Clinical trial results:
A PHASE II STUDY ON THE ACTIVITY OF TRABECTEDIN IN PRETREATED EPITHELIOID OR BIPHASIC/SARCOMATOID MALIGNANT PLEURAL MESOTHELIOMA (MPM)
ATREUS TRIAL

Summary

EudraCT number	2011-006330-16
Trial protocol	IT
Global end of trial date	09 December 2019

Results information

Result version number	v1 (current)
This version publication date	17 June 2022
First version publication date	17 June 2022

Trial information

Trial identification

Sponsor protocol code	IRFMN-MPM-6077

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02194231
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Istituto di Ricerche Farmacologiche Mario Negri IRCCS
Sponsor organisation address	Via Mario Negri 2, Milan, Italy,
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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	24 June 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 June 2019
Global end of trial reached?	Yes
Global end of trial date	09 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a phase II, single arm, multicentre study.
The primary objective of the study is to assess the activity of trabectedin in patients with epithelioid MPM relapsing after treatment with pemetrexed plus platinum-based drugs.

Protection of trial subjects:

NA

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 March 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 145
Worldwide total number of subjects	145
EEA total number of subjects	145

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)	55
From 65 to 84 years	90
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall, 145 patients were enrolled in seven sites in Italy: 78 patients (53.8%) with epithelioid MPM and 67 (46.2%) with biphasic or sarcomatoid MPM.

Pre-assignment

Screening details:

NA

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	epithelioid MPM (A)

Arm description:

Recruited patients will receive 1.1 mg/m2 intravenous trabectedin infusion over 3 hours every 21 days until disease progression or development of side-effects requiring treatment discontinuation.

Arm type	Experimental
Investigational medicinal product name	Trabectedin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

1.1 mg/mq over 3 hours infusion every 21 days

Arm title	biphasic/sarcomatoid MPM (B)

Arm description:

Recruited patients will receive 1.1 mg/m2 intravenous trabectedin infusion over 3 hours every 21 days until disease progression or development of side-effects requiring treatment discontinuation.

Arm type	Experimental
Investigational medicinal product name	Trabectedin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

1.1 mg/mq over 3 hours infusion every 21 days

Number of subjects in period 1	epithelioid MPM (A)	biphasic/sarcomatoid MPM (B)
Started	78	67
Completed	66	54
Not completed	12	13
Treatment not started	2	4
Protocol major violations	3	4
Treatment discontinuation	7	5

Baseline characteristics

Reporting groups	
Reporting group title	epithelioid MPM (A)
Reporting group description:	
Recruited patients will receive 1.1 mg/m2 intravenous trabectedin infusion over 3 hours every 21 days until disease progression or development of side-effects requiring treatment discontinuation.	
Reporting group title	biphasic/sarcomatoid MPM (B)
Reporting group description:	
Recruited patients will receive 1.1 mg/m2 intravenous trabectedin infusion over 3 hours every 21 days until disease progression or development of side-effects requiring treatment discontinuation.	

Reporting group values	epithelioid MPM (A)	biphasic/sarcomatoid MPM (B)	Total
Number of subjects	78	67	145
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)	33	22	55
From 65-84 years	45	45	90
85 years and over	0	0	0
Age continuous			
Units: years			
median	66.4	67.9	
inter-quartile range (Q1-Q3)	62 to 72	63 to 74.4	-
Gender categorical			
Units: Subjects			
Female	22	15	37
Male	56	52	108

Subject analysis sets	
Subject analysis set title	ITT set A
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT set A includes all subjects with epithelioid MPM who provided informed consent and were enrolled in the study, with no major violations of the eligibility criteria.	
Subject analysis set title	ITT set B
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT set B includes all subjects with biphasic or sarcomatoid MPM who provided informed consent and were enrolled in the study, with no major violations of the eligibility criteria.	
Subject analysis set title	Safety set A
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety set A includes all subjects with epithelioid MPM who provided informed consent and were enrolled in the study, with no major violations of the eligibility criteria, who received at least one dose of study treatment and had at least one safety follow-up, whether withdrawn prematurely or not.

Subject analysis set title	Safety set B
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety set B includes all subjects with biphasic or sarcomatoid MPM who provided informed consent and were enrolled in the study, with no major violations of the eligibility criteria, who received at least one dose of study treatment and had at least one safety follow-up, whether withdrawn prematurely or not.

Subject analysis set title	PP set A
Subject analysis set type	Per protocol

Subject analysis set description:

The PP set A includes all subjects with epithelioid MPM who provided informed consent and were enrolled in the study, with no major violations of the eligibility criteria, who received at least 12 weeks of treatment or who interrupted treatment before 12 weeks for progressive disease or death, and whose disease was assessed.

Subject analysis set title	PP set B
Subject analysis set type	Per protocol

Subject analysis set description:

The PP set B includes all subjects with biphasic or sarcomatoid MPM who provided informed consent and were enrolled in the study, with no major violations of the eligibility criteria, who received at least 12 weeks of treatment or who interrupted treatment before 12 weeks for progressive disease or death, and whose disease is assessed.

Reporting group values	ITT set A	ITT set B	Safety set A
Number of subjects	75	63	73
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)	33	22	31
From 65-84 years	45	45	42
85 years and over	0	0	0
Age continuous Units: years			
median	66.3	67.9	66.3
inter-quartile range (Q1-Q3)	61.3 to 72.0	63.0 to 74.4	61 to 72
Gender categorical Units: Subjects			
Female	22	15	22
Male	53	48	51

Reporting group values	Safety set B	PP set A	PP set B
Number of subjects	59	66	54
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)	19	29	14
From 65-84 years	40	37	40
85 years and over	0	0	0
Age continuous			
Units: years			
median	67.9	65.9	68.3
inter-quartile range (Q1-Q3)	63 to 74.6	60.3 to 71.9	64.2 to 74.6
Gender categorical			
Units: Subjects			
Female	13	21	12
Male	46	45	42

End points

End points reporting groups

Reporting group title	epithelioid MPM (A)

Reporting group description:

Recruited patients will receive 1.1 mg/m2 intravenous trabectedin infusion over 3 hours every 21 days until disease progression or development of side-effects requiring treatment discontinuation.

Reporting group title	biphasic/sarcomatoid MPM (B)

Reporting group description:

Recruited patients will receive 1.1 mg/m2 intravenous trabectedin infusion over 3 hours every 21 days until disease progression or development of side-effects requiring treatment discontinuation.

Subject analysis set title	ITT set A
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT set A includes all subjects with epithelioid MPM who provided informed consent and were enrolled in the study, with no major violations of the eligibility criteria.

Subject analysis set title	ITT set B
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT set B includes all subjects with biphasic or sarcomatoid MPM who provided informed consent and were enrolled in the study, with no major violations of the eligibility criteria.

Subject analysis set title	Safety set A
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety set A includes all subjects with epithelioid MPM who provided informed consent and were enrolled in the study, with no major violations of the eligibility criteria, who received at least one dose of study treatment and had at least one safety follow-up, whether withdrawn prematurely or not.

Subject analysis set title	Safety set B
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety set B includes all subjects with biphasic or sarcomatoid MPM who provided informed consent and were enrolled in the study, with no major violations of the eligibility criteria, who received at least one dose of study treatment and had at least one safety follow-up, whether withdrawn prematurely or not.

Subject analysis set title	PP set A
Subject analysis set type	Per protocol

Subject analysis set description:

The PP set A includes all subjects with epithelioid MPM who provided informed consent and were enrolled in the study, with no major violations of the eligibility criteria, who received at least 12 weeks of treatment or who interrupted treatment before 12 weeks for progressive disease or death, and whose disease was assessed.

Subject analysis set title	PP set B
Subject analysis set type	Per protocol

Subject analysis set description:

The PP set B includes all subjects with biphasic or sarcomatoid MPM who provided informed consent and were enrolled in the study, with no major violations of the eligibility criteria, who received at least 12 weeks of treatment or who interrupted treatment before 12 weeks for progressive disease or death, and whose disease is assessed.

Primary: PFS

End point title	PFS[1]

End point description:

PFS12w is <25%, and at the same time reveal, at a β level of 15%, whether PFS12w is >40%.
The PFS12w and response rate will be reported descriptively as counts, percents and using 80% and 95% confidence intervals for the epithelioid cohort.

End point type	Primary

End point timeframe:

PFS12w - Patients alive and free of progression at 12 weeks

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoints are reported by arm

End point values	epithelioid MPM (A)	PP set A		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	62	62		
Units: patients	27	27		

Statistical analyses

Statistical analysis title	PFS rate 12weeks

Statistical analysis description:

Patients who interrupted trt for progressive disease or death before 12 weeks were included in the analysis as failures. Patients who did not progress or die within 12 weeks from trt start and without a disease evaluation between the 11th and the 13th week were considered as not evaluable, unless the absence of disease progression was confirmed in the disease evaluations after the 13th week. The 80% and 95% confidence intervals (CI) for PFS12w were computed by means of exact binomial methods

Comparison groups	epithelioid MPM (A) v PP set A
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	PFS12w
Point estimate	43.5
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	34.9
upper limit	52.5

Primary: PFS

End point title	PFS[2]

End point description:

With a one-sided α level of 5%, the null hypothesis that PFS12w is <15% and to have 95% power to reveal whether PFS12w is >35%.
The PFS12w and response rate will be reported descriptively as counts, percents and using 90% and 95% confidence intervals for the biphasic/sarcomatoid cohort.

End point type	Primary

End point timeframe:

PFS12w - Patients alive and free of progression at 12 weeks

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoints are reported by arm

End point values	biphasic/sarcomatoid MPM (B)	PP set B		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	52	52		
Units: patients	16	16		

Statistical analyses

Statistical analysis title	PFS rate 12weeks

Statistical analysis description:

Patients who interrupted trt for progressive disease or death before 12 weeks were included in the analysis as failures. Patients who did not progress or die within 12 weeks from trt start and without a disease evaluation between the 11th and the 13th week were considered as not evaluable, unless the absence of disease progression was confirmed in the disease evaluations after the 13th week. The 80% and 95% confidence intervals (CI) for PFS12w were computed by means of exact binomial methods.

Comparison groups	biphasic/sarcomatoid MPM (B) v PP set B
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	PFS12w
Point estimate	30.8
Confidence interval	
level	90 %
sides	2-sided
lower limit	20.3
upper limit	42.9

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During treatment

Assessment type	Systematic

Dictionary used

Dictionary name	NCI-CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Overall

Reporting group description: -

Serious adverse events	Overall		
Total subjects affected by serious adverse events			
subjects affected / exposed	46 / 145 (31.72%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pericardial effusion			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vena cava thrombosis			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Venous thrombosis			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	2 / 145 (1.38%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	2 / 2		
Ischaemic cardiomyopathy			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	1 / 1		
Left ventricular dysfunction			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pericardial effusion			
subjects affected / exposed	2 / 145 (1.38%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pulmonary oedema (cardiogenic)			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Loss of consciousness			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	2 / 145 (1.38%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Leukopenia			

subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 145 (2.07%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	2 / 145 (1.38%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Multi-organ failure			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Pyrexia			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sudden death			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 145 (1.38%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

Diarrhoea				
subjects affected / exposed	1 / 145 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	1 / 145 (0.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Oesophageal achalasia				
subjects affected / exposed	1 / 145 (0.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oesophageal obstruction				
subjects affected / exposed	1 / 145 (0.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Stomatitis				
subjects affected / exposed	1 / 145 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 145 (0.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Orchitis				
subjects affected / exposed	1 / 145 (0.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Alanine aminotransferase increased				
subjects affected / exposed	1 / 145 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Cholecystitis				
subjects affected / exposed	1 / 145 (0.69%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory failure				
subjects affected / exposed	1 / 145 (0.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnea				
subjects affected / exposed	7 / 145 (4.83%)			
occurrences causally related to treatment / all	1 / 7			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	4 / 145 (2.76%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 1			
Pleural effusion				
subjects affected / exposed	1 / 145 (0.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	1 / 145 (0.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	1 / 1			
Pneumothorax				
subjects affected / exposed	1 / 145 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	1 / 145 (0.69%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			

Pulmonary embolism			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Sternal fracture			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	5 / 145 (3.45%)		
occurrences causally related to treatment / all	3 / 5		
deaths causally related to treatment / all	0 / 2		
Sepsis			
subjects affected / exposed	2 / 145 (1.38%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	1 / 1		
Septic shock			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Overall		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	137 / 145 (94.48%)		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	106 / 145 (73.10%)		
occurrences (all)	576		
General disorders and administration site conditions			

Fatigue subjects affected / exposed occurrences (all)	93 / 145 (64.14%) 251		
Hepatobiliary disorders Hepatotoxicity subjects affected / exposed occurrences (all)	133 / 145 (91.72%) 755		
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all)	49 / 145 (33.79%) 148		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 January 2014	PRINCIPAL CHANGES: 1.OBJECTIVES -> adding a secondary objective 2.ENDOPINTS -> adding a secondary outcome 3.CENTERS -> adding a clinical centre 4.INCLUSION CRITERIA -> changes in inclusion criteria 5.STUDY PROCEDURE -> changes in study procedures (Hematological evaluation added) 6.PREMEDICATION AND CONCOMITANT THERAPIES -> changes in study procedures and concomitant therapies 7.PAIN EVALUATION -> changes in study procedures, its scientific relevance, in data collection 8.STATISTICAL ANALYSIS -> changes in primary and secondary statistical analysis 9.BLOOD MACROPHAGES ANALYSIS -> changes in study procedures and CRF 10.TRANSLATIONAL STUDY PROCEDURES -> changes in study procedures and CRF
27 October 2015	PRINCIPAL CHANGES: 1.SAMPLE SIZE -> changes in sample size calculation 2.STUDY PROCEDURE -> changes regarding the length of the study 3.PRIMARY ENDPOINT -> definition of the timing for TAC evaluation 4.TAC EVALUATION -> changes in TAC evaluation according to the modified RECIST criteria 5.TRABECTEDINE -> Trabectedine dose reduction 6.CENTERS -> adding clinical centres
16 November 2016	PRINCIPAL CHANGES: 1.TAC EVALUATION -> adding a TAC centralized review 2.ECG -> exam modified in the study 3.STATISTICAL ANALYSIS -> more details about sample size and statistical analysis of the translational study 4.INFORMED CONSENT -> update of the document

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/32732073