Clinical trial results:
A Randomised Stratified Multicentre Phase II Clinical Trial of Single-Agent ADI-PEG 20 (Pegylated Arginine Deiminase) in Patients with Malignant Pleural Mesothelioma.

Summary

EudraCT number	2006-004592-35
Trial protocol	GB
Global end of trial date	30 April 2015

Results information

Result version number	v1
This version publication date	16 September 2017
First version publication date	16 September 2017
Summary attachment (see zip file)	ADAM Publication_Sep2016 (Arginine Deprivation With Pegylated Arginine Deiminase in Patients With Argininosuccinate Synthetase 1–Deficient Malignant Pleural Mesothelioma A Randomized Clinical Trial.pdf)

Trial information

Trial identification

Sponsor protocol code	6836

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01279967
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Barts Health NHS Trust
Sponsor organisation address	5 Walden Street, London, United Kingdom, E1 2EF
Public contact	CECM Trials Team, Queen Mary University London, 0044 02078828197, bci-cecmmonitoring@qmul.ac.uk
Scientific contact	CECM Trials Team, Queen Mary University London, 0044 02078828197, bci-cecmmonitoring@qmul.ac.uk

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 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 September 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 April 2015
Global end of trial reached?	Yes
Global end of trial date	30 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the time to disease progression between the control group receiving best supportive care and the group receiving ADI-PEG 20 and best supportive care.

Protection of trial subjects:

The Trial Management Group consisted of an independent chairperson, the Chief Investigator, trial co-ordination team, collaborators, and the trial statistician and provided review of cumulative reports of all Serious Adverse Events (SAEs) on a minimum 6 monthly basis to identify patterns or trends of events or identify safety issues, which would not be apparent on an individual basis.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 January 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 68
Worldwide total number of subjects	68
EEA total number of subjects	68

Notes:

Subjects enrolled per age group

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)	29
From 65 to 84 years	39
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From March 2, 2011 to March 21, 2013 201 patients were screened to take part in ADAM.

Pre-assignment

Screening details:

From March 2, 2011 to March 21, 2013 201 patients were screened to take part in ADAM. Of these 97 were found to be ASS1 negative and 70 were randomised into the trial. 2 patients were subsequently found to be ineligible so that the total number of patients randomised into the trial is 68.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	ADI-PEG20 + BSC

Arm description:

Patients randomised into this arm received a weekly intramuscular injection of ADI-PEG20 (36.8mg/m2) for up to 6 months (cycles) plus best supportive care (BSC). Patients continued to receive study treatment, with regular blood sampling, until disease progression, withdrawal of consent, or unacceptable toxic effects. ADI-PEG20–treated patients with disease control were allowed to exceed 6 cycles. Chemotherapy-naive patients were offered chemotherapy on progression.

Arm type	Experimental
Investigational medicinal product name	Pegylated arginine deiminase (ADI-PEG 20)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Weekly intramuscular injection of ADI-PEG20 dose of 36.8mg/m2 (equivalent to 320IU/m2) for up to 6 months.

Arm title	BSC alone

Arm description:

Best supportive care

Arm type	Control

No investigational medicinal product assigned in this arm

Number of subjects in period 1	ADI-PEG20 + BSC	BSC alone
Started	44	24
Completed	44	24

Baseline characteristics

Reporting groups

Reporting group title	ADI-PEG20 + BSC

Reporting group description:

Patients randomised into this arm received a weekly intramuscular injection of ADI-PEG20 (36.8mg/m2) for up to 6 months (cycles) plus best supportive care (BSC). Patients continued to receive study treatment, with regular blood sampling, until disease progression, withdrawal of consent, or unacceptable toxic effects. ADI-PEG20–treated patients with disease control were allowed to exceed 6 cycles. Chemotherapy-naive patients were offered chemotherapy on progression.

Reporting group title	BSC alone

Reporting group description:

Best supportive care

Reporting group values	ADI-PEG20 + BSC	BSC alone	Total
Number of subjects	44	24	68
Age categorical Units: Subjects			
Adults (18-64 years)	17	13	30
From 65-84 years	27	11	38
Gender categorical Units: Subjects			
Female	8	5	13
Male	36	19	55
ECOG Units: Subjects			
PS 0	9	7	16
PS 1	35	17	52
Smoking history Units: Subjects			
Never smoker	18	7	25
Current smoker	1	1	2
Ex-smoker	25	16	41
Histological sub-type Units: Subjects			
Sarcomatoid	1	1	2
Non-sarcomatoid	43	23	66
Prior Chemotherapy Units: Subjects			
None	17	11	28
Platinum based	27	13	40

Subject analysis sets

Subject analysis set title	All analyses
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All eligible patients that had been randomised (excludes 2 patients who were randomised but not eligible, as ascertained after randomisation)

Reporting group values	All analyses		
Number of subjects	68		
Age categorical Units: Subjects			
Adults (18-64 years)	30		
From 65-84 years	38		
Gender categorical Units: Subjects			
Female			
Male			
ECOG Units: Subjects			
PS 0			
PS 1			
Smoking history Units: Subjects			
Never smoker			
Current smoker			
Ex-smoker			
Histological sub-type Units: Subjects			
Sarcomatoid			
Non-sarcomatoid			
Prior Chemotherapy Units: Subjects			
None			
Platinum based			

End points

End points reporting groups

Reporting group title	ADI-PEG20 + BSC
Reporting group description:	
Patients randomised into this arm received a weekly intramuscular injection of ADI-PEG20 (36.8mg/m2) for up to 6 months (cycles) plus best supportive care (BSC). Patients continued to receive study treatment, with regular blood sampling, until disease progression, withdrawal of consent, or unacceptable toxic effects. ADI-PEG20–treated patients with disease control were allowed to exceed 6 cycles. Chemotherapy-naive patients were offered chemotherapy on progression.	
Reporting group title	BSC alone
Reporting group description:	
Best supportive care	
Subject analysis set title	All analyses
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All eligible patients that had been randomised (excludes 2 patients who were randomised but not eligible, as ascertained after randomisation)	

Primary: Progression free survival

End point title	Progression free survival
End point description:	
End point type	Primary
End point timeframe:	
Until end of follow up	

End point values	ADI-PEG20 + BSC	BSC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	24		
Units: Months				
median (inter-quartile range (Q1-Q3))	3.2 (1.8 to 5.5)	2 (1.8 to 3.6)		

Statistical analyses

Statistical analysis title	ADI-PEG20 analyses
Comparison groups	ADI-PEG20 + BSC v BSC alone
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.15 [1]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.56

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	0.96

Notes:

[1] - randomised phase II trial

Secondary: Overall Survival

End point title	Overall Survival

End point description:

End point type	Secondary

End point timeframe:

Until end of follow up

End point values	ADI-PEG20 + BSC	BSC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	24		
Units: Months				
median (inter-quartile range (Q1-Q3))	11.5 (4.2 to 22.9)	11.1 (6.9 to 14.2)		

Statistical analyses

Statistical analysis title	Overall survival
Comparison groups	ADI-PEG20 + BSC v BSC alone
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.15 [3]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	1.16

Notes:

[2] - The Kaplan-Meier curves did not show proportional hazards. Therefore restricted mean survival times also provided:
RMST ADI-PEG20: 15.7 months
BSC: 12.1 months
Difference in RMST 3.6 (95% CI -1.0 to 8.1), p=0.6 (one-sided), p=0.13 (two-sided)

[3] - p=0.15 (2-sided) or 0.08 (one-sided)

Secondary: Objective Response Rate

End point title	Objective Response Rate

End point description:

Proportion of evaluable subjects who achieve a confirmed SD, CR or PR per modified RECIST guidelines for plain CT and by EORTC guidelines for PET-CT. The number and percentage of subjects falling into each response category will be descriptively tabulated. At 4 months, the best response observed by patients was stable disease (SD), there were no CR or PR.

End point type	Secondary

End point timeframe:

Those with evaluable disease at 4 months

End point values	ADI-PEG20 + BSC	BSC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	9		
Units: Percentage	12	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse events

End point title	Adverse events

End point description:

Assessed from adverse event and SUSAR reporting. Based on the highest grade of toxicity (grade 1 to 4) for each patient and each event type.

End point type	Secondary

End point timeframe:

Until end of follow up

End point values	ADI-PEG20 + BSC	BSC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	24		
Units: Number of patients	40	14		

Attachments (see zip file)	ADAM trial - Eudract toxicity table.docx

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From consent date to 30 days post last dose of IMP.

Adverse event reporting additional description:

SAEs are as defined in the regulations.
Non-serious adverse events are all grades 1 to 2. The uploaded table shows grade 1-2 and grade 3-4 separately.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	ADI-PEG20 + BSC

Reporting group description:

Patients randomised into this arm received a weekly intramuscular injection of ADI-PEG20 (36.8mg/m2) for up to 6 months (cycles) plus best supportive care (BSC). Patients continued to receive study treatment, with regular blood sampling, until disease progression, withdrawal of consent, or unacceptable toxic effects. ADI-PEG20–treated patients with disease control were allowed to exceed 6 cycles. Chemotherapy-naive patients were offered chemotherapy on progression.

Reporting group title	BSC alone

Reporting group description:

Best supportive care

Serious adverse events	ADI-PEG20 + BSC	BSC alone	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 44 (20.45%)	2 / 24 (8.33%)	
number of deaths (all causes)	35	20	
number of deaths resulting from adverse events			
Investigations			
Neutropenia			
subjects affected / exposed	1 / 44 (2.27%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Neuropathy			
subjects affected / exposed	1 / 44 (2.27%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			

subjects affected / exposed	0 / 44 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drowsiness			
subjects affected / exposed	0 / 44 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Unwell	Additional description: pale, clammy, BP low 70/35, chest pressure and rash		
subjects affected / exposed	1 / 44 (2.27%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain	Additional description: abdominal pain due to pericardial effusion		
subjects affected / exposed	1 / 44 (2.27%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever			
subjects affected / exposed	1 / 44 (2.27%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 44 (2.27%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergic reaction	Additional description: Allopurinol allergy with renal impairment		
subjects affected / exposed	2 / 44 (4.55%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactoid reaction			
subjects affected / exposed	1 / 44 (2.27%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Difficulty swallowing			
subjects affected / exposed	0 / 44 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 44 (2.27%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adult respiratory distress syndrome			
subjects affected / exposed	1 / 44 (2.27%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Myositis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Rash			
subjects affected / exposed	1 / 44 (2.27%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Purpuric rash legs			
subjects affected / exposed	1 / 44 (2.27%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	ADI-PEG20 + BSC	BSC alone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 44 (97.73%)	21 / 24 (87.50%)	

Investigations			
Abnormal haematologic test result			
subjects affected / exposed	12 / 44 (27.27%)	2 / 24 (8.33%)	
occurrences (all)	47	2	
Neutropenia			
subjects affected / exposed	4 / 44 (9.09%)	0 / 24 (0.00%)	
occurrences (all)	4	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 44 (4.55%)	0 / 24 (0.00%)	
occurrences (all)	4	0	
Nervous system disorders			
Dizzy spell			
subjects affected / exposed	6 / 44 (13.64%)	0 / 24 (0.00%)	
occurrences (all)	6	0	
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	16 / 44 (36.36%)	0 / 24 (0.00%)	
occurrences (all)	21	0	
Chest pain and/or trouble breathing			
subjects affected / exposed	24 / 44 (54.55%)	8 / 24 (33.33%)	
occurrences (all)	45	8	
Fatigue			
subjects affected / exposed	19 / 44 (43.18%)	6 / 24 (25.00%)	
occurrences (all)	36	6	
Fever			
subjects affected / exposed	1 / 44 (2.27%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Pain			
subjects affected / exposed	22 / 44 (50.00%)	4 / 24 (16.67%)	
occurrences (all)	33	5	
Swelling in limbs			
subjects affected / exposed	3 / 44 (6.82%)	0 / 24 (0.00%)	
occurrences (all)	5	0	
Immune system disorders			
Allergic reaction and/or anaphylaxis			

subjects affected / exposed	1 / 44 (2.27%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
GI events			
subjects affected / exposed	23 / 44 (52.27%)	6 / 24 (25.00%)	
occurrences (all)	73	14	
Infections and infestations			
Infection			
subjects affected / exposed	12 / 44 (27.27%)	3 / 24 (12.50%)	
occurrences (all)	19	3	
Rash			
subjects affected / exposed	17 / 44 (38.64%)	1 / 24 (4.17%)	
occurrences (all)	24	1	
Metabolism and nutrition disorders			
Abnormal biochemical test result			
subjects affected / exposed	6 / 44 (13.64%)	1 / 24 (4.17%)	
occurrences (all)	42	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 October 2010	- Changes to primary endpoint (TTP to PFS) - Increased sample size - IMP dose adjustment in line with recent published data
10 November 2010	IMPD updates
18 February 2011	Inclusion of patients with prior platinum therapy
19 September 2011	Changes to screening timeframe
29 March 2012	Updates to IMP thawing process, clarification of registration, screening, withdrawal and follow-up processes
18 May 2012	Change to Sponsor name
19 October 2012	- Change of requirement to check serum uric acid levels on every day of dosing to Day 1 of each cycle - Inclusion of study schedule for patients who wish to extend treatment beyond 6 months - New Investigator Brochure

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/27584578