2)
Muscular weakness	1 (0.2)	1 (0.5)	2 (0.3)
Musculoskeletal pain	2 (0.5)	0	2 (0.3)
Pain in extremity	0	1 (0.5)	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	44 (10.5)	11 (5.3)	55 (8.7)
Brain cancer metastatic	1 (0.2)	0	1 (0.2)
Hepatic neoplasm	1 (0.2)	0	1 (0.2)
Hepatocellular carcinoma	1 (0.2)	1 (0.5)	2 (0.3)
Liver carcinoma ruptured	1 (0.2)	0	1 (0.2)
Malignant neoplasm progression	28 (6.7)	5 (2.4)	33 (5.2)

System Organ Class Preferred Term[a]	ADI-PEG 20 N = 421 N (%)	Placebo N = 209 N (%)	Total N = 630 N (%)
Metastases to bone	1 (0.2)	1 (0.5)	2 (0.3)
Metastases to central nervous system	5 (1.2)	1 (0.5)	6 (1.0)
Metastases to lung	2 (0.5)	0	2 (0.3)
Metastases to spine	0	2 (1.0)	2 (0.3)
Metastases to spleen	1 (0.2)	0	1 (0.2)
Neoplasm malignant	1 (0.2)	0	1 (0.2)
Neoplasm progression	1 (0.2)	1 (0.5)	2 (0.3)
Tumour embolism	1 (0.2)	0	1 (0.2)
Tumour haemorrhage	1 (0.2)	1 (0.5)	2 (0.3)
Nervous system disorders	37 (8.8)	9 (4.3)	46 (7.3)
Brain stem infarction	1 (0.2)	0	1 (0.2)
Cerebral haemorrhage	0	1 (0.5)	1 (0.2)
Coma hepatic	2 (0.5)	0	2 (0.3)
Depressed level of consciousness	1 (0.2)	0	1 (0.2)
Encephalopathy	4 (1.0)	2 (1.0)	6 (1.0)
Haemorrhage intracranial	3 (0.7)	0	3 (0.5)
Headache	1 (0.2)	0	1 (0.2)
Hepatic encephalopathy	21 (5.0)	4 (1.9)	25 (4.0)
Hyperammonaemic encephalopathy	1 (0.2)	0	1 (0.2)
Lacunar infarction	1 (0.2)	0	1 (0.2)
Spinal cord compression	2 (0.5)	1 (0.5)	3 (0.5)
Syncope	0	1 (0.5)	1 (0.2)
Transient ischaemic attack	1 (0.2)	0	1 (0.2)
Psychiatric disorders	4 (1.0)	1 (0.5)	5 (0.8)
Confusional state	1 (0.2)	0	1 (0.2)
Disorientation	0	1 (0.5)	1 (0.2)
Insomnia	1 (0.2)	0	1 (0.2)
Mental status changes	2 (0.5)	0	2 (0.3)
Renal and urinary disorders	1 (0.2)	2 (1.0)	3 (0.5)
Acute kidney injury	0	2 (1.0)	2 (0.3)
Renal colic	1 (0.2)	0	1 (0.2)
Urinary tract obstruction	1 (0.2)	0	1 (0.2)
Reproductive system and breast disorders	1 (0.2)	0	1 (0.2)
Pelvic pain	1 (0.2)	0	1 (0.2)

System Organ Class Preferred Term[a]	ADI-PEG 20 N = 421 N (%)	Placebo N = 209 N (%)	Total N = 630 N (%)
Respiratory, thoracic and mediastinal disorders	15 (3.6)	8 (3.8)	23 (3.7)
Cough	1 (0.2)	0	1 (0.2)
Dyspnoea	6 (1.4)	4 (1.9)	10 (1.6)
Haemoptysis	1 (0.2)	1 (0.5)	2 (0.3)
Haemothorax	0	1 (0.5)	1 (0.2)
Hypoxia	1 (0.2)	0	1 (0.2)
Laryngeal haemorrhage	1 (0.2)	0	1 (0.2)
Mediastinal haemorrhage	0	1 (0.5)	1 (0.2)
Pharyngeal inflammation	1 (0.2)	0	1 (0.2)
Pleural effusion	4 (1.0)	2 (1.0)	6 (1.0)
Pleuritic pain	0	1 (0.5)	1 (0.2)
Pneumonitis	1 (0.2)	0	1 (0.2)
Pulmonary haemorrhage	0	1 (0.5)	1 (0.2)
Pulmonary oedema	1 (0.2)	0	1 (0.2)
Respiratory failure	1 (0.2)	1 (0.5)	2 (0.3)
Skin and subcutaneous tissue disorders	2 (0.5)	1 (0.5)	3 (0.5)
Dermatitis allergic	1 (0.2)	0	1 (0.2)
Rash	0	1 (0.5)	1 (0.2)
Rash macular	1 (0.2)	0	1 (0.2)
Vascular disorders	3 (0.7)	0	3 (0.5)
Hypertension	2 (0.5)	0	2 (0.3)
Superior vena cava syndrome	1 (0.2)	0	1 (0.2)

Abbreviations: ADI-PEG 20, arginine deiminase-polyethylene glycol of 20,000 molecular weight; TEAE, treatment-emergent adverse event.

Note: Unless otherwise noted, the denominator for percentages is the total number of subjects (N) in each treatment arm overall. Treatment-emergent adverse events included all adverse events that started on or after the first dose date of study drug, or adverse events that were present prior to the first dose of study drug, but their severity or relationship increased after the first dose of study drug, up to and including 30 days after the final study drug dosing date. At each level of summarization, a subject was only counted once if the subject reported 1 or more events.

[a] Events were mapped to the Medical Dictionary for Regulatory Activities (MedDRA Version 18.0) system for reporting (preferred term and body system).

Source: Table 14.3.1.4.

12.3.1.3 Other Significant Adverse Events

In the ADI-PEG 20 treatment group, 70 (16.6%) subjects experienced TEAEs that led to study drug discontinuation, compared with 31 (14.8%) in the Placebo treatment group.

Treatment-emergent AEs leading to discontinuation of study drug are summarized for each treatment group by subject in Table 12-11. The only TEAEs leading to discontinuation of study drug in ≥1% of subjects overall were malignant neoplasm progression (11 [1.7%] subjects), disease progression (7 [1.1%] subjects), and hepatic encephalopathy (6 [1.0%] subjects).

Treatment-emergent AEs resulting in study drug discontinuation are presented in Table 14.3.2.3.

Table 12-11 Treatment-Emergent Adverse Events Causing Discontinuation of Study Drug (Safety Population)

System Organ Class Preferred Term[a]	ADI-PEG 20 N = 421 N (%)	Placebo N = 209 N (%)	Total N = 630 N (%)
Total number of TEAEs causing discontinuation of study drug	73	31	104
Number of subjects with at least 1 TEAE causing discontinuation of study drug	70 (16.6)	31 (14.8)	101 (16.0)
Blood and lymphatic system disorders	0	1 (0.5)	1 (0.2)
Anaemia	0	1 (0.5)	1 (0.2)
Cardiac disorders	1 (0.2)	0	1 (0.2)
Cardiac arrest	1 (0.2)	0	1 (0.2)
Gastrointestinal disorders	8 (1.9)	2 (1.0)	10 (1.6)
Abdominal distension	1 (0.2)	0	1 (0.2)
Ascites	1 (0.2)	1 (0.5)	2 (0.3)
Gastrointestinal haemorrhage	1 (0.2)	1 (0.5)	2 (0.3)
Haematochezia	1 (0.2)	0	1 (0.2)
Oesophageal varices haemorrhage	3 (0.7)	0	3 (0.5)
Vomiting	1 (0.2)	0	1 (0.2)
General disorders and administration site conditions	10 (2.4)	5 (2.4)	15 (2.4)
Disease progression	4 (1.0)	3 (1.4)	7 (1.1)
Face oedema	1 (0.2)	0	1 (0.2)
Fatigue	2 (0.5)	0	2 (0.3)
General physical health deterioration	1 (0.2)	1 (0.5)	2 (0.3)
Generalised oedema	1 (0.2)	0	1 (0.2)
Injection site pain	1 (0.2)	0	1 (0.2)
Performance status decreased	0	1 (0.5)	1 (0.2)
Hepatobiliary disorders	5 (1.2)	5 (2.4)	10 (1.6)
Hepatic failure	2 (0.5)	2 (1.0)	4 (0.6)
Hepatic haemorrhage	1 (0.2)	1 (0.5)	2 (0.3)

System Organ Class Preferred Term[a]	ADI-PEG 20 N = 421 N (%)	Placebo N = 209 N (%)	Total N = 630 N (%)
Hyperbilirubinaemia	0	2 (1.0)	2 (0.3)
Jaundice	1 (0.2)	0	1 (0.2)
Liver injury	1 (0.2)	0	1 (0.2)
Immune system disorders	3 (0.7)	0	3 (0.5)
Anaphylactic reaction	1 (0.2)	0	1 (0.2)
Hypersensitivity	2 (0.5)	0	2 (0.3)
Infections and infestations	2 (0.5)	2 (1.0)	4 (0.6)
Abdominal infection	0	1 (0.5)	1 (0.2)
Biliary tract infection	1 (0.2)	0	1 (0.2)
Liver abscess	0	1 (0.5)	1 (0.2)
Sepsis	1 (0.2)	0	1 (0.2)
Injury, poisoning and procedural complications	1 (0.2)	0	1 (0.2)
Wound complication	1 (0.2)	0	1 (0.2)
Investigations	10 (2.4)	1 (0.5)	11 (1.7)
Alanine aminotransferase increased	2 (0.5)	0	2 (0.3)
Aspartate aminotransferase increased	3 (0.7)	1 (0.5)	4 (0.6)
Blood bilirubin increased	5 (1.2)	0	5 (0.8)
Transaminases increased	1 (0.2)	0	1 (0.2)
Metabolism and nutrition disorders	1 (0.2)	4 (1.9)	5 (0.8)
Diabetes mellitus	0	1 (0.5)	1 (0.2)
Fluid overload	0	1 (0.5)	1 (0.2)
Hypercalcaemia	0	1 (0.5)	1 (0.2)
Hypercholesterolaemia	0	1 (0.5)	1 (0.2)
Hyperkalaemia	1 (0.2)	0	1 (0.2)
Musculoskeletal and connective tissue disorders	0	1 (0.5)	1 (0.2)
Muscular weakness	0	1 (0.5)	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	15 (3.6)	3 (1.4)	18 (2.9)
Brain cancer metastatic	1 (0.2)	0	1 (0.2)
Hepatic neoplasm	1 (0.2)	0	1 (0.2)
Malignant neoplasm progression	8 (1.9)	3 (1.4)	11 (1.7)
Metastases to central nervous system	4 (1.0)	0	4 (0.6)
Neoplasm progression	1 (0.2)	0	1 (0.2)
Nervous system disorders	10 (2.4)	3 (1.4)	13 (2.1)
Brain stem infarction	1 (0.2)	0	1 (0.2)
Depressed level of consciousness	1 (0.2)	0	1 (0.2)
Encephalopathy	2 (0.5)	0	2 (0.3)
Haemorrhage intracranial	2 (0.5)	0	2 (0.3)

System Organ Class Preferred Term[a]	ADI-PEG 20 N = 421 N (%)	Placebo N = 209 N (%)	Total N = 630 N (%)
Hepatic encephalopathy	4 (1.0)	2 (1.0)	6 (1.0)
Spinal cord compression	0	1 (0.5)	1 (0.2)
Renal and urinary disorders	0	1 (0.5)	1 (0.2)
Acute kidney injury	0	1 (0.5)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	4 (1.0)	3 (1.4)	7 (1.1)
Dyspnoea	1 (0.2)	2 (1.0)	3 (0.5)
Haemoptysis	0	1 (0.5)	1 (0.2)
Hypoxia	1 (0.2)	0	1 (0.2)
Pleural effusion	1 (0.2)	0	1 (0.2)
Pulmonary oedema	1 (0.2)	0	1 (0.2)
Respiratory failure	1 (0.2)	0	1 (0.2)
Skin and subcutaneous tissue disorders	1 (0.2)	0	1 (0.2)
Rash macular	1 (0.2)	0	1 (0.2)

Abbreviations: ADI-PEG 20, arginine deiminase-polyethylene glycol of 20,000 molecular weight; TEAE, treatment-emergent adverse event.

Note: Unless otherwise noted, the denominator for percentages is the total number of subjects (N) in each treatment arm overall. Treatment-emergent adverse events included all adverse events that started on or after the first dose date of study drug, or adverse events that were present prior to the first dose of study drug, but their severity or relationship increased after the first dose of study drug, up to and including 30 days after the final study drug dosing date. At each level of summarization, a subject was counted only once if the subject reported 1 or more events.

[a] Events were mapped to the Medical Dictionary for Regulatory Activities (MedDRA Version 18.0) system for reporting (preferred term and body system).

Source: Table 14.3.1.9.

12.3.1.4 Adverse Events of Special Interest or Concern

ADI is found only in microbes and not in humans. As a foreign protein, ADI is highly immunogenic in humans as it is a non-human protein; however, the modification of ADI with PEG reduces the immunogenicity of ADI. Allergic reactions do, however, occur with biologics, even in their pegylated forms. Adverse events resembling allergy, hypersensitivity reactions and anaphylactic reactions have been observed in ADI-PEG 20 studies. Therefore, because Adverse Events of Special Interest (AESI) are those events thought to be [potentially] associated with the investigational compound the following AESI have been documented, for which narratives are written (Section 14.3.3), include hypersensitivity, allergic reation, anaphylaxis, and allergic rash.

Adverse Events of Special Interest occurred at a low frequency, and included hypersensitivity (9 [2.1%] subjects in the ADI-PEG 20 treatment group vs 0 [0.0%] in the Placebo treatment group), rash macular (3 [0.7%] subjects in the ADI-PEG 20 treatment group vs 1 [0.5%]

in the Placebo treatment group), dermatitis allergic (2 [0.5%] subjects in the ADI-PEG 20 treatment group vs 0 [0.0%] in the Placebo treatment group), anaphylactic reaction and anaphylactic shock (each in 1 [0.2%] subject in the ADI-PEG 20 treatment group vs 0 [0.0%] in the Placebo treatment group), drug hypersensitivity (1 [0.2%] subject in the ADI-PEG 20 treatment group and 1 [0.5%] subject in the Placebo treatment group). Of these, only 8 events were serious, all in the ADI-PEG 20 treatment group.

12.3.1.5 Relationship between Arginine and Citrulline Levels and Selected Safety Variables

The relationship between the arginine levels and selected safety variables is summarized in Table 14.2.8.7. The relationship between the citrulline levels and selected safety variables is summarized in Table 14.2.8.8.

The change from baseline at Week 4 in the arginine level was clinically significant for neutropenia ($P = 0.0112$). For citrulline, the change from baseline at Week 4 was clinically significant for neutropenia and thrombocytopenia ($P = 0.0017$ and 0.0027, respectively). Although these associations are significant, the odds ratios indicate the associations are not strong. Also, the overall incidence rate of both neutropenia and thrombocytopenia is not high (both 3.2%). Due to the limited number of events, this association may not be considered especially robust.

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

Narratives are provided in Section 14.3.3 for subjects who experienced the following:

- Death within 30 days from last administration of study drug, with the exception of deaths related to progression of disease understudy,
- Serious Adverse Events judged related to study drug,
- Adverse Events judged related to study drug and that lead to study drug discontinuation,
- Adverse Events of Special Interest included events of anaphylaxis and or hypersensitivity judged related to study drug.

Table 12-12 lists the subjects for whom narratives are written and the reason(s) for the narratives.

Table 12-12 Subject Narratives

Subject Number	Death Within Study or 30 Days Following Study Drug Discontinuation	Related Serious Adverse Event(s)	Related Adverse Event(s) Leading to Study Drug Discontinuation	Related Adverse Event(s) of Special Interest
e	X (Dyspnoea)			
102-0008	X (Cardiac arrest)			
205-0012	X (Upper gastrointestinal haemorrhage)			
257-0012	X (Sepsis)			
302-0011	X (Blood bilirubin increased)			
302-0022	X (Haemorrhage intracranial)			
305-0019	X (Upper gastrointestinal haemorrhage)			
305-0028	X (Encephalopathy)			

Subject Number	Death Within Study or 30 Days Following Study Drug Discontinuation	Related Serious Adverse Event(s)	Related Adverse Event(s) Leading to Study Drug Discontinuation	Related Adverse Event(s) of Special Interest
305-0039	X (Coma hepatic)			
305-0047	X (Hepatic encephalopathy)			
404-0001	X (Abdominal pain)			
405-0002	X (Oesophageal varices haemorrhage)			
502-0002	X (Respiratory failure)			
503-0004	X (Liver injury)			
309-0004	X (Malignant neoplasm progression)	X (Esophageal varices haemorrhage)		
513-0004	X (Gastrointestinal haemorrhage)	X (Gastrointestinal haemorrhage)	X (Gastrointestinal haemorrhage)	
307-0011	X (Sepsis)	X (Hypersensitivity, Stomatitis, Dermatitis allergic)	X (Hypersensitivity)	X (Hypersensitivity) (Dermatitis allergic)
201-0018		X (Hepatic failure)		
203-0005		X (Hepatic encephalopathy)		
307-0045		X (Hyperammonaemic encephalopathy)		
309-0003		X (Hepatic encephalopathy)		
309-0010		X (Hepatic encephalopathy)		
405-0021		X (Headache, Alanine & Aspartate		

Subject Number	Death Within Study or 30 Days Following Study Drug Discontinuation	Related Serious Adverse Event(s)	Related Adverse Event(s) Leading to Study Drug Discontinuation	Related Adverse Event(s) of Special Interest
		aminotransferase increased)		
101-0041		X (Vomiting)	X (Vomiting)	
101-0042		X (Hepatic encephalopathy)	X (Encephalopathy)	
201-0017		X (Hepatic failure)	X (Hepatic failure)	
252-0002		X (Muscular weakness, Rash macular)	X (Rash macular)	
257-0015		X (Arthralgia, Injection site pain)	X (Injection site pain)	
258-0015		X (Hepatic encephalopathy)	X (Hepatic encephalopathy)	
302-0025		X (Hemorrhage intracranial)	X (Hemorrhage intracranial)	
201-0020		X (Hypersensitivity)	X (Hypersensitivity)	X (Hypersensitivity)
257-0002		X (Anaphylactic reaction)	X (Anaphylactic reaction)	X (Anaphylactic reaction)
302-0008		X (Anaphylactic shock)		X (Anaphylactic shock)
302-0023		X (Hypersensitivity)		X (Hypersensitivity)
403-0002		X (Hypersensitivity)		X (Hypersensitivity)
203-0001			X (Face oedema)	
253-0002			X (Fatigue)	
259-0001			X (Fatigue)	
306-0036			X	

Subject Number	Death Within Study or 30 Days Following Study Drug Discontinuation	Related Serious Adverse Event(s)	Related Adverse Event(s) Leading to Study Drug Discontinuation	Related Adverse Event(s) of Special Interest
			(Alanine & Aspartate aminotransferase increased)	
114-0007				X (Hypersensitivity)
115-0001				X (Hypersensitivity)
257-0008				X (Hypersensitivity)
307-0025				X (Hypersensitivity)

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

On-study deaths are summarized in Table 14.3.2.1. Serious AEs are summarized in Table 14.3.2.2. The rate of on-study deaths (15.2% in the ADI-PEG 20 treatment group compared to 10.5% in the Placebo treatment group) and serious TEAEs (45.6% in the ADI-PEG 20 treatment group compared to 37.8% in the Placebo treatment group) were similar between the treatment groups. The on-study deaths were most commonly related to disease progression. There were some allergic-type reactions (AESI) in the ADI-PEG 20 treatment group, which contributed to the slightly higher incidence of serious TEAEs compared to the Placebo treatment group.

12.4 Clinical Laboratory Evaluation

As would be expected in this subject population as the disease progresses, there was a worsening over time in hematology, chemistry, and urinalysis parameters. Most had no apparent treatment-related trend, and no clinically relevant changes were seen in hematology, clinical chemistry, or urinalysis parameters. No abnormalities of potential clinical concern were reported for any laboratory test parameters.

12.4.1 Listing of Individual Laboratory Measurements by Subject and Each Abnormal Laboratory Value

Serum chemistry and hematology are presented by subject in Listing 16.2.8.1 and Listing 16.2.8.2, respectively. Hepatitis B and Hepatitis C laboratory results are presented by subject in Listing 16.2.8.3.

12.4.2 Evaluation of Individual Laboratory Parameters

12.4.2.1 Laboratory Values over Time

Clinical laboratory test results over time are presented for for serum chemistry in Listing 16.2.8.1, and for hematology in Listing 16.2.8.2.

12.4.2.2 Individual Subject Changes

Shifts from baseline in hematology parameters are summarized as follows:

- For ungraded CTCAE by high/low flag (Table 14.3.4.3)
- By CTCAE grade (Table 14.3.4.4)
- By concomitant antiviral therapy use for ungraded CTCAE by high/low flag (Table 14.3.4.7)
- By concomitant antiviral therapy use by CTCAE grade (Table 14.3.4.8)

As expected with the course of the disease, there was a worsening over time in subjects for all hematology parameters. For neutrophils, there were larger shifts from baseline to worst post-baseline CTCAE grade in the ADI-PEG 20 treatment group compared to the Placebo treatment group. All shifts from baseline to worst post-baseline CTCAE grade were generally unchanged by concomitant antiviral therapy use, although larger shifts in the ADI-PEG 20 treatment group versus the Placebo treatment group were seen for leukocytes in the subset of subjects with antiviral therapy use than in the subset without antiviral therapy use. Shifts from baseline in serum chemistry parameters are summarized as follows:

- For ungraded CTCAE by high/low flag (Table 14.3.4.5)
- By CTCAE grade (Table 14.3.4.6)
- By concomitant antiviral therapy use for ungraded CTCAE by high/low flag (Table 14.3.4.9)
- By concomitant antiviral therapy use by CTCAE grade (Table 14.3.4.10)

No treatment effect was apparent in serum chemistry parameters shifts from baseline to worst post-baseline CTCAE grade. All shifts from baseline to worst post-baseline CTCAE grade were generally unchanged by concomitant antiviral therapy use, although larger shifts in the ADI-PEG 20 treatment group versus the Placebo treatment group were seen for glucose in the subset of subjects with antiviral therapy use than in the subset without, and larger shifts in the Placebo treatment group versus the ADI-PEG 20 treatment group were seen for alkaline phosphatase in the subset of subjects with antiviral therapy use than in the subset without antiviral therapy use.

12.4.2.3 Individual Clinically Significant Abnormalities

Although ALT increased, AST increased, and blood bilirubin increased were reported as TEAEs in >7.5% of subjects overall, the percentages were similar between the ADI-PEG 20 treatment group and the Placebo treatment group (37 [8.8%] subjects and 17 [8.1%] subjects, respectively for ALT increased; 62 [14.7%] subjects and 29 [13.9%] subjects, respectively for AST increased; and 41 [9.7%] subjects and 18 [8.6%] subjects, respectively for blood bilirubin increased). Other than anemia (46 [10.9%] subjects in the ADI-PEG 20 treatment group and 24 [11.5%] subjects in the Placebo treatment group), no hematology or urinalysis laboratory abnormalities were reported as TEAEs in >7.5% of subjects overall.

12.5 Vital Sign Measurements, Physical Findings, and Other Observations Related to Safety

12.5.1 Vital Sign Measurements

Change from baseline in vital sign measurements are summarized in Table 14.3.5.1 and presented by subject in Listing 16.2.8.4. In general, there was no difference between the ADI-PEG 20 treatment group and the Placebo treatment group. Both hypotension and hypertension were reported as TEAEs in <5% of subjects overall, and were similar in the ADI-PEG 20 treatment group and the Placebo treatment group.

12.5.2 Other Safety Analyses

12.5.2.1 Physical Examination Results

Physical examination results are presented by subject in Listing 16.2.8.5. In general, there was no difference between the ADI-PEG 20 treatment group and the Placebo treatment group.

12.5.2.2 Eastern Cooperative Oncology Group Scores

Shift from baseline in ECOG scores is presented by subject in Listing 16.2.8.6. The ECOG scores tended to either remain the same, or to worsen over time, which would be expected over the course of the disease. In general, there was no difference between the ADI-PEG 20 treatment group and the Placebo treatment group.

12.5.2.3 Electrocardiogram Parameters

Shift from baseline in overall ECG interpretation is summarized in Table 14.3.5.3. Shift from baseline in QTc category is summarized in Table 14.3.5.4. ECG results are presented by subject in Listing 16.2.8.7. In general, there was no difference between the ADI-PEG 20 treatment group and the Placebo treatment group.

12.6 Pregnancies

No pregnancies were reported during the study.

12.7 Safety Conclusions

The mean (Std Dev) number of doses was 13.97 (14.54) and 16.47 (16.58) for the ADI-PEG 20 and Placebo treatment group, respectively. The mean (Std Dev) duration of exposure was 12.7 (14.38) weeks for the ADI-PEG 20 treatment group and 14.98 (16.06) weeks for the Placebo treatment group. The number of subjects with at least one dose delay was 174 (41.0%) in the ADI-PEG 20 treatment group and 72 (34.1%) in the Placebo treatment group. The most common reasons for dose delays were adverse event, laboratory abnormality, and other.

The incidence of subjects experiencing an AE was similar among the 2 treatment groups. A total of 406 (96.4%) subjects reported TEAEs in the ADI-PEG 20 treatment group and 201 (96.2%) in the Placebo treatment group. Among the TEAEs, 241 (57.2%) subjects reported drug-related TEAEs in the ADI-PEG 20 treatment group and 110 (52.6%) in the Placebo treatment group, although it was determined after database lock that the grade 5 gastric hemorrhage experienced by subject 513-0004 was not related to treatment with ADI-PEG 20. A total of 192 (45.6%) subjects reported serious TEAEs in the ADI-PEG 20 treatment group and 79 (37.8%) in the Placebo treatment group.

On-therapy TEAEs were more frequently reported under the gastrointestinal disorders, and General disorders and administration site conditions SOCs in both treatment groups. Fatigue was the most common TEAE under the General disorders and administration site conditions SOC and overall, with a similar event rate in the ADI-PEG 20 treatment group and in the Placebo treatment group (23.3% and 26.8%, respectively). Decreased appetite under the Metabolism and nutrition disorders SOC was the second most common TEAE overall, with a similar event rate in the ADI-PEG 20 treatment group and in the Placebo treatment group (22.8% and 19.6%, respectively).

Although the incidence of other commonly occurring TEAEs was generally similar between the treatment groups, an imbalance was observed for the Skin and subcutaneous tissue disorders SOC, where events were more common in the ADI-PEG 20 treatment group than the Placebo treatment group (34.9% vs 25.8%, respectively).

The number of subjects reporting at least one TEAE who received antiviral therapy or not (223 and 384, respectively) closely mirrors the number of subjects who received antiviral therapy or not (231 [36.4%] vs 404 [63.6%], respectively). The distribution of commonly

occurring TEAEs among the SOCs was generally similar between the ADI-PEG 20 and Placebo treatment groups whether or not antiviral therapy was received.

The incidence of subjects with TEAEs causing discontinuation of study drug was similar in the ADI-PEG 20 treatment group (16.6%) and the Placebo treatment group (14.8%). The only TEAEs leading to discontinuation of study drug in ≥1% of subjects overall were malignant neoplasm progression (11 [1.7%] subjects), disease progression (7 [1.1%] subjects), and hepatic encephalopathy (6 [1.0%] subjects). The incidence of on-study deaths (deaths that occurred within 30 days of the last dose of study drug) was 15.2% in the ADI-PEG 20 treatment group and 10.5% the Placebo treatment group

Most TEAEs were CTCAE grade 1. The total number of subjects who reported TEAEs with a CTCAE grade >3 was 88 (20.9%) in the ADI-PEG 20 treatment group and 31 (14.8%) in the Placebo treatment group. The most frequently reported on-therapy grade 4 and 5 TEAEs were under the Neoplasms benign, malignant and unspecified (incl cysts and polyps); Investigations; and Metabolism and nutrition disorders SOCs in both treatment groups. Malignant neoplasm progression was the most common CTCAE grade >3 TEAE under the Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC and overall, with a similar event rate in the ADI-PEG 20 treatment group and in the Placebo treatment group (5.0% and 1.9%, respectively). Disease progression was the second most common CTCAE grade >3 TEAE overall, with an event rate equal in the ADI-PEG 20 treatment group and in the Placebo treatment group (1.9% each).

Other than disease progression and malignant neoplasm progression, no individual TEAE of grade 5 intensity was experienced by more than 3 subjects in either treatment group. Two events were experienced by more than 20% of subjects in either treatment group; fatigue (98 [23.3%] subjects in the ADI-PEG 20 treatment group, and 56 [26.8%] subjects in the Placebo treatment group), and decreased appetite (96 [22.8%] subjects in the ADI-PEG 20 treatment group, and 41 [19.6%] subjects in the Placebo treatment group). No events occurred more frequently (at least 10% higher) in one treatment group versus the other.

The overall incidence of TEAEs considered related to study drug by the investigator was 57.2% in the ADI-PEG 20 treatment group and 52.6% in the Placebo treatment group (although it was determined after database lock that the grade 5 gastric hemorrhage experienced by subject 513-0004 was not related to treatment with ADI-PEG 20). Most TEAEs considered related to study drug were reported in no more than 7.5% of subjects.

The number of subjects with at least 1 drug-related TEAE with a grade >3 was low in both groups at 8 (1.9%) in the ADI-PEG 20 treatment group and 1 (0.5%) in the Placebo treatment

group (although as noted, it was determined after database lock that the grade 5 gastric hemorrhage experienced by subject 513-0004 was not related to treatment with ADI-PEG 20). On-therapy, drug-related grade 4 and 5 TEAEs were most frequently reported under the Investigations SOC in the ADI-PEG 20 treatment group. Hepatic failure and Blood cholesterol increased were the most common drug-related CTCAE grade >3 TEAEs under the Hepatobiliary disorders and Investigations SOCs, respectively, and overall, with a similar event rate in the ADI-PEG 20 treatment group and in the Placebo treatment group (0.5% and 0.0%, respectively).

In the ADI-PEG 20 treatment group, 192 (45.6%) subjects experienced serious TEAEs during the study compared with 79 (37.8%) subjects in the Placebo treatment group. The most commonly reported preferred term was malignant neoplasm progression, with 28 (6.7%) subjects in the ADI-PEG 20 treatment group, compared with 5 (2.4%) subjects in the Placebo treatment group, and was the most frequent event in the Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC (which was also the most commonly reported SOC). The next most commonly reported preferred terms were hepatic encephalopathy (21 [5.0%] subjects in the ADI-PEG 20 treatment group compared with 4 [1.9%] subjects in the Placebo treatment group), and disease progression (15 [3.6%] subjects in the ADI-PEG 20 treatment group compared with 10 [4.8%] subjects in the Placebo treatment group), both at 25 (4.0%) subjects overall.

The number of subjects with at least 1 drug-related, serious TEAE with a grade >3 was 4 (1.0%) in the ADI-PEG 20 treatment group and 0 (0.0%) in the Placebo treatment group, although as noted, it was determined after database lock that the grade 5 gastric hemorrhage experienced by subject 513-0004 was not related to treatment with ADI-PEG 20. On therapy, drug-related, serious grade 4 and 5 TEAEs were most frequently reported under the Hepatobiliary disorders SOC in the ADI-PEG 20 treatment group. Hepatic failure was the most common drug related, serious CTCAE grade >3 TEAE under the Hepatobiliary disorders SOC and overall, with a similar event rate in the ADI-PEG 20 treatment group and in the Placebo treatment group (0.5% and 0.0%, respectively).

The overall incidence of serious TEAEs considered related to study drug by the investigator was 5.0% in the ADI-PEG 20 treatment group and 1.4% in the Placebo treatment group. Most serious TEAEs considered related to study drug were reported in less than 1.0% of subjects, with the exception of hypersensitivity in 1.0% and hepatic encephalopathy in 1.2% of subjects in the ADI-PEG 20 treatment group.

In the ADI-PEG 20 treatment group, 64 (15.2%) subjects died during the study (deaths that occurred within 30 days of the last dose of study drug) and 22 (10.5%) in the Placebo treatment group.

Adverse Events of Special Interest occurred at a low frequency, and included hypersensitivity (9 [2.1%] subjects in the ADI-PEG 20 treatment group vs 0 [0.0%] in the Placebo treatment group), rash macular (3 [0.7%] subjects in the ADI-PEG 20 treatment group vs 1 [0.5%] in the Placebo treatment group), dermatitis allergic (2 [0.5%] subjects in the ADI-PEG 20 treatment group vs 0 [0.0%] in the Placebo treatment group), anaphylactic reaction and anaphylactic shock (each in 1 [0.2%] subject in the ADI-PEG 20 treatment group vs 0 [0.0%] in the Placebo treatment group), drug hypersensitivity (1 [0.5%] subject in the ADI-PEG 20 treatment group and 1 [2.0%] subject in the Placebo treatment group). Of these, only 8 events were serious, all in the ADI-PEG 20 treatment group.

Although various changes in hematology and chemistry laboratory values were observed as would be expected in this subject population as the disease progresses, there was a worsening over time in hematology, chemistry, and urinalysis parameters. For neutrophils, there were larger shifts from baseline to worst post-baseline CTCAE grade in the ADI-PEG 20 treatment group compared to the Placebo treatment group. All shifts from baseline to worst post-baseline CTCAE grade were generally unchanged by concomitant antiviral therapy use, although larger shifts in the ADI-PEG 20 treatment group versus the Placebo treatment group were seen for leukocytes in the subset of subjects with antiviral therapy use than in the subset without antiviral therapy use. No treatment effect was apparent in serum chemistry parameters shifts from baseline to worst post-baseline CTCAE grade. All shifts from baseline to worst post-baseline CTCAE grade were generally unchanged by concomitant antiviral therapy use, although larger shifts in the ADI-PEG 20 treatment group versus the Placebo treatment group were seen for glucose in the subset of subjects with antiviral therapy use than in the subset without, and larger shifts in the Placebo treatment group versus the ADI-PEG 20 treatment group were seen for alkaline phosphatase in the subset of subjects with antiviral therapy use than in the subset without antiviral therapy use.

Although ALT increased, AST increased, and blood bilirubin increased were reported as TEAEs in >7.5% of subjects overall, the percentages were similar between the ADI-PEG 20 treatment group and the Placebo treatment group (37 [8.8%] subjects and 17 [8.1%] subjects, respectively for ALT increased; 62 [14.7%] subjects and 29 [13.9%] subjects, respectively for AST increased; and 41 [9.7%] subjects and 18 [8.6%] subjects, respectively for blood bilirubin increased). Other than anemia (46 [10.9%] subjects in the ADI-PEG 20 treatment

group and 24 [11.5%] subjects in the Placebo treatment group), no hematology or urinalysis laboratory abnormalities were reported as TEAEs in >7.5% of subjects overall.

The change from baseline at Week 4 in the arginine level was clinically significant for neutropenia ($P = 0.0112$). For citrulline, the change from baseline at Week 4 was clinically significant for neutropenia and thrombocytopenia ($P = 0.0017$ and 0.0027, respectively). Although these associations are significant, the odds ratios indicate the associations are not strong. Also, the overall incidence rate of both neutropenia and thrombocytopenia is not high (both 3.2%). Due to the limited number of events, this association may not be considered especially robust.

In general, there was no difference between the ADI-PEG 20 treatment group and the Placebo treatment group for vital signs, physical examination results, shift from baseline in ECOG scores, or shifts from baseline in ECG parameters.

13 Discussion and Conclusions

This was a multi-center, multi-national, Phase 3, double-blind (subject, caregiver, investigator, and outcomes assessor), placebo-controlled study of ADI-PEG 20 in subjects with advanced HCC who had failed prior systemic therapy. Failure was defined as having progressed radiographically on, or been intolerant to, prior systemic therapy. Intolerance was defined as discontinuation due to an AE(s) on prior systemic therapy that was unacceptable to the treating physician and/or subject, with or without dose interruption and modification. For sorafenib or any other systemic antineoplastic agent, failure generally required at least 14 days of treatment for the agent that defined failure. Thus, ADI-PEG 20 was being evaluated as second line, and in some cases third line or later systemic chemotherapy.

Eligible subjects received ADI-PEG 20 at 18 mg/m^2 or placebo by IM injection (1 cycle = 4 weekly treatments). Subjects in both groups continued to receive best supportive care. Computed tomography or MRI scans were performed at baseline and at the end of every 12 weeks (3 cycles) for assessment of tumor response according to RECIST 1.1 criteria. Subjects could continue to receive treatments unless one of the following occurred at any time during the course of therapy: unacceptable AEs, death, or PD. Subjects with a CR may have received 1 additional cycle (4 weekly treatments).

13.1 Efficacy

The primary efficacy endpoint for this study, median OS using the ITT Population, was not met. Overall survival (at the time of 487 deaths) was estimated at 7.8 months (range 0.37 to 41.8+ months) for the ADI-PEG 20 treatment group and 7.4 months (range 0.67 to 47.73+ months) for the Placebo treatment group, which did not reach statistical significance ($P = 0.884$).

For the sensitivity analysis (all 525 deaths), using the ITT Population (635 subjects), median OS was estimated at 7.3 months (range 0.37 to 41.8+ months) for the ADI-PEG 20 treatment group and 7.2 months (range 0.67 to 47.73+ months) for the Placebo treatment group, which did not reach statistical significance ($P = 0.775$).

The ADI-PEG 20 treatment group did not demonstrate improvement relative to the Placebo treatment group on any of the secondary efficacy endpoints for any of the analyses.

Differences between the ADI-PEG 20 and Placebo treatment groups were not statistically significant (P values were ≥ 0.5) for PFS, BOTR at all timepoints, TTP, BODC, and decline in AFP. Additionally, results were not statistically significant for analyses of OS by the subgroups of region – sorafenib treatment status (Asia and non-sorafenib failure, Asia

and sorafenib failure, NA and Europe and non-sorafenib failure, and NA and Europe and sorafenib failure), geographical region (Asia vs NA and Europe), sorafenib treatment status (non-sorafenib failure and sorafenib failure), ECOG performance status at screening (0 vs 1 and 2), presence or absence of macroscopic vascular invasion (portal vein or branches), presence or absence of extrahepatic spread, etiology of HCC (hepatitis C, hepatitis B, alcohol, NASH, and other), or antiviral therapy use (yes or no).

As expected, the null hypothesis that the ADI-PEG 20 blood levels and arginine blood levels were not correlated was rejected for the change from baseline at all time points through 16 weeks. Therefore, ADI-PEG 20 and arginine blood levels can be considered as correlated. The null hypothesis that the ADI-PEG 20 blood levels and citrulline blood levels were not correlated was rejected for the change from baseline at all time points through 16 weeks. Therefore, ADI-PEG 20 and citrulline blood levels can be considered as correlated.

Compared to the subjects with arginine depletion for ≤ 3 weeks (median OS: 5.7 months), subjects who experienced arginine depletion for >3 to ≤7 weeks or for >7 weeks had a longer OS (median: 8.3 months, $P = 0.9603$; median: 12.5 months, $P = 0.0002$, respectively), after adjusting for treatment duration ($P < 0.0001$). Compared to the subjects with citrulline increase for ≤3 weeks (median OS: 5.2 months), subjects with citrulline increase for >3 to ≤7 weeks, or for >7 weeks had a longer OS (median: 6.3 months, $P = 0.955$; median: 13.0 months, $P < 0.0006$, respectively), after adjusting for treatment duration ($P < 0.0001$).

13.2 Safety

Almost all subjects (96.3%) experienced at least one TEAE during the study, and was similar between the treatment groups.

The incidence of subjects experiencing a TEAE was similar among the 2 treatment groups, as was the incidence of drug-related TEAEs. Subjects in the ADI-PEG 20 treatment group and the Placebo treatment group had similar distribution of grade >3 TEAEs (20.9% and 14.8%, respectively), drug-related TEAEs with grade >3 (1.9% and 0.5%, respectively), serious TEAEs (45.9% and 37.8%, respectively), serious drug-related TEAEs (5.0% and 1.4%, respectively), TEAEs causing discontinuation of study drug (16.6% and 14.8%, respectively), and on-study deaths (15.2% and 10.5%, respectively).

Most TEAEs were CTCAE grade 1. Two events were experienced by more than 20% of subjects in either treatment group; fatigue (98 [23.3%] subjects in the ADI-PEG 20 treatment group, and 56 [26.8%] subjects in the Placebo treatment group), and decreased appetite (96 [22.8%] subjects in the ADI-PEG 20 treatment group, and 41 [19.6%] subjects in the

Placebo treatment group). No events occurred more frequently (at least 10% higher) in one treatment group versus the other.

On-therapy TEAEs were more frequently reported under the gastrointestinal disorders, and General disorders and administration site conditions SOCs in both treatment groups. Fatigue was the most common TEAE under the General disorders and administration site conditions SOC and overall, with a similar event rate in the ADI-PEG 20 treatment group and in the Placebo treatment group (23.3% and 26.8%, respectively). Although the incidence of other commonly occurring TEAEs was generally similar between the treatment groups, an imbalance was observed for the Skin and subcutaneous tissue disorders SOC, where events were more common in the ADI-PEG 20 treatment group (34.9% vs 25.8%, respectively). No events occurred more frequently (at least 10% higher) in one treatment group versus the other. Most TEAEs considered related to study drug were reported in less than 7.5% of subjects, and most serious TEAEs considered related to study drug were reported in no more than 1.0% of subjects, with the exception of hypersensitivity in 1.0% and hepatic encephalopathy in 1.2% of subjects in the ADI-PEG 20 treatment group.

The number of subjects reporting at least one TEAE who received antiviral therapy or not (223 and 384, respectively) closely mirrors the number of subjects who received antiviral therapy or not (231 [36.4%] vs 404 [63.6%], respectively). The distribution of commonly occurring TEAEs among the SOCs was generally similar between the ADI-PEG 20 and Placebo treatment groups whether or not antiviral therapy was received.

Adverse Events of Special Interest occurred at a low frequency, and included hypersensitivity (9 [2.1%] subjects in the ADI-PEG 20 treatment group vs 1 [0.5%] in the Placebo treatment group), rash macular (3 [0.7%] subjects in the ADI-PEG 20 treatment group vs 1 [0.5%] in the Placebo treatment group), dermatitis allergic (2 [0.5%] subjects in the ADI-PEG 20 treatment group vs 0 [0.0%] in the Placebo treatment group), anaphylactic reaction and anaphylactic shock (each in 1 [0.2%] subject in the ADI-PEG 20 treatment group vs 0 [0.0%] in the Placebo treatment group), drug hypersensitivity (1 [0.2%] subject in the ADI-PEG 20 treatment group and 1 [0.5%] subject in the Placebo treatment group).

Although various changes in hematology and chemistry laboratory values were observed as would be expected in this subject population as the disease progresses, there was a worsening over time in hematology, chemistry, and urinalysis parameters. For neutrophils, there were larger shifts from baseline to worst post-baseline CTCAE grade in the ADI-PEG 20 treatment group compared to the Placebo treatment group. All shifts from baseline to worst post-baseline CTCAE grade were generally unchanged by concomitant antiviral therapy use,

although larger shifts in the ADI-PEG 20 treatment group versus the Placebo treatment group were seen for leukocytes in the subset of subjects with antiviral therapy use than in the subset without antiviral therapy use. No treatment effect was apparent in serum chemistry parameters shifts from baseline to worst post-baseline CTCAE grade. All shifts from baseline to worst post-baseline CTCAE grade were generally unchanged by concomitant antiviral therapy use, although larger shifts in the ADI-PEG 20 treatment group versus the Placebo treatment group were seen for glucose in the subset of subjects with antiviral therapy use than in the subset without, and larger shifts in the Placebo treatment group versus the ADI-PEG 20 treatment group were seen for alkaline phosphatase in the subset of subjects with antiviral therapy use than in the subset without antiviral therapy use.

Although ALT increased, AST increased, and blood bilirubin increased were reported as TEAEs in >7.5% of subjects overall, the percentages were similar between the ADI-PEG 20 treatment group and the Placebo treatment group (37 [8.8%] subjects and 17 [8.1%] subjects, respectively for ALT increased; 62 [14.7%] subjects and 29 [13.9%] subjects, respectively for AST increased; and 41 [9.7%] subjects and 18 [8.6%] subjects, respectively for blood bilirubin increased). Other than anemia (46 [10.9%] subjects in the ADI-PEG 20 treatment group and 24 [11.5%] subjects in the Placebo treatment group), no hematology or urinalysis laboratory abnormalities were reported as TEAEs in > 7.5% of subjects overall.

For citrulline, the change from baseline at Week 4 was clinically significant for neutropenia and thrombocytopenia. Although these associations are significant, the odds ratios indicate the associations are not strong. Also, the overall incidence rate of both neutropenia and thrombocytopenia is not high (both 3.2%). Due to the limited number of events, this association may not be considered especially robust.

In general, there was no difference between the ADI-PEG 20 treatment group and the Placebo treatment group for vital signs, physical examination results, shift from baseline in ECOG scores, or shifts from baseline in ECG parameters.

13.3 Overall Conclusions

- In subjects with advanced HCC who had failed prior systemic therapy, multiple-cycle treatment with ADI-PEG 20 did not meet the primary endpoint of the study. The ADI-PEG 20 treatment group did not have a greater length of OS compared with the Placebo group. In addition, the difference between the treatment groups was not statistically significant (ie, all *P* values ≥0.05) for PFS, BOTR at all timepoints, TTP, BODC, and decline in AFP. Additionally, results were not statistically significant for analyses of OS by all pre-defined subgroups.

- As expected, there was a correlation between ADI-PEG 20 blood levels and arginine blood levels, with a survival benenfit associated with arginine depletion. There was also a correlation between ADI-PEG 20 blood levels and citrulline blood levels, with a survival benefit associated with citrulline increase.
- In general, the incidence of drug-related TEAEs, grade ≥3 TEAEs, serious TEAEs, serious drug-related TEAEs, drug-related TEAEs causing discontinuation, and on-study deaths were similar in the ADI-PEG 20 treatment group and in the Placebo treatment group.
- Adverse Events of Special Interest occurred at a low frequency (≤2.1%), and included hypersensitivity, rash macular, dermatitis allergic, anaphylactic reaction, anaphylactic shock, and drug hypersensitivity.
- Overall, treatment with ADI-PEG 20 did not demonstrate clinical benefit with regard to efficacy as determined by OS in the population of advanced HCC with failed prior systemic therapy enrolled in this study.
- Treatment with ADI-PEG 20 did, however, demonstrate an increased OS in those subjects with prolonged (>7 weeks) arginine depletion or prolonged (>7 weeks) citrulline increase.
- The safety of treatment with ADI-PEG 20 in this population was acceptable, and generally similar to that of placebo. Most frequently occurring TEAEs were fatigue and decreased appetite. The most frequently occurring drug-related TEAEs were fatigue and rash.
- Strategies to enhance prolonged arginine depletion (or citrulline increase), which has correlated with increased OS in a population with advanced HCC, are warranted.

14 Tables and Figures Referred to but not Included in the Text

14.1 Demographic Data

Number	Title
Table 14.1.1	Subject Disposition (Intent-to-Treat Population)
Table 14.1.2.1	Protocol Deviations (Intent-to-Treat Population
Table 14.1.2.2	Demographics and Baseline Characteristics (Intent-to-Treat Population)
Table 14.1.3	Prior Medications (Safety Population)
Table 14.1.4	Concomitant Medications (Safety Population)
Table 14.1.5.1	Drug Exposure (Intent-to-Treat Population)

14.2 Efficacy Data

14.3 Safety Data

14.3.1 Displays of Adverse Events

14.3.2 Listings of Deaths and Other Serious and Significant Adverse Events

By-subject listings of death and other serious and significant AEs are provided in Section 16.2.7.

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

Narratives are provided for subjects who experienced the following:

- Death within 30 days from last administration of study drug, with the exception of deaths related to progression of disease understudy,
- Serious Adverse Events judged related to study drug,
- Adverse Events judged related to study drug and that lead to study drug discontinuation,
- Adverse Events of Special Interest included events of anaphylaxis and or hypersensitivity judged related to study drug.

Sponsor assessments of causality are only provided in the narratives when required (i.e. narratives written for SAE(s)).

Reason(s) for Narrative: Death
Subject ID: 101-0018
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Dyspnoea	Death	2012-03-28 / 2012-03-31	5	Dose not changed	Fatal	Not Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:
Subject 101-0018 was a 51-year-old Asian-mainland China male randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2012-02-21; and received once-weekly treatment with study drug between 2012-02-21 and 2012-03-06. The subject received a total of 3 injections of ADI-PEG 20.

The subject was first diagnosed with stage IV hepatocellular carcinoma on 2011-07-28. The subject received prior systemic chemotherapy with sorafenib from 2011-08-00 to 2012-01-31. Other therapies the subject received included transarterial chemoembolization with doxorubicin-eluting beads. The subject underwent surgery for right lower lobe VATS

(video-assisted thoracoscopic surgery) with a wedge resection of pulmonary nodule on 2011-07-28. Prior to the start of study treatment, the subject's ongoing medical conditions included hepatitis B, hepatomegaly, and pleural effusion.

Concomitant medications (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug and during the study, included azithromycin, ceftriaxone, ciprofloxacin, docusate, enoxaparin, furosemide, guaifenesin, ipratropium, levosalbutamol magnesium sulfate, morphine sulfate, ondansetron, pantoprazole, paracetamol, piperacillin, salbutamol, sennoside a/b, simeticone, spironolactone, vancomycin.

Starting 2012-02-29, the subject developed Grade 3 dyspnea. No action was taken with study therapy; and no hospitalization or treatment was required. On 2012-03-12, the dyspnea worsened to Grade 3 dyspnea, and subject experienced Grade 3 pleural effusion. The subject was hospitalized as a result of the events. The subject's last dose of study drug prior to the event was administered on 06MAR2012.

Diagnostics included a chest radiography which showed possible bilateral pleural effusion on admission; a CT scan of chest, abdomen, and pelvis which revealed enlarged pulmonary metastases since 2012-02-16, with increased small left and moderate to large right pleural effusions resulting in increased compressive atelectasis. There was a new small to moderate pericardial effusion, with an increase in the thoracic adenopathy, left posterior iliac bone metastasis, and multifocal hepatocellular carcinoma. A tumor thrombus with new extension into the intrahepatic inferior vena cava (IVC); and the number of splenic infarcts was also increased. On 2012-03-14, a thoracic ultrasound and thoracentesis revealed pleural effusion along medial border of scapula and right pleural fluid at level of hemidiaphragm; pleural fluid cytology indicated right pleural fluid negative for malignant cells (mesothelia atypia, inflammation present); and an echocardiography showed ejection fraction >55%, trace mitral regurgitation, and trace aortic regurgitation. According to the CIOMS, treatment during the hospitalization included acetaminophen, albuterol inhalant, azithromycin, ceftriaxone, ciprofloxacin, docusate, enoxaparin, furosemide, guaifenesin, magnesium sulfate, morphine sulfate, ondansetron, pantoprazole, piperacillin, simethicone, and vancomycin.

On 2012-03-21, the event of dyspnea was considered recovered/resolved with sequelae and pleural effusion was considered not recovered/not resolved; the subject was discharged from the hospital the same day. The dyspnea and pleural effusion events were considered to be unrelated to study with an alternate etiology of disease progression. The study drug was interrupted as a result of the events.

On 2012-03-28, 22 days after the last dose of study drug, the subject was hospitalized under hospice care as a result of worsening dyspnea. No action was taken with study treatment as a result of the worsening dyspnea; however, the study drug was withdrawn as a result of disease progression. Three days later, the subject died as a result of Grade 5 dyspnea. According to the CIOMS, no autopsy was performed and no death certificate was available. The Investigator determined the cause of death to be malignant disease.

The Investigator considered the fatal event of dyspnea to be not related to ADI-PEG 20; an alternate etiology of disease progression was reported. The Polaris Medical Monitor agreed with the Investigator's assessment.

No abnormal laboratory values were recorded during the adverse events.

Reason(s) for Narrative: Death
Subject ID: 102-0008
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Cardiac arrest	Death	2014-02-09 / 2014-02-10	5	Drug withdrawn	Fatal	Unlikely Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:
Subject 102-0008 was a 64-year-old black or african american male randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2014-01-02; and received once-weekly treatment with study drug between 2014-01-08 and 2014-02-05. The subject received a total of 5 injections of ADI-PEG 20.

The subject was first diagnosed with stage IIIA hepatocellular carcinoma on 2009-09-30. The subject received prior systemic chemotherapy with sorafenib from 2013-08-20 to 2013-12-17. Other therapies the subject received included laparoscopic microwave ablation of liver mass. Prior to the start of study treatment, the subject's medical history included epidermal cyst, and a kidney stone. The subject's ongoing medical conditions included alcohol abuse in remission, allergic rhinitis, gouty arthritis, cholelithiasis, cocaine

dependence in remission, depressive disorder, dry skin, emphysema, essential hypertension, fatigue - grade 1, gastroesophageal reflux disorder, gout, high cholesterol, low back pain, male erectile disorder, male hypogonadism, marginal zone lymphoma, nausea/vomiting, normocytic anemia, peripheral neuropathy, Peyronie's disease, and thrombocytopenia.

Concomitant medications, (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug and during the study, included allopurinol, ascorbic acid w/biotin/calcium/carb, citalopram, colestipol hydrochloride, flunisolide, furosemide, gabapentin, metoprolol, mirtazapine, omeprazole, ondansetron, urea.
On 2014-01-23, the subject was dispensed darbepoetin alfa for anemia / low hemoglobin (result was not reported).

On 2014-02-09, the subject experienced a cardiac arrest and was hospitalized for the event. The subject's last dose (week 5) of study drug prior to the event was administered on 05FEB2014. Treatment was not reported; however, the study drug was withdrawn as a result of the event. On 2014-02-10, 5 days after the last dose of study drug was administered, the subject died as a result of a Grade 5 cardiac arrest event. The site was unable to obtain authorization from family for additional death information.

The Investigator considered the event of cardiac arrest to be unlikely related to ADI-PEG 20; an alternate etiology of cardiac (unspecified) was reported (in CIOMS). The Polaris Medical Monitor agreed with the Investigator's assessment.

No abnormal laboratory values were recorded during the adverse events.

Reason(s) for Narrative: Death
Subject ID: 205-0012
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Upper gastrointestinal haemorrhage	Death	2013-01-08 / 2013-01-08	5	Dose not changed	Fatal	Unlikely Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:
Subject 0012 was a 73-year-old white /caucasian/european heritage female randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2012-11-27; and received once-weekly treatment with study drug between 2012-12-06 and 2012-12-20. The subject received a total of 3 injections of ADI-PEG 20.

The subject was first diagnosed with stage IIIA hepatocellular carcinoma on 2006-01-27. The subject received prior systemic chemotherapy with SORAFENIB from 2012-07-25 to 2012-11-08 and radiotherapy. Other therapies the subject received included transcatheter arterial chemoembolization. The subject underwent surgery for liver biopsy on 2001-09-17, liver biopsy on 2006-01-27, liver biopsy on 2006-02-14, liver resection on 2006-02-14, cholecystectomy on 2007-07-23, liver biopsy on 2007-07-23. Prior to the start of study treatment, the subject's medical history and conditions included appendicectomy, cholecystic calculus with biliary sludge, cholecystectomy, esophageal varices, left carotid artery thromboendarterectomy, left mammary nodulectomy, and transient ischemic attack. Ongoing medical conditions included atrioventricular block grade 1, cirrhosis, discopathy, gastritis, hcv infection, hepatic steatosis, hiatal hernia, hypertension, insomnia, low albumin value, low potassium value, menopause, right carotid artery stenosis, spondyloarthrosis, uterine fibromas, and vasculopathy.

Concomitant medications, (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug and during the study included acetylsalicylic acid, ceftriaxone sodium, clarithromycin, furosemide, lorazepam, methylprednisolone, omeprazole, pantoprazole sodium sesquihydrate, primox plus, rosuvastatin calcium, spironolactone, trophicard, and ursodeoxycholic acid.

On 2013-01-08, the subject experienced upper gastrointestinal hemorrhage and was hospitalized for this event. The subject's last dose of study drug prior to the event was administered on 2012-12-20. No additional treatment was administered and the study drug was permanently withdrawn as a result of disease progression.

On 2013-01-08, the subject presented with a complaint of abdominal pain and was noted to fall asleep during initial evaluation. According to the CIOMS, the laboratory results on admission showed hemoglobin level of 6.3 (unit and normal range was not reported). Treatment included 1-unit of erythrocytes and morphine; however, the subject experienced hematemesis and her condition continued to deteriorate. The subject died as a result of Grade 5 upper gastrointestinal hemorrhage the same day. No additional information was reported.

The Investigator considered the event of upper gastrointestinal hemorrhage to be unlikely related to ADI-PEG 20; an alternate etiology of disease progression was reported. The Polaris Medical Monitor agreed with the Investigator's assessment.

No other abnormal laboratory values were recorded during the adverse events.

Reason(s) for Narrative: Death
Subject ID: 257-0012
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Sepsis	Death	2013-06-20 / 2013-06-25	4	Drug withdrawn	Fatal	Unlikely Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:
Subject 257-0012 was a 75-year-old white /caucasian/european heritage male randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2013-05-09; and received once-weekly treatment with study drug between 2013-05-13 and 2013-06-07. The subject received a total of 4 injections of ADI-PEG 20.

The subject was first diagnosed with stage IV hepatocellular carcinoma on 2012-02-16. The subject received prior systemic chemotherapy with sorafenib from 2012-11-08 to 2013-02-21. Other therapies the subject received included transcatheter arterial chemoemboization. Prior to the start of study treatment, the subject's ongoing medical conditions included atrial fibrillation, type 2 diabetes mellitus, hypertension, palpable liver edge, proteinuria, and gout.

Concomitant medications, (antiviral therapy will be included below if applicable) within 14 days prior to the first dose of study drug and during the study, included allopurinol, antibacterial for systemic use (unspecified), bisoprolol, digoxin, furosemide, intravenous solutions (unspecified), insulin, metformin, omeprazole, paracetamol, perindopril, pioglitazone, piperacillin / tazobactam, sennoside a/b, spironolactone, succinylated gelatin, and trimethoprim.

On 2013-06-20, the subject experienced a Grade 3 atrial fibrillation and Grade 4 sepsis; and was hospitalized for these events. The subject's last dose of study drug prior to the event was administered on 2013-06-07. According to the CIOMS, the initial symptoms included tachypnea, dyspnea, lethargy, and tachycardia. The electrocardiogram showed atrial fibrillations with a rate of 140 beats per minute. The atrial fibrillation was considered unrelated to study treatment with an alternative cause of concomitant disease. The subject reported missing the bisoprolol dose for 2 days prior to admission. Additionally, the subject had approximately 10-year history of atrial fibrillation and type 2 diabetes mellitus. While the subject was hospitalized, the atrial fibrillation was treated with digoxin and sepsis was treated with piperacillin / tazobactam, succinylated gelatin, and antibacterial for systemic use (unspecified).

On 2013-06-25, 18 days after the last dose (week 4) of study treatment, the subject died as a result of the sepsis event. That day, the atrial fibrillation was considered recovered/resolved. According to the CIOMS, the death notification reported the cause of death as sepsis. No additional information was reported.

The Investigator considered the event of sepsis to be unlikely related to ADI-PEG 20; an alternate etiology of concomitant disease was reported. The Polaris Medical Monitor agreed with the Investigator's assessment.

Laboratory values recorded as abnormal during the adverse events are presented in the following table.

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Aspartate Aminotransferase (U/L)	11 / 36	66	43	1	20JUN2013
Eosinophils/Leukocytes (%)	0 / 6.8	1.7	9.3	Not reported	20JUN2013
Glucose (mmol/L)	3.9 / 5.6	7.6	7.4	1	20JUN2013
Leukocytes (10^9/L)	3.8 / 10.7	4.7	3.41	1	20JUN2013
Neutrophils (10^9/L)	1.96 / 7.23	3.51	1.29	2	20JUN2013
Neutrophils/Leukocytes (%)	40.5 / 75	74.8	38	Not reported	20JUN2013
Platelets (10^9/L)	130 / 394	179	118	1	20JUN2013
Protein (g/L)	60 / 80	85	84	Not reported	20JUN2013
Prothrombin Time (sec)	9.7 / 12.3	11.9	15.1	Not reported	20JUN2013

Reason(s) for Narrative: Death
Subject ID: 302-0011
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Blood bilirubin increased	Death	2012-06-05 / 2012-06-06	4	Dose not changed	Fatal	Not Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:
Subject 302-0011 was a 52-year-old asian-taiwan male randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2012-04-17; and received once-weekly treatment with study drug between 2012-04-24 and 2012-05-15. The subject received a total of 4 injections of ADI-PEG 20.

The subject was first diagnosed with stage IV hepatocellular carcinoma on 2011-12-09. The subject received prior systemic chemotherapy with sorafenib from 2012-02-16 to 2012-03-22. The subject underwent surgery for cholecystectomy on 2011-12-12; and s6/7/8 trisegmentectomy of liver on 2011-12-12. Prior to the start of study treatment, the subject's ongoing medical conditions included chronic hepatitis B, lung metastasis, and sinus tachycardia.

Concomitant medications, (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug and during the study, included aldioxa, entecavir, furosemide, kimotab, lorazepam, silybum marianum, and tramadol.

On 2012-05-15, the same day as week 4 study drug was administered, the subject experienced a Grade 2 blood bilirubin increased (results were not reported). On 2012-05-29, the subject refused to continue the study and withdrew consent.

On 2012-06-05, the subject experienced a Grade 4 blood bilirubin increase. The subject's last dose (week 4) of study drug prior to the event was administered on 2012-05-15. No additional information was available to the Investigator.

The Investigator considered the event of blood bilirubin increased to be unrelated to ADI-PEG 20; an alternate etiology of progressive disease was reported. The Polaris Medical Monitor agreed with the Investigator's assessment.

Laboratory values recorded as abnormal during the adverse events are presented in the following table.

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Alanine Aminotransferase (U/L)	0 / 40	62	213	3	05JUN2012
Albumin (g/L)	37 / 53	47	33	1	05JUN2012
Aspartate Aminotransferase (U/L)	5 / 45	96	600	3	05JUN2012
Bilirubin (umol/L)	3.42 / 27.36	17.1	248.463	3	05JUN2012

Reason(s) for Narrative: Death
Subject ID: 302-0022
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Haemorrhage intracranial	Death	2013-09-22 / 2013-10-05	4	Drug withdrawn	Fatal	Not Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:
Subject 302-0022 was a 65-year-old asian-taiwan male randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2013-07-02; and received once-weekly treatment with study drug between 2013-07-09 and 2013-09-17. The subject received a total of 11 injections of ADI-PEG 20.

The subject was first diagnosed with stage IV hepatocellular carcinoma on 2011-04-12. The subject received prior systemic chemotherapy with sorafenib from 2012-05-10 to 2012-05-18; cisplatin from 2012-07-13 to 2012-08-06; doxorubicin from 2012-07-13

to 2012-08-06; etoposide from 2012-07-13 to 2012-08-06; fluorouracil from 2012-07-13 to 2012-08-06; and sorafenib from 2012-08-23 to 2012-12-27. Other therapies the subject received included radiofrequency ablation. Prior to the start of study treatment, the subject's medical history and conditions included chronic bronchitis. The subject's ongoing medical conditions included chronic hepatitis B, chronic liver parenchymal disease, esophageal varices, gastric ulcers, gastroesophageal reflux disease, glaucoma, hypertension, multiple lung metastases, portal hypertensive gastropathy, and type 2 diabetes mellitus with polyneuropathy.

Concomitant medications, (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug and during the study, included acarbose, alprazolam, ambroxol hydrochloride, amlodipine, betamethasone, calamine, cefuroxime, chlorphenamine, clotrimazole, co-diovan, codeine phosphate, dexamethasone, enemas, entecavir, epinephrine, epinephrine hydrochloride, etofenamate, famotidine, glycerol, insulin glargine, insulin human, labetalol, lactulose, magnesium oxide, nicardipine hydrochloride, repaglinide, saxagliptin, sennoside a+b, tranexamic acid, urokinase, valsartan, and zinc oxide.

On 2013-09-22, the subject experienced a Grade 4 hemorrhage intracranial and was hospitalized for this event. The subject's last dose (week 11) of study drug prior to the event was administered on 2013-09-17. According to the CIOMS, the day of admission, the subject had fallen down at home and was found lying on the floor approximately 1 to 2 hours later.

Prior to the event, it was reported in the clinical database that the subject had a brain CT performed on the day of the week 10 study treatment administration (2013-09-10). Additional testing prior to hospitalization included a sensation testing on 2013-09-13; MRI of the brain with emg, mncv(ue), mncv(le), sncv, and f wav performed on 2013-09-18.

The vital signs and examinations on 2013-09-22 showed a temperature of 36OC, heart rate of 106 beats per minute, blood pressure of 188/104 mmHg, Glasgow Coma Score of E4V4M5, and the electrocardiogram showed normal sinus rhythm. The subject was acutely ill-looking, with no specific trauma, fracture, headache, or dizziness. The light reflex showed +/+, pupils: 4/4, left side hemiplegia, motor potency (left/right): upper: 0/5, lower: 1/5, no paresthesia of extremities and face, Babinski sign was positive at left leg. Laboratory results on admission showed an elevated glucose of 247 mg/dL; ALT: 32 U/L; CRP: 0.52 mg/L; and PT/APTT was normal. Brain CT showed a 4.1cm acute intracerebral hemorrhage (ICH) and minimal subarachnoid hemorrhage (SAH) at right high frontal region; another small high-density nodule 1.1cm, at left parasagittal parietal lobe with no ventricular dilatation

or midline shift. Subject was admitted to surgical intensive care unit (SICU). The study drug was permanently discontinued on 2013-09-23 and the subject was withdrawn from the study due to disease progression.

During SICU admission, subject was treated with glyceron, decadron, perdipine, and insulin. A MRI of the brain performed 4 days after admission showed a new hematoma at right frontal lobe, in favor of tumor bleeding; most of the metastatic lesions showed regression change; however, a 9 mm enhancing nodule at left frontal lobe (Se/Im: 7/48) showed mild enlargement as compared with previous MRI. Subsequently, radiotherapy was administered for palliative treatment. The subject gradually developed productive cough and chest radiography showed a consolidative mass in right lower lobe and other small nodules in bilateral lung fields. Laboratory results between 2013-09-30 and 2013-10-03 showed leukocytosis with left shift.

Despite antibiotic treatment, infection quickly progressed, and the subject's blood pressure dropped (result not reported). Respiratory failure developed, and after discussions with relatives, a do not resuscitate form and against advice discharge form were signed on 2013-10-04. The following day, 18 days after the final study drug was administered, the subject died as a result of the intracranial hemorrhage, considered fatal on 2013-10-05. The urinary tract infection, hyperglycemia, and hypertensive events were considered resolved at the time of death.

The Investigator considered the fatal event of intracranial hemorrhage to be not related to ADI-PEG 20; an alternate etiology of disease progression was reported. The Polaris Medical Monitor agreed with the Investigator's assessment.

Laboratory values recorded as abnormal during the adverse events are presented in the following table.

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Chloride (mmol/L)	100 / 114	103	96	Not reported	22SEP2013
Glucose (mmol/L)	3.6075 / 6.3825	8.0475	13.7085	2	22SEP2013
Lymphocytes/Leukocytes (%)	20 / 45	29.9	16.7	Not reported	22SEP2013
Platelets (10^9/L)	150 / 350	122	115	1	22SEP2013
Blood Urea Nitrogen (mmol/L)	2.499 / 7.14	7.14	9.282	Not reported	30SEP2013
Hematocrit (%)	37 / 47	42.2	53.4	Not reported	30SEP2013

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Hemoglobin (g/L)	120 / 160	146	171	0	30SEP2013
Leukocytes (10^9/L)	4500000 / 11000000	7.33	14400000	0	30SEP2013
Lymphocytes (10^9/L)	900000 / 4950000	2.19167	777600	1	30SEP2013
Lymphocytes/Leukocytes (%)	20 / 45	29.9	5.4	Not reported	30SEP2013
Neutrophils (10^9/L)	2025000 / 8250000	4.55926	13204800	0	30SEP2013
Neutrophils/Leukocytes (%)	45 / 75	62.2	91.7	Not reported	30SEP2013
Platelets (10^9/L)	150 / 350	122	149	1	30SEP2013
Blood Urea Nitrogen (mmol/L)	2.499 / 7.14	7.14	9.996	Not reported	03OCT2013
Erythrocytes (10^12/L)	4.2 / 5.4	5.08	6.2	Not reported	03OCT2013
Hematocrit (%)	37 / 47	42.2	54.1	Not reported	03OCT2013
Hemoglobin (g/L)	120 / 160	146	177	0	03OCT2013
Leukocytes (10^9/L)	4500000 / 11000000	7.33	40200000	0	03OCT2013
Leukocytes (10^9/L)	4500000 / 11000000	7.33	44300000	0	03OCT2013
Lymphocytes (10^9/L)	900000 / 4950000	2.19167	443000	1	03OCT2013
Lymphocytes (10^9/L)	900000 / 4950000	2.19167	804000	1	03OCT2013
Lymphocytes/Leukocytes (%)	20 / 45	29.9	1	Not reported	03OCT2013
Lymphocytes/Leukocytes (%)	20 / 45	29.9	2	Not reported	03OCT2013
Monocytes (10^9/L)	0 / 990000	0.41781	1608000	Not reported	03OCT2013
Monocytes (10^9/L)	0 / 990000	0.41781	1772000	Not reported	03OCT2013
Neutrophils (10^9/L)	2025000 / 8250000	4.55926	35778000	0	03OCT2013
Neutrophils (10^9/L)	2025000 / 8250000	4.55926	38984000	0	03OCT2013
Neutrophils Band Form (10^9/L)	0 / 550000	0	2010000	Not reported	03OCT2013
Neutrophils Band Form (10^9/L)	0 / 550000	0	3101000	Not reported	03OCT2013
Neutrophils Band Form/Leukocytes (%)	0 / 5	0	7	Not reported	03OCT2013
Neutrophils/Leukocytes (%)	45 / 75	62.2	88	Not reported	03OCT2013

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Neutrophils/Leukocytes (%)	45 / 75	62.2	89	Not reported	03OCT2013
Platelets (10^9/L)	150 / 350	122	117	1	03OCT2013
Sodium (mmol/L)	135 / 147	143	131	1	03OCT2013
Alpha Fetoprotein (ug/L)	0 / 20	17897	30326.6	Not reported	04OCT2013

Reason(s) for Narrative: Death
Subject ID: 305-0019
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Upper gastrointestinal haemorrhage	Death	2012-11-08 / 2012-11-13	4	Dose not changed	Fatal	Not Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:

Subject 305-0019 was a 35-year-old asian-taiwan male randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2012-09-04; and received once-weekly treatment with study drug between 2012-09-11 and 2012-10-16. The subject received a total of 6 injections of ADI-PEG 20.

The subject was first diagnosed with stage II hepatocellular carcinoma on 2007. The subject received prior systemic chemotherapy with sorafenib from 2012-07-17 to 2012-08-21. Other therapies the subject received included hepatic artery infusion chemotherapy, percutaneous ethanol injection, and transcatheter arterial chemoembolization. The subject underwent surgery for liver segmentectomy on 2000-06-04. Just prior to the start of treatment, the subject had hepatic artery infusion catheter removed on 2012-09-05. The subject's ongoing medical conditions included ascites, chronic duodenitis, chronic gastritis, duodenal ulcer scar, esophageal varices, gastric varices, hepatitis B virus carrier, liver cirrhosis, microcytic anemia, and splenomegaly.

Concomitant medications, (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug and during the study, included albumin

human, baramycin, dicloxacillin sodium monohydrate, entecavir, furosemide, lansoprazole, mosapride citrate, paracetamol, propranolol, silybum marianum, spironolactone, tramadol, and ursodeoxycholic acid.

On 2012-10-30, 14 days after the week 6 dose of study drug, the subject experienced a Grade 3 blood bilirubin increased (refer to the laboratory values in table below narrative).

No hospitalization was required; however, the subject was discontinued from the study due to the event. The event was considered unlikely in relationship to ADI-PEG 20 study treatment and remained ongoing.

On 2012-11-08, 23 days after the last administration of study treatment, the subject experienced a Grade 4 upper gastrointestinal hemorrhage and was hospitalized for this event.

Procedures and medications used to treat the event were not reported. On 2012-11-13, 28 days after the last administration of study treatment, the subject died as a result of the hemorrhage event. The increased bilirubin event was considered resolved at the time of death. No additional information at the time of death was reported.

The Investigator considered the fatal event of upper gastrointestinal hemorrhage to be not related to ADI-PEG 20; an alternate etiology was disease progression. The Polaris Medical Monitor agreed with the Investigator's assessment.

Laboratory values recorded as abnormal during the adverse events are presented in the following table.

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Activated Partial Thromboplastin Time (sec)	24.3 / 32.7	34	35	1	30OCT2012
Alanine Aminotransferase (U/L)	0 / 36	42	59	1	30OCT2012
Alanine Aminotransferase (U/L)	0 / 41	42	62	1	30OCT2012
Albumin (g/L)	35 / 55	32	24.8	2	30OCT2012
Albumin (g/L)	35 / 52	32	26	2	30OCT2012
Alkaline Phosphatase (U/L)	40 / 129	507	869	3	30OCT2012
Alpha Fetoprotein (ug/L)	0 / 14.99	12868.05	24482.8	Not reported	30OCT2012
Aspartate Aminotransferase (U/L)	0 / 34	101	429	3	30OCT2012

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Aspartate Aminotransferase (U/L)	0 / 37	101	435	3	30OCT2012
Bilirubin (umol/L)	5.13 / 22.23	22.23	107.73	3	30OCT2012
Bilirubin (umol/L)	0 / 22.23	22.23	111.15	3	30OCT2012
Chloride (mmol/L)	98 / 107	96	89	Not reported	30OCT2012
Cholesterol (mmol/L)	38.199 / 71.043	77.112	90.678	4	30OCT2012
Creatinine (umol/L)	56.576 / 112.268	47.736	39.78	Not reported	30OCT2012
Creatinine (umol/L)	61.88 / 106.08	47.736	58.344	Not reported	30OCT2012
Direct Bilirubin (umol/L)	0 / 8.55	10.26	82.08	Not reported	30OCT2012
Eosinophils (10^9/L)	0.04 / 0.66	0.03288	0	Not reported	30OCT2012
Eosinophils/Leukocytes (%)	1 / 6	0.4	0	Not reported	30OCT2012
Hematocrit (%)	39 / 53	31	30.3	Not reported	30OCT2012
Hematocrit (%)	41 / 53	31	30.9	Not reported	30OCT2012
Hemoglobin (g/L)	135 / 175	102	103	1	30OCT2012
Hemoglobin (g/L)	123 / 183	102	105	1	30OCT2012
Indirect Bilirubin (umol/L)	0 / 13.68	11.97	25.65	Not reported	30OCT2012
Lactate Dehydrogenase (U/L)	135 / 225	171	377	Not reported	30OCT2012
Leukocytes (10^9/L)	4 / 11	8.22	11.07	0	30OCT2012
Leukocytes (10^9/L)	3.9 / 10.6	8.22	11.3	0	30OCT2012
Lymphocytes/Leukocytes (%)	20 / 56	10.9	11.1	Not reported	30OCT2012
Lymphocytes/Leukocytes (%)	20 / 45	10.9	14	Not reported	30OCT2012
Neutrophils (10^9/L)	1.6 / 8.25	6.4938	8.7453	0	30OCT2012
Neutrophils (10^9/L)	1.638 / 7.844	6.4938	9.0965	0	30OCT2012
Neutrophils/Leukocytes (%)	40 / 75	79	79	Not reported	30OCT2012
Neutrophils/Leukocytes (%)	42 / 74	79	80.5	Not reported	30OCT2012
Platelets (10^9/L)	150 / 400	246	511	0	30OCT2012
Platelets (10^9/L)	120 / 400	246	642	0	30OCT2012
Prothrombin Time (sec)	8 / 12	12.9	16.6	Not reported	30OCT2012
Sodium (mmol/L)	136 / 145	132	126	3	30OCT2012
Alanine Aminotransferase (U/L)	0 / 36	42	69	1	06NOV2012

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Aspartate Aminotransferase (U/L)	0 / 34	101	579	3	06NOV2012
Bilirubin (umol/L)	0 / 22.23	22.23	116.28	3	06NOV2012

Reason(s) for Narrative: Death
Subject ID: 305-0028
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Encephalopathy	Death	2013-06-14 / 2013-06-16	3	Dose not changed	Fatal	Not Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:
Subject 305-0028 was a 73-year-old asian-taiwan female randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2013-03-13; and received once-weekly treatment with study drug between 2013-03-15 and 2013-05-29. The subject received a total of 12 injections of ADI-PEG 20.

The subject was first diagnosed with stage IV hepatocellular carcinoma on 2012-10-24. The subject received prior systemic chemotherapy with sorafenib from 2012-11-21 to 2013-02-27. Prior to the start of study treatment, the subject's medical history and conditions included abdominal distension, anemia, chronic apical periodontitis, left neck pain, mucositis oral, right upper quadrant pain, and skin itching. The subject's ongoing medical conditions included anorexia, arthralgia of knee, cachexia, chronic hepatitis C, dental caries, fatigue, hypertension, insomnia, liver cirrhosis, osteoarthrosis, platelet count decreased, type 2 diabetes mellitus, and white blood cell decreased grade 2.

Concomitant medications, (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug and during the study included amlodipine, amoxi-clavulanico, celecoxib, codeine phsphate, ipratropium bromide / albuterol sulfate, famotidine, fentanyl, fleet, fludiazepam, flurbiprofen, ibuprofen, lactulose, lorazepam, losartan potassium, medroxyprogesterone acetate, meloxicam, metformin, metoclopramide,

mirtazapine, neomycin, paracetamol, tramadol hydrochloride, acetaminophen / tramadol hydrochloride, and zolpidem.

On 2013-06-14, the subject experienced a Grade 3 encephalopathy and was hospitalized for this event. The subject's last dose (week 12) of study drug prior to the event was administered on 2013-05-29 At the time of admission the subject was also diagnosed with Grade 3 pneumonitis and Grade 1 vomiting. Events were not considered serious.

The subject was administered oxygen support between 2013-06-14 and 2013-06-16. No action was taken with study drug as a result of the event; however, the subject was withdrawn from the study due to disease progression.

On 2013-06-16, 18 days after the final dose of study drug was administered, the subject died as a result of the encephalopathy, considered fatal on 2013-06-16. The pneumonitis and vomiting events were considered resolved at the time of death. No additional information at the time of death was reported.

The Investigator considered the fatal event of encephalopathy to be not related to ADI-PEG 20; an alternate etiology of disease progression was reported. The Polaris Medical Monitor agreed with the Investigator's assessment.

Laboratory values recorded as abnormal during the adverse events are presented in the following table.

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Alanine Aminotransferase (U/L)	0 / 36	84	44	1	14JUN2013
Albumin (g/L)	35 / 55	42	33.6	1	14JUN2013
Aspartate Aminotransferase (U/L)	0 / 34	101	88	1	14JUN2013
Bilirubin (umol/L)	0 / 22.23	10.26	30.78	1	14JUN2013
Blood Urea Nitrogen (mmol/L)	2.142 / 7.497	4.2483	20.5275	Not reported	14JUN2013
Lymphocytes (10^9/L)	0.78 / 5.936	0.6888	0.5952	2	14JUN2013
Lymphocytes/Leukocytes (%)	20 / 56	24.6	6.2	Not reported	14JUN2013
Neutrophils (10^9/L)	1.638 / 7.844	1.792	8.5248	0	14JUN2013
Neutrophils/Leukocytes (%)	42 / 74	64	88.8	Not reported	14JUN2013
Platelets (10^9/L)	150 / 400	60	82	1	14JUN2013

Reason(s) for Narrative: Death
Subject ID: 305-0039
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Coma hepatic	Death	2013-12-21 / 2013-12-26	5	Dose not changed	Fatal	Not Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:
Subject 305-0039 was a 36-year-old asian-taiwan male randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2013-11-06; and received once-weekly treatment with study drug between 2013-11-28 and 2013-12-19. The subject received a total of 4 injections of ADI-PEG 20.

The subject was first diagnosed with stage IV hepatocellular carcinoma on 2012-12-11. The subject received prior systemic chemotherapy with sorafenib from 2013-02-05 to 2013-10-31; and radiotherapy from 2013-02-19 to 2013-04-02. Prior to the start of study treatment, the subject's ongoing medical and conditions included ascites, chronic hepatitis B, cirrhosis, duodenal polyp, gastroesophageal reflux disease, and splenomegaly.

Concomitant medications, (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug and during the study, included acetylcysteine, ambroxol hydrochloride, aminophylline, amoxi-clavulanic, antacids, brown mixture, ceftriaxone, dextromethorphan, dextrose and sodium chloride injection, entecavir, famotidine, furosemide, glucose, lactulose, loperamide, pantoprazole, pinaverium bromide, silybum marianum, spironolactone, tramadol hydrochloride/acetaminophen, and vasoprotectives.

On 2013-12-21, the subject experienced a coma hepatic and was subsequently hospitalized for this event 3 days later. The subject's last dose of study drug prior to the event was administered on 2013-12-19. On admission, the subject reported a history of conscious disturbance for 3 days and greenish stool passage. According to the CIOMS, the examination showed no evidence of pain, icteric, cachexia, acute ill appearance, pupil size: 3+/3+, and conscious examination: E4V2M5. Subject was then admitted under the impression

of hepatic encephalopathy and liver cirrhosis. The family decided to sign do not resuscitate form. Treatment included lactulose, ceftriaxone (for abdominal infection), transfusion of 2-units of packaged red blood cells and 2-units of fresh frozen plasma. The subject was also treated with nil per os and oxygen inhalation therapy between 2013-12-24 and 2013-12-26. Study drug was not changed. On 2013-12-26, 7 days after the final study dose was administered, the subject died as a result of Grade 5 coma hepatic.

The Investigator considered the event of coma hepatic to be not related to ADI-PEG 20; an alternate etiology of disease progression was reported. The Polaris Medical Monitor agreed with the Investigator's assessment.

Laboratory values recorded as abnormal during the adverse events are presented in the following table.

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Alanine Aminotransferase (U/L)	0 / 36	36	205	3	24DEC2013
Aspartate Aminotransferase (U/L)	0 / 34	77	532	3	24DEC2013
Bilirubin (umol/L)	0 / 22.23	22.23	153.9	3	24DEC2013
Blood Urea Nitrogen (mmol/L)	2.142 / 7.497	5.1408	35.8785	Not reported	24DEC2013
Creatinine (umol/L)	56.576 / 112.268	65.416	162.656	Not reported	24DEC2013
Erythrocytes (10^12/L)	4.5 / 5.9	4.05	4.48	Not reported	24DEC2013
Leukocytes (10^9/L)	3.9 / 10.6	6.54	18.8	0	24DEC2013
Lymphocytes (10^9/L)	0.78 / 5.936	0.68016	0.376	3	24DEC2013
Lymphocytes/Leukocytes (%)	20 / 56	10.4	2	Not reported	24DEC2013
Neutrophils (10^9/L)	1.638 / 7.844	5.22546	17.86	0	24DEC2013
Neutrophils/Leukocytes (%)	42 / 74	79.9	95	Not reported	24DEC2013
Platelets (10^9/L)	150 / 400	138	38	3	24DEC2013

Reason(s) for Narrative: Death
Subject ID: 305-0047
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Hepatic encephalopathy	Death	2015-01-16 / 2015-01-28	5	Drug withdrawn	Fatal	Not Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:
Subject 305-0047 was a 58-year-old asian-taiwan male randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2014-12-23; and received once-weekly treatment with study drug between 2014-12-25 and 2015-01-14. The subject received a total of 4 injections of ADI-PEG 20.

The subject was first diagnosed with stage IV hepatocellular carcinoma on 2013-02-04. The subject received prior systemic chemotherapy with thalidomide. The subject underwent surgery for right hepatectomy on 2014-02-04. Prior to the start of study treatment, the subject's medical history and conditions included tongue cancer. The subject's ongoing medical conditions included abdominal fullness, abdominal pain, bilateral lower limb varicose vein, chronic hepatitis B carrier, chronic hepatitis C carrier, insomnia, leg edema, liver cirrhosis, mild ascites, status post cholecystectomy, status post lymph node, and right supraomohyoid neck dissection.

Concomitant medications, (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug and during the study, included amlodipine, codeine phosphate, diprogent, electrolytes NOS, esomeprazole, famotidine, fleet, flurbiprofen, ibuprofen, ketoconazole, labetalol, lactulose, magnesium oxide, meloxicam, metoclopramide, morphine hydrochloride, mosapride citrate, paracetamol, phytomenadione, prochlorperazine, propranolol, spironolactone, sulindac, tramadol hydrochloride, tranexamic acid, and zolpidem.

On 2015-01-16, the subject experienced hepatic encephalopathy and was hospitalized for this event. According to the CIOMS report, the subject was initially hospitalized for hepatic encephalopathy Grade 1 with drowsy consciousness, noted 2 days prior. Lactulose was

prescribed; however, no change in consciousness level was noted. The day after admission, the subject developed Grade 3 hypertension (considered serious). The subject's last dose of study drug prior to both events was administered on 2015-01-14.

Study drug was interrupted (week 5) as a result of the hypertension event. A nasogastric tube was inserted and irrigated with 100 cc normal saline on 2015-01-21; and 2-unit transfusion of fresh frozen plasma per day between 2015-01-21 and 2015-01-23. According to the CIOMS, the subject's condition continued to deteriorate due to elevated ammonia levels (262 ug/dL on 2015-01-21; additional laboratory results are listed in the table below this narrative). The hepatic encephalopathy event was upgraded to Grade 2 on 2015-01-23. That day, nasogastric feedings and oxygen therapy was initiated through 2015-01-28. According to the CIOMS, the subject's ammonia level continued to increase from 262 to 382 ug/dL; and the hepatic encephalopathy event was again upgraded to Grade 3 on 2015-01-27. That day, the study drug was permanently discontinued as a result of the hepatic encephalopathy event. The following day (2015-01-28), 14 days after the final dose of study drug was administered, the subject died of Grade 5 hepatic encephalopathy. The serious event of hypertension, considered to be related to disease progression, resolved at death. No additional information at the time of death was reported.

The Investigator considered the event of hepatic encephalopathy to be not related to ADI-PEG 20; an alternate etiology of disease progression was reported. The Polaris Medical Monitor agreed with the Investigator's assessment.

Laboratory values recorded as abnormal during the adverse events are presented in the following table.

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Erythrocytes (10^12/L)	4.5 / 5.9	3.99	4.13	Not reported	16JAN2015
Hematocrit (%)	41 / 53	38.2	39.4	Not reported	16JAN2015
Alanine Aminotransferase (U/L)	0 / 36	37	44	1	17JAN2015
Bilirubin (umol/L)	0 / 22.23	17.1	39.33	2	17JAN2015
Potassium (mmol/L)	3.6 / 5	4.1	3.5	1	17JAN2015
Albumin (g/L)	35 / 55	33	32.3	1	21JAN2015
Aspartate Aminotransferase (U/L)	0 / 34	54	58	1	21JAN2015

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Erythrocytes (10^12/L)	4.5 / 5.9	3.99	3.8	Not reported	21JAN2015
Hematocrit (%)	41 / 53	38.2	36.2	Not reported	21JAN2015
Hemoglobin (g/L)	135 / 175	129	121	1	21JAN2015
Aspartate Aminotransferase (U/L)	0 / 34	54	65	1	23JAN2015
Bilirubin (umol/L)	0 / 22.23	17.1	29.07	1	23JAN2015
Creatinine (umol/L)	56.576 / 112.268	64.532	55.692	Not reported	23JAN2015
Erythrocytes (10^12/L)	4.5 / 5.9	3.99	3.99	Not reported	23JAN2015
Hematocrit (%)	41 / 53	38.2	38.4	Not reported	23JAN2015
Hemoglobin (g/L)	135 / 175	129	132	1	23JAN2015
Platelets (10^9/L)	150 / 400	149	144	1	23JAN2015
Alanine Aminotransferase (U/L)	0 / 36	37	49	1	27JAN2015
Aspartate Aminotransferase (U/L)	0 / 34	54	82	1	27JAN2015
Bilirubin (umol/L)	0 / 22.23	17.1	25.65	1	27JAN2015
Blood Urea Nitrogen (mmol/L)	2.142 / 7.497	8.1039	7.8183	Not reported	27JAN2015
Erythrocytes (10^12/L)	4.5 / 5.9	3.99	3.85	Not reported	27JAN2015
Hematocrit (%)	41 / 53	38.2	37	Not reported	27JAN2015
Hemoglobin (g/L)	135 / 175	129	127	1	27JAN2015

Reason(s) for Narrative: Death
Subject ID: 404-0001
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Abdominal pain	Death	2013-09-11 / 2013-09-11	5	Dose not changed	Fatal	Not Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:
Subject 404-0001 was a 71-year-old asian-north east asian heritage male randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2013-07-04; and received once-weekly treatment with study drug between 2013-07-22 and 2013-08-12. The subject received a total of 4 injections of ADI-PEG 20.

The subject was first diagnosed with stage IV hepatocellular carcinoma on 2011-04-07. The subject received prior systemic chemotherapy with sorafenib from 2013-05-14 to 2013-07-03; and radiotherapy from 2013-03-08 to 2013-04-28. Other therapies the subject received included percutaneous ethanol injection, radiofrequency ablation, and transarterial chemoembolization (pei-rfa-tace). The subject underwent surgery for diaphragm wedge resection on 2012-07-26; extended right posterior sectionectomy on 2012-07-26; and inferior vena cava (ivc) wedge resection on 2012-07-26. Prior to the start of study treatment, the subject's medical history and conditions included Grade 3 back pain, and left eye cataract surgery. The subject's ongoing medical conditions included abdominal pain, hepatitis C, hypothyroidism, liver cirrhosis, multiple compression fracture (L1), Grade 2 right shoulder pain, and splenomegaly.

Concomitant medications, (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug and during the study, included acetylcysteine, acyclovir, albumin human, bisacodyl, cefazedone, cefepime, ertapenem, fentanyl, furosemide, gabapentin, lactulose, levothyroxine sodium, lipids nos, lorazepam, magnesium hydroxide, megestrol acetate, metoclopramide hydrochloride, morphine sulfate, mupirocin, nature's way primadophilus original, ornithine aspartate, oxycodone hydrochloride, paracetamol, pethidine, phloroglucinol, primaxin, ropivacaine, silybum

marianum, spironolactone, targin teicoplanin, tiropramide, tuberculin, ultracet, unacid, ursodeoxycholic acid, vancomycin, and vitamins NOS.

The subject entered the study with a history of multiple compression fracture (L1) and Grade 2 right shoulder pain. Following study enrollment, an unspecified kyphoplasty was performed on 2013-07-08.

On 2013-07-22, the subject experienced a Grade 3 abdominal pain (associated with back pain) and was hospitalized for this event. According to the CIOMS, the first dose of study drug (week 1) was administered the same day, after the subject was hospitalized.

On 2013-07-24, a thoracic epidural block was performed with improvement of back pain reported. While hospitalized, the subject was administered the week 2 to week 4 study drug weekly as planned (34.0 mg each time). The week 4 study treatment was administered on 2013-08-12. The following day, a chest and liver CT scan revealed disease progression (specifics not reported); and the subject was discontinued from study treatment. That same day, a thoracic epidural block on percutaneous nephrostomy was performed from 2013-08-13 and right pcn tube was inserted.

According to the CIOMS, subject was prescribed and treated with general supportive care during the hospitalization. However, the subject's disease and symptoms progressively worsened. On 2013-09-11, the End-of-treatment (EOT) visit was performed. Later that day, 30 days after the last dose of study drug was administered, the subject died of Grade 5 abdominal pain. Specifics were not reported.

The Investigator considered the Grade 3 and Grade 5 abdominal pain events to be not related to ADI-PEG 20; an alternate etiology of disease progression was reported. The Polaris Medical Monitor agreed/ with the Investigator's assessment.

Laboratory values recorded as abnormal during the adverse events are presented in the following table.

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Albumin (g/L)	35 / 52	29	26	2	29JUL2013
Calcium (mmol/L)	2.1956 / 2.6447	2.07085	2.02095	1	29JUL2013
Cholesterol (mmol/L)	46.41 / 85.6443	42.84	45.339	4	29JUL2013
Erythrocytes (10^12/L)	4.5 / 5.9	3.54	3.38	No reported	29JUL2013
Glucose (mmol/L)	4.107 / 5.883	5.4945	7.659	1	29JUL2013

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Hematocrit (%)	37 / 51	35.2	34.2	No reported	29JUL2013
Hemoglobin (g/L)	126 / 174	120	116	1	29JUL2013
Lactate Dehydrogenase (U/L)	238 / 422	449	424	No reported	29JUL2013
Leukocytes (10^9/L)	4.5 / 11	4.82	11.59	0	29JUL2013
Lymphocytes/Leukocytes (%)	13 / 44	18.9	8.1	No reported	29JUL2013
Monocytes (10^9/L)	0.18 / 0.99	0.49164	0.99674	No reported	29JUL2013
Neutrophils/Leukocytes (%)	40 / 75	69.7	83	No reported	29JUL2013
Prothrombin Intl. Normalized Ratio	0.92 / 1.09	1.03	1.26	1	29JUL2013
Prothrombin Time (sec)	12.3 / 14	13.4	15.7	No reported	29JUL2013
Sodium (mmol/L)	136 / 146	138	133	1	29JUL2013
Albumin (g/L)	35 / 52	29	30	1	12AUG2013
Blood Urea Nitrogen (mmol/L)	2.499 / 8.211	1.9278	8.8893	No reported	12AUG2013
Calcium (mmol/L)	2.1956 / 2.6447	2.07085	2.07085	1	12AUG2013
Carbon Dioxide (mmol/L)	21 / 31	22	18	No reported	12AUG2013
Cholesterol (mmol/L)	46.41 / 85.6443	42.84	30.702	4	12AUG2013
Creatinine (umol/L)	61.88 / 127.296	55.692	136.136	No reported	12AUG2013
Erythrocytes (10^12/L)	4.5 / 5.9	3.54	3.2	No reported	12AUG2013
Hematocrit (%)	37 / 51	35.2	30.9	No reported	12AUG2013
Hemoglobin (g/L)	126 / 174	120	105	1	12AUG2013
Lactate Dehydrogenase (U/L)	238 / 422	449	485	No reported	12AUG2013
Leukocytes (10^9/L)	4.5 / 11	4.82	15.32	0	12AUG2013
Lymphocytes/Leukocytes (%)	13 / 44	18.9	8	No reported	12AUG2013
Monocytes (10^9/L)	0.18 / 0.99	0.49164	1.34816	No reported	12AUG2013
Neutrophils/Leukocytes (%)	40 / 75	69.7	82.8	No reported	12AUG2013
Prothrombin Intl. Normalized Ratio	0.92 / 1.09	1.03	1.34	1	12AUG2013
Prothrombin Time (sec)	12.3 / 14	13.4	16.4	No reported	12AUG2013
Sodium (mmol/L)	136 / 146	138	133	1	12AUG2013

Reason(s) for Narrative: Death
Subject ID: 405-0002
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Oesophageal varices haemorrhage	Death	2013-04-30 / 2013-05-12	3	Drug withdrawn	Fatal	Unlikely Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:

Subject 405-0002 was a 46-year-old asian-north east asian heritage male randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2013-04-10; and received once-weekly treatment with study drug between 2013-04-16 and 2013-04-30. The subject received a total of 3 injections of ADI-PEG 20.

The subject was first diagnosed with stage I hepatocellular carcinoma on 2012-12-28. The subject received prior systemic chemotherapy with sorafenib from 2012-12-00 to 2013-03-18. Prior to the start of study treatment, the subject's medical history included appendectomy. The subject's ongoing medical conditions included Grade 2 abdominal pain, Grade 1, dyspepsia, Grade 2 headache, and hepatitis B virus carrier.

Concomitant medications, (antiviral therapy will be included below if applicable) within 14 days prior to the first dose of study drug and during the study, included albumin human, aluminum silicate, alverine, cefotaxime sodium, cefpodoxime proxetil, cimetropium, cimetropium bromide, durabac, fentanyl, levofloxacin, meropenem, metoclopramide hydrochloride, metronidazole, morphine hydrochloride, osmotan, oxycodone, pantoprazole, pethidine hydrochloride, phloroglucinol, simethicone, sodium chloride, sucralfate, targin, tenofovir, and terlipressin acetate.

On 2013-04-20, 4 days after the first dose of study drug (week 1) was administered, the subject experienced a Grade 3 portal hypertensive gastropathy and was hospitalized on 2013-04-22 for the event. The event was considered to be unlikely related to ADI-PEG 20. While hospitalized, the subject was treated with terlipressin acetate, transfusion, and prophylactic antibiotics. On 2013-04-23, the subject was discharged with the event

resolved. No action was taken with the study drug; and week 2 study drug was administered the following day.

On 2013-04-30, the same day the study drug (week 3) was administered, the subject experienced a Grade 3 esophageal varices hemorrhage and was hospitalized for this event. According to the CIOMS, the subject reported experiencing 2 episodes of hematemesis immediately following return home from the study drug administration. An L-tube irrigation and direct rectal examination were performed in the ER that day. The direct rectal examination was negative. A gastrofibroscopy showed ulcer and spurt bleeding of esophageal varice. Endoscopic varice ligation was performed and 3-units of fresh frozen plasma was transfused. On 2013-05-01, the subject had several hematochezia episodes.
A Sengstaken-Blakemore tube was inserted and additional 2-units of packaged red blood cells were transfused. Additionally, the subject was treated with metoclopramide, terlipressin acetate, pantoprazole, cefotaxime sodium, morphine, aluminum silicate, and pethidine HCL.

On 2013-05-03, study therapy was permanently withdrawn as a result of the event.

On 2013-05-06, the subject was discharged from the hospital. However, according to the CIOMS, the subject was transferred to a local hospital for continued treatment.
On 2013-05-11, the subject developed an episode of sudden hematemesis and progressive deterioration (confusion) was reported. The family refused resuscitation, and subject died the following day as a result of esophageal varices hemorrhage. The event occurred 12 days after the final dose of study drug was administered. The Investigator judged the event a consequence of subject's disease progression.

The Investigator considered the fatal event of esophageal varices hemorrhage to be unlikely related to ADI-PEG 20; an alternate etiology of disease progression was reported. The Polaris Medical Monitor agreed with the Investigator's assessment.

No abnormal laboratory values were recorded during the adverse events.

Reason(s) for Narrative: Death
Subject ID: 502-0002
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Respiratory failure	Death	2014-01-19 / 2014-01-19	5	Dose not changed	Fatal	Not Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:
Subject 502-0002 was a 65-year-old asian-mainland china male randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2014-01-08 and received once-weekly treatment with study drug on 2014-01-10. The subject received only 1 injection of ADI-PEG 20.

The subject was first diagnosed with stage IV hepatocellular carcinoma on 2006-12-08. The subject received prior systemic chemotherapy with sorafenib from 2012-10-25 to 2013-11-30; and radiotherapy from 2011-11-30 to 2013-07-30. Other therapies the subject received included percutaneous radiofrequency ablation of lung cancer and radiofrequency ablation and transarterial chemo embolization of hcc. The subject underwent surgery for residual cholecystectomy and right hepatectomy on 2006-12-08. Prior to the start of study treatment, the subject's medical history and conditions included cerebral infarction. The subject's ongoing medical and conditions included chronic hepatitis, cough, hypertension, and schistosomiasis.

Concomitant medications, (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug and during the study, included albumin human, ambroxol hydrochloride, carbamazepine, ceftazidime, celecoxib, codeine, codeine phosphate, diazepam, electrolyte solutions, fats NOS, granulocyte macrophage colony stim factor, magnesium isoglycyrrhizinate, mannitol, megestrol acetate, methylprednisolone, nifedipine, omeprazole sodium, phenobarbital, sodium bicarbonate, thymalfasin, unspecified herbal, and zolpidem tartrate.

On 2014-01-16, 6 days after the first dose of study drug was administered, the subject experienced a Grade 4 respiratory failure. The subject presented with a cough, expectoration

and lethargic sleep. Study drug was withdrawn as a result of the event. The subject received symptomatic treatment without improvement. On 2014-01-17, the subject became comatosed. On 2014-01-19, 9 days after a single dose of study drug was administered, the subject died as a result of Grade 5 respiratory failure. No additional information was reported.

The Investigator considered the fatal event of respiratory failure to be not related to ADI-PEG 20; an alternate etiology of disease progression was reported. The Polaris Medical Monitor agreed with the Investigator's assessment.

No abnormal laboratory values were recorded during the adverse events.

Reason(s) for Narrative: Death
Subject ID: 503-0004
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Liver injury	Death	2014-03-22 / 2014-04-05	5	Drug withdrawn	Fatal	Unlikely Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:
Subject 503-0004 was a 49-year-old asian-mainland china male randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2014-03-06; and received once-weekly treatment with study drug between 2014-03-11 and 2014-03-25. The subject received a total of 3 injections of ADI-PEG 20.

The subject was first diagnosed with stage IIIA hepatocellular carcinoma on 2013-10-24. The subject received prior systemic chemotherapy with fluorouracil from 2014-02-06 to 2014-02-07; oxaliplatin from 2014-02-06 to 2014-02-06; fluorouracil from 2014-02-20 to 2014-02-21; and oxaliplatin from 2014-02-20 to 2014-02-20. The subject received radiotherapy from 2014-02-06 to 2014-02-20. Other therapies the subject received included transcatheter arterial chemoembolization. The subject underwent surgery for expand left liver resection on 2013-10-24. Prior to the start of study treatment, the subject's ongoing medical

and conditions included abdominal dropsy, abdominal pain, chronic hepatitis B, hepatitis A, left side of the ilium metastatic tumor, liver cirrhosis, and offside cervical lymph node metastatic.

Concomitant medications, (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug and during the study, included ademetionine, ascorbic acid, diammonium glycyrrhizinate, entecavir, furosemide, lactulose, metoclopramide, morphine, omeprazole, ondansetron, ornithine, oxycodone hydrochloride, pantoprazole, potassium chloride, pyridoxine hydrochloride, spironolactone, tiopronin, torasemide, tropisetron, and an unspecified herbal therapy.

On 2014-03-22, 4 days after the study drug (week 2) was administer, the subject was hospitalized with liver injury. The liver function test results showed an ALT of 121 U/L, AST of 557 U/L, total bilirubin of 234.7 UMOL/L, direct bilirubin of 105.4 UMOL/L, IBIL 129.3 UMOL/L, ALP 320 U/L, and GGT of 420 U/L. On 2014-03-25, the study drug (week 3) was administered. According to the CIOMS, the subject was discharged from the hospital 2014-03-26. Study treatment was permanently discontinued as a result of the liver injury.

On 2014-04-05, 11 days after the final study dose was administered, the subject died of Grade 5 liver injury. No additional information was reported.

The Investigator considered the event of liver injury to be unlikely related to ADI-PEG 20; an alternate etiology of disease progression (reported as liver cancer or hepatitis B) was reported. The Polaris Medical Monitor agreed with the Investigator's assessment.

Laboratory values recorded as abnormal during the adverse events are presented in the following table.

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Alanine Aminotransferase (U/L)	10 / 40	12	121	2	22MAR2014
Albumin (g/L)	35 / 55	26.2	27.8	2	22MAR2014
Alkaline Phosphatase (U/L)	40 / 150	No reported	320	1	22MAR2014
Aspartate Aminotransferase (U/L)	10 / 40	75	557	3	22MAR2014
Bilirubin (umol/L)	3.4 / 17.1	29.8	234.7	4	22MAR2014
Indirect Bilirubin (umol/L)	0 / 10	10	129.3	No reported	22MAR2014
Alanine Aminotransferase (U/L)	10 / 40	12	73	1	25MAR2014
Albumin (g/L)	35 / 55	26.2	22	2	25MAR2014

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Aspartate Aminotransferase (U/L)	10 / 40	75	204	3	25MAR2014
Bilirubin (umol/L)	3.4 / 17.1	29.8	288.7	4	25MAR2014
Direct Bilirubin (umol/L)	0 / 6.8	19.8	215.3	No reported	25MAR2014
Indirect Bilirubin (umol/L)	0 / 10	10	73.4	No reported	25MAR2014
Phosphate (mmol/L)	0.9 / 1.61	0.87	0.66	2	25MAR2014
Potassium (mmol/L)	3.5 / 5.5	4.11	3.25	1	25MAR2014
Protein (g/L)	60 / 80	58.7	55.1	No reported	25MAR2014
Calcium (mmol/L)	2.12 / 2.58	1.75	1.75	2	26MAR2014
Erythrocytes (10^12/L)	3.5 / 5	2.72	2.75	No reported	26MAR2014
Hematocrit (%)	35 / 50	27	27	No reported	26MAR2014
Hemoglobin (g/L)	110 / 150	89	89	2	26MAR2014
Lymphocytes (10^9/L)	0.8 / 4	0.56925	0.69336	2	26MAR2014
Lymphocytes/Leukocytes (%)	20 / 40	22.5	8.1	No reported	26MAR2014
Neutrophils (10^9/L)	2 / 7	1.52	7.04	0	26MAR2014
Neutrophils/Leukocytes (%)	50 / 75	60.1	80.6	No reported	26MAR2014
Platelets (10^9/L)	100 / 300	127	73	2	26MAR2014

Reason(s) for Narrative: Death, and Related SAE

Subject ID: 309-0004

Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Esophageal varices haemorrhage	SAE	2012-06-27 / 2012-07-19	3	Dose not changed	Recovered/ Resolved	Possibly Related
Malignant neoplasm progression	Death	2012-07-19 / 2012-07-19	5	Dose not changed	Fatal	Not Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:

Subject 309-0004 was a 55-year-old asian-taiwan male randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2012-06-14;

and received once-weekly treatment with study drug between 2012-06-25 and 2012-07-03. The subject received a total of 2 injections of ADI-PEG 20.

The subject was first diagnosed with stage IV hepatocellular carcinoma on 2011-04-15. The subject received prior systemic chemotherapy with sorafenib from 2011-12-30 to 2012-05-20. Other therapies the subject received included hepatic artery infusion chemotherapy with cisplatin and fluorouracil. Prior to the start of study treatment, the subject's medical history and conditions included esophageal varices bleeding, gastro-esophageal reflux disease, and gastric xanthomas. Ongoing medical conditions included abdominal fullness, anemia, anorexia, back pain, chronic cystitis, constipation, degenerative with l-spine, diabetes mellitus type 2, duodenal diverticulum, enlargement of prostate gland, esophageal varices, fatigue, fatty liver, gastric ulcers, gastric varices, gastritis, gastroesophageal varices, hand foot syndrome, hemorrhoid, hepatitis B, hiatus hernia, intermittent ascites, intermittent hematuria, liver cirrhosis, liver nodule, metastatic lymph nodes, nodule in right lower lung, osteoporosis, portal hypertensive gastropathy, portal vein thrombosis, right hydronephrosis, splenomegaly, spur formation of l-spine, thrombosis of inferior vena cava, and thrombosis of right renal vein.

Concomitant medications, (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug and during the study included albumin human, amino acids nos w/xylitol, chlorpromazine hydrochloride, codeine, dicycloverine hydrochloride, dimeticone, diphenhydramine, entecavir, flomoxef sodium, furosemide, glyceol, glycyrrhiza glabra, heparin, hydrocortisone sodium succinate, hyoscine butylbromide, insulin, lansoprazole, lidocaine, magnesium oxide, metoclopramide hydrochloride, morphine, mosapride, pantoprazole sodium sesquihydrate, phytomenadione, pioglitazone hydrochloride, potassium chloride, propranolol hydrochloride, rondec tr, spironolactone, tamsulosin hydrochloride, terlipressin, tramadol hydrochloride, tranexamic acid, triamcinolone acetonide, tropisetron hydrochloride, unspecified herbal, and zingiber officinale rhizome.

On 2012-06-27, 2 days after week 1 study drug was administered, the subject presented with nausea and coffee ground vomiting and was hospitalized for Grade 3 esophageal varices hemorrhage. According to the CIOMS, the subject's level of consciousness was E4V5M6 and anemic conjunctiva was assessed. Laboratory results showed HGB of 7.2g/dl, HCT of 21.4%, PT of 14.4 sec, and platelet count of 107 103/ul. A panendoscopy showed moderate esophageal varices, congestive gastropathy and small antral ulcers. Endoscopy showed esophageal varices at lower esophagus with recent bleeding and small gastric shallow ulcers.

According to the CIOMS, the subject's history included esophageal varices and gastric ulcers (since late 2001); gastroesophageal varices (since 2011-04-15), and portal hypertensive gastrophy with mucosal hemorrhages, and esophageal varices with suspected recent bleeding (since 2011-05-26).

While hospitalized, the week 2 study drug was administered on 2012-07-03. The following day, the subject experienced nausea and 3 episodes of fresh blood vomiting (approximately 420 ml). Laboratory results that day showed a HGB of 8.6 g/dl (from 9.9 g/dl), PT: 14.5 sec, and platelet count of 77 103/µl. A follow-up endoscopy revealed esophageal varices ligation and esophageal ulcers. 2012-07-08, the subject again experienced an episode of fresh blood vomiting (approximately 1200 ml). The follow-up endoscope showed 1 esophageal varices bleeding, esophageal varices with ligation and esophageal ulcers. The laboratory results that day showed hgb: 10.5 g/dl, pt: 15.9 sec, platelets: 87 103/µl.

While hospitalized, the subject developed 2 additional SAEs: Grade 4 blood bilirubin increased on 2012-07-10 and 7 days later Grade 4 hepatic encephalopathy. That day, the subject was reported as having jaundice, consciousness change (to E2-3V2M5) and ammonia level of 186 µmo/l. Study drug was not changed as a result of the events.

The subject's condition remained unstable, and a transfer to hospice care was suggested. On 2012-07-18, the subject was discharged from the hospital with jaundice and change inconsciousness(E3V2M5).

The Investigator considered the event of esophageal varices hemorrhage to be possibly related to ADI-PEG 20. The Polaris Medical Monitor agreed with the Investigator's assessment. The hepatic encephalopathy and blood bilirubin increased events were considered to be related to disease progression.

Following the discharge, the subject experienced a fatal Grade 5 malignant neoplasm progression on 2012-07-19. The last dose of study drug (week 2) was administered 16 days prior to the event. The esophageal varices hemorrhage, hepatic encephalopathy, and blood bilirubin increased events were considered resolved at the time of death. No additional information was reported.

The Investigator considered the event of malignant neoplasm progression to be not related to ADI-PEG 20; an alternate etiology of disease progression was reported. The Polaris Medical Monitor agreed with the Investigator's assessment.

Laboratory values recorded as abnormal during the adverse events are presented in the following table.

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Hematocrit (%)	40 / 49	25.4	21.4	Not reported	27JUN2012
Hemoglobin (g/L)	135 / 175	86	72	3	27JUN2012
Leukocytes (10^9/L)	3.4 / 9.1	6.34	13.7	0	27JUN2012
Platelets (10^9/L)	150 / 400	52	107	1	27JUN2012
Albumin (g/L)	35 / 52	41	28	2	03JUL2012
Alkaline Phosphatase (U/L)	40 / 129	265	261	1	03JUL2012
Bilirubin (umol/L)	5.13 / 22.23	15.39	80.37	3	03JUL2012
Calcium (mmol/L)	2.1457 / 2.5449	2.2455	1.9461	2	03JUL2012
Chloride (mmol/L)	98 / 107	98	94	Not reported	03JUL2012
Cholesterol (mmol/L)	38.199 / 71.043	44.982	37.128	4	03JUL2012
Direct Bilirubin (umol/L)	0 / 8.55	6.84	56.43	Not reported	03JUL2012
Erythrocytes (10^12/L)	4.2 / 6.2	2.66	3.57	Not reported	03JUL2012
Hematocrit (%)	39 / 53	25.4	32.6	Not reported	03JUL2012
Hemoglobin (g/L)	123 / 183	86	110	1	03JUL2012
Indirect Bilirubin (umol/L)	0 / 13.68	8.55	23.94	Not reported	03JUL2012
Lymphocytes (10^9/L)	0.8 / 4.95	0.6023	0.6307	2	03JUL2012
Lymphocytes/Leukocytes (%)	20 / 45	9.5	7	Not reported	03JUL2012
Neutrophils/Leukocytes (%)	40 / 75	79.7	86	Not reported	03JUL2012
Phosphate (mmol/L)	0.87183 / 1.45305	1.16244	0.67809	2	03JUL2012
Platelets (10^9/L)	120 / 400	52	54	2	03JUL2012
Potassium (mmol/L)	3.5 / 5.1	3.94	3.38	1	03JUL2012
Prothrombin Time (sec)	8 / 12	12.1	15.1	Not reported	03JUL2012
Sodium (mmol/L)	136 / 145	136	130	1	03JUL2012
Hemoglobin (g/L)	135 / 175	86	99	2	04JUL2012
Platelets (10^9/L)	150 / 400	52	77	1	04JUL2012
Hemoglobin (g/L)	135 / 175	86	105	1	08JUL2012
Platelets (10^9/L)	150 / 400	52	34	3	08JUL2012
Platelets (10^9/L)	150 / 400	52	87	1	08JUL2012
Bilirubin (umol/L)	3.42 / 20.52	15.39	195.111	3	09JUL2012
Direct Bilirubin (umol/L)	0 / 6.84	6.84	150.822	Not reported	09JUL2012

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Bilirubin (umol/L)	3.42 / 20.52	15.39	227.088	4	10JUL2012
Direct Bilirubin (umol/L)	0 / 6.84	6.84	171.684	Not reported	10JUL2012
Bilirubin (umol/L)	3.42 / 20.52	15.39	388.683	4	15JUL2012
Direct Bilirubin (umol/L)	0 / 6.84	6.84	290.358	Not reported	15JUL2012
Potassium (mmol/L)	3.5 / 5	3.94	2.38	4	15JUL2012
Bilirubin (umol/L)	3.42 / 20.52	15.39	429.039	4	17JUL2012
Potassium (mmol/L)	3.5 / 5	3.94	3.1	1	17JUL2012

Reason(s) for Narrative: Death, Related SAE, Related AE Leading to Study Drug Discontinuation (AEDD)
Subject ID: 513-0004
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Gastrointestinal haemorrhage	Death, SAE, AEDD	2014-07-13 / 2014-07-26	5	Drug withdrawn	Fatal	Possibly Related*

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

* This relationship was changed by the investigator to not related to study drug but this change occurred after the closure of the database

Narrative:

Subject 513-0004 was a 46-year-old asian-mainland china male randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2014-06-16; and received once-weekly treatment with study drug between 2014-06-18 and 2014-07-08. The subject received a total of 4 injections of ADI-PEG 20.

The subject was first diagnosed with stage IV hepatocellular carcinoma on 2012-11-14. The subject received prior systemic chemotherapy with sorafenib from 2013-05-10 to 2014-02-08. Other therapies the subject received included transcatheter arterial chemoembolization by digital subtraction angiography (DSA)-. The subject underwent surgery for the left hepatic lobe resection on 2012-11-12; abdominal mass excision of sections of small intestine; excision of descending colon excision on 2013-03-28; abdominal mass removal and intestinal adhesion; and debonding and excision of descending colon

and enterocoelli on 2014-02-08. The subject had abdominocentesis and catheterization on 2014-07-16; peritoneal perfusion: hemocoagulase on 2014-07-17; transfusion: red cells suspension 2u on 2014-07-17. Prior to the start of study treatment, the subject's medical history and conditions included lower gastrointestinal hemorrhage. The subject's ongoing medical conditions included chronic superficial gastritis, chronic hepatic b virus, decompensated hepatic cirrhosis, and upper abdomen tenderness.

Concomitant medications, (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug and during the study, included alanyl glutamine, albumin human, amino acids – not otherwise specified (nos), aminomethylbenzoic acid, azintamide, benzylpenicillin sodium, bucinnazine hydrochloride, ceftriaxone sodium, coenzyme complex, dopamine, entecavir, etamsilate, fats nos, electrolyte solution, furosemide, glutathione sodium, haemocoagulase, invert sugar, lansoprazole, lidocaine hydrochloride, lipids nos, magnesium isoglycyrrhizinate, metoclopramide, mosapride citrate, octreotide acetate, omeprazole sodium, ornithine, phytomenadione, polyene 201-0018 phosphatidylcholine, potassium chloride, promethazine hydrochloride, tropisetron hydrochloride, unspecified herbal, veramid, and vidarabine sodium phosphate.

On 2014-07-13, 5 days after the last dose (week 4) of study drug was administered, the subject experienced gastrointestinal hemorrhage (10 ml fresh blood). According to the CIOMS, the subject was treated with unspecific dosage of yunnan baiyao herbal therapy. The event was considered serious.

The following day, the subject again experienced gastrointestinal hemorrhage (10 ml fresh blood and 3 x 3cm soft tissue) and was hospitalized for this event. The subject was treated with aminomethylbenzoic acid injections for the promotion of blood clotting. According to the CIOMS, the subject was assessed as having disease progression with massive degree of ascites by B ultrasonography (on 2014-07-16). Study drug was withdrawn as a result of the gastrointestinal hemorrhage event; however, the subject was permanently discontinued from the study due to disease progression.

On 2014-07-18, 10 days after the last dose (week 4) of study drug was administered, the subject also experienced a Grade 2 hepatic encephalopathy. No action was taken with study treatment as a result of the hepatic encephalopathy event. According to the CIOMS, the treatment (unspecified) was ineffective and the subject was subsequently discharged from the hospital on 2014-07-26. That same day, 18 days after the last dose of study treatment, the subject died as a result of Grade 5 gastrointestinal hemorrhage. The event of hepatic

encephalopathy was considered recovered/resolved at the time of death. No additional information at the time of death was reported.

The Investigator considered the event of gastrointestinal hemorrhage to be possibly related to ADI-PEG 20; however, the assessment was revised by the Investigator following database lock to unrelated. The Investigator considered the event of hepatic encephalopathy to be not related to ADI-PEG 20. The Polaris Medical Monitor agreed with the Investigator's assessments.

Laboratory values recorded as abnormal during the adverse events are presented in the following table.

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Uric Acid (umol/L)	210 / 430	180	186	No reported	15JUL2014

Reason(s) for Narrative: Death, Related SAE(s), Related AE Leading to Study Drug Discontinuation (AEDD), and AE(s) of Special Interest (AESI)
Subject ID: 307-0011
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Hypersensitivity	SAE, AESI, AEDD	2012-03-16 / 2012-03-24	3	Drug withdrawn	Recovering/ Resolving	Probably Related
Stomatitis	SAE	2012-03-19 / 2012-04-02	3	Dose not changed	Recovered/ Resolved	Possibly Related
Hypersensitivity	AESI	2012-03-24 / 2012-03-24	2	Dose not changed	Recovering/ Resolving	Definitely Related
Dermatitis allergic	SAE, AESI	2012-03-25 / 2012-04-02	3	Dose not changed	Recovered/ Resolved	Probably Related
Sepsis	SAE, Death	2012-03-29 / 2012-04-02	4	Dose not changed	Fatal	Not Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:
Subject 307-0011 was a 75-year-old asian-taiwan male randomly assigned to the ADI-PEG 20 treatment group. The subject was enrolled in Study POLARIS2009-001 on 2012-01-31; and received once-weekly treatment with study drug between 2012-02-07 and 2012-03-16. The subject received a total of 5 injections of ADI-PEG 20 (week 5 dose was missed for a pruritic rash).

The subject was first diagnosed with stage IIIA hepatocellular carcinoma on 2011-05-18. Prior systemic chemotherapy with sorafenib was reported. No other therapies were reported.

Prior to the start of study treatment, the subject's medical history and conditions included hepatitis B, left parotid tumor, right parotid tumor, and ureteral stone; and ongoing medical conditions included abdominal distension, abdominal pain, ascites, bilateral leg edema, bilateral pleural effusion, bilateral renal stone, cholelithiasis, diabetes mellitus, gallbladder stone, gastritis, hepatitis C, hiatus hernia, hypertension, hyperuricemia, liver cirrhosis, osteophytes in thoracolumbar spine, reflux esophagitis, and right bundle branch block.

Concomitant medications, (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug and during the study, included acetylcysteine, allopurinol, cefotaxime sodium, cyproheptadine hydrochloride, fexofenadine hydrochloride, furosemide, hydrocortisone acetate, irbesartan, metformin hydrochloride, methylprednisolone sodium succinate, mometasone furoate, nifedipine, pantoprazole sodium sesquihydrate, paracetamol, prednisolone, silybum marianum, spersin, topaal, triamcinolone, triamcinolone acetonide, ursodeoxycholic acid, and xylocaine-epinephrine.

On 2012-02-23, 2 days after the week 3 study drug was administered, the subject developed a Grade 2 pruritic rash. On 2012-03-06, 6 days after the week 4 study drug administration, the pruritic rash event worsened to Grade 3. The study treatment was interrupted (week 5) and resulted in an improvement of symptoms to Grade 1 on 2012-03-13. Study treatment (week 6 dose) was subsequently resumed on the day of hospitalization (16MAR2012).

On 2012-03-16, the subject experienced Grade 3 hypersensitivity and Grade 1 pyrexia and was hospitalized for the events. The subject's last dose (week 6) of study drug prior to the events was administered the same day (on 16MAR2012). No additional doses of study treatment were administered to the subject. Diagnostic testing included a blood culture, chest x-ray, skin biopsy, urine analysis, and urine culture performed on 2012-03-16. According to the safety report, a skin biopsy reported "features consistent with drug reaction" and the blood culture was positive for Gram-positive cocci. No additional laboratory results were

reported. While hospitalized, on 2012-03-19, 3 days after the last dose of study treatment, the subject developed SAE of Grade 3 stomatitis.

On 2012-03-24, the event of hypersensitivity was downgraded to Grade 2 and the subject was discharged from the hospital the same day (the Grade 2 event resolved the same day). The study drug was permanently withdrawn as result of the Grade 3 hypersensitivity serious adverse event. No action was taken as a result of the pyrexia and stomatitis events. The day after discharge, the subject developed a Grade 3 allergic dermatitis event (not serious). The pyrexia, stomatitis, and allergic dermatitis events were considered resolved on 2012-04-02.

The Investigator considered the Grade 3 hypersensitivity to be probably related, and the stomatitis to be possibly related. The pyrexia was considered not related to ADI-PEG 20; however, is was considered related to the hypersensitivity event. The Polaris Medical Monitor agreed with the Investigator's assessments. The Investigator considered the Grade 2 hypersensitivity event to be definitely related to ADI-PEG 20.

On 2012-03-25, 1 day after the subject was discharged; the subject was readmitted for a Grade 3 dermatitis allergic, a 6-day history of Grade 3 stomatitis, and a 9-day history of Grade 1 fever. The last dose of study drug was administered 9 days prior to the events.

According to the safety report, the subject's condition did not improve in spite of the antibiotic therapy for positive blood culture, intravenous steroids for allergic reaction, and nutritional supportive for stomatitis. On 2012-03-29, the subject developed Grade 4 sepsis which resulted in death 3 days later. The death occurred 17 days after the final dose of study treatment. The dermatitis allergic, stomatitis, and pyrexia were considered recovered/resolved at the time of death.

The Investigator considered the event of dermatitis allergic to be probably related to ADI-PEG 20. The Investigator considered the event of sepsis to be not related to ADI-PEG 20. The Polaris Medical Monitor agreed with the Investigator's assessments.

Laboratory values recorded as abnormal during the adverse events are presented in the following table.

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Alanine Aminotransferase (U/L)	0 / 54	112	236	2	25MAR2012

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Alanine Aminotransferase (U/L)	0 / 54	112	416	3	28MAR2012
Aspartate Aminotransferase (U/L)	0 / 39	119	203	3	28MAR2012
Blood Urea Nitrogen (mmol/L)	2.499 / 7.497	8.4609	21.777	Not reported	28MAR2012
Platelets (10^9/L)	138 / 353	216	53	2	28MAR2012
Alanine Aminotransferase (U/L)	0 / 54	112	300	3	01APR2012
Aspartate Aminotransferase (U/L)	0 / 39	119	161	2	01APR2012
Blood Urea Nitrogen (mmol/L)	2.499 / 7.497	8.4609	42.126	Not reported	01APR2012
Creatinine (umol/L)	61.88 / 132.6	95.472	134.368	Not reported	01APR2012
Hemoglobin (g/L)	135 / 170	115	80	2	01APR2012
Platelets (10^9/L)	138 / 353	216	32	3	01APR2012
Potassium (mmol/L)	3.5 / 5	4.02	6.2	3	01APR2012
Sodium (mmol/L)	135 / 148	137	168	4	01APR2012
Potassium (mmol/L)	3.5 / 5	4.02	6.5	3	02APR2012
Sodium (mmol/L)	135 / 148	137	166	4	02APR2012

Reason(s) for Narrative: Related SAE
Subject ID: 201-0018
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Hepatic failure	SAE	2013-12-24 / 2014-01-08	4	Dose not changed	Recovered/ Resolved	Possibly Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:
Subject 201-0018 was a 78-year-old white /caucasian/european heritage female randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2013-11-26; and received once-weekly treatment with study drug between 2013-12-06 and 2013-12-19. The subject received a total of 3 injections of ADI-PEG 20.

The subject was first diagnosed with stage IV hepatocellular carcinoma on 2009-12. The subject received prior systemic chemotherapy with sorafenib from 2010-08 to 2013-05-00. Other therapies the subject received included percutaneous ethanol injection of two lesions to iv liver segment. The subject had liver biopsy on 2013-11-27. Prior to the start of study treatment, the subject's medical history and conditions included drug-eluting stent in the right coronary artery, heart attack, and percutaneous transluminal coronary angioplasty (PTCA). The subject's ongoing medical conditions included anemia, arterial hypertension, ascites slight, chronic ischemic heart disease, cirrhosis, gallstones, hcv positive, and menopausal since 1983.

Concomitant medications, (antiviral therapy will be included below if applicable) therapy taken within 14 days prior to the first dose of study drug and during the study, included allopurinol, atorvastatin, bisoprolol, ciprofloxacin, clognil plus, furosemide, lactulose, omeprazole, potassium canrenoate, rifaximin, spironolactone, ursodeoxycholic acid, and zofenopril.

On 2013-12-24, the subject experienced a Grade 4 hepatic failure and was hospitalized for this event. The subject's last dose of study drug prior to the event was administered on 19DEC2013.

Treatment for the event was not reported in the clinical database. On 2014-01-08, the hepatic failure was considered recovered/resolved, and the subject was discharged the same day. No action was taken with the study drug. The subject withdrew consent for treatment prior to the event.

The Investigator considered the event of hepatic failure to be possibly related to ADI-PEG 20. The Polaris Medical Monitor agreed with the Investigator's assessment.

No abnormal laboratory values were recorded during the adverse events.

Reason(s) for Narrative: Related SAE
Subject ID: 203-0005
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Hepatic encephalopathy	SAE	2012-04-16 / 2012-04-20	4	Drug interrupted	Recovered/ Resolved	Possibly Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:
Subject 203-0005 was a 53-year-old white/caucasian/european heritage male randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2012-03-29; and received once-weekly treatment with study drug between 2012-04-05 and 2012-07-05. The subject received a total of 9 injections of ADI-PEG 20 (week 3 and 4 doses were missed).

The subject was first diagnosed with stage IV hepatocellular carcinoma on 2011-10-24. The subject received prior systemic chemotherapy with sorafenib from 2011-11-15 to 2012-02.

Prior to the start of study treatment, the subject's ongoing medical conditions included alcohol abuse, dyspnea, hcv infection, leg cramps, legs edema, and portal hypertension.

Concomitant medications, (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug and during the study, included acetylcysteine, amino acids nos, amlodipine, chlorphenamine maleate, corticosteroid NOS, enemas, furosemide, hydrocortisone, lactitol, lactulose, levofloxacin, lorazepam, magnesium, methylprednisolone, methylprednisolone sodium succinate, potassium canrenoate, rifaximin, and zolpidem tartrate.

On 2012-04-16, the subject experienced Grade 4 hepatic encephalopathy and was hospitalized for this event. The subject's last dose of study drug prior to the event was administered on 2012-04-12. At the time of admission, the subject also experienced Grade 1 anxiety. The event was not considered serious. According to the CIOMS, the subject symptoms also included mood disturbance, psychomotor retardation, and altered level of consciousness. The symptoms resolved following treatment with potassium canrenoate, levofloxacin, magnesium, and rifaximin.

The clinical database reports treatment at the time of hospitalization also included lactulose, lactitol, lorazepam, and amino-acids NOS. On 2012-04-18, the anxiety event resolved. Two days later, on 2012-04-20, the event of hepatic encephalopathy was considered recovered/resolved and the subject was discharged from the hospital the same day.

Study drug was interrupted (week 3 and 4); and the administration was resumed on 2012-05-04 and continued without interruption though 2012-07-05. Treatment was permanently discontinued at that time as a result of disease progression. Following discontinuation from treatment, the subject received system treatment with capecitabine between 2012-10-17 and 2012-12-04.

The Investigator considered the event of hepatic encephalopathy to be possibly related to ADI-PEG 20. The Polaris Medical Monitor agreed with the Investigator's assessment. According to the CIOMS, the Investigator confirmed that both the background cirrhosis and the study drug could have worked conjunctly as cofactors in precipitating encephalopathy. The background cirrhosis was thought to have a relevant role; however, the subject's liver function was very good. Additionally, the Investigator confirmed that an isolate hepatic encephalopathy was unusual as only related to cirrhosis.

No abnormal laboratory values were recorded during the adverse events.

Reason(s) for Narrative: Related SAE
Subject ID: 307-0045
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Hyperammonaemic encephalopathy	SAE	2014-07-31 / 2014-08-08	3	Drug interrupted	Recovered/resolved	Probably Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:
Subject 307-0045 was a 48-year-old asian-taiwan male randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2014-06-27; and received once-weekly treatment with study drug between 2014-07-07 and 2014-09-22. The subject received a total of 10 injections of ADI-PEG 20 (week 5 and 6 doses were missed).

The subject was first diagnosed with stage IV hepatocellular carcinoma on 2012-01-06. The subject received prior systemic chemotherapy with sorafenib from 2013-08-02 to 2014-04-23; and radiotherapy from 2012-12 to 2013-11-15. Other therapies the subject received included radiofrequency ablation transcatheter arterial chemoembolization. The subject underwent surgery for liver segment 8 segmentectomy on 2012-01-06; and bilateral vsat wedge resection of left upper, right lower, and left lower lung; liver segment 3 and 4 segmentectomy and cholecystectomy; and lymph node resection and enterolysis (all on 2013-12-31). Prior to the start of study treatment, the subject's medical history and conditions included liver abscess. The subject's ongoing medical conditions included ascites, atherosclerosis of abdominal aorta, gastric and esophageal varices, hepatitis B, hypertension, insomnia, intermittent fever, left pleural effusion, liver cirrhosis, lung metastasis, osteophytes, right bundle branch block, splenomegaly, spondylosis, and unspecified functional disorder of stomach.

Concomitant medications, (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug and during the study, included ciprofloxacin, dimeticone, entecavir, lactulose, lorazepam, paracetamol, ranitidine, silybum marianum, sucralfate, ursodeoxycholic acid, and zolpidem tartrate.

On 2014-07-31, the subject experienced a Grade 3 hyperammonemic encephalopathy and was hospitalized for this event. The subject's last dose of study drug prior to the event was administered on 2014-07-28. According to the CIOMS, the subject had an 8-day history of elevated ammonia levels. On admission, the subject's laboratory results showed an elevated ammonia with 282 ug/ml, subsequently 238 ug/ml on 2014-08-02, and 179 ug/ml on 2014-08-04. After admission, subject's condition improved; however, specific treatments were not reported.

On 2014-08-08, the event of hyperammonemic encephalopathy was downgraded to Grade 2 and the subject was discharged from the hospital the same day. The Grade 2 event was reported as improving on 2014-08-12; however, a second Grade 3 event was reported in the clinical database starting the same day. This event was not considered serious. Study drug was interrupted as a result of both Grade 3 events.

Study treatment was resumed (week 7) on 2014-08-19. That day, the subject again experienced a Grade 2 hyperammonemic encephalopathy event which resolved on 2014-08-25. Study treatment remained ongoing and the next dose (week 8) was administered on 2014-08-25. Following the week 12 study drug administration (2014-09-22), the treatment is permanently withdrawn as a result of disease progression.

The Investigator considered the event of hyperammonemic encephalopathy to be probably related to ADI-PEG 20. The Polaris Medical Monitor agreed with the Investigator's assessment.

Reason(s) for Narrative: Related SAE
Subject ID: 309-0003
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Hepatic encephalopathy	SAE	2012-06-23 / 2012-06-28	3	Drug interrupted	Recovered/ Resolved	Possibly Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:
Subject 309-0003 was a 52-year-old asian-taiwan female randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2012-06-11: and received once-weekly treatment with study drug between 2012-06-20 and 2012-08-29. The subject received a total of 9 injections of ADI-PEG 20 (week 2 and 5 doses were missed).

The subject was first diagnosed with stage IIIA hepatocellular carcinoma on 2009-05-01. The subject received prior systemic chemotherapy with hepatic encephalopathy with sorafenib from 2010-10-27 to 2011-03-12. Other therapies the subject received included hepatic artery infusion chemotherapy with fluorouracil and cisplatin; transcatheter arterial chemoembolization at bilareral hepatic lobe; and transcatheter arterial chemoembolization at right hepatic lobe.

Prior to the start of study treatment, the subject's medical history and conditions included common bile duct stone, esophageal varices bleeding, gall bladder polyp, intermittent ascites, intermittent hepatic encephalopathy, perianal abscess with fistula, right kidney stone, right pleural effusion, and right renal cysts. The subject's ongoing medical and conditions included anemia, congestive gastropathy, duodenal ulcers, esophageal ulcer, esophageal varices, fatty liver, gastric ulcers, gastric varices, hemorrhoid, hepatic cysts, hepatitis B, ileus, intermittent gall bladder stone, intermittent gastritis, intermittent leg edema, left pleural effusion, liver cirrhosis, marginal spur of t-l spine, platelet count decreased, portal vein thrombosis, reflux esophagitis, right spondylosis, spider angioma, splenomegaly, and telangectasia of esophagus.

Concomitant medications, (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug and during the study, included betamethasone valerate, diclofenac sodium, furosemide, lactulose, lansoprazole, mucaine, opium derivatives and expectorants, propranolol hydrochloride, sennoside a+b calcium, and spironolactone.

On 2012-06-23, 3 days after the initial week 1 study drug was administered, the subject experienced a Grade 3 hepatic encephalopathy and was hospitalized for this event. The subject has a prior history of intermittent hepatic encephalopathy starting 2010-10-27.

According to the CIOMS, the subject had 2-day history of nausea and dizziness with associated hand tremor, yellowish skin, and consciousness changes. On admission, the subject had a level of consciousness of E4V5M6. Laboratory results included PT of 11.8 sec,

SGOT of 58 IU/L, total bilirubin of 1.22 mg/dl, and ammonia level of 178 µmol/L. Treatment for the event included hemodynamic management and lactulose treatment. A chest x-ray was performed on 2012-06-23; oxygen therapy from 2012-06-23 to 2012-06-28; and a stool occult blood on 2012-06-24 (results were not reported).

According to the CIOMS, the ammonia laboratory result was 146 µmol/L on 2012-06-26. The subject's consciousness gradually improved (E4V5M6) and hemodynamic status stabilized. On 2012-06-28, the hepatic encephalopathy was considered recovered/resolved and the subject was discharged from the hospital the same day. Study drug was interrupted as a result of the event and was resumed (week 3) on 2012-07-04. The event did not recur despite reintroduction to ADI-PEG 20 for an additional 8 weeks.

Following the event, an abdominal ultrasound, blood culture, chest x-ray, and urine analysis were performed on 2012-07-16 (results and rationale were not reported). Following the week 11 (2012-08-29) study drug administration, the treatment was permanently withdrawn as a result of disease progression. During follow-up, is was reported the subject was treated with systemic chemotherapy sorafenib between 2012-10-24 and 2012-11-28. No additional information was reported.

The Investigator considered the event of hepatic encephalopathy to be possibly related to ADI-PEG 20. The Polaris Medical Monitor agreed with the Investigator's assessment.

Laboratory values recorded as abnormal during the adverse events are presented in the following table.

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Aspartate Aminotransferase (U/L)	10 / 50	44	58	1	23JUN2012
Bilirubin (umol/L)	3.42 / 20.52	20.52	20.862	1	23JUN2012
Indirect Bilirubin (umol/L)	0 / 6.84	13.68	10.26	Not reported	23JUN2012
Alkaline Phosphatase (U/L)	35 / 104	151	114	1	27JUN2012
Aspartate Aminotransferase (U/L)	0 / 31	44	49	1	27JUN2012
Bilirubin (umol/L)	5.13 / 22.23	20.52	27.36	1	27JUN2012
Cholesterol (mmol/L)	38.199 / 71.043	83.181	87.822	4	27JUN2012

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Eosinophils/Leukocytes (%)	1 / 6	6.5	8.5	Not reported	27JUN2012
Erythrocytes (10^12/L)	3.7 / 5.5	3.19	3.49	Not reported	27JUN2012
Indirect Bilirubin (umol/L)	0 / 13.68	13.68	18.81	Not reported	27JUN2012
Leukocytes (10^9/L)	4 / 11	2.47	2.34	2	27JUN2012
Lymphocytes (10^9/L)	0.8 / 4.95	0.58045	0.48906	3	27JUN2012
Neutrophils (10^9/L)	1.6 / 8.25	1.54869	1.42272	2	27JUN2012
Platelets (10^9/L)	120 / 400	66	61	2	27JUN2012
Potassium (mmol/L)	3.5 / 5.1	4.4	3.43	1	27JUN2012
Prothrombin Time (sec)	8 / 12	11.8	13.5	Not reported	27JUN2012

Reason(s) for Narrative: Related SAE
Subject ID: 309-0010
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Hepatic encephalopathy	SAE	2013-04-06 / 2013-04-12	3	Drug interrupted	Recovered/	Hepatic encephalopathy

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:

Subject 309-0010 was a 47-year-old asian-taiwan male randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2013-03-25; and received once-weekly treatment with study drug between 2013-03-25 and 2014-10-20. The subject received a total of 82 injections of ADI-PEG 20 (week 3 dose was missed).

The subject was first diagnosed with stage IIIA hepatocellular carcinoma on 2009-05-22. The subject received prior systemic chemotherapy with sorafenib from 2013-01-10 to 2013-02-25. Other therapies the subject received included transcatheter arterial chemoembolization. Prior to the start of study treatment, the subject's medical history and conditions included ascites, coronary varices, duodenal ulcer with bleeding hemostasis, gallbladder sludge, gastric ulcers, and lymph nodes metastasis. The subject's ongoing medical conditions included alcoholic liver damage, anemia, ascites, bilateral renal cysts,

degenerative joint disease change of l-spine, duodenal ulcers, esophageal varices, gastric ulcer, hepatitis B, intermittent mixed hemorrhoid, liver cirrhosis, mixed piles, and splenomegaly.

Concomitant medications, (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug and during the study included alcos-anal, aldioxa, betamethasone, desloratadine, dimethicone, diphenhydramine, fleet, hyoscine, iron, lactulose, lansoprazole, lidocaine, lorazepam, magnesium oxide, metoclopramide hydrochloride, pantoprazole sodium sesquihydrate, paracetamol, phytomenadione, silybum marianum, telbivudine, tranexamic acid, and vitamin b complex.

On 2013-04-06, the subject presented with confusion associated with epistaxis which progressed to combative behavior. The subject was hospitalized with Grade 3 hepatic encephalopathy two days later. The subject's last dose (week 2) of study drug prior to the event was administered on 2013-04-01. On admission, the consciousness level was E3V3M4 to E4V4M5. Laboratory results showed a hemoglobin of 8.5 g/dL, HCT 27.2%, PT 12.1 sec, SGOT 62 IU/l, total bilirubin of 0.95 mg/dL, and ammonia level of 150 µmol/L.
On 2013-04-09, ammonia level was 139 µmol/L.

While hospitalized, treatment for the event included lactulose, lorazepam, phytomenadione, tranexamic acid, pantoprazole sodium sesquihydrate, and Vitamin B complex.
On 2013-04-12, the event of hepatic encephalopathy was considered recovered/resolved and the subject was discharged from the hospital the same day. Study drug was interrupted and administration was resumed on 2013-04-15. According to the CIOMS, the Investigator reported since that since the subject had never developed hepatic encephalopathy before receiving the study drug and it abated after stopping the study drug, the hepatic encephalopathy was judged as possibly related. However, the study drug remained ongoing through week 83 (2014-10-20); and no additional encephalopathy or serious adverse events were reported.

The Investigator considered the event of hepatic encephalopathy to be possibly related to ADI-PEG 20. The Polaris Medical Monitor agreed with the Investigator's assessment.

Laboratory values recorded as abnormal during the adverse events are presented in the following table.

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Aspartate Aminotransferase (U/L)	10 / 50	50	62	1	08APR2013
Erythrocytes (10^12/L)	4.26 / 5.56	4.07	3.66	Not reported	08APR2013
Hematocrit (%)	40 / 49	32	27.2	Not reported	08APR2013
Hemoglobin (g/L)	135 / 175	99	85	2	08APR2013
Platelets (10^9/L)	150 / 400	95	96	1	08APR2013

Reason(s) for Narrative: Related SAE(s)
Subject ID: 405-0021
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Headache	SAE	2013-10-09 / 2013-10-10	2	Dose not changed	Recovered/ Resolved	Possibly Related
Alanine aminotransferase increased	SAE	2013-10-11 / 2013-10-12	3	Drug interrupted	Recovered/ Resolved	Possibly Related
Aspartate aminotransferase increased	SAE	2013-10-11 / 2013-10-12	2	Dose not changed	Recovered/ Resolved	Possibly Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:

Subject 405-0021 was a 47-year-old asian-north east asian heritage male randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2013-06-12; and received once-weekly treatment with study drug between 2013-06-19 and 2014-07-14. The subject received a total of 51 injections of ADI-PEG 20 (week 17, 38, 49, 54, and 55 doses were missed).

The subject was first diagnosed with stage IV hepatocellular carcinoma on 2009-05-16. The subject received prior systemic chemotherapy with sorafenib from 2009-10-09 to 2010-03; and again from 2011-03-21 to 2011-07-20. Radiotherapy was performed from

2010-06-07 to 2013-04-15. Other therapies the subject received: 4 transcatheter arterial chemoembolization treatments. The subject underwent surgery for palliative seeding nodule excision; excision of lesion of retroperitoneum/peritoneum on 2010-11-15; mass excision on 2011-02-11; lysis of peritoneal adhesions; and resection of small intestine and anastomosis on 2012-09-19. Prior to the start of study treatment, the subject's medical history and conditions included lumbar herniated inter-vertebral disc. The subject's ongoing medical conditions included Grade 2 abdominal pain, anemia, atrophic gastritis, hepatitis B virus, iron deficiency anemia, mild dizziness, Grade 2 pelvic pain, and reflux esophagitis.

Concomitant medications, (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug and during the study, included cebetabs ,cefotaxime sodium, chlorphenamine, desonide, dexamethasone, dextrose and sodium chloride injection, domperidone, durabac, entecavir, esomeprazole, fentanyl, feroba, freamine, glucose, godex, lactulose, metoclopramide hydrochloride, morphine hydrochloride, multivitamins, myprodol, ornithine, osmotan, oxycodone, oxycodone hydrochloride, pantoprazole, pethidine hydrochloride, pip/tazo, ringer-lactate, sodium chloride, targin, terlipressin acetate, tranexamic acid, trimebutine maleate, and ursodeoxycholic acid.

On 2013-10-09, the subject experienced a Grade 2 headache; onset was abrupt and accompanied with nausea. The event was considered serious. The following day, the headache was resolved. However, the clinical laboratory results showed a glucose of 116 mg/dL; AST 171 IU/L; ALT 297 IU/L; and total bilirubin was 0.9 mg/dL (table below narrative contains additional clinical laboratory results). As a result, on 2013-10-11, the subject was hospitalized for the Grade 3 alanine aminotransferase increased and Grade 2 aspartate aminotransferase increased (both were considered serious). According to the CIOMS, the hospital evaluation also included the recent headache. The subject's last dose of study drug (week 16) prior to the events was administered on 2013-10-02.

On admission, a MRI brain showed no evidence of brain metastasis; and abdominal/chest CTs showed no significant changes in comparison with prior scans. Treatment included metoclopramide hydrochloride and solution of dextrose 10%/sodium and potassium. On 2013-10-12, the alanine aminotransferase increased and aspartate aminotransferase increased events were considered resolved and the subject was discharged from the hospital.

Study drug was interrupted as a result of the alanine aminotransferase increased event; and study drug (week 18) was administered on 2013-10-16. No action was required as a result of the headache and aspartate aminotransferase increased events.

The Investigator considered the events of headache, alanine aminotransferase increased, and aspartate aminotransferase increased events to be possibly related to ADI-PEG 20. The Polaris Medical Monitor agreed with the Investigator's assessment.

Laboratory values recorded as abnormal during the adverse events are presented in the following table.

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Eosinophils (10^9/L)	40000 / 700000	29700	26800	Not reported	01MAR2014
Eosinophils/Leukocytes (%)	1 / 7	1.1	0.4	Not reported	01MAR2014
Erythrocytes (10^12/L)	4.2E12 / 6.3E12	3.53E12	2.91E12	Not reported	01MAR2014
Hematocrit (%)	39 / 52	30.3	23.9	Not reported	01MAR2014
Hemoglobin (g/L)	130 / 170	95	82	2	01MAR2014
Lymphocytes (10^9/L)	800000 / 4400000	758700	763800	1	01MAR2014
Lymphocytes/Leukocytes (%)	20 / 44	28.1	11.4	Not reported	01MAR2014
Neutrophils/Leukocytes (%)	50 / 75	61.5	80.6	Not reported	01MAR2014
Alanine Aminotransferase (U/L)	0 / 40	127	285	3	03MAR2014
Albumin (g/L)	35 / 52	38	29	2	03MAR2014
Alkaline Phosphatase (U/L)	40 / 120	188	153	1	03MAR2014
Aspartate Aminotransferase (U/L)	0 / 40	89	189	2	03MAR2014
Bilirubin (umol/L)	3.42 / 20.52	6.84	23.94	1	03MAR2014
Blood Urea Nitrogen (mmol/L)	3.57 / 9.282	3.57	1.785	Not reported	03MAR2014
Calcium (mmol/L)	2.1457 / 2.5449	2.1457	1.996	2	03MAR2014

Reason(s) for Narrative: Related SAE, Related AE Leading to Study Drug Discontinuation (AEDD)
Subject ID: 101-0041
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Vomiting	SAE, AEDD	2013-08-12 / 2013-08-16	3	Drug withdrawn	Recovered/ Resolved	Possibly Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:
Subject 101-0041 was a 54-year-old white-white/caucasian/european heritage male randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2013-07-15; and received once-weekly treatment with study drug between 2013-07-30 and 2013-08-06. The subject received a total of 2 injections of ADI-PEG 20 prior to the following SAE.

The subject was first diagnosed with stage IV hepatocellular carcinoma on 2011-09-23. The subject received prior systemic chemotherapy with sorafenib from 2013-02-15 to 2013-07-15. Other therapies the subject received included bland embolization of right hepatic tumor mass and chemoembolization therapy to right hepatic tumor. The subject underwent surgery for core liver biopsy on 2012-12-21. Prior to the start of study treatment, the subject's medical history conditions included bilateral inguinal hernia repairs as a child, bleeding esophageal varices (banded), multiple skin cancers; basal cell and squamous cell, orthopedic surgery to right leg with metal plate placement, and two cataract surgeries. The subject's ongoing medical conditions included benign colon polyps, congestive heart failure, diabetes, hepatitis B, hypertension, medically controlled ascites, non-alcoholic steatohepatitis, and peripheral vascular disease.

Concomitant medications, (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug included propranolol, rifaximin, furosemide, insulin, insulin glargine, and esomeprazole.

On 2013-08-12, the subject experienced a Grade 3 vomiting and was hospitalized for this event the following day. The subject's last dose of study drug prior to the event was

administered on 06AUG2013. According to the CIOMS, on admission, the subject presented with Grade 3 elevated bilirubin (no clinical or safety laboratory results were reported); a 1-day history of shaking, chills, nausea, right upper quadrant pain, vomiting and diarrhea; and 3-week history of productive cough. A computerized tomography (CT) scan of the abdomen-pelvis was performed to rule out biliary obstruction (no infective or obstructive process was identified). Blood, sputum, and urine cultures were negative. Concomitant medications used to treat symptoms, included ciprofloxacin, enoxaparin, loperamide, lorazepam, magnesium sulfate, metronidazole, morphine sulfate, omeprazole, ondansetron, potassium chloride, prochlorperazine, and sodium chloride intravenous fluids for the dehydration.

On 2013-08-16, the subject was discharged from the hospital. The event of vomiting was considered recovered/resolved on 2013-08-16. According to the CIOMS, the bilirubin improved to Grade 1; however, no laboratory results were reported.

Study drug was initially interrupted (week 3 and 4) as a result of the vomiting event. Subsequently, the study drug was withdrawn due to the vomiting event.

No laboratory results were reported at the time of the event per PPD template for this patient

The Investigator considered the event of vomiting to be possibly related to ADI-PEG 20. The Polaris Medical Monitor did not agree with the Investigator's assessment.

No abnormal laboratory values were reported during the adverse events.

Reason(s) for Narrative: Related SAE, Related AE Leading to Study Drug Discontinuation (AEDD),
Subject ID: 101-0042
Treatment Group: ADI-PEG 20
Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Hepatic encephalopathy	SAE	2013-08-15 / 2013-08-18	2	Dose not changed	Recovered/ Resolved	Possibly Related
Encephalopathy	AEDD	2013-09-10 / 2013-09-23	3	Drug withdrawn	Recovered/ Resolved	Possibly Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:
Subject 101-0042 was a 64-year-old white-white/caucasian/european heritage male randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2013-08-05; and received once-weekly treatment with study drug between 2013-08-05 and 2013-09-03. The subject received a total of 5 injections of ADI-PEG 20 prior to discontinuation for an adverse event.

The subject was first diagnosed with stage IIIA hepatocellular carcinoma on 2012-05-22. The subject received prior systemic chemotherapy with sorafenib from 2012-06-05 to 2013-07-16. The subject underwent surgery for liver biopsy on 2012-05-22. Prior to the start of study treatment, the subject's medical history included biliary ductal injury with multiple reconstructive surgeries, choledochojejunoectomy, sepsis post-periodontal surgery, and splenectomy. The subject's ongoing medical conditions included biliary obstruction, esophageal varices, hypertension, lower back pain, psoriatic arthritis, right foot drop, and ulcerative colitis/proctitis.

Concomitant medications, (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug and during the study, included acetylsalicylic acid, amlodipine, bupropion hydrochloride, calcium, hydrochlorothiazide, lactulose, magnesium sulfate, mesalazine, metoprolol, multivitamins, potassium chloride, sodium chloride, valsartan, and vitamin d nos.

On 2013-08-15, the subject experienced a Grade 2 hepatic encephalopathy and was hospitalized for the event. The subject's last dose (week 2) of study drug prior to the event was administered on 13AUG2013. According to the CIOMS, the subject was assessed with dehydration, mental status changes, and confusion; the CT scan was normal; however, the ammonia level was 236 (normal range 0 – 50 mcM/L). An additional symptom included dehydration, identified after admission and considered to be a trigger for the encephalopathy. Treatment for the event included lactulose. According to the CIOMS, treatment also included magnesium sulfate, mesalamine, intravenous normal saline, and oral valsartan. Ammonia levels remained elevated throughout the hospitalization with 236 mcM/L noted on 08-15, 206 mcM/L on 08-16, 189 mcM/L on 08-17, and 190 mcM/L on 08-18.

On 2013-08-16, the subject's mental status improved and ammonia levels were trending lower. On 2013-08-18, event of hepatic encephalopathy was considered recovered/resolved and the subject was discharged from the hospital the same day. No action was taken with the

study drug and the next dose was administered on 2013-08-20 (week 3). According to the CIOMS, that day, the ammonia levels remained elevated at 263 mcM/L.

The Investigator considered the event of hepatic encephalopathy to be possibly related to ADI-PEG 20. The Polaris Medical Monitor did not agree with the Investigator's assessment.

On 2013-09-10, the subject experienced a Grade 3 encephalopathy. The subject's last dose (week 5) of study drug prior to the event was administered on 03SEP2013.

The event was not considered serious and the subject was not hospitalized. The lactulose treatment received during the prior hospitalization remained ongoing. No additional event details or treatment were reported. The event of encephalopathy was considered recovered/resolved on 2013-09-23.

The study drug was permanently withdrawn as a result of the event. Following discontinuation from study treatment, the subject initiated systemic chemotherapy with cabozantinib vs placebo from 2013-11-18 to 2013-12-29.

The Investigator considered the event of encephalopathy to be possibly related to ADI-PEG 20.

Laboratory values recorded as abnormal during the adverse events are presented in the following table.

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Alanine Aminotransferase (U/L)	5 / 37	67	56	1	10SEP2013
Albumin (g/L)	40 / 52	29	34	1	10SEP2013
Alkaline Phosphatase (U/L)	45 / 129	277	176	1	10SEP2013
Aspartate Aminotransferase (U/L)	10 / 37	70	57	1	10SEP2013
Cholesterol (mmol/L)	71.3999643 / 85.6800357	56.049	51.408	4	10SEP2013
Erythrocytes (10^12/L)	4.2 / 5.6	3.52	3.4	Not reported	10SEP2013
Glucose (mmol/L)	3.885 / 5.4945	7.326	8.9355	2	10SEP2013
Hematocrit (%)	38 / 52	34.3	33.1	Not reported	10SEP2013
Hemoglobin (g/L)	130 / 170	112	107	1	10SEP2013
Monocytes/Leukocytes (%)	0 / 12	13.2	15	Not reported	10SEP2013

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Potassium (mmol/L)	3.5 / 5.1	3.4	3.3	1	10SEP2013
Protein (g/L)	63 / 81	59	58	Not reported	10SEP2013
Prothrombin Intl. Normalized Ratio	0.89 / 1.2	1.3	1.4	1	10SEP2013
Prothrombin Time (sec)	9.4 / 12.8	14	15.2	Not reported	10SEP2013
Alanine Aminotransferase (U/L)	5 / 37	67	60	1	23SEP2013
Albumin (g/L)	40 / 52	29	31	1	23SEP2013
Alkaline Phosphatase (U/L)	45 / 129	277	211	1	23SEP2013
Alpha Fetoprotein (ug/L)	0 / 6.1	55	42	Not reported	23SEP2013
Aspartate Aminotransferase (U/L)	10 / 37	70	71	1	23SEP2013
Calcium (mmol/L)	2.12075 / 2.61975	2.17065	2.0958	1	23SEP2013
Cholesterol (mmol/L)	71.3999643 / 85.6800357	56.049	51.051	4	23SEP2013
Eosinophils/Leukocytes (%)	0 / 7	10	10.2	Not reported	23SEP2013
Erythrocytes (10^12/L)	4.2 / 5.6	3.52	2.93	Not reported	23SEP2013
Glucose (mmol/L)	3.885 / 5.4945	7.326	7.659	1	23SEP2013
Hematocrit (%)	38 / 52	34.3	29	Not reported	23SEP2013
Hemoglobin (g/L)	130 / 170	112	95	2	23SEP2013
Lactate Dehydrogenase (U/L)	12 / 246	224	317	Not reported	23SEP2013
Monocytes/Leukocytes (%)	0 / 12	13.2	12.3	Not reported	23SEP2013
Protein (g/L)	63 / 81	59	62	Not reported	23SEP2013
Prothrombin Intl. Normalized Ratio	0.89 / 1.2	1.3	1.39	1	23SEP2013
Prothrombin Time (sec)	9.4 / 12.8	14	15	Not reported	23SEP2013

Reason(s) for Narrative: Related SAE, and Related AE Leading to Study Drug Discontinuation (AEDD)

Subject ID: 201-0017

Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Hepatic failure	SAE, AEDD	2013-12-13 / 2013-12-24	4	Drug withdrawn	Recovered/ Resolved	Possibly Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:

Subject 201-0017 was an 82-year-old white/caucasian/european heritage male randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2013-11-06; and received once-weekly treatment with study drug between 2013-11-28 and 2013-12-06. The subject received a total of 2 injections of ADI-PEG 20.

The subject was first diagnosed with stage II hepatocellular carcinoma on 2012-07.
The subject received prior systemic chemotherapy with sorafenib, which resulted in skin toxicity and hyperbilirubinemia, from 2013-07 to 2013-09. Other therapies the subject received included percutaneous ethanol injection and radiofrequency ablation of two lesions to iv and viii liver segments, and transarterial chemoembolization for multifocal HCC.
The subject underwent liver biopsy surgery on 2013-10-21. Prior to the start of study treatment, the subject's medical history and conditions included appendectomy. The subject's ongoing medical conditions included adenomyomatosis gallbladder, allergy to intravenous contrast media, arterial hypertension, broncopneumopathy chronic, chondropathy, cirrhosis, gallstones, hcv positive, ischemic cardiopathy, left gonarthrosis, meniscosi, poisoning phyto-drugs, prostatic hypertrophy, pulmonary emphysema, spondylo-disk-arthrosis, and thrombocytopenia.

Concomitant medications, (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug and during the study, included bisoprolol fumarate, doxazosin, glyceryl trinitrate, lactitol, lansoprazole, paracetamol, potassium canrenoate, and torasemide.

On 2013-12-13, the subject experienced a Grade 4 hepatic failure and was hospitalized for this event. The subject's last dose of study drug prior to the event was administered on 06DEC2013. Study drug was permanently withdrawn as a result of the event. No treatment or diagnostics were reported. On 2013-12-24, event of hepatic failure was considered recovered/resolved, and the subject was discharged from the hospital the same day.

The Investigator considered the event of hepatic failure to be possibly related to ADI-PEG 20. The Polaris Medical Monitor agreed with the Investigator's assessment.

No abnormal laboratory values were recorded during the adverse events.

Reason(s) for Narrative: Related SAE(s), Related AE Leading to Study Drug Discontinuation (AEDD)
Subject ID: 252-0002
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Muscular weakness	SAE	2012-09-09 / 2012-09-16	3	Dose not changed	Recovered/ Resolved	Possibly Related
Muscular weakness	SAE	2012-09-09 / 2012-09-16	3	Dose not changed	Recovered/ Resolved	Possibly Related
Rash macular	SAE, AEDD	2012-09-09 / 2012-09-17	3	Drug withdrawn	Recovered/ Resolved	Definitely Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:
Subject 252-0002 was a 76-year-old white /caucasian/european heritage male randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2012-07-24; and received once-weekly treatment with study drug between 2012-08-28 and 2012-09-04. The subject received a total of 2 injections of ADI-PEG 20.

The subject was first diagnosed with stage IV hepatocellular carcinoma on 2011-06.
The subject received prior systemic chemotherapy with sorafenib from 2011-12 to 2012-06.
Prior to the start of study treatment, the subject's medical history and conditions included prostate cancer. The subject's ongoing medical and conditions included hay fever, hypertension, indigestion, pulmonary embolism, and type 2 diabetes mellitus.

Concomitant medications, (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug and during the study, included amlodipine, dexamethasone, enalapril, flucloxacillin, gliclazide, intravenous solutions, indapamide,

loperamide, metformin, omeprazole, other emollients and protectives, paracetamol, and tinzaparin.

On 2012-09-09, the subject experienced Grade 3 muscular weakness (bilateral lower extremities), Grade 3 muscular weakness (bilateral upper extremities), and Grade 3 rash macular (erythromacular leg and buttocks). Subsequently, the subject was hospitalized for these events. The subject's last dose (week 2) of study drug prior to the 3 events was administered on 2012-09-04. Treatment during hospitalization included intravenous solutions, and paracetamol (none specific to events were reported). On 2012-09-11, the subject was discharged from the hospital with the events ongoing. However, the muscular weakness events were considered recovered/resolved 5 days later, on 2012-09-16. The event of rash macular resolved the following day, on 2012-09-17. However, on 2012-09-18, an event of Grade 1 leg rash was reported which resolved on 2012-09-20.

No action was taken with study therapy as a result of the Grade 3 muscular weakness (bilateral lower and upper extremities). The treatment was permanently discontinued as a result of the Grade 3 macular rash event.

The Investigator considered the 2 events of muscular weakness to be possibly related to ADI-PEG 20. The Investigator rash macular event to be definitely related to ADI-PEG 20. The Polaris Medical Monitor agreed with the Investigator's assessment. According to the CIOMS, the Investigator considered the definite relationship of causality because the event developed immediately after administration of study drug and increased in severity in the days after study drug administration. It was also noted that there was no recurrence following cessation of study drug.

No abnormal laboratory values were recorded during the adverse events.

Reason(s) for Narrative: Related SAE(s), Related AE Leading to Study Drug Discontinuation (AEDD)
Subject ID: 257-0015
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Arthralgia	SAE	2014-04-24 / 2014-04-25	3	Dose not changed	Recovered/ Resolved	Definitely Related
Injection site pain	SAE, AEDD	2014-04-24 / 2014-04-25	3	Drug withdrawn	Recovered/ Resolved	Definitely Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:

Subject 257-0015 was a 69-year-old black or african american female randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2014-03-31; and received once-weekly treatment with study drug received a total of 1 injection of ADI-PEG 20 on 2014-04-14.

The subject was first diagnosed with stage IV hepatocellular carcinoma on 2013-10-09. The subject received prior systemic chemotherapy with sorafenib from 2013-11-18 to 2014-02-10. Prior to the start of study treatment, the subject's medical history and conditions included fatigue (2013-12 to 2014-04-23); and ongoing medical conditions included anemia, arthritis of right knee, hepatitis B infection, hypertension, sterilization, and both upper abdominal pain and vaginal bleeding (since 2014-03-15). On 2014-04-15, 1 day after the final dose of study treatment, subject had endometrial biopsy performed; however, the results were not reported.

Concomitant medications, (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug and during the study, included amlodipine, amoxicillin, amoxicillin with clavulanate potassium, bendroflumethiazide, carbohydrates NOS w/fats nos/minera, codeine phosphate, electrolytes NOS with macrogol 3350, entecavir, folic acid, ketoprofen, morphine, morphine sulfate, paracetamol, sodium chloride, and solutions affecting the electrolyte balance.

On 2014-04-24, the subject was assessed at the week 2 study visit with events of fatigue, anorexia, nausea, and vomiting (all Grade 2; none serious); and jaundice, pruritus, and ascites (all Grade 1; none serious). According to the CIOMS, the subject also experienced an infection at the site of the study drug administration. An ultrasound showed no abscess; however, the CRP was 142 mg/L (range was not reported). Earlier in the day, the subject was assessed at the week 2 visit, that day, the subject was hospitalized for Grade 3 arthralgia and Grade 3 injection site pain. The subject's last and only dose of study drug prior to the events was administered on 2014-04-14. No treatment was reported for the event. On 2014-04-25,

the events of arthralgia and injection site pain were considered recovered/resolved and the subject was discharged from the hospital the same day. No action was taken with the study drug as a result of the arthralgia; however, the study drug was withdrawn as a result of the injection site pain event. The outcome of the fatigue, anorexia, nausea, vomiting, jaundice, pruritus, and ascites events was unknown.

Two days after discharge, the subject was readmitted for Grade 3 arthritis. The event of arthritis was considered recovered/resolved on 2014-05-08 and the subject was discharged the same day. The event was considered to be unlikely related to ADI-PEG 20. According to the CIOMS, 41 days following a single dose of study drug administration, the subject died on 2014-05-25 as a result of malignant disease.

The Investigator considered the events of arthralgia and injection site pain to be definitely related to ADI-PEG 20. The Polaris Medical Monitor agreed with the Investigator's assessments.

No abnormal laboratory values were recorded during the adverse events.

Reason(s) for Narrative: Related SAE, Related AE Leading to Study Drug Discontinuation (AEDD),
Subject ID: 258-0015
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Hepatic encephalopathy	SAE, AEDD	2015-01-05 / 2015-01-12	2	Drug withdrawn	Recovered/ Resolved	Possibly Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:
Subject 258-0015 was a 65-year-old white-white/caucasian/european heritage male randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2014-11-28; and received once-weekly treatment with study drug between 2014-12-03 and 2015-01-02. The subject received a total of 3 injections of ADI-PEG 20 (week 3 and 4 doses were missed).

The subject was first diagnosed with stage IIIA hepatocellular carcinoma on 2013-06-21. The subject received prior systemic chemotherapy with sorafenib from 2014-08 to 2014-10-22. Other therapies the subject received included transcatheter arterial chemoembolization (tace). Prior to the start of study treatment, the subject's ongoing medical conditions included enlarged prostate, hemochromatosis, hypertension, pruritus, raised cholesterol, and right side abdomen pain.

Concomitant medications, (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug and during the study, included candesartan, cough and cold preparations, dolo mobilat, dutas-t, ezetimibe, lactulose, omeprazole, and oseltamivir phosphate.

On 2015-01-05, the subject experienced a Grade 2 hepatic encephalopathy and was hospitalized for this event. The last dose of study drug prior to the event was administered on 2015-01-02. According to the CIOMS, the subject was taken to emergency department with increasing confusion and was subsequently admitted to hospital for further investigations. The subject underwent blood tests, a chest x-ray and CT scan of the head (specific results were not reported). This event was preceded by Grade 2 increased ammonia levels on 2015-01-02. No specific treatment for the hepatic encephalopathy event was reported. On 2015-01-12, the event of hepatic encephalopathy was considered recovered/resolved and the subject was discharged from the hospital the same day. Study drug was withdrawn as a result of the event.

The Investigator considered the event of hepatic encephalopathy to be possibly related to ADI-PEG 20. The Polaris Medical Monitor did not agree with the Investigator's assessment. The Investigator considered rationale for the possible relationship to the study drug to the subject's history of similar symptoms, though less severe, following the first two doses of the study drug. Elevated ammonia levels were recorded; however, this had not been tested prior to study, as it was not routine. Additionally, no other adverse events were reported by the Investigator for this subject.

No abnormal laboratory values were recorded during the adverse events.

Reason(s) for Narrative: Related SAE, Related AE Leading to Study Drug Discontinuation (AEDD)
Subject ID: 302-0025
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Hemorrhage intracranial	SAE, AEDD	2013-11-08 / 2014-07-06	3	Drug withdrawn	Recovered/ Resolved	Possibly Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:
Subject 302-0025 was a 40-year-old asian-taiwan male randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2013-10-15; and received once-weekly treatment with study drug between 2013-10-22 and 2013-11-05. The subject received a total of 3 injections of ADI-PEG 20.

The subject was first diagnosed with stage IV hepatocellular carcinoma on 2011-09-13. The subject received prior systemic chemotherapy with sorafenib from 2011-10-12 to 2012-02-13; thalidomide from 2013-03-19 to 2013-05-09; cisplatin from 2013-06-03 to 2013-09-24; doxorubicin from 2013-06-03 to 2013-09-24; etoposide from 2013-06-03 to 2013-09-26; and fluorouracil from 2013-06-03 to 2013-09-26. Other therapies the subject received included transarterial chemoembolization. A left lobectomy of liver surgery was performed on 2011-09-06. Prior to the start of study treatment, the subject's medical history included cholecystectomy, and hypothyroidism; and ongoing medical conditions included chronic hepatitis B, gastroesophageal reflux disease, lung metastasis, mediastinal lap, and superficial gastritis.

Concomitant medications, (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug and during the study, included acetylsalicylic acid, dexamethasone, entecavir, glyceol, lorazepam, and sodium chloride.

According to the CIOMS, on 2013-11-08, the subject experienced a sudden onset of right side paresthesia; first noted on the right side of the face, then shoulders, and spreading down into the legs. The subject reported being able to walk, speak, swallow and grasp; however, the coordination of hands and legs was poor. That day, the subject was hospitalized for

Grade 3 hemorrhage intracranial. The last dose of study drug prior to the event was administered on 2013-11-05. At the time of admission, the vital signs were as follows; blood pressure: 137/95 mmHg; pulse: 77 beats/min, respiratory rate: 18 breaths/min. Brain MRI taken on 10-Nov-2013 showed one 2.8cm acute intracranial hemorrhage (ICH) in left postcentral gyrus with perifocal edema. No obvious abnormal enhancing lesion was seen. On 2013-11-09, an MRI of the brain was performed. According to the CIOMS, treatment included glycerol and dexamethasone for symptom control and brain edema prevention. On 2013-11-14, the event of hemorrhage intracranial was considered recovering/resolving and subject was discharged from the hospital the same day. Study drug was withdrawn as a result of the event. According to the CIOMS, no obvious abnormal enhancing lesion was seen in the MRI/MRA, subject reports progression of right side paresthesia in recent weeks after discharge, and to rule out the hepatocellular carcinoma brain metastases impressed by the neurologist, investigator decided admit the subject on 2013-12-12 for further evaluation and management. At admission, neurologic examinations found the following sensory functions: paresthesia over right side, and upper and lower extremities; reflex: superficial, deep and pathological; motor functions: 5 (RUL) 5 (LUL), 5 (RLL) 5 (LLL); cranial nerves: intact; cerebral function: normal, no abnormal gait. Initial management and treatment included close observation, follow-up of Glasgow coma scale (GCS), vital signs, and administration of Glycerol and Decadron. Relevant laboratory data on admission showed WBC 7000/CUMM; HGB 14.0 g/dl; PLT 158000/CUMM; SEG 85.3%; LYMP 12.7%; CREAT 0.82 mg/dL; ALT 23 U/L; Na 139 mmol/L; K 4.3 mmol/L; and CK of 54 U/L (normal ranges were not reported). Additional radiotherapy was performed between 2013-12-16 and 2014-01-22.

According to the CIOMS, the symptoms improved and subject was discharged in stable condition on 2013-12-18. Additionally, the subject experienced intermittent dizziness and nausea, and repeated admissions were noted after 2014-02. However, specific events and details were not reported. On 2014-07-06, the subject died as a result of malignant disease. The event of hemorrhage intracranial was considered resolved at the time of death. No additional details were reported.

The Investigator considered the event of hemorrhage intracranial to be possibly related to ADI-PEG 20. The Polaris Medical Monitor agreed with the Investigator's assessment. According to the CIOMS, the Investigator reported the causal relationship considering the subject had no relevant medical history or other reason (history) to cause the event.

Laboratory values recorded as abnormal during the adverse events are presented in the following table.

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Alpha Fetoprotein (ug/L)	0 / 20	14937.5	32360.1	Not reported	10DEC2013
Erythrocytes (10^12/L)	4.6 / 6.2	3.96	4.12	Not reported	10DEC2013
HCV Viral Load (IU/mL)	15 / not reported	14.9999	14.9999	Not reported	10DEC2013
Leukocytes (10^9/L)	4500000 / 11000000	3700000	4400000	1	10DEC2013

Reason(s) for Narrative: Related SAE, Related AE Leading to Study Drug Discontinuation (AEDD), AE of Special Interest (AESI)
Subject ID: 201-0020
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Hypersensitivity	SAE, AEDD, AESI	2014-01-30 / 2014-01-30	2	Drug withdrawn	Recovered/ Resolved	Definitely Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:
Subject 201-0020 was a 67-year-old white-white/caucasian/european heritage male randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2014-01-17; and received once-weekly treatment with study drug between 2014-01-23 and 2014-01-30. The subject received a total of 2 injections of ADI-PEG 20.

The subject was first diagnosed with stage IV hepatocellular carcinoma on 2013-04. The subject underwent surgery for cholecystectomy on 2013-06-27; liver biopsy on 2013-06-27; and liver resection on 2013-06-27. The subject received prior systemic chemotherapy with sorafenib from 2013-10-28 to 2013-11-18. The subject's ongoing medical conditions included hepatitis B positive history since 1987. Concomitant medications, including antiviral therapy taken during the study, are reported in the following SAE.

On 2014-01-30, following the week 2 administration of study treatment, the subject experienced Grade 2 hypersensitivity. According to the safety report, the subject experienced tongue tingling and difficulty in swallowing within 10 minutes after the administration of

study drug. Treatment for the event included an intravenous infusion 0.9% 250 ml solution with 10 mg of chlorphenamine maleate, and 4 mg of dexamethasone sodium phosphate. The subject remained under observation for approximately 2 hours following the event. Later that same day, the hypersensitivity symptoms completely resolved, and the subject was sent home. No hospitalization was reported; however, the event was considered an important medical event. As a result of the event, the subject was permanently withdrawn from study treatment.

The Investigator considered the event of hypersensitivity to be definitely related to ADI-PEG 20. The Polaris Medical Monitor agreed with the Investigator's assessment.

Laboratory values recorded as abnormal during the adverse events are presented in the following table.

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Alanine Aminotransferase (U/L)	6 / 43	58	44	1	30JAN2014
Aspartate Aminotransferase (U/L)	11 / 36	52	48	1	30JAN2014
Glucose (mmol/L)	3.9 / 5.6	6	6.7	1	30JAN2014
Protein (g/L)	60 / 80	82	84	Not reported	30JAN2014

Reason(s) for Narrative: Related SAE, Related AE Leading to Study Drug Discontinuation (AEDD), AE of Special Interest (AESI)
Subject ID: 257-0002
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Anaphylactic reaction	SAE, AEDD, AESI	2012-05-17 / 2012-05-20	3	Drug withdrawn	Recovered/ Resolved	Definitely Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:
Subject 257-0002 was a 56-year-old white/caucasian/european heritage male randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2012-04-12; and received once-weekly treatment with study drug between 2012-04-19 and 2012-05-17. The subject received a total of 3 injections of ADI-PEG 20 (week 3 and 4 doses was missed for the following event).

The subject was first diagnosed with stage IV hepatocellular carcinoma on 2008-07-14. The subject received prior systemic chemotherapy with sorafenib from 2010-06-11 to 2011-05-00. Other therapies the subject received included radiofrequency ablation. The subject underwent surgery for left lateral segmentectomy on 2008-07-11; and excision of peritoneal nodules on 2010-01-18. At the start of study treatment, the subject's ongoing medical conditions included alcoholic liver disease and emphysema.

Concomitant medications, (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug and during the study, included avena sativa fluid extract, chlorphenamine, chlorphenamine maleate, dermatologicals, hydrocortisone, ibuprofen, omeprazole, other dermatological preparations, paracetamol, and prednisolone.

On 2012-04-27, 1 day after the week 2 study drug administration, the subject developed Grade 2 injection site pain, Grade 1 pruritus (general), and Grade 2 rash (trunk and all extremities). Events were not considered serious and probably related to study treatment. Initially, the subject was treated with topical aveeno cream, aqueous cream, and epiderm; and ibuprophen, paracetamol, and chlorphenamine maleate. The week 3 and 4 study treatment administration was stopped temporarily as a result of the rash event. On 2012-05-03, oral prednisolone was introduced and 2 days later oral chlorphenamine was started. On 2012-05-10, the injection site pain and rash events resolved. The outcome of the pruritus event was unknown.

On 2012-05-17, the week 5 study dose was resumed. The same day, the subject experienced a Grade 3 anaphylactic reaction and was hospitalized for this event. According to the safety report, the subject's symptoms included breathlessness, rash all over body, loose stools, stomach pains, vomiting, hypotension, and being hot and sweaty. Treatment for the event included intravenous hydrocortisone (NOS) solution, chlorphenamine, and prednisolone. On 2012-05-20, the anaphylactic reaction was considered recovered/resolved, and the subject was discharged from the hospital the same day. As a result of the event, the study drug was permanently withdrawn.

The Investigator considered the event of anaphylactic reaction to be definitely related to ADI-PEG 20. The Polaris Medical Monitor agreed with the Investigator's assessment.

No abnormal laboratory values were reported during the adverse events.

Reason(s) for Narrative: Related SAE, Related AE of Special Interest (AESI)
Subject ID: 302-0008
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Anaphylactic shock	SAE, AESI	2012-05-01 / 2012-05-02	3	Dose not changed	Recovered/ Resolved	Definitely Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:
Subject 302-0008 was a 37-year-old asian-taiwan male randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2012-02-21; and received once-weekly treatment with study drug between 2012-02-28 and 2012-05-08. The subject received a total of 9 injections of ADI-PEG 20 (week 3 and 4 doses were missed).

The subject was first diagnosed with stage IV hepatocellular carcinoma on 2009-09-07. The subject received prior systemic chemotherapy with sorafenib from 2010-10-19 to 2011-03-08; brivanib from 2011-03-08 to 2011-05-20; cisplatin from 2011-11-09 to 2012-01-28; etoposide from 2011-11-09 to 2012-01-30, and fluorouracil from 2011-11-09 to 2012-01-30; and radiotherapy from 2011-11-14 to 2011-11-29. The subject underwent surgery for hepatic segmentectomy on 2009-09-07; hepatic segmentectomy on 2010-02; and a hepatic segmentectomy on 2010-05-10. The subject had multiple blood transfusions (all packed red blood cell) between 2012-03-14 and 2012-05-31; and a thoracentesis on 2012-05-29. Prior to the start of study treatment, the subject's medical history and conditions included hypertension, posterior reversible and encephalopathy syndrome. The subject's ongoing conditions included brain metastasis, chronic hepatitis B, and lung metastasis.

Concomitant medications, (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug and during the study, included acetylcysteine, aldioxa, amoxicillin/clavulanic acid, betamethasone valerate, brown mixture, cefmetazole, cefuroxime, chlorphenamine maleate, codeine phosphate, ipratropium bromide/albuterol, dexamethasone, dextromethorphan, dextrose and sodium chloride injection, diclofenac, dimeticone, diosmectite, enemas, entecavir, etofenamate, flomoxef sodium, furosemide, heparin, heparinoid, hetastarch, indometacin, kaopectate, lactulose, lorazepam, magnesium oxide, metoclopramide hydrochloride, morphine hydrochloride, naproxen, paracetamol, phytomenadione, sennoside a/b, sodium chloride, solutions affecting the electrolyte balance, spironolactone, thalidomide, tramadol hydrochloride, tranexamic acid, tramadol/acetaminophen, and unacid.

On 2012-05-01, the subject experienced Grade 3 anaphylactic shock. The subject's last dose (week 10) of study drug prior to the event was administered the same day.

On 2012-05-01, the subject was hospitalized for this event. Associated events included Grade 1 fever (however, reported as a temperature of 36.9o), Grade 1 vomiting, and Grade 1 anorexia. According to the CIOMS, the pre-dose vital signs showed a blood pressure 137/88 mm/hg and pulse of 99 beats per minute (bpm). Approximately 10 minutes after study drug was administered, the subject experienced a sudden onset of dizziness, rapid drop of blood pressure (60/40 mm/hg), vomiting, and low abdominal cramping pain. The initial assessment on admission showed a blood pressure 128/92 mm/hg, pulse of 134 bpm, and respiratory rate of 22/min. The ECG showed sinus tachycardia (heart rate: 122/min). Laboratory results showed a hemoglobin of 10.2 g/dL, platelets138000/ mm3, lymphocytes 7.5%, AST: 57 U/L, DBil: 0.57 mg/dL, T.Bil: 3.05 mg/dL, and the CRP was 4.45 mg/dL. No breathing difficulty, cyanosis, skin reactions, change or loss of consciousness, persistent gastrointestinal events or other cardiovascular symptoms were noted. Subject was admitted with an impression of suspected vasovagal syncope for further evaluation, monitoring, and intravenous hydration. The following day (2012-05-02), the event was considered recovered/resolved and the subject was discharged from the hospital the same day. Study drug was not changed; the study drug was administered on and was resumed on 2012-05-08. This event term of suspected vasovagal syncope was later changed to anaphylactic shock. The events of fever and vomiting resolved at discharge; whereas, the anorexia event resolved 2012-05-10.

The Investigator considered the event of anaphylactic shock to be definitely related to ADI-PEG 20. The Polaris Medical Monitor agreed with the Investigator's assessment.

Laboratory values recorded as abnormal during the adverse events are presented in the following table.

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Activated Partial Thromboplastin Time (sec)	24.3 / 32.7	28	37.2	1	20MAR2012
Albumin (g/L)	35 / 52	46	28	2	20MAR2012
Bilirubin (umol/L)	5.13 / 22.23	15.39	46.17	2	20MAR2012
Calcium (mmol/L)	2.1457 / 2.5449	2.22055	1.996	2	20MAR2012
Carbon Dioxide (mmol/L)	22 / 29	25.4	34.8	Not reported	20MAR2012
Cholesterol (mmol/L)	38.199 / 71.043	63.546	34.986	4	20MAR2012
Creatinine (umol/L)	61.88 / 106.08	70.72	37.128	Not reported	20MAR2012
Direct Bilirubin (umol/L)	0 / 8.55	5.13	27.36	Not reported	20MAR2012
Erythrocytes (10^12/L)	4.2 / 6.2	3.5	2.68	Not reported	20MAR2012
Glucose (mmol/L)	4.107 / 6.0495	5.6055	9.1575	2	20MAR2012
Hematocrit (%)	39 / 53	31.7	24	Not reported	20MAR2012
Hemoglobin (g/L)	123 / 183	111	82	2	20MAR2012
Indirect Bilirubin (umol/L)	0 / 13.68	10.26	18.81	Not reported	20MAR2012
Lactate Dehydrogenase (U/L)	135 / 225	207	440	Not reported	20MAR2012
Lymphocytes (10^9/L)	0.8 / 4.95	0.48848	0.31005	3	20MAR2012
Lymphocytes/Leukocytes (%)	20 / 45	14.2	6.5	Not reported	20MAR2012
Neutrophils/Leukocytes (%)	40 / 75	77	83	Not reported	20MAR2012
Platelets (10^9/L)	120 / 400	103	113	1	20MAR2012
Protein (g/L)	66 / 87	71	54	Not reported	20MAR2012
Prothrombin Time (sec)	8 / 12	11.1	12.2	Not reported	20MAR2012
Uric Acid (umol/L)	178.44 / 475.84	386.62	148.7	Not reported	20MAR2012
Aspartate Aminotransferase (U/L)	0 / 37	40	40	1	01MAY2012
Bilirubin (umol/L)	5.13 / 22.23	15.39	34.2	2	01MAY2012
Calcium (mmol/L)	2.1457 / 2.5449	2.22055	2.0958	1	01MAY2012
Creatinine (umol/L)	61.88 / 106.08	70.72	46.852	Not reported	01MAY2012

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Direct Bilirubin (umol/L)	0 / 8.55	5.13	13.68	Not reported	01MAY2012
Erythrocytes (10^12/L)	4.2 / 6.2	3.5	3.22	Not reported	01MAY2012
Hematocrit (%)	39 / 53	31.7	29.2	Not reported	01MAY2012
Hemoglobin (g/L)	123 / 183	111	100	1	01MAY2012
Indirect Bilirubin (umol/L)	0 / 13.68	10.26	20.52	Not reported	01MAY2012
Lactate Dehydrogenase (U/L)	135 / 225	207	272	Not reported	01MAY2012
Lymphocytes (10^9/L)	0.8 / 4.95	0.48848	0.468	3	01MAY2012
Lymphocytes/Leukocytes (%)	20 / 45	14.2	10	Not reported	01MAY2012
Neutrophils/Leukocytes (%)	40 / 75	77	81	Not reported	01MAY2012

Reason(s) for Narrative: Related SAE, Related AE(s) of Special Interest (AESI)
Subject ID: 302-0023
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Hypersensitivity	SAE, AESI	2013-09-10 / 2013-09-11	2	Dose not changed	Recovered/ Resolved	Definitely Related
Hypersensitivity	AESI	2013-10-08 / 2013-10-15	2	Dose not changed	Recovered/ Resolved	Definitely Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:

Subject 302-0023 was a 68-year-old asian-taiwan male randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2013-08-30; and received once-weekly treatment with study drug between 2013-09-10 and 2013-10-15. The subject received a total of 6 injections of ADI-PEG 20.

The subject was first diagnosed with stage IIIA hepatocellular carcinoma on 2009-09-15. The subject received prior systemic chemotherapy with sorafenib from 2013-06-26 to 2013-08-21. Other therapies the subject received included radiofrequency tumor ablation transcatheter arterial chemoembolization, surgery for liver s5/s6/s7 trisegmentectomy on

2009-09-15, s2 segmentectomy on 2010-11-09, and s4 sub-segmentectomy on 2010-11-09. Prior to the start of study treatment, the subject's medical history and conditions included bloody bile, cholangitis, cholecystectomy, and tea color urine. The subject's ongoing medical conditions included chronic hepatitis B, gastritis, gastroesophageal reflux disease, left renal cyst, liver cirrhosis, low back pain, peptic ulcer, portal hypertensive gastropathy, and suspicion tumor invasion to common bile duct, with percutaneous transhepatic cholangial drainage. According to the CIOMS, the subject also has a history of seafood allergy and reaction to some Chinese foods (unspecified).

Concomitant medications, (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug and during the study, included chlorphenamine, cyproheptadine, dexamethasone, diflucortolone, fexofenadine, hydrocortisone, hydroxyzine, levocetirizine, metoclopramide, neomycin, paracetamol, piroxicam, prednisolone, tranexamic acid, and ultracet.

On 2013-09-10, the subject experienced a Grade 2 hypersensitivity and was hospitalized for this event. The subject's initial dose (week 1) of study drug prior to the event was administered the same day (on 10SEP2013). According to the clinical database, 3 hours after the subject was administered the study treatment, a sudden onset of multiple itchy, erythematous papules (round, 3mm in diameter) was reported over all extremities. Additionally, the subject experienced tongue numbness. Symptoms progressed from distal to proximal part quickly, bilateral eye lid edematous and swelling showing up later. Treatment included chlorpheniramine injection which resulted in an improvement of symptoms. On 2013-09-11, the event of hypersensitivity was considered recovered/resolved and the subject was discharged the same day.

According to safety report, the subject was discharged with prophylactic medication medications for allergy of chlorpheniramine, prednisolone, and dexamethasone (continuously administered between 2013-09-11 and 2013-10-04). The study drug dose was not changed and the Investigator reported the study treatment was administered on week 2 (2013-09-17), week 3 (2013-09-24), and week 4 (2013-10-04) without any abnormalities.

The Investigator considered the event of hypersensitivity to be definitely related to ADI-PEG 20. The Polaris Medical Monitor agreed with the Investigator's assessment.

On 2013-10-08, the subject experienced Grade 2 intermittent hypersensitivity. The subject's last dose (week 5) of study drug prior to the event was administered the same day (on 2013-10-08). According to the safety report, prophylactic pre-medication prior to study treatment administration included normal saline intravenous, chlorpheniramine and

dexamethasone injections; prednisolone, and chlorpheniramine orally; and focus gel topical. The subject was not hospitalized; and the intermittent hypersensitivity event was not considered serious. However, the subject required treatment in the emergency department (ED) for 6 to 7 hours.

The prophylactic medication pre-medications remained ongoing for approximately 2 to 4 days following the subject's discharge. Between 2013-10-09 and 10-12, the subject was prescribed levocetirizine and hydroxyzine for allergic reaction. The event of hypersensitivity was considered recovered/resolved on 2013-10-15. That day, study drug (week 6) was administered and prophylactic pre-medications included prednisolone, levocetirizine, and hydroxyzine. The Investigator again reported the study drug was administered without any abnormal effect.

According to the clinical database, the week 7 dose of study drug was not administered as the subject withdrew consent for treatment. However, according to the safety reported, following communication with Polaris/CRO medical monitor on 2013-10-15, the Investigator withdrew the subject from the study, reporting "no more allergic reactions persist for this subject."

The Investigator considered the event of hypersensitivity to be definitely related to ADI-PEG 20.

Following the discontinuation of study treatment, the subject was treated with a percutaneous transhepatic cholangical drainage revision on 2013-10-20 and 2013-10-25; and systemic chemotherapy with thalidomide between 2013-11-05 and 2014-01-14.

Laboratory values recorded as abnormal during the adverse events are presented in the following table.

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Alanine Aminotransferase (U/L)	0 / 40	52	45	1	15OCT2013
Albumin (g/L)	37 / 53	32	26	2	15OCT2013
Alkaline Phosphatase (U/L)	10 / 100	183	248	1	15OCT2013
Cholesterol (mmol/L)	44.625 / 85.68	47.124	37.485	4	15OCT2013
Direct Bilirubin (umol/L)	0 / 7.695	14.193	12.654	Not reported	15OCT2013
Erythrocytes (10^12/L)	4.6 / 6.2	4.04	3.71	Not reported	15OCT2013
Hematocrit (%)	40 / 54	36.3	32.9	Not reported	15OCT2013
Hemoglobin (g/L)	140 / 180	122	110	1	15OCT2013

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Lymphocytes/Leukocytes (%)	20 / 45	15	14.8	Not reported	15OCT2013
Monocytes/Leukocytes (%)	0 / 9	10.5	9.2	Not reported	15OCT2013
Potassium (mmol/L)	3.4 / 4.7	3.8	3.3	1	15OCT2013

Reason(s) for Narrative: Related SAE, AE of Special Interest (AESI)
Subject ID: 403-0002
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Hypersensitivity	SAE, AESI	2013-08-13 / 2013-08-13	3	Dose not changed	Recovered/ Resolved	Probably Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:
Subject 403-0002 was a 52-year-old asian-north east asian heritage male randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2013-05-27; and received once-weekly treatment with study drug between 2013-06-12 and 2013-08-13. The subject received a total of 10 injections of ADI-PEG 20.

The subject was first diagnosed with stage IV hepatocellular carcinoma on 2011-05-07. The subject received prior systemic chemotherapy with sorafenib from 2009-11-25 to 2011-01-12; fluorouracil from 2011-03-07 to 2011-10-19; fluorouracil from 2012-07-03 to 2013-01-04 sorafenib from 2013-01-28 to 2013-04-29; and radiotherapy from 2011-03-07 to 2011-04-01. Other therapies the subject received included transcatheter arterial chemoembolization, surgery for left lateral segmentectomy on 2007-05-07, and left hemihepatectomy on 2009-10-21. No additional records were found on this subject. Prior to the start of study treatment, the subject's ongoing medical history and conditions included diabetes mellitus, hepatitis B, and hypertension.

Concomitant medications, (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug and during the study, included amlodipine

orotate, atenolol, dalteparin sodium, epinephrine hydrochloride, glimepiride, hydrocortisone sodium succinate, naproxen sodium, oxycodone hydrochloride, sucralfate, sultamicillin tosilate, ultracet, warfarin sodium, and zolpidem tartrate.

On 2013-08-13, the subject experienced Grade 3 hypersensitivity. The subject's last (week 10) of study drug prior to the event was administered the same day (on 2013-08-13).

The event was considered an important medical event. According to the CIOMS, immediately following study drug administration, the subject reported chest discomfort, pelvic pain, and chills. Symptoms also included nausea, vomiting, and dyspnea. Subject's blood pressure was 59/31 mmHg and saturation was 90%. Treatment for the event included intravenous hydrocortisone and epinephrine, unspecified hydration, and oxygen therapy (4L) to control relevant symptoms. Subsequent to treatment, the symptoms improved. The event of hypersensitivity was considered recovered/resolved the day of onset. According to the clinical database, the study drug was not changed; however, study treatment was not resumed and was discontinued for disease progression.

The Investigator considered the event of hypersensitivity to be probably related to ADI-PEG 20. The Polaris Medical Monitor agreed with the Investigator's assessment.

Laboratory values recorded as abnormal during the adverse events are presented in the following table.

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Albumin (g/L)	33 / 53	37	30	1	13AUG2013
Alkaline Phosphatase (U/L)	40 / 122	103	124	1	13AUG2013
Chloride (mmol/L)	98 / 110	102	96	Not reported	13AUG2013
Glucose (mmol/L)	3.885 / 6.105	8.436	16.206	3	13AUG2013
Hematocrit (%)	40 / 52	46.6	37.6	Not reported	13AUG2013
Hemoglobin (g/L)	130 / 170	146	121	1	13AUG2013
Lactate Dehydrogenase (U/L)	119 / 247	217	252	Not reported	13AUG2013
Monocytes/Leukocytes (%)	3.3 / 9	10.2	9.5	Not reported	13AUG2013
Sodium (mmol/L)	135 / 145	136	133	1	13AUG2013

Reason(s) for Narrative: Related AE Leading to Study Drug Discontinuation (AEDD)
Subject ID: 203-0001
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Face oedema	AEDD	2012-04-13 / 2012-04-15	3	Drug withdrawn	Recovered/ Resolved	Probably Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:

Subject POL2009001-203-0001 was a 61-year-old white /caucasian/european heritage female randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2012-02-21; and received once-weekly treatment with study drug between 2012-03-06 and 2012-04-13. The subject received a total of 5 injections of ADI-PEG 20 (week 2 dose was missed).

The subject was first diagnosed with stage IV hepatocellular carcinoma on 2011-04-06. The subject received prior systemic chemotherapy with sorafenib from 2011-06-17 to 2011-08-10 capecitabine from 2011-10-15 to 2011-12-22. Other therapies the subject received included radiofrequency. The subject underwent surgery for liver biopsy on 2010-04-06. Prior to the start of study treatment, the subject's medical history and conditions included cholecystectomy, hysterectomy, ovarian surgery, and uterine carcinoma. The subject's ongoing medical conditions included diabetes mellitus, gastritis, hcv infection, and hypertension.

Concomitant medications, (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug and during the study included amlodipine besylate, beclomethasone dipropionate, betamethasone valerate, corticosteroids for systemic use, hydrocortisone, hyzaar, insulin, insulin human injection isophane, ipratropium bromide, other nutrients (dietary supplement containing extract of fish eggs), paracetamol, propranolol hydrochloride, and torasemide.

On 2012-04-13, the subject experienced Grade 3 face edema. The subject's last dose (week 6) of study drug prior to the event was administered the same day (on 2012-04-13). Just prior to the event (on 2012-04-11), the subject developed groin and thigh rash

(both Grade 1, not serious; probably related). Both resolved on 2012-04-13. At the onset of the Grade 3 face edema, the subject also experienced Grade 2 dyspnea and Grade 1 lip edema (both not serious; probably related).

The face edema event was not assessed as serious and hospitalization was not required. Treatment was not required. The event of face edema was considered recovered/resolved on 2012-04-15. The dyspnea and lip edema both also resolved on 2012-04-15. Study drug was withdrawn as a result of the face edema event. No action was taken with study treatment as a result of the other events.

The Investigator considered the event of face edema to be probably related to ADI-PEG 20.

Laboratory values recorded as abnormal during the adverse events are presented in the following table.

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Albumin (g/L)	33 / 49	31	27	2	13APR2012
Aspartate Aminotransferase (U/L)	9 / 34	56	47	1	13APR2012
Cholesterol (mmol/L)	4.86 / 8.28	2.56	2.21	0	13APR2012
Glucose (mmol/L)	3.9 / 5.6	5.6	7.2	1	13APR2012
Lactate Dehydrogenase (U/L)	53 / 234	241	256	No reported	13APR2012

Reason(s) for Narrative: Related AE Leading to Study Drug Discontinuation (AEDD)
Subject ID: 253-0002
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Fatigue	AEDD	2012-05-11 / 2012-05-25	3	Drug withdrawn	Recovered/ Resolved	Possibly Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:
Subject 253-0002 was a 63-year-old white /caucasian/european heritage male randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2012-03-02; and received once-weekly treatment with study drug between 2012-03-09 and 2012-05-04. The subject received a total of 8 injections of ADI-PEG 20 (week 5 dose was interrupted).

The subject was first diagnosed with stage IIIA hepatocellular carcinoma on 2010-11-26. No prior systemic chemotherapy, other therapies, or surgery was reported for the subject.

Prior to the start of study treatment, the subject's medical history and conditions included a myocardial infarction. The subject's ongoing medical conditions included hypercholesterolemia, hypertension, ischemic heart disease, raised AST levels (Grade 2), and type 2 diabetes.

Concomitant medications, (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug and during the study, included AKWA tears, allopurinol, amlodipine, atenolol, furosemide, lisinopril, loperamide, metformin, paracetamol, simvastatin, and tramadol.

On 2012-04-04, the subject experienced a Grade 3 fatigue that resulted in study treatment interruption (week 5). On 2012-04-10, the event resolved and study dose (week 6) was administered on 2012-04-13. The week 7 and 8 study drug was administered without event (2012-04-20 and 2012-04-27).

On 2012-05-04, the same day as the week 9 study dose administration, the subject again developed Grade 2 fatigue. No action was taken with study drug.

On 2012-05-11, the fatigue event worsened to Grade 3. The subject's last dose (week 9) was administered on 2012-05-04. The event was not considered serious and the subject was not hospitalized. Study drug was withdrawn as a result of the Grade 3 event. No treatment was required and the fatigue was downgraded to Grade 2 on 2012-05-25 (outcome unknown).

The Investigator considered the event of fatigue to be possibly related to ADI-PEG 20.

Laboratory values recorded as abnormal during the adverse events are presented in the following table.

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Alanine Aminotransferase (U/L)	6 / 43	46	59	1	11MAY2012
Albumin (g/L)	33 / 49	35	29	2	11MAY2012
Alkaline Phosphatase (U/L)	35 / 125	217	500	2	11MAY2012
Aspartate Aminotransferase (U/L)	11 / 36	110	161	2	11MAY2012
Bilirubin (umol/L)	3 / 21	17	41	2	11MAY2012
Blood Urea Nitrogen (mmol/L)	1.4 / 8.6	7.3	11.6	No reported	11MAY2012
Cholesterol (mmol/L)	4.53 / 7.71	2.86	3.22	0	11MAY2012
Creatinine (umol/L)	40 / 119	90	123	No reported	11MAY2012
Direct Bilirubin (umol/L)	0 / 7	10	25	No reported	11MAY2012
Erythrocytes (10^12/L)	4 / 5.8	4.2	3.8	No reported	11MAY2012
Glucose (mmol/L)	3.9 / 5.6	8.2	9.6	2	11MAY2012
Hematocrit (%)	37 / 51	39	35	No reported	11MAY2012
Hemoglobin (g/L)	125 / 170	133	115	1	11MAY2012
Lactate Dehydrogenase (U/L)	53 / 234	259	334	No reported	11MAY2012
Neutrophils/Leukocytes (%)	40.5 / 75	70.3	77.1	No reported	11MAY2012
Potassium (mmol/L)	3.4 / 5.4	4.8	5.5	1	11MAY2012

Reason(s) for Narrative: AE Leading to Study Drug Discontinuation (AEDD)

Subject ID: 259-0001

Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Fatigue	AEDD	2014-06-18 / 2014-07-16	3	Drug withdrawn	Recovered/ Resolved	Probably Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:

Subject 259-0001 was a 68-year-old white /caucasian/european heritage female randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2013-05-24; and received once-weekly treatment with study drug between 2013-06-05 and 2014-06-11 (week 54). The subject received a total of 33 injections of ADI-PEG 20 (week 5, 7, 13, 15, 16, 21, 24, 25, 27, 29, 30, 31, 34, 35, 39, 43, 44, 47, 49, 50, and 53 doses were missed).

The subject was first diagnosed with stage II hepatocellular carcinoma on 2011-06-20. The subject received prior systemic chemotherapy with sorafenib from 2011-07 to 2012-03-00. Other therapies the subject received included gc33/ placebo. Prior to the start of study treatment, the subject's medical history and conditions included abdominal pain, fatigue, nausea, and osteoarthritis. The subject's ongoing medical conditions included constipation, depression, dry eyes, essential hypertension, gastroesophageal reflux disease, hepatocellular cancer, hypothyroidism, insomnia, iron deficiency - anemia, osteoporosis, pruritus, and stress incontinence.

Concomitant medications, (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug and during the study included amoxicillin, balneum hermal plus, carbohydrates NOS with fats and minerals, carbomer, chlorphenamine maleate, citalopram, clobetasone butyrate, cholestyramine, diazepam, docusate, domperidone, electrolytes NOS with macrogol 3350, ferrous fumarate, haloperidol, hydromol, ibuprofen, lansoprazole, levomepromazine, loratadine, metoclopramide, naproxen, ondansetron, oxybutynin hydrochloride, oxycodone hydrochloride, panadeine co, peptac, perindopril, prednisolone, sennoside a+b, unspecified herbal, and zopiclone.

Starting 2013-06-12, the subject experienced 22 events of fatigue (Grades 1 through 3). Nine of the events led to a study treatment interruption. All events were considered probably related to study treatment, none required treatment, none were serious, and all events resolved. On 2014-06-11, the subject, with a prior to treatment history of fatigue, experienced Grade 2 fatigue. The subject's last dose (week 54) of study drug prior to the event was administered the same day (on 2014-06-11). Seven days later (on 2014-06-18), the fatigue worsened to Grade 3. The event was not considered serious. Study drug was permanently withdrawn as a result of the event. On 2014-07-16, event of fatigue was considered recovered/resolved.

The Investigator considered the event of fatigue to be probably related to ADI-PEG 20.

No abnormal laboratory values were recorded during the adverse events.

Reason(s) for Narrative: AE(s) Leading to Study Drug Discontinuation (AEDD)
Subject ID: 306-0036
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Alanine aminotransferase increased	AEDD	2013-08-27 / 2013-09-10	3	Drug withdrawn	Recovered/ Resolved	Possibly Related
Aspartate aminotransferase increased	AEDD	2013-09-03 / 2013-11-25	3	Drug withdrawn	Recovered/ Resolved	Possibly Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:
Subject 306-0036 was a 73-year-old asian-taiwan male randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2013-07-02; and received once-weekly treatment with study drug between 2013-07-09 and 2013-08-20. The subject received a total of 7 injections of ADI-PEG 20.

The subject was first diagnosed with stage IV hepatocellular carcinoma on 2012-03-22. The subject received prior systemic chemotherapy with sorafenib from 2013-05-08 to 2013-06-14. Other therapies the subject received included transcatheter arterial embolization. The subject underwent surgery for left hepatic lobectomy, and s8 tumor wide excision on 2012-06-25. Prior to the start of study treatment, the subject's medical history and conditions included gall bladder chronic inflammation, left inguinal hernia, and right inguinal cystic. The subject's ongoing medical conditions included diabetes mellitus, duodenal ulcers, esophagitis, hepatitis B, hypertension, liver cirrhosis, and splenomegaly.

Concomitant medications, (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug and during the study, included aluminum silicate, amlodipine, belbarb, ceftibuten, ceftriaxone, esomeprazole, furosemide, glimepiride, lactulose, loperamide, metformin, mosapride citrate, paracetamol, potassium chloride, silybum marianum, spironolactone, telbivudine, and ultracet.

On 2013-08-13, the same day as the week 6 study treatment administration, the subject experienced Grade 3 aspartate aminotransferase (AST) increased and Grade 2 alanine aminotransferase increased (ALT). No action was taken with study drug as a result of events. On 2013-08-27, 7 days after day after the week 7 study treatment administration, the subject experienced Grade 3 ALT increase and Grade 4 AST increase events (refer to the laboratory values in table below narrative). Study drug was withdrawn as a result of the Grade 3 ALT event; however, no action was taken with study drug as a result of Grade 4 AST increase. No additional study treatment was administered.

On 2013-09-03, the subject developed Grade 3 AST increased which also resulted in study drug withdrawal. However, the primary reason the subject was discontinued from the study drug was due to disease progression. The subject's last dose of study drug prior to the treatment discontinuation events was administered on 20AUG2013. The event of ALT increase was downgraded to a Grade 2 on 2013-09-10 and resolved on 2013-11-25. That day, the AST increase was also considered resolved. The subject was not hospitalized and none of the laboratory events were not considered serious.

The Investigator considered the events of alanine aminotransferase increased and aspartate aminotransferase increased to be possibly related to ADI-PEG 20.

Laboratory values recorded as abnormal during the adverse events are presented in the following table.

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Alanine Aminotransferase (U/L)	0 / 41	56	386	3	27AUG2013
Alanine Aminotransferase (U/L)	0 / 40	56	387	3	27AUG2013
Albumin (g/L)	35 / 52	41	33	1	27AUG2013
Alkaline Phosphatase (U/L)	40 / 140	98	181	1	27AUG2013
Alkaline Phosphatase (U/L)	40 / 129	98	187	1	27AUG2013
Alpha Fetoprotein (ug/L)	0 / 14.99	14.81	209.8	Not reported	27AUG2013
Aspartate Aminotransferase (U/L)	0 / 37	62	572	3	27AUG2013
Aspartate Aminotransferase (U/L)	0 / 37	62	585	3	27AUG2013
Bilirubin (umol/L)	5.13 / 22.23	6.84	32.49	1	27AUG2013
Bilirubin (umol/L)	3.42 / 23.94	6.84	39.33	2	27AUG2013

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Chloride (mmol/L)	98 / 107	103	96	Not reported	27AUG2013
Direct Bilirubin (umol/L)	0 / 8.55	3.42	18.81	Not reported	27AUG2013
Erythrocytes (10^12/L)	4.2 / 6.2	4.48	4.06	Not reported	27AUG2013
Hematocrit (%)	39 / 53	37	33.6	Not reported	27AUG2013
Hemoglobin (g/L)	123 / 183	125	115	1	27AUG2013
Lactate Dehydrogenase (U/L)	135 / 225	180	317	Not reported	27AUG2013
Monocytes/Leukocytes (%)	2 / 10	15	15	Not reported	27AUG2013
Phosphate (mmol/L)	0.87183 / 1.45305	0.74267	0.80725	1	27AUG2013
Potassium (mmol/L)	3.5 / 5.1	3.21	3.25	1	27AUG2013
Prothrombin Time (sec)	8 / 12	11.2	12.8	Not reported	27AUG2013
Alanine Aminotransferase (U/L)	0 / 40	56	308	3	03SEP2013
Albumin (g/L)	35 / 52	41	30	1	03SEP2013
Alkaline Phosphatase (U/L)	40 / 140	98	234	1	03SEP2013
Aspartate Aminotransferase (U/L)	0 / 37	62	473	3	03SEP2013
Bilirubin (umol/L)	3.42 / 23.94	6.84	41.04	2	03SEP2013
Erythrocytes (10^12/L)	4.3 / 6.1	4.48	4.2	Not reported	03SEP2013
Hematocrit (%)	41 / 53	37	34.4	Not reported	03SEP2013
Hemoglobin (g/L)	135 / 175	125	117	1	03SEP2013
Leukocytes (10^9/L)	3.9 / 10.6	3.87	3.7	1	03SEP2013
Alanine Aminotransferase (U/L)	0 / 40	56	248	3	07SEP2013
Aspartate Aminotransferase (U/L)	0 / 37	62	342	3	07SEP2013
Bilirubin (umol/L)	3.42 / 23.94	6.84	78.66	3	07SEP2013
Creatinine (umol/L)	56.576 / 112.268	83.096	117.572	Not reported	07SEP2013
Glucose (mmol/L)	3.885 / 5.55	7.548	9.768	2	07SEP2013
Hematocrit (%)	41 / 53	37	37.7	Not reported	07SEP2013
Hemoglobin (g/L)	135 / 175	125	127	1	07SEP2013
Lymphocytes (10^9/L)	0.78 / 5.936	1.40094	0.4235	3	07SEP2013
Lymphocytes/Leukocytes (%)	20 / 56	36.2	5.5	Not reported	07SEP2013
Neutrophils/Leukocytes (%)	42 / 74	44.9	89.9	Not reported	07SEP2013

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Activated Partial Thromboplastin Time (sec)	24.3 / 32.7	27.3	32.9	1	24SEP2013
Alanine Aminotransferase (U/L)	0 / 41	56	136	2	24SEP2013
Albumin (g/L)	35 / 52	41	27	2	24SEP2013
Alkaline Phosphatase (U/L)	40 / 129	98	494	2	24SEP2013
Alpha Fetoprotein (ug/L)	0 / 14.99	14.81	554.06	Not reported	24SEP2013
Aspartate Aminotransferase (U/L)	0 / 37	62	271	3	24SEP2013
Bilirubin (umol/L)	5.13 / 22.23	6.84	114.57	3	24SEP2013
Calcium (mmol/L)	2.1457 / 2.5449	2.2455	2.07085	1	24SEP2013
Chloride (mmol/L)	98 / 107	103	92	Not reported	24SEP2013
Direct Bilirubin (umol/L)	0 / 8.55	3.42	87.21	Not reported	24SEP2013
Erythrocytes (10^12/L)	4.2 / 6.2	4.48	3.79	Not reported	24SEP2013
Hematocrit (%)	39 / 53	37	31	Not reported	24SEP2013
Hemoglobin (g/L)	123 / 183	125	112	1	24SEP2013
Indirect Bilirubin (umol/L)	0 / 13.68	3.42	27.36	Not reported	24SEP2013
Lactate Dehydrogenase (U/L)	135 / 225	180	302	Not reported	24SEP2013
Lymphocytes (10^9/L)	0.8 / 4.95	1.40094	0.7095	2	24SEP2013
Lymphocytes/Leukocytes (%)	20 / 45	36.2	15	Not reported	24SEP2013
Monocytes/Leukocytes (%)	2 / 10	15	17	Not reported	24SEP2013
Phosphate (mmol/L)	0.87183 / 1.45305	0.74267	0.77496	2	24SEP2013
Prothrombin Time (sec)	8 / 12	11.2	12.4	Not reported	24SEP2013
Sodium (mmol/L)	136 / 145	142	127	3	24SEP2013
Uric Acid (umol/L)	178.44 / 475.84	226.024	130.856	Not reported	24SEP2013

Reason(s) for Narrative: AE of Special Interest (AESI)
Subject ID: 114-0007
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Hypersensitivity	AESI	2014-12-29 / Stop date not reported	1	Dose not changed	Not recovered/ Not resolved	Probably Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:
Subject 114-0007 was a 60-year-old white-white/caucasian/european heritage female randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2014-11-14; and received once-weekly treatment with study drug between 2014-11-19 and 2015-07-07. The subject received a total of 32 injections of ADI-PEG 20 (week 16 dose was missed).

The subject was first diagnosed with stage IV hepatocellular carcinoma on 2014-01-30. The subject received prior systemic chemotherapy with sorafenib from 2014-04-17 to 2014-05-14. The subject's ongoing medical conditions included bicuspid aortic valve, constipation, dry eyes, dyspepsia, hepatocellular carcinoma, migraines, and rash - maculopapular.

Concomitant medications, (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug and during the study, included artificial tears, camellia sinensis, fish oil, lactobacillus acidophilus, lactulose, linum usitatissimum seed oil, magnesium, mecobalamin, minerals with vitamins nos, paracetamol, prochlorperazine, and simethicone.

On 2014-12-29, 6 days following the week 6 study drug dose administration, the subject experienced intermittent Grade 1 hypersensitivity, reporting redness at injection site. Study dose was not changed as a result of the hypersensitivity event; and study drug administration remained ongoing through 2015-07-07. Other adverse events at the time of the event included abdominal pain and difficulty swallowing (both Grade 1, onset 2015-01-01). Both were considered probably related to study treatment. The outcome of the hypersensitivity, abdominal pain, and difficulty swallowing events were all reported as

unknown at the end of treatment. The subject was not hospitalized and none of the events were considered serious. No additional allergic reaction events were reported while the subject remained on study and no follow-up was reported subsequently to the study treatment discontinuation.

The Investigator considered the event of hypersensitivity to be probably related to ADI-PEG 20.

Laboratory values recorded as abnormal during the adverse events are presented in the following table.

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Activated Partial Thromboplastin Time (sec)	23 / 35.3	22.6	22.6	0	06JAN2015
Leukocytes (10^9/L)	3.8 / 10.7	3.85	3.56	1	20JAN2015
Monocytes/Leukocytes (%)	2.6 / 10.1	8.2	15	Not reported	04FEB2015
Activated Partial Thromboplastin Time (sec)	23 / 35.3	22.6	22.9	0	18FEB2015
Bilirubin (umol/L)	3.42 / 20.52	5.13	3.41829	0	18FEB2015
Activated Partial Thromboplastin Time (sec)	23 / 35.3	22.6	22.2	0	31MAR2015
Glucose (mmol/L)	3.885 / 5.55	4.2735	5.994	1	28APR2015
Glucose (mmol/L)	3.885 / 5.55	4.2735	7.104	1	12MAY2015
Glucose (mmol/L)	3.885 / 5.55	4.2735	5.7165	1	26MAY2015

Reason(s) for Narrative: AE of Special Interest (AESI)
Subject ID: 115-0001
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Hypersensitivity	AESI	2012-11-27 / 2013-02-14	2	Dose not changed	Recovered/ Resolved	Definitely Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:

Subject 115-0001 was a 59-year-old asian-south east asian heritage female randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2012-11-14; and received once-weekly treatment with study drug between 2012-11-27 and 2013-02-05. The subject received a total of 11 injections of ADI-PEG 20.

The subject was first diagnosed with stage IV hepatocellular carcinoma on 2011-07-15. The subject received prior systemic chemotherapy with sorafenib from 2012-08-14 to 2012-10-18. Other therapies included a transcatheter arterial chemoembolization of doxorubicin. The subject underwent surgery for a partial right hepatectomy on 2011-07-28. Prior to the start of study treatment, the subject's medical history and conditions included cholecystectomy, and right and left cataract removal. The subject's ongoing medical conditions included arthralgia, hepatitis B, hypertension, intermittent abdominal pain, and intermittent vertigo.

Concomitant medications, (antiviral therapy will be included below if applicable) within 14 days prior to the first dose of study drug and during the study, included amlodipine, chondroitin, dexamethasone, diphenhydramine, docusate sodium, entecavir, hydromorphone, multivitamins, omega-3 fatty acids, oxycodone, prochlorperazine, pyridoxine, ranitidine hydrochloride, tocopherol, and trolamine.

On 2012-11-27, the first day of study treatment, the subject experienced Grade 2 hypersensitivity. No additional details at the time of the event were reported. The hypersensitivity event was not considered serious and treatment for the event was not reported. The study drug and dose remained unchanged as a result of the event. No additional adverse events were reported for the subject while on study treatment (subject completed

week 11). The hypersensitivity event was considered recovered/resolved on 2013-02-14 (9 days after the final dose of study treatment).

The Investigator considered the event of hypersensitivity to be definitely related to ADI-PEG 20.

Laboratory values recorded as abnormal during the adverse event are presented in the following table.

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Alanine Aminotransferase (U/L)	6 / 34	43	49	1	04DEC2012
Alkaline Phosphatase (U/L)	35 / 123	201	245	1	04DEC2012
Aspartate Aminotransferase (U/L)	9 / 34	68	61	1	04DEC2012
Cholesterol (mmol/L)	61.047 / 103.887	62.832	60.333	4	04DEC2012
Leukocytes (10^9/L)	3.8 / 10.7	3.69	2.73	2	04DEC2012
Neutrophils (10^9/L)	1.96 / 7.23	2	1.48	2	04DEC2012
Alanine Aminotransferase (U/L)	6 / 34	43	122	2	18DEC2012
Alkaline Phosphatase (U/L)	35 / 123	201	323	2	18DEC2012
Aspartate Aminotransferase (U/L)	9 / 34	68	113	2	18DEC2012
Glucose (mmol/L)	3.885 / 5.55	4.995	5.883	1	18DEC2012
Alanine Aminotransferase (U/L)	6 / 34	43	94	1	02JAN2013
Alkaline Phosphatase (U/L)	35 / 123	201	425	2	02JAN2013
Aspartate Aminotransferase (U/L)	9 / 34	68	100	1	02JAN2013

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Glucose (mmol/L)	3.885 / 5.55	4.995	7.77	1	02JAN2013
Alanine Aminotransferase (U/L)	6 / 34	43	71	1	15JAN2013
Alkaline Phosphatase (U/L)	35 / 123	201	392	2	15JAN2013
Aspartate Aminotransferase (U/L)	9 / 34	68	94	1	15JAN2013
Glucose (mmol/L)	3.885 / 5.55	4.995	6.1605	1	15JAN2013
Alanine Aminotransferase (U/L)	6 / 34	43	69	1	29JAN2013
Alkaline Phosphatase (U/L)	35 / 123	201	372	2	29JAN2013
Aspartate Aminotransferase (U/L)	9 / 34	68	103	2	29JAN2013
Alanine Aminotransferase (U/L)	6 / 34	43	61	1	14FEB2013
Alkaline Phosphatase (U/L)	35 / 123	201	325	2	14FEB2013
Aspartate Aminotransferase (U/L)	9 / 34	68	116	2	14FEB2013
Sodium (mmol/L)	135 / 145	142	146	1	14FEB2013

Reason(s) for Narrative: AE(s) of Special Interest (AESI)
Subject ID: 257-0008
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Hypersensitivity	AESI	2013-04-04 / 2013-04-21	2	Drug interrupted	Recovered/ Resolved	Definitely Related
Hypersensitivity	AESI	2013-04-30 / 2013-05-08	2	Drug interrupted	Recovered/ Resolved	Definitely Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:
Subject 257-0008 was an 80-year-old white/caucasian/european heritage female randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2013-02-28; and received once-weekly treatment with study drug between 2013-03-28 and 2013-06-13. The subject received a total of 9 injections of ADI-PEG 20.

The subject was first diagnosed with stage IIIA hepatocellular carcinoma on 2011-10-06. The subject received prior systemic chemotherapy with sorafenib from 2011-11-03 to 2012-04-15. Other therapies the subject received included transcatheter arterial chemoembolization (tace); and tace with dc beads. Prior to the start of study treatment, the subject's ongoing medical conditions included asthma, hypertension, lethargy, osteoporosis, primary biliary cirrhosis, and right shoulder pain.

Concomitant medications, (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug and during the study, included alendronate sodium, budesonide, chlorphenamine, hydrocortisone, indapamide, irbesartan, lekovit ca, paracetamol, prednisolone, raloxifene, terbutaline, and ursodeoxycholic acid.

On 2013-04-04, the subject experienced a Grade 2 hypersensitivity. The subject's last dose (week 2) of study drug prior to the events was administered the same day (on 2013-04-04). The following day (2013-04-05), the subject also developed a Grade 2 injection site rash. The subject was not hospitalized and the event was not considered serious. No treatment was required for the event. The event of hypersensitivity was considered recovered/resolved on 2013-04-21. Study drug (week 3 and 4) was interrupted as a result of the event; and the

week 5 treatment dose was resumed on 2013-04-25. The rash remained and did not resolve until 2013-05-15.

The Investigator considered the event of hypersensitivity to be definitely related to ADI-PEG 20. The event did not meet the criteria for seriousness.

On 2013-04-30, 5 days after the most recent study drug was administered, the subject experienced a Grade 2 hypersensitivity. The subject was not hospitalized and the event was not considered serious. No treatment was required for the event. The event of hypersensitivity was considered recovered/resolved on 2013-05-08. Study drug (week 6) was interrupted as a result of the event; and the week 7 treatment dose was resumed on 2013-05-09. Treatment remained ongoing through week 12 (2013-06-13). The subject discontinued study drug administration as a result of disease progression.

The Investigator considered the event of hypersensitivity to be definitely related to ADI-PEG 20. The event did not meet the criteria for seriousness.

Laboratory values recorded as abnormal during the adverse events are presented in the following table.

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Aspartate Aminotransferase (U/L)	9 / 34	43	38	1	04APR2013
Glucose (mmol/L)	3.9 / 5.6	6	6.7	1	04APR2013
Alanine Aminotransferase (U/L)	6 / 32	34	36	1	18APR2013
Alpha Fetoprotein (ug/L)	0 / 9	3480.5	5157.5	Not reported	18APR2013
Aspartate Aminotransferase (U/L)	9 / 34	43	38	1	18APR2013
Glucose (mmol/L)	3.9 / 5.6	6	5.9	1	18APR2013
Alanine Aminotransferase (U/L)	6 / 32	34	45	1	02MAY2013
Aspartate Aminotransferase (U/L)	9 / 34	43	39	1	02MAY2013

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Glucose (mmol/L)	3.9 / 5.6	6	8.9	1	02MAY2013

Reason(s) for Narrative: AE(s) of Special Interest (AESI)
Subject ID: 307-0025
Treatment Group: ADI-PEG 20

Event(s):

Preferred Term (MedDRA 18.0)	Reason for Narrative	Start Date/Stop Date or Ongoing	Intensity (CTCAE Grade)	Action Taken	Outcome	Relationship
Hypersensitivity	AESI	2013-03-20 2013-03-20	2	Dose not changed	Recovering/ Resolving	Probably Related
Hypersensitivity	AESI	2013-03-20 2013-03-21	1	Dose not changed	Recovered/ Resolved	Probably Related

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; CTCAE, Common terminology criteria for adverse events

Narrative:
Subject 307-0025 was a 68-year-old asian-taiwan male randomly assigned to the ADI-PEG 20 group. The subject was enrolled in Study POLARIS2009-001 on 2012-12-13; and received once-weekly treatment with study drug between 2012-12-18 and 2013-05-30. The subject received a total of 24 injections of ADI-PEG 20.

The subject was first diagnosed with stage IV hepatocellular carcinoma on 2010-08-13. Prior to the start of study treatment, the subject's medical history and conditions included coagulopathy, constipation, fatigue, and thrombocytopenia. The subject's ongoing medical conditions included abdominal pain, abdominal fullness, bilateral renal cysts, hepatitis C, insomnia, liver cirrhosis, and lymphadenopathy.

Concomitant medications, (antiviral therapy will be included below if applicable) taken within 14 days prior to the first dose of study drug and during the study, included alprazolam, brotizolam, cefazolin, cefixime, diclofenac sodium, dimeticone, esomeprazole, estazolam, fexofenadine hydrochloride, furosemide, hydrocortisone sodium succinate, lorazepam, magnesium oxide, medroxyprogesterone acetate, metoclopramide, metoclopramide hydrochloride, paracetamol, propranolol hydrochloride, silybum marianum, somatostatin,

spironolactone, sucralfate, terlipressin, trazodone hydrochloride, ultracet, ursodeoxycholic acid, and zolpidem tartrate.

On 2013-03-20, the subject experienced Grade 2 hypersensitivity (trunk and hands). The subject's last dose (week 14) of study drug prior to the events was administered the same day (on 2013-03-20). The subject was not hospitalized, no treatment was required, and the event was not considered serious. The event of hypersensitivity was considered recovering/resolving the day of onset. However, according to the clinical database, the subject also experienced Grade 1 hypersensitivity (trunk and hands) on 2013-03-20. The event was not considered serious and recovered/resolved the following day (on 2013-03-21). Study drug was not changed for either event; and week 15 study treatment was administered on 2013-03-28. The study treatment remained ongoing through 2013-05-30 (week 24). Study treatment was discontinued as a result of disease progression.

The Investigator considered both events of hypersensitivity (Grade 1 and Grade 2) to be probably related to ADI-PEG 20.

Laboratory values recorded as abnormal during the adverse events are presented in the following table.

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Alanine Aminotransferase (U/L)	0 / 41	123	115	1	16MAY2013
Alanine Aminotransferase (U/L)	0 / 54	123	135	1	16MAY2013
Alanine Aminotransferase (U/L)	0 / 54	123	151	1	16MAY2013
Alkaline Phosphatase (U/L)	30 / 110	108	127	1	16MAY2013
Aspartate Aminotransferase (U/L)	0 / 37	128	147	2	16MAY2013
Aspartate Aminotransferase (U/L)	0 / 39	128	164	2	16MAY2013
Blood Urea Nitrogen (mmol/L)	2.856 / 8.211	5.0337	14.2443	Not reported	16MAY2013
Chloride (mmol/L)	98 / 107	104	109	Not reported	16MAY2013
Creatinine (umol/L)	61.88 / 106.08	62.764	53.924	Not reported	16MAY2013
Creatinine (umol/L)	61.88 / 132.6	62.764	58.344	Not reported	16MAY2013
Eosinophils/Leukocytes (%)	1 / 6	1.7	0.8	Not reported	16MAY2013
Erythrocytes (10^12/L)	4.2 / 6.2	3.91	3.42	Not reported	16MAY2013

Parameter (units)	Normal Range	Screening	Result	Grade	Date
Hematocrit (%)	39 / 53	39.7	35.4	Not reported	16MAY2013
Hemoglobin (g/L)	123 / 183	142	116	1	16MAY2013
Hemoglobin (g/L)	135 / 170	142	98	2	16MAY2013
Lymphocytes/Leukocytes (%)	27 / 47	36.4	21.2	Not reported	16MAY2013
Neutrophils/Leukocytes (%)	43 / 64	52.2	70.4	Not reported	16MAY2013
Platelets (10^9/L)	138 / 353	63	63	2	16MAY2013
Platelets (10^9/L)	120 / 400	63	93	1	16MAY2013
Potassium (mmol/L)	3.5 / 5	3.97	5.3	1	16MAY2013
Protein (g/L)	66 / 87	74	65	Not reported	16MAY2013
Prothrombin Time (sec)	8 / 12	12.2	12.7	Not reported	16MAY2013
Hemoglobin (g/L)	135 / 170	142	96	2	17MAY2013

14.3.4 Abnormal Laboratory Value Listing

15 Reference List

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