



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 |
| Arm title | 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.

| | |
|------------------|----------------------|
| Arm title | 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 |

| | | | |
|---|--------|--|--|
| Reporting group values | 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. | |

| End point values | 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

| | |
|---|--|
| Statistical analysis title | 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 %

| Non-serious adverse events | 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">• 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).• Mandatory contraception was extended from 3 months to 12 months after the last study drug administration.• 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. |
| 23 January 2018 | Main changes included: <ul style="list-style-type: none">• A syphilis test was added at screening and the hepatitis A test was removed to align with the information in the IMPD.• 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. |
| 25 April 2018 | Main changes included: <ul style="list-style-type: none">• 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.• Modified RECIST criteria were removed as diagnostic criteria. |
| 09 May 2018 | Main changes included: <ul style="list-style-type: none">• 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. |
| 02 December 2019 | Main changes included: <ul style="list-style-type: none">• Circumstances in which delayed leukapheresis could be permitted were defined.• Procedures for manufactured product out of date were defined. 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"> • 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). • 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. • 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. • 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). • A number of additional sensitivity analysis were added. |
|-------------|--|

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: