Clinical trial results:
A Trial of Intra-pleuraL OK-432 Therapy in mesothelioma (TILT): A feasibility study using the 'trial within a cohort' methodology

Summary

EudraCT number	2016-004727-23
Trial protocol	GB
Global end of trial date	19 November 2019

Results information

Result version number	v1 (current)
This version publication date	23 January 2021
First version publication date	23 January 2021

Trial information

Trial identification

Sponsor protocol code	3850

Additional study identifiers

ISRCTN number	ISRCTN10432197
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	North Bristol NHS Trust
Sponsor organisation address	Southmead Hospital, Bristol, United Kingdom, BS10 5NB
Public contact	Research & Innovation, North Bristol NHS Trust, 0044 1174149329, researchsponsor@nbt.nhs.uk
Scientific contact	Research & Innovation, North Bristol NHS Trust, 0044 1174149329, researchsponsor@nbt.nhs.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	25 February 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of this study is to answer the question “Is it possible (feasible) to undertake a trial within a cohort to investigate the effect of OK432, administered directly into the chest in people with mesothelioma, and is it acceptable to patients and relatives?”

This research will determine whether a full-scale version of the trial is possible. If it is, the results of this research will inform the design of the subsequent full-scale trial.

The long-term goal is to determine whether OK432 is an effective treatment for mesothelioma, and whether the trial within a cohort design is appropriate for mesothelioma trials.

Protection of trial subjects:

Known safety risks were minimised where possible by excluding high risk patients and using close patient monitoring to identify adverse events as soon as possible. The TwiC (Trial within a Cohort) design was discussed with the PPI group and seen as preferable to traditional randomised methods as patients would only be informed of the intervention once selected to receive it. The number of trial visits was also discussed with the PPI group to balance the need for clinical follow up with patient burden. To minimise potential distress to patients participating in the qualitative interviews a topic guide was developed in collaboration with the PPI group to ensure acceptability.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 January 2018
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: 7
Worldwide total number of subjects	7
EEA total number of subjects	0

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)	2
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled between 30/01/2018 and 30/11/2019 and recruitment was based at three NHS sites in the UK.

Pre-assignment

Screening details:

There were 43 patients in the cohort during the recruitment period at the trial sites of which 7 met the eligibility criteria.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	All participants

Arm description:

All participants

Arm type	Baseline
Investigational medicinal product name	OncoTice
Investigational medicinal product code	BCG
Other name	Bacillus Calmette-Guérin (BCG)
Pharmaceutical forms	Powder and solvent for intravesical solution
Routes of administration	Intrapleural use

Dosage and administration details:

BCG original dose: 0.4-1.6 x 10^7 CFU instilled intra-pleurally via indwelling pleural catheter
BCG dose reduced to 0.2-0.8 x 10^7 CFU after urgent safety measure passed

Investigational medicinal product name	OK432
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intrapleural use

Dosage and administration details:

Original dose 10 Klinishe Einheirt (KE) delivered intra-pleurally via indwelling pleural catheter
Dose reduced to 5KE after urgent safety measure.

Number of subjects in period 1	All participants
Started	7
Completed	7

Period 2

Period 2 title	Overall trial
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

A key tenet of the TwiC design is that participants are only informed about the trial intervention once they have been selected to receive it, whilst controls are blinded to the existence of the trial.

Arms

Are arms mutually exclusive?	No
Arm title	IMP-BCG

Arm description:

BCG is a live attenuated, low-virulence strain of Mycobacterium bovis prepared from a culture of Bacillus Calmette-Guérin (OncoTice, Merck Sharp & Dohme Ltd, Netherlands).

Arm type	Experimental
Investigational medicinal product name	OncoTice
Investigational medicinal product code	BCG
Other name	Bacillus Calmette-Guérin (BCG)
Pharmaceutical forms	Powder and solvent for intravesical solution
Routes of administration	Intrapleural use

Dosage and administration details:

BCG original dose: 0.4-1.6 x 10^7 CFU instilled intra-pleurally via indwelling pleural catheter
BCG dose reduced to 0.2-0.8 x 10^7 CFU after urgent safety measure passed

Arm title	Control

Arm description:

Eligible patients from the longitudinal, observational cohort study. A key tenet of the TwiC design is that participants are only informed about the trial intervention once they have been selected to receive it, whilst controls are blinded to the existence of the trial.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	IMP-OK432

Arm description:

OK432 consists of heat-treated, penicillin-killed, freeze-dried Streptococcus pyogenes group A2 (Picibanil, Chugai Pharmaceutical Ltd, Japan).

Arm type	Experimental
Investigational medicinal product name	OK432
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intrapleural use

Dosage and administration details:

Original dose 10 Klinishe Einheirt (KE) delivered intra-pleurally via indwelling pleural catheter
Dose reduced to 5KE after urgent safety measure.

Arm title	All participants

Arm description: -

Arm type	All participants

No investigational medicinal product assigned in this arm

Arm title	,03 ERWK

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3DWLHQWV ZKR UHFHLYHG HLWKHU 2. RU %&*

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2WKHU QDPH	%DFLOOXV &DOPHWWH *XpULQ %&*
3KDUPDFHXWLFDO IRUPV	3RZGHU DQG VROYHQW IRU LQWUDYHVLFDO VROXWL
5RXWHV RI DGPLQLVWUDWLRQ	,QWUDSOHXUDO XVH

'RVDJH DQG DGPLQLVWUDWLRQ GHWDLOV

%&* RULJLQDO GRVH [A &)8 LQVWLOOHG LQWUD SOHXUDOO\ YLD LQGZ
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,QYHVWLJDWLRQDO PHGLFLQDO SURGXFW QDPH	2QH SURGXFW QDPH
,QYHVWLJDWLRQDO PHGLFLQDO SURGXFW FRGH	
2WKHU QDPH	
3KDUPDFHXWLFDO IRUPV	3RZGHU IRU VROXWLRQ IRU LQMHFWLRQ LQIXVLRQ
5RXWHV RI DGPLQLVWUDWLRQ	,QWUDSOHXUDO XVH

'RVDJH DQG DGPLQLVWUDWLRQ GHWDLOV

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Number of subjects in period 2	,03 %&*	&RQWURO	,03 2.
6WDUWHG			
&RPSOHWHG			
1RW FRPSOHWHG			
GHFOLQHG WR SDUWLFLSDWH			

Number of subjects in period 2	$OO SDUWLFLSDQWV	,QW9 VERWK
6WDUWHG		
&RPSOHWHG		
1RW FRPSOHWHG		
GHFOLQHG WR SDUWLFLSDWH		

Baseline characteristics

Reporting groups

Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	7	7	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
median	73		
full range (min-max)	60 to 83	-	
Gender categorical Units: Subjects			
Female	1	1	
Male	6	6	
Asbestos exposure Units: Subjects			
None recalled	1	1	
Transient	1	1	
Light/passive	1	1	
Heavy/active	4	4	
Duration of symptoms Units: Subjects			
< 1 month	3	3	
1-3 months	1	1	
> 3 months	2	2	
Not recorded	1	1	
Method of diagnosis Units: Subjects			
CT-guided biopsy	1	1	
Medical thoracoscopy	5	5	
VATS	1	1	
Laterality Units: Subjects			
Left	2	2	

Right	5	5	
Tumour histology Units: Subjects			
Epithelioid	7	7	
Brims prognostic score Units: Subjects			
1 (best prognosis)	1	1	
02	5	5	
03	0	0	
4 (worst prognosis)	1	1	

End points

End points reporting groups

Reporting group title	All participants
Reporting group description:	
All participants	
Reporting group title	IMP-BCG
Reporting group description:	
BCG is a live attenuated, low-virulence strain of Mycobacterium bovis prepared from a culture of Bacillus Calmette-Guérin (OncoTice, Merck Sharp & Dohme Ltd, Netherlands).	
Reporting group title	Control
Reporting group description:	
Eligible patients from the longitudinal, observational cohort study. A key tenet of the TwiC design is that participants are only informed about the trial intervention once they have been selected to receive it, whilst controls are blinded to the existence of the trial.	
Reporting group title	IMP-OK432
Reporting group description:	
OK432 consists of heat-treated, penicillin-killed, freeze-dried Streptococcus pyogenes group A2 (Picibanil, Chugai Pharmaceutical Ltd, Japan).	
Reporting group title	All participants
Reporting group description: -	
Reporting group title	IMP- both
Reporting group description:	
Patients who received either OK432 or BCG	

Primary: Recruitment rate

End point title	Recruitment rate[1]
End point description:	
End point type	Primary
End point timeframe:	
Randomisation	
Notes:	
[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: No analyses planned - a feasibility trial	

End point values	All participants			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: Participants				
Target	12			
Randomised	7			

Statistical analyses

No statistical analyses for this end point

Primary: Attrition Rate

End point title	Attrition Rate[2]

End point description:

Attrition was defined as participants who declined to receive an IMP following randomisation or who declined or failed to complete follow up in the cohort if allocated to control.

End point type	Primary

End point timeframe:

Final follow up

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No analyses planned - a feasibility trial

End point values	All participants			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: Participants				
Randomised	7			
Completed	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of control participants who were unblinded

End point title	Number of control participants who were unblinded

End point description:

End point type	Secondary

End point timeframe:

Final follow up

End point values	Control			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Participants				
Number of control patients	3			
Number of control patients who were unblinded	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Survival

End point title	Survival

End point description:

End point type	Secondary

End point timeframe:

Survival was calculated as date of diagnosis with MPM to date of death, as recorded on the death certificate. Surviving participants were censored on 02/06/2020 (7.5 months after final patient visit)

End point values	Control	IMP- both		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: months				
median (inter-quartile range (Q1-Q3))	29 (5.2 to 45.0)	18.1 (12.1 to 23.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Radiological tumour response rates

End point title	Radiological tumour response rates

End point description:

End point type	Secondary

End point timeframe:

Baseline and final follow up (week 12)

End point values	All participants			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: Participants				
progressive disease	3			
stable disease	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Pleural fluid drainage volumes

End point title	Pleural fluid drainage volumes

End point description:

End point type	Secondary

End point timeframe:

Until final follow up at 12 weeks

End point values	All participants			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: ml				
arithmetic mean (full range (min-max))	436.7 (0 to 1500)			

Statistical analyses

No statistical analyses for this end point

Secondary: Successful pleurodesis

End point title	Successful pleurodesis

End point description:

End point type	Secondary

End point timeframe:

Censored from cohort on 02/06/2020

End point values	All participants			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: Participants	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to pleurodesis

End point title	Time to pleurodesis

End point description:

End point type	Secondary

End point timeframe:

Final follow up at 12 weeks

End point values	All participants			
Subject group type	Reporting group			
Number of subjects analysed	6[3]			
Units: days				
median (inter-quartile range (Q1-Q3))	42 (30 to 132)			

Notes:

[3] - 6 patients achieved pleurodesis

Statistical analyses

No statistical analyses for this end point

Secondary: Breathlessness

End point title	Breathlessness

End point description:

End point type	Secondary

End point timeframe:

Baseline, weeks 3, 6 and 12

End point values	All participants			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: mm				
median (inter-quartile range (Q1-Q3))	18.3 (8.3 to 25)			

Statistical analyses

No statistical analyses for this end point

Secondary: Chest pain

End point title	Chest pain

End point description:

End point type	Secondary

End point timeframe:

baseline and weeks 3, 6 and 12

End point values	All participants			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: mm				
median (inter-quartile range (Q1-Q3))	4.7 (1.5 to 11.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Sweats

End point title	Sweats

End point description:

End point type	Secondary

End point timeframe:
baseline and weeks 3, 6 and 12

End point values	All participants			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: mm				
median (inter-quartile range (Q1-Q3))	2.2 (0.3 to 7.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life

End point title	Quality of Life

End point description:

End point type	Secondary

End point timeframe:
baseline and weeks 3, 6 and 12

End point values	All participants			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: mm				
median (inter-quartile range (Q1-Q3))	80 (76.9 to 81.7)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Randomisation until datalock (participants continued to be monitored for adverse events when they had returned to the cohort)

Assessment type	Systematic

Dictionary used

Dictionary name	SNOMED CT
Dictionary version	1.36.4

Reporting groups

Reporting group title	OK432
Reporting group description: -	
Reporting group title	IMP-BCG
Reporting group description: -	
Reporting group title	Control
Reporting group description: -	

Serious adverse events	OK432	IMP-BCG	Control
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	1 / 2 (50.00%)	1 / 2 (50.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
Systemic inflammatory response syndrome	Additional description: Fever, malaise and anorexia with raised inflammatory markers.		
subjects affected / exposed	1 / 1 (100.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural infection bacterial	Additional description: Infection of indwelling pleural catheter		
subjects affected / exposed	0 / 1 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	OK432	IMP-BCG	Control
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	1 / 2 (50.00%)	2 / 2 (100.00%)
General disorders and administration site conditions			
Systemic inflammatory response syndrome	Additional description: Fever, malaise and raised inflammatory markers		
subjects affected / exposed	0 / 1 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Pleural infection bacterial	Additional description: Infected indwelling pleural catheter, treated as outpatient.		
subjects affected / exposed	0 / 1 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Pain	Additional description: Rib pain		
subjects affected / exposed	0 / 1 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 1 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 October 2017	Addition of BCG arm
25 July 2018	Updated BCG SmPC Change to CTA to use Pharmaceutical Solutions as QP
21 January 2019	Urgent Safety Measure to allow half dose IMP

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported