



## Clinical trial results:

### **RANDOMIZED, DOUBLE-BLIND, PHASE 2/3 STUDY IN SUBJECTS WITH MALIGNANT PLEURAL MESOTHELIOMA TO ASSESS ADI-PEG 20 WITH PEMETREXED AND CISPLATIN (ATOMIC-MESO PHASE 2/3 STUDY)**

#### **Summary**

EudraCT number	2015-004281-28
Trial protocol	GB IT
Global end of trial date	18 August 2022

#### **Results information**

Result version number	v1 (current)
This version publication date	19 December 2025
First version publication date	19 December 2025
Summary attachment (see zip file)	Clinical Study Report - Polaris2015-003 (study-report-polaris2015-003.pdf) subject-disposition (subject-disposition.pdf) demographic-data (demographic-data.pdf) End Points (individual-efficacy-response-data.pdf) Adverse Events (adverse-event-listings.pdf) More Information - Protocol and Protocol Amendments (protocol-and-protocol-amendments.pdf)

#### **Trial information**

##### **Trial identification**

Sponsor protocol code	POLARIS2015-003
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##### **Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02709512
WHO universal trial number (UTN)	U1111-1170-6516

Notes:

##### **Sponsors**

Sponsor organisation name	Polaris Group
Sponsor organisation address	9990 Mesa Rim Road, Suite 110, San Diego, CA, United States, 92121
Public contact	Mirla Langlois, Designe Rx Europe Limited, 1 858-452-6688, mlanglois@polarispharma.com
Scientific contact	Mirla Langlois, Designe Rx Europe Limited, 1 858-452-6688, mlanglois@polarispharma.com

Notes:

##### **Paediatric regulatory details**

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No	No

Notes:

**Results analysis stage**

Analysis stage	Final
Date of interim/final analysis	14 September 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 August 2022
Global end of trial reached?	Yes
Global end of trial date	18 August 2022
Was the trial ended prematurely?	No

Notes:

**General information about the trial**

Main objective of the trial:

Determine efficacy as determined by RR, measured by modified RECIST criteria for unresectable MPM and RECIST 1.1 criteria (phase 2 portion) and OS (phase 3 portion)

Protection of trial subjects:

Key Protections for Participants:

Informed Consent: Participants voluntarily agreed to participate after being fully informed about the trial's risks, benefits, and procedures.

Right to Withdraw: Participants could change their minds and withdraw from a trial at any time without penalty.

Privacy and Confidentiality: Personal and health information was kept private and secure, with only authorized personnel having access to the data.

Independent Data Safety Monitoring Board had oversight and reviewed data to ensure safety of participants

Background therapy:

Pemetrexed is a folate analog metabolic inhibitor

Cisplatin is a heavy metal compound containing platinum

Carboplatin is a platinum-based n ankylating agent

Pemetrexed (500 mg/m<sup>2</sup>), Cisplatin (75 mg/m<sup>2</sup>), Carboplatin (AUC 5)

Evidence for comparator:

This is a randomized, double-blind, multi-center, phase 2/3 trial of ADI-PEG 20 in combination with pemetrexed and cisplatin or Carboplatin in subjects with unresectable MPM of sarcomatoid or biphasic histologies. Placebo comparator was used.

Actual start date of recruitment	01 August 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

**Population of trial subjects****Subjects enrolled per country**

Country: Number of subjects enrolled	Australia: 18
Country: Number of subjects enrolled	Italy: 30
Country: Number of subjects enrolled	Taiwan: 4
Country: Number of subjects enrolled	United Kingdom: 144
Country: Number of subjects enrolled	United States: 53

Worldwide total number of subjects	249
EEA total number of subjects	30

Notes:

<b>Subjects enrolled per age group</b>	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	58
From 65 to 84 years	191
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Recruitment started in 01st August 2017 and ended 15th August 2021. The planned enrollment period was 36 months. Enrollment took place in US, UK, Australia, Italy and Taiwan.

### Pre-assignment

Screening details:

Recording age, gender, race, ethnicity (i.e. demographics). Taking a medical history, noting any medications you may be taking and if you have had any side effects from them.

Completing a physical exam. Performance status assessment, to see how well you are able to perform your normal daily activities. Blood sampling for routine laboratory test.

### Period 1

Period 1 title	Treatment and Follow-up Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	ADI-PEG 20

Arm description:

Active Arm

Arm type	Experimental
Investigational medicinal product name	Pegargiminase
Investigational medicinal product code	
Other name	ADI-PEG 20
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

36 mg/m<sup>2</sup> weekly, Intramuscularly

<b>Arm title</b>	Placebo
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Arm description:

Placebo arm

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

36 mg/m<sup>2</sup> equivalent Placebo weekly, Intramuscularly

<b>Number of subjects in period 1</b>	ADI-PEG 20	Placebo
Started	125	124
Completed	125	124

## Baseline characteristics

### Reporting groups

Reporting group title	ADI-PEG 20
Reporting group description:	
Active Arm	
Reporting group title	Placebo
Reporting group description:	
Placebo arm	

Reporting group values	ADI-PEG 20	Placebo	Total
Number of subjects	125	124	249
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	28	30	58
From 65-84 years	97	94	191
85 years and over	0	0	0
Age < 65	0	0	0
Age > 65	0	0	0
Age continuous			
Units: years			
median	71.0	70.0	
standard deviation	± 69.5	± 69.4	-
Gender categorical			
Units: Subjects			
Female	23	20	43
Male	102	104	206
Race			
Units: Subjects			
Asian	5	5	10
Black or African American	3	0	3
White	116	116	232
Other	1	3	4

### Subject analysis sets

Subject analysis set title	ADI PEM Platinum
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Active Group	
Subject analysis set title	ADI PEM Platinum

Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Placebo Group	

Reporting group values	ADI PEM Platinum	ADI PEM Platinum	
Number of subjects	125	124	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	28	30	
From 65-84 years	97	94	
85 years and over	0	0	
Age < 65	0	0	
Age > 65	0	0	
Age continuous			
Units: years			
median	71.0	70.0	
standard deviation	± 69.5	± 69.4	
Gender categorical			
Units: Subjects			
Female	23	20	
Male	102	104	
Race			
Units: Subjects			
Asian	5	5	
Black or African American	3	0	
White	116	116	
Other	1	3	

## End points

### End points reporting groups

Reporting group title	ADI-PEG 20
Reporting group description:	
Active Arm	
Reporting group title	Placebo
Reporting group description:	
Placebo arm	
Subject analysis set title	ADI PEM Platinum
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Active Group	
Subject analysis set title	ADI PEM Platinum
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Placebo Group	

### Primary: OS

End point title	OS
End point description:	
Overall Survival	
End point type	Primary
End point timeframe:	
36 months	

End point values	ADI-PEG 20	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	124		
Units: months				
median (standard deviation)	9.3 (± 2.02)	7.66 (± 1.7)		

### Statistical analyses

Statistical analysis title	Overall Survival
Comparison groups	ADI-PEG 20 v Placebo
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	equivalence <sup>[1]</sup>
P-value	= 0.0234
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.71



Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	0.93
Variability estimate	Standard deviation
Dispersion value	0.5

Notes:

[1] - 125 subjects in the ADI-PEG 20 group

## Secondary: PFS

End point title	PFS
End point description: Progression Free Survival	
End point type	Secondary
End point timeframe: 36 months	

End point values	ADI-PEG 20	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	124		
Units: months				
median (standard deviation)	6.24 (± 0.8)	5.65 (± 0.9)		

## Statistical analyses

<b>Statistical analysis title</b>	Progression Free Survival
Comparison groups	ADI-PEG 20 v Placebo
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	equivalence <sup>[2]</sup>
P-value	= 0.0193
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	0.9
Variability estimate	Standard deviation
Dispersion value	0.65

Notes:

[2] - 125 subjects in the ADI-PEG 20 group

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

After the first dose and until 30 days after the last dose.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.1
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### Reporting groups

Reporting group title	ADIPemPlatinum
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Reporting group description: -

Reporting group title	PlaceboPemPlatinum
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Reporting group description: -

Serious adverse events	ADIPemPlatinum	PlaceboPemPlatinum	
Total subjects affected by serious adverse events			
subjects affected / exposed	62 / 125 (49.60%)	61 / 124 (49.19%)	
number of deaths (all causes)	7	12	
number of deaths resulting from adverse events	7	11	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed <sup>[1]</sup>	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed <sup>[2]</sup>	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed <sup>[3]</sup>	1 / 1 (100.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed <sup>[4]</sup>	1 / 1 (100.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Orthostatic hypotension subjects affected / exposed <sup>[5]</sup> occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 1 (100.00%) 0 / 1 0 / 0	0 / 1 (0.00%) 0 / 0 0 / 0	
General disorders and administration site conditions Pyrexia subjects affected / exposed <sup>[6]</sup> occurrences causally related to treatment / all deaths causally related to treatment / all	5 / 5 (100.00%) 0 / 1 0 / 0	8 / 8 (100.00%) 0 / 1 0 / 0	
Non-cardiac chest pain subjects affected / exposed <sup>[7]</sup> occurrences causally related to treatment / all deaths causally related to treatment / all	6 / 6 (100.00%) 0 / 1 0 / 0	3 / 3 (100.00%) 0 / 1 0 / 0	
Fatigue subjects affected / exposed <sup>[8]</sup> occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 1 (100.00%) 0 / 1 0 / 0	2 / 2 (100.00%) 0 / 1 0 / 0	
Sudden death subjects affected / exposed <sup>[9]</sup> occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 2 (100.00%) 0 / 1 0 / 2	0 / 1 (0.00%) 0 / 1 0 / 0	
Pain subjects affected / exposed <sup>[10]</sup> occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 1 (100.00%) 0 / 1 0 / 0	0 / 1 (0.00%) 0 / 0 0 / 0	
Immune system disorders Anaphylactic reaction subjects affected / exposed <sup>[11]</sup> occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 2 (100.00%) 0 / 2 0 / 0	0 / 1 (0.00%) 0 / 0 0 / 0	
Drug hypersensitivity subjects affected / exposed <sup>[12]</sup> occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 1 (100.00%) 0 / 1 0 / 0	0 / 1 (0.00%) 0 / 0 0 / 0	

Hypersensitivity			
subjects affected / exposed <sup>[13]</sup>	1 / 1 (100.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed <sup>[14]</sup>	2 / 2 (100.00%)	2 / 2 (100.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed <sup>[15]</sup>	2 / 2 (100.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed <sup>[16]</sup>	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cough			
subjects affected / exposed <sup>[17]</sup>	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed <sup>[18]</sup>	1 / 1 (100.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed <sup>[19]</sup>	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed <sup>[20]</sup>	6 / 6 (100.00%)	2 / 2 (100.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Psychiatric disorders			
Confusional state			
subjects affected / exposed <sup>[21]</sup>	1 / 1 (100.00%)	2 / 2 (100.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed <sup>[22]</sup>	0 / 1 (0.00%)	2 / 2 (100.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed <sup>[23]</sup>	1 / 1 (100.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed <sup>[24]</sup>	1 / 1 (100.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter test positive			
subjects affected / exposed <sup>[25]</sup>	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed <sup>[26]</sup>	2 / 2 (100.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed <sup>[27]</sup>	1 / 1 (100.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			

subjects affected / exposed <sup>[28]</sup>	1 / 1 (100.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin abrasion			
subjects affected / exposed <sup>[29]</sup>	1 / 1 (100.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed <sup>[30]</sup>	4 / 4 (100.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed <sup>[31]</sup>	1 / 1 (100.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed <sup>[32]</sup>	2 / 2 (100.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Myocardial infarction			
subjects affected / exposed <sup>[33]</sup>	1 / 1 (100.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed <sup>[34]</sup>	1 / 1 (100.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed <sup>[35]</sup>	1 / 1 (100.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Cerebrovascular accident subjects affected / exposed <sup>[36]</sup>	1 / 1 (100.00%)	3 / 3 (100.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 2	
Lethargy subjects affected / exposed <sup>[37]</sup>	2 / 2 (100.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome subjects affected / exposed <sup>[38]</sup>	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure subjects affected / exposed <sup>[39]</sup>	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope subjects affected / exposed <sup>[40]</sup>	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed <sup>[41]</sup>	0 / 1 (0.00%)	5 / 5 (100.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia subjects affected / exposed <sup>[42]</sup>	1 / 1 (100.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia subjects affected / exposed <sup>[43]</sup>	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Febrile neutropenia			
subjects affected / exposed <sup>[44]</sup>	2 / 2 (100.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eyelid function disorder			
subjects affected / exposed <sup>[45]</sup>	1 / 1 (100.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed <sup>[46]</sup>	1 / 1 (100.00%)	7 / 7 (100.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed <sup>[47]</sup>	2 / 2 (100.00%)	5 / 5 (100.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed <sup>[48]</sup>	2 / 2 (100.00%)	3 / 3 (100.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed <sup>[49]</sup>	2 / 2 (100.00%)	2 / 2 (100.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed <sup>[50]</sup>	1 / 1 (100.00%)	2 / 2 (100.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed <sup>[51]</sup>	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	



Enterocolitis			
subjects affected / exposed <sup>[52]</sup>	1 / 1 (100.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed <sup>[53]</sup>	1 / 1 (100.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed <sup>[54]</sup>	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed <sup>[55]</sup>	6 / 6 (100.00%)	4 / 4 (100.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed <sup>[56]</sup>	1 / 1 (100.00%)	3 / 3 (100.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed <sup>[57]</sup>	1 / 1 (100.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed <sup>[58]</sup>	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gouty tophus			
subjects affected / exposed <sup>[59]</sup>	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Muscular weakness subjects affected / exposed <sup>[60]</sup> occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 1 (0.00%) 0 / 0 0 / 0	1 / 1 (100.00%) 0 / 1 0 / 0	
Infections and infestations			
Pneumonia subjects affected / exposed <sup>[61]</sup> occurrences causally related to treatment / all deaths causally related to treatment / all	5 / 5 (100.00%) 1 / 1 0 / 1	6 / 6 (100.00%) 1 / 1 0 / 3	
Sepsis subjects affected / exposed <sup>[62]</sup> occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 1 (100.00%) 1 / 1 0 / 0	6 / 6 (100.00%) 1 / 1 0 / 0	
Lower respiratory tract infection subjects affected / exposed <sup>[63]</sup> occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 2 (100.00%) 0 / 1 0 / 0	3 / 3 (100.00%) 0 / 1 0 / 0	
Neutropenic sepsis subjects affected / exposed <sup>[64]</sup> occurrences causally related to treatment / all deaths causally related to treatment / all	3 / 3 (100.00%) 0 / 1 0 / 0	2 / 2 (100.00%) 0 / 1 0 / 0	
COVID-19 subjects affected / exposed <sup>[65]</sup> occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 1 (100.00%) 0 / 1 0 / 0	2 / 2 (100.00%) 0 / 1 0 / 2	
Septic shock subjects affected / exposed <sup>[66]</sup> occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 1 (100.00%) 0 / 1 0 / 0	2 / 2 (100.00%) 0 / 2 0 / 0	
Urinary tract infection subjects affected / exposed <sup>[67]</sup> occurrences causally related to treatment / all deaths causally related to treatment / all	3 / 3 (100.00%) 0 / 1 0 / 0	0 / 1 (0.00%) 0 / 0 0 / 0	
Lung infection			

subjects affected / exposed <sup>[68]</sup>	2 / 2 (100.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural infection			
subjects affected / exposed <sup>[69]</sup>	1 / 1 (100.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed <sup>[70]</sup>	1 / 1 (100.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed <sup>[71]</sup>	1 / 1 (100.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed <sup>[72]</sup>	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed <sup>[73]</sup>	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed <sup>[74]</sup>	0 / 1 (0.00%)	3 / 3 (100.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed <sup>[75]</sup>	3 / 3 (100.00%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			

subjects affected / exposed <sup>[76]</sup>	1 / 1 (100.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia			
subjects affected / exposed <sup>[77]</sup>	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The number of subjects exposed to this adverse event is equal to the total number of subjects exposed to this adverse event. This discrepancy is due to the number of subjects for each reporting group (ADI and Placebo)

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The number of subjects exposed to this adverse event is equal to the total number of subjects exposed to this adverse event. This discrepancy is due to the number of subjects for each reporting group (ADI and Placebo)

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The number of subjects exposed to this adverse event is equal to the total number of subjects exposed to this adverse event. This discrepancy is due to the number of subjects for each reporting group (ADI and Placebo)

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The number of subjects exposed to this adverse event is equal to the total number of subjects exposed to this adverse event. This discrepancy is due to the number of subjects for each reporting group (ADI and Placebo)

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The number of subjects exposed to this adverse event is equal to the total number of subjects exposed to this adverse event. This discrepancy is due to the number of subjects for each reporting group (ADI and Placebo)

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The number of subjects exposed to this adverse event is equal to the total number of subjects exposed to this adverse event. This discrepancy is due to the number of subjects for each reporting group (ADI and Placebo)

[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The number of subjects exposed to this adverse event is equal to the total number of subjects exposed to this adverse event. This discrepancy is due to the number of subjects for each reporting group (ADI and Placebo)

[8] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The number of subjects exposed to this adverse event is equal to the total number of subjects exposed to this adverse event. This discrepancy is due to the number of subjects for each reporting group (ADI and Placebo)

[9] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The number of subjects exposed to this adverse event is equal to the total number of subjects exposed to this adverse event. This discrepancy is due to the number of subjects for each reporting group (ADI and Placebo)

[10] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: The number of subjects exposed to this adverse event is equal to the total number of subjects exposed to this adverse event. This discrepancy is due to the number of subjects for each reporting group (ADI and Placebo)



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<b>Non-serious adverse events</b>	ADIPemPlatinum	PlaceboPemPlatinum	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	123 / 125 (98.40%)	123 / 124 (99.19%)	
Investigations			
Neutrophil count decreased			
subjects affected / exposed <sup>[78]</sup>	24 / 24 (100.00%)	10 / 10 (100.00%)	
occurrences (all)	1	1	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed <sup>[79]</sup>	14 / 14 (100.00%)	18 / 18 (100.00%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed <sup>[80]</sup>	66 / 66 (100.00%)	62 / 62 (100.00%)	
occurrences (all)	1	1	
Pyrexia			
subjects affected / exposed <sup>[81]</sup>	17 / 17 (100.00%)	13 / 13 (100.00%)	
occurrences (all)	1	1	
Non-cardiac chest pain			
subjects affected / exposed <sup>[82]</sup>	26 / 26 (100.00%)	17 / 17 (100.00%)	
occurrences (all)	1	1	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed <sup>[83]</sup>	28 / 28 (100.00%)	10 / 10 (100.00%)	
occurrences (all)	1	1	
Anaemia			
subjects affected / exposed <sup>[84]</sup>	34 / 34 (100.00%)	38 / 38 (100.00%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed <sup>[85]</sup>	65 / 65 (100.00%)	67 / 67 (100.00%)	
occurrences (all)	1	1	
Constipation			
subjects affected / exposed <sup>[86]</sup>	54 / 54 (100.00%)	41 / 41 (100.00%)	
occurrences (all)	1	1	
Vomiting			

subjects affected / exposed <sup>[87]</sup>	23 / 23 (100.00%)	32 / 32 (100.00%)	
occurrences (all)	1	1	
Diarrhoea			
subjects affected / exposed <sup>[88]</sup>	20 / 20 (100.00%)	24 / 24 (100.00%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed <sup>[89]</sup>	19 / 19 (100.00%)	20 / 20 (100.00%)	
occurrences (all)	1	1	
Dyspnoea			
subjects affected / exposed <sup>[90]</sup>	35 / 35 (100.00%)	30 / 30 (100.00%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	24 / 125 (19.20%)	18 / 124 (14.52%)	
occurrences (all)	1	1	
Infections and infestations			
Oral candidiasis			
subjects affected / exposed <sup>[91]</sup>	11 / 11 (100.00%)	14 / 14 (100.00%)	
occurrences (all)	1	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed <sup>[92]</sup>	26 / 26 (100.00%)	44 / 44 (100.00%)	
occurrences (all)	1	1	

Notes:

[78] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The number of subjects exposed to this adverse event is equal to the total number of subjects exposed to this adverse event. This discrepancy is due to the number of subjects for each reporting group (ADI and Placebo)

[79] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The number of subjects exposed to this adverse event is equal to the total number of subjects exposed to this adverse event. This discrepancy is due to the number of subjects for each reporting group (ADI and Placebo)

[80] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The number of subjects exposed to this adverse event is equal to the total number of subjects exposed to this adverse event. This discrepancy is due to the number of subjects for each reporting group (ADI and Placebo)

[81] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: The number of subjects exposed to this adverse event is equal to the total number of subjects exposed to this adverse event. This discrepancy is due to the number of subjects for each reporting group (ADI and Placebo)



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 November 2019	<p>1. Removed "with Low Argininosuccinate Synthetase 1 Expression" from the protocol title. Rationale: ASS1 testing will no longer be required or conducted as ASS1 expression level is no longer considered important when ADI-PEG 20 is combined with chemotherapy.</p> <p>2. Removed requirement for tumor samples for ASS1 testing as an eligibility criterion and other study-specific sections and references related to tumor sample collection and ASS1 testing. Rationale: ASS1 deficiency is no longer considered important when ADI-PEG 20 is combined with chemotherapy.</p> <p>3. Removed response rate (RR), duration of response (DOR) and disease control rate (DCR) as secondary efficacy endpoints for the phase 3 portion Rationale: RR will only be analyzed once at the first interim analysis at the end of phase 2 portion to support accelerated approval and will not be analyzed again at the end of phase 3. Progression free survival (PFS) is the key secondary efficacy endpoint for the phase 3.</p> <p>4. Removed requirement for confirmation of measurable disease by blinded independent central review (BICR) Rationale: Sites are fully capable of determining measurable disease (to-date, only 2% were found ineligible and 1% as borderline cases by BICR). This would reduce logistic issues at sites (potential delay in subject enrollment) and vendor management cost.</p> <p>5. Removed requirement for confirmational scans 4 weeks after the scheduled scans showing tumor response (PR and CR) Rationale: The conformational scan is unnecessary for a randomized, double-blind, controlled study with BICR and with 6-week intervals for tumor scans scheduled for all subjects on study. This would also reduce complexity of scheduling for the sites.</p> <p>6. Removed requirement for BICR to determine PFS in phase 3 portion Rationale: Simplification for logistics management and reduction of vendor management cost.</p>

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/38358753>

<http://www.ncbi.nlm.nih.gov/pubmed/34589965>

