



## Clinical trial results:

### A Randomized, Open-Label Phase II/III Study With Dendritic Cells Loaded With Allogeneic Tumour Cell Lysate (PheraLys) in Subjects With Mesothelioma as Maintenance Treatment (MesoPher) After Chemotherapy.

## DENIM (DENDritic Cell Immunotherapy for Mesothelioma)

### Summary

EudraCT number	2017-001774-41
Trial protocol	NL GB BE FR IT
Global end of trial date	24 June 2022

### Results information

Result version number	v1 (current)
This version publication date	24 June 2023
First version publication date	24 June 2023

### Trial information

#### Trial identification

Sponsor protocol code	MM04
-----------------------	------

#### Additional study identifiers

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

Notes:

### Sponsors

Sponsor organisation name	Amphera BV
Sponsor organisation address	Onderwijsboulevard 225, 's-Hertogenbosch, Netherlands, 5223 DE
Public contact	Clinical trial office, Amphera B.V., Info@amphera.nl
Scientific contact	Clinical trial office, Amphera B.V., Info@amphera.nl

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 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 June 2022
Global end of trial reached?	Yes
Global end of trial date	24 June 2022
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the overall survival rate (determined from the time of randomization in the study) of subjects who receive dendritic cell immunotherapy with MesoPher plus best supportive care (BSC) compared to BSC alone.

Protection of trial subjects:

From earlier studies it is known that the adverse event profile of MesoPher is very benign. Adverse events consisted mainly of mild to moderate, transient injection site reactions and infusion related reactions. In previous studies MesoPher did not induce any product related serious adverse events. An Independent Data Monitoring Committee met every 6 months to review the safety and efficacy data of the study.

Background therapy:

-

Evidence for comparator:

-

Actual start date of recruitment	18 June 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	Netherlands: 127
Country: Number of subjects enrolled	Belgium: 33
Country: Number of subjects enrolled	France: 16
Worldwide total number of subjects	176
EEA total number of subjects	176

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)	53
From 65 to 84 years	123
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

A total of 6 study centers in 5 countries were initiated in this study. Due to COVID-19 restrictions, 2 centers did not recruit any patients.

### Pre-assignment

Screening details:

For inclusion in the study, patients had to have stable disease or better after standard chemotherapy treatment. After screening (medical history, physical exam, CT-scan), eligible patients were randomised. Patients assigned to the MesoPher arm travelled to the EMC for leukapheresis and MesoPher production.

### 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:

The study was masked as formal blinding was not possible due to the nature of the treatment. The sponsor, lead statistician and coordinating investigator were blinded to aggregate data until database lock to ensure study decisions were not affected by knowledge of treatment assignment.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	MesoPher + Best supportive care

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Autologous dendritic cells pulsed with allogeneic tumour cell lysate
Investigational medicinal product code	
Other name	MesoPher
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use, Intradermal use

Dosage and administration details:

Patients received a maximum of 5 administrations of MesoPher, 3 doses every other week and 2 more doses at week 18 and week 30. MesoPher was given in addition to best supportive care. The dose of 25 million viable cells per administration was given 2/3 intravenous and 1/3 intradermal.

<b>Arm title</b>	Best supportive care
------------------	----------------------

Arm description: -

Arm type	Best supportive care
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	MesoPher + Best supportive care	Best supportive care
Started	88	88
Completed	23	27
Not completed	65	61
Consent withdrawn by subject	2	2
Death	61	59

Lost to follow-up	2	-
-------------------	---	---

## Baseline characteristics

### Reporting groups

Reporting group title	MesoPher + Best supportive care
Reporting group description: -	
Reporting group title	Best supportive care
Reporting group description: -	

Reporting group values	MesoPher + Best supportive care	Best supportive care	Total
Number of subjects	88	88	176
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)	23	30	53
From 65-84 years	65	58	123
85 years and over	0	0	0
Age continuous			
Age (mean)			
Units: years			
arithmetic mean	68.8	67.2	
standard deviation	± 7.53	± 8.97	-
Gender categorical			
Units: Subjects			
Female	10	17	27
Male	78	71	149
Histology			
Histologic type of mesothelioma			
Units: Subjects			
Epithelioid	73	75	148
Sarcomatoid	7	4	11
Biphasic	8	8	16
Other	0	1	1
ECOG performance			
Units: Subjects			
ECOG 0	38	27	65
ECOG 1	50	60	110
Not reported	0	1	1

### Subject analysis sets

Subject analysis set title	FAS
Subject analysis set type	Full analysis

<b>Reporting group values</b>	FAS		
Number of subjects	176		
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)	53		
From 65-84 years	123		
85 years and over	0		
Age continuous			
Age (mean)			
Units: years			
arithmetic mean	68.0		
standard deviation	± 8.30		
Gender categorical			
Units: Subjects			
Female	27		
Male	149		
Histology			
Histologic type of mesothelioma			
Units: Subjects			
Epithelioid	148		
Sarcomatoid	11		
Biphasic	16		
Other	1		
ECOG performance			
Units: Subjects			
ECOG 0	65		
ECOG 1	110		
Not reported	1		

## End points

### End points reporting groups

Reporting group title	MesoPher + Best supportive care
Reporting group description: -	
Reporting group title	Best supportive care
Reporting group description: -	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
Includes all randomised patients	

### Primary: Overall survival

End point title	Overall survival
End point description:	
End point type	Primary
End point timeframe:	
From randomization (about 3 to 4 months after diagnosis) until death. For subjects who were alive at the end of the study or lost to follow-up, OS was censored on the last date when subjects were known to be alive.	

End point values	MesoPher + Best supportive care	Best supportive care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	88		
Units: days				
median (confidence interval 95%)	513 (377 to 620)	558 (435 to 668)		

### Statistical analyses

Statistical analysis title	OS analysis
Comparison groups	MesoPher + Best supportive care v Best supportive care
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6185
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.765
upper limit	1.572



Variability estimate	Standard error of the mean
----------------------	----------------------------

## Secondary: Progression free survival

End point title	Progression free survival
End point description: The time of disease progression was the time of the first CT scan showing progressive disease in either the target or non-target lesions or if there where new lesions.	
End point type	Secondary
End point timeframe: From randomisation until disease progression; in the absence of progression, until death or end of study.	

End point values	MesoPher + Best supportive care	Best supportive care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	88		
Units: days				
median (confidence interval 95%)	166 (99 to 178)	99 (93 to 136)		

## Statistical analyses

Statistical analysis title	PFS analysis
Comparison groups	MesoPher + Best supportive care v Best supportive care
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5963
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.656
upper limit	1.232
Variability estimate	Standard error of the mean

## Secondary: Disease control rate

End point title	Disease control rate
End point description: Subjects with either CR, PR or SD as best disease response during the study.	

End point type	Secondary
End point timeframe:	
From randomisation until disease progression; in the absence of progression, until death or end of the study.	

<b>End point values</b>	MesoPher + Best supportive care	Best supportive care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	88		
Units: Subjects	50	35		

### Statistical analyses

<b>Statistical analysis title</b>	Disease control rate
Comparison groups	MesoPher + Best supportive care v Best supportive care
Number of subjects included in analysis	176
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0203
Method	Cochran-Mantel-Haenszel

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from randomisation until progressive disease, death or end of the study, whichever came first.

Assessment type	Systematic
-----------------	------------

### Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	24.0
--------------------	------

### Reporting groups

Reporting group title	MesoPher
-----------------------	----------

Reporting group description:

All subjects randomised to Arm A who underwent at least eukapheresis. If they did not (and consequently did not receive MesoPher either) they are excluded from the safety analysis set

Reporting group title	Best standard of care
-----------------------	-----------------------

Reporting group description:

All subjects randomised to arm B.

Serious adverse events	MesoPher	Best standard of care	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 87 (8.05%)	8 / 88 (9.09%)	
number of deaths (all causes)	61	59	
number of deaths resulting from adverse events	0	0	
Investigations			
Blood potassium decreased			
subjects affected / exposed	1 / 87 (1.15%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 87 (1.15%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 87 (1.15%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Hip fracture			
subjects affected / exposed	0 / 87 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	1 / 87 (1.15%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 87 (1.15%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 87 (1.15%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 87 (1.15%)	0 / 88 (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	0 / 87 (0.00%)	1 / 88 (1.14%)	
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 / 87 (1.15%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			

subjects affected / exposed	0 / 87 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 87 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	1 / 87 (1.15%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 87 (1.15%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 87 (0.00%)	3 / 88 (3.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypomagnesaemia			
subjects affected / exposed	1 / 87 (1.15%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	MesoPher	Best standard of care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	82 / 87 (94.25%)	52 / 88 (59.09%)	
Cardiac disorders			

Chest pain subjects affected / exposed occurrences (all)	13 / 87 (14.94%) 16	11 / 88 (12.50%) 11	
General disorders and administration site conditions Injection site reaction subjects affected / exposed occurrences (all)	73 / 87 (83.91%) 202	0 / 88 (0.00%) 0	
Infusion related reaction subjects affected / exposed occurrences (all)	64 / 87 (73.56%) 143	0 / 88 (0.00%) 0	
Fatigue subjects affected / exposed occurrences (all)	10 / 87 (11.49%) 11	6 / 88 (6.82%) 6	
Influenza like illness subjects affected / exposed occurrences (all)	4 / 87 (4.60%) 4	5 / 88 (5.68%) 5	
Pyrexia subjects affected / exposed occurrences (all)	5 / 87 (5.75%) 6	1 / 88 (1.14%) 2	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	2 / 87 (2.30%) 3	5 / 88 (5.68%) 5	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	5 / 87 (5.75%) 5	2 / 88 (2.27%) 3	
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	13 / 87 (14.94%) 13	14 / 88 (15.91%) 16	
Cough subjects affected / exposed occurrences (all)	8 / 87 (9.20%) 9	8 / 88 (9.09%) 8	
Upper respiratory tract infection			

subjects affected / exposed occurrences (all)	5 / 87 (5.75%) 6	2 / 88 (2.27%) 2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	12 / 87 (13.79%)	2 / 88 (2.27%)	
occurrences (all)	12	2	
Back pain			
subjects affected / exposed	8 / 87 (9.20%)	6 / 88 (6.82%)	
occurrences (all)	9	6	
Flank pain			
subjects affected / exposed	7 / 87 (8.05%)	4 / 88 (4.55%)	
occurrences (all)	8	4	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 January 2018	Main changes included: <ul style="list-style-type: none"><li>• Data collection after the follow-up period was extended to include not only subject's survival status but also subsequent anticancer treatment data and response (if available).</li><li>• Mandatory contraception was extended from 3 months to 12 months after the last study drug administration.</li><li>• As the primary endpoint is overall survival, survival data had to be collected within the remit of the protocol. Therefore, follow-up after week 30 was until death for each subject.</li></ul>
23 January 2018	Main changes included: <ul style="list-style-type: none"><li>• A syphilis test was added at screening and the hepatitis A test was removed to align with the information in the IMPD.</li><li>• It was clarified that subjects had to undergo of DTH skin test after 3 DC treatments to determine if DC treatment resulted in a detectable immune response.</li></ul>
25 April 2018	Main changes included: <ul style="list-style-type: none"><li>• Additional immunomonitoring and biomarker samples were added at leukapheresis. Further, it was specified that leukapheresis could be repeated if MesoPher production failed or did not meet release specifications. Serology had to be within 4 weeks of leukapheresis procedure.</li><li>• Modified RECIST criteria were removed as diagnostic criteria.</li></ul>
09 May 2018	Main changes included: <ul style="list-style-type: none"><li>• It was clarified that concurrent bevacizumab during chemotherapy and during the first 6 weeks after completion of chemotherapy was allowed but subjects who received bevacizumab were only eligible if they stopped bevacizumab due to non-tolerance before or by the end of the chemotherapy period. Subjects who benefitted from bevacizumab use could continue treatment with bevacizumab and were consequently not eligible for the study.</li></ul>
02 December 2019	Main changes included: <ul style="list-style-type: none"><li>• Circumstances in which delayed leukapheresis could be permitted were defined.</li><li>• Procedures for manufactured product out of date were defined.</li></ul> Procedures for cases in which repeat leukapheresis was not possible were defined.



15 May 2021	<p>Main changes included:</p> <ul style="list-style-type: none"> <li>• It was clarified that the intention is that subjects would continue to be followed-up for survival, tumour response and possibly subsequent treatments after the end of study (12 months after randomization of the last subject into the study, when at least 101 events had occurred).</li> <li>• The COVID-19 pandemic had a serious effect on the recruitment rate in the study. To reach the originally planned 230 subjects would take unrealistically long. Hence the number of patients to be recruited was reduced to at least 164.</li> <li>• In view of the reduction in sample size, the interim analysis with the aim to re-estimate the sample size, was no longer relevant and was thus removed.</li> <li>• As a consequence of travel restrictions in relation to the COVID-19 pandemic, 4 instead of 6 study centers were involved in the study (centers in the UK and Italy were closed without having recruited subjects).</li> <li>• A number of additional sensitivity analysis were added.</li> </ul>
-------------	--

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
16 March 2020	Recruitment of new patients was temporarily halted due to the COVID-19 pandemic.	06 May 2020

Notes:

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None
------

Notes: