



Clinical trial results:

Multi-center phase 2 study to assess the safety, tolerability and early signs of efficacy of tid orally administered BAY63-2521 in adult deltaF508 homozygous Cystic Fibrosis patients

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2013-004595-35 |
| Trial protocol | GB DE NL BE |
| Global end of trial date | 22 September 2017 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 02 September 2018 |
| First version publication date | 02 September 2018 |

Trial information

Trial identification

| | |
|-----------------------|------------------|
| Sponsor protocol code | BAY63-2521/17020 |
|-----------------------|------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02170025 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Bayer AG |
| Sponsor organisation address | Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368 |
| Public contact | Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com |
| Scientific contact | Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com |

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 | 22 September 2017 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|-------------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 22 September 2017 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

- 1) To assess the safety and tolerability versus placebo in adult deltaF508 homozygous Cystic Fibrosis patients not on treatment with Orkambi
- 2) To assess early signs of efficacy versus placebo in adult deltaF508 homozygous Cystic Fibrosis patients not on treatment with Orkambias observed by change from baseline in sweat chloride content (applicable for part 2 only)

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 30 September 2014 |
| 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: 1 |
| Country: Number of subjects enrolled | United Kingdom: 4 |
| Country: Number of subjects enrolled | Belgium: 1 |
| Country: Number of subjects enrolled | France: 2 |
| Country: Number of subjects enrolled | Germany: 3 |
| Country: Number of subjects enrolled | Canada: 4 |
| Country: Number of subjects enrolled | United States: 6 |
| Worldwide total number of subjects | 21 |
| EEA total number of subjects | 11 |

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) | 21 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted at multiple centers in 7 countries worldwide between 30-Sep-2014 (first subject first visit) and 31-Jan-2017 (last subject last visit).

Pre-assignment

Screening details:

Of 31 participants who were screened, 10 failed screening, 21 were randomized.

Period 1

| | |
|------------------------------|---|
| Period 1 title | Overall study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Arms

| | |
|------------------------------|--------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Riociguat (Adepas, BAY63-2521) |

Arm description:

Participants received 0.5 mg BAY63-2521 three times daily (tid) for 14 days. The dose would be increased to 1 mg BAY63-2521 for an additional 14 days, if this was considered safe and tolerable on the basis of the available data for a given patient.

| | |
|--|--------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Riociguat (Adepas, BAY63-2521) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received 0.5 mg BAY63-2521 three times daily (tid) for 14 days. The dose would be increased to 1 mg BAY63-2521 for an additional 14 days, if this was considered safe and tolerable on the basis of the available data for a given patient.

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

Arm description:

Participants received matching placebo tid.

| | |
|--|----------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received matching placebo tid.

| Number of subjects in period 1 | Riociguat (Adempas, BAY63-2521) | Placebo |
|---------------------------------------|------------------------------------|---------|
| Started | 14 | 7 |
| Completed | 12 | 7 |
| Not completed | 2 | 0 |
| Adverse Event | 2 | - |

Baseline characteristics

Reporting groups

| | |
|--|---------------------------------|
| Reporting group title | Riociguat (Adempas, BAY63-2521) |
| Reporting group description: Participants received 0.5 mg BAY63-2521 three times daily (tid) for 14 days. The dose would be increased to 1 mg BAY63-2521 for an additional 14 days, if this was considered safe and tolerable on the basis of the available data for a given patient. | |
| Reporting group title | Placebo |
| Reporting group description: Participants received matching placebo tid. | |

| Reporting group values | Riociguat (Adempas, BAY63-2521) | Placebo | Total |
|--|---------------------------------|---------|-------|
| Number of subjects | 14 | 7 | 21 |
| 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 | | | |
| arithmetic mean | 27.1 | 29.1 | |
| standard deviation | ± 6.9 | ± 7.2 | - |
| Gender categorical Units: Subjects | | | |
| Female | 4 | 1 | 5 |
| Male | 10 | 6 | 16 |
| Sweat chloride content Units: mmol/L | | | |
| arithmetic mean | 96.33 | 94.50 | |
| standard deviation | ± 17.28 | ± 12.82 | - |

End points

End points reporting groups

| | |
|--|------------------------------------|
| Reporting group title | Riociguat (Adempas, BAY63-2521) |
| Reporting group description: Participants received 0.5 mg BAY63-2521 three times daily (tid) for 14 days. The dose would be increased to 1 mg BAY63-2521 for an additional 14 days, if this was considered safe and tolerable on the basis of the available data for a given patient. | |
| Reporting group title | Placebo |
| Reporting group description: Participants received matching placebo tid. | |
| Subject analysis set title | Pharmacodynamic analysis set (PDS) |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Pharmacodynamic analysis set (N=16) included patients who received the medication and who had valid sweat chloride data for efficacy analysis. | |
| Subject analysis set title | Safety analysis set (SAF) |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Safety analysis set (N=21) included patients who had taken at least one dose of the study medication. | |

Primary: Change of sweat chloride content from baseline

| | |
|---|--|
| End point title | Change of sweat chloride content from baseline |
| End point description: Sweat chloride samples were obtained by using a Macroduct induction and collection device according to standard procedures. | |
| End point type | Primary |
| End point timeframe: Baseline, at day 14 and day 28 in study part 1 | |

| End point values | Riociguat (Adempas, BAY63-2521) | Placebo | | |
|--------------------------------------|---------------------------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 9 ^[1] | 7 ^[2] | | |
| Units: mmol/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change at day 14 in part 1 | 7.06 (± 10.26) | 8.71 (± 8.20) | | |
| Change at day 28 in part 1 | 3.44 (± 11.04) | 9.00 (± 12.71) | | |

Notes:

[1] - PDS

[2] - PDS

Statistical analyses

| | |
|---|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: Treatment effect describes the difference in outcomes between 0.5 mg riociguat and placebo on Day 14. This was an exploratory analysis. For sample size determination a probabilistic assessment on predicted point estimates and width of credible intervals was performed. | |

| | |
|---|---|
| Comparison groups | Riociguat (Adempas, BAY63-2521) v Placebo |
| Number of subjects included in analysis | 16 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Bayesian analysis |
| Point estimate | -1.3 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -8.7 |
| upper limit | 6 |

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

Treatment effect describes the difference in outcomes between 1.0 mg riociguat and placebo on Day 28. This was an exploratory analysis. For sample size determination a probabilistic assessment on predicted point estimates and width of credible intervals was performed.

| | |
|---|---|
| Comparison groups | Riociguat (Adempas, BAY63-2521) v Placebo |
| Number of subjects included in analysis | 16 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Bayesian analysis |
| Point estimate | -5 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -12.4 |
| upper limit | 2.4 |

Secondary: Change of FEV1 from baseline

| | |
|-----------------|------------------------------|
| End point title | Change of FEV1 from baseline |
|-----------------|------------------------------|

End point description:

Spirometry was performed according to the American Thoracic Society Guidelines 1995 at the time points screening/
baseline, treatment period and follow up.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline to Day 14, Day 28 and Follow-up

| End point values | Riociguat (Adempas, BAY63-2521) | Placebo | | |
|--------------------------------------|---------------------------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 9 ^[3] | 7 ^[4] | | |
| Units: % predicted value | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change at day 14 | 0.86 (± 4.59) | 2.00 (± 7.28) | | |
| Change at day 28 | -0.79 (± 6.04) | 2.43 (± 9.55) | | |
| Change at follow-up visit | -0.46 (± 5.51) | 2.63 (± 9.50) | | |

Notes:

[3] - PDS

[4] - PDS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first treatment until 14 days after last treatment

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 19.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Participants received matching placebo tid

| | |
|-----------------------|---------------------------------|
| Reporting group title | Riociguat (Adempas, BAY63-2521) |
|-----------------------|---------------------------------|

Reporting group description:

Participants received 0.5 mg three times daily (tid) BAY63-2521 for 14 days. The dose would be increased to 1 mg BAY63-2521 for an additional 14 days, if this was considered safe and tolerable on the basis of the available data for a given patient.

| Serious adverse events | Placebo | Riociguat (Adempas, BAY63-2521) | |
|---|----------------|---------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 1 / 14 (7.14%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Gastrointestinal disorders | | | |
| Distal intestinal obstruction syndrome | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 14 (7.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Infective pulmonary exacerbation of cystic fibrosis | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 14 (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: 0 %

| Non-serious adverse events | Placebo | Riociguat (Adempas, BAY63-2521) | |
|---|--|---|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 7 / 7 (100.00%) | 13 / 14 (92.86%) | |
| Vascular disorders Flushing subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 14 (0.00%) 0 | |
| General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) Vessel puncture site bruise subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 0 / 7 (0.00%) 0 1 / 7 (14.29%) 1 0 / 7 (0.00%) 0 | 2 / 14 (14.29%) 2 1 / 14 (7.14%) 1 1 / 14 (7.14%) 1 1 / 14 (7.14%) 3 | |
| Immune system disorders Jarisch-Herxheimer reaction subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 14 (0.00%) 0 | |
| Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Sinus congestion subjects affected / exposed occurrences (all) Haemoptysis | 0 / 7 (0.00%) 0 1 / 7 (14.29%) 1 0 / 7 (0.00%) 0 | 1 / 14 (7.14%) 1 3 / 14 (21.43%) 3 1 / 14 (7.14%) 1 | |

| | | | |
|--|---------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 14 (7.14%) 1 | |
| Sputum discoloured subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 2 / 14 (14.29%) 3 | |
| Sputum increased subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 1 / 14 (7.14%) 2 | |
| Increased viscosity of bronchial secretion subjects affected / exposed occurrences (all) | 2 / 7 (28.57%) 2 | 0 / 14 (0.00%) 0 | |
| Product issues Device occlusion subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 14 (0.00%) 0 | |
| Investigations C-reactive protein increased subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 14 (7.14%) 1 | |
| Serum ferritin decreased subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 14 (7.14%) 1 | |
| Pseudomonas test positive subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 14 (0.00%) 0 | |
| Injury, poisoning and procedural complications Ligament sprain subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 14 (7.14%) 1 | |
| Skin injury subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 14 (7.14%) 1 | |
| Face injury subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 14 (7.14%) 1 | |
| Nervous system disorders | | | |

| | | | |
|---|---------------------|----------------------|--|
| Dizziness subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 1 / 14 (7.14%) 1 | |
| Headache subjects affected / exposed occurrences (all) | 2 / 7 (28.57%) 4 | 3 / 14 (21.43%) 4 | |
| Paraesthesia subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 14 (0.00%) 0 | |
| Orthostatic intolerance subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 14 (7.14%) 1 | |
| Blood and lymphatic system disorders Iron deficiency anaemia subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 14 (7.14%) 1 | |
| Eye disorders Eye allergy subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 14 (0.00%) 0 | |
| Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 14 (7.14%) 4 | |
| Abdominal pain subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 3 / 14 (21.43%) 3 | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 14 (7.14%) 3 | |
| Constipation subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 1 / 14 (7.14%) 1 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 2 / 14 (14.29%) 2 | |
| Dyspepsia | | | |

| | | | |
|---|----------------|-----------------|--|
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 14 (7.14%) | |
| occurrences (all) | 0 | 2 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 2 / 14 (14.29%) | |
| occurrences (all) | 0 | 2 | |
| Nausea | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 0 / 14 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 2 / 14 (14.29%) | |
| occurrences (all) | 0 | 2 | |
| Faecal volume decreased | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 14 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Faeces soft | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 14 (7.14%) | |
| occurrences (all) | 0 | 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 14 (7.14%) | |
| occurrences (all) | 0 | 1 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 1 / 14 (7.14%) | |
| occurrences (all) | 1 | 1 | |
| Myalgia | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 14 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 14 (7.14%) | |
| occurrences (all) | 0 | 1 | |
| Tendonitis | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 14 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Musculoskeletal chest pain | | | |

| | | | |
|---|----------------|-----------------|--|
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 14 (7.14%) | |
| occurrences (all) | 0 | 1 | |
| Musculoskeletal stiffness | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 14 (7.14%) | |
| occurrences (all) | 0 | 1 | |
| Infections and infestations | | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 14 (7.14%) | |
| occurrences (all) | 0 | 1 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 2 / 14 (14.29%) | |
| occurrences (all) | 2 | 2 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 14 (7.14%) | |
| occurrences (all) | 0 | 1 | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 14 (7.14%) | |
| occurrences (all) | 0 | 1 | |
| Vulvovaginal mycotic infection | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 1 / 14 (7.14%) | |
| occurrences (all) | 0 | 1 | |
| Infective pulmonary exacerbation of cystic fibrosis | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | 2 / 14 (14.29%) | |
| occurrences (all) | 2 | 2 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 15 April 2015 | Amendment 5 (dated 15 Apr 2015) to the original clinical study protocol Version 1.0, forming current integrated protocol version 2.0. <ul style="list-style-type: none">- A "positive sputum culture for Staphylococcus aureus either currently or within the previous year" was removed as exclusion criterion (part of exclusion criterion 5) |
| 28 September 2015 | Amendment 7 (dated 28 Sep 2015) to the integrated protocol version 2.0 (15 Apr 2015) <ul style="list-style-type: none">- FEV1 range for inclusion extended from 60-90% predicted (p) to 40 to 100%p- The range of acceptable blood pressure for inclusion was extended (upper limit of SBP from 140 to 160 mmHg, upper limit of DBP from 90 to 100 mmHg.- Removal of two barrier methods as acceptable contraception- Switching 2 site visits into telephone contacts- NPD measurement was made optional (and related exclusion criterion removed)- Removal of determination of reticulocytes- Inclusion of pharmacokinetic (PK) data into DSMB assessment |
| 18 August 2016 | Amendment 8 (dated 18 Aug 2016) to protocol version 3.0 (28 Sep 2015) <ul style="list-style-type: none">- Shortening of safety monitoring period from 12 to 4 h if DSMB review of the data of Cohort 1 did not reveal any safety concerns- LCI measurement was made optional and LCI as well as NPD were changed from secondary endpoints to additional endpoints- Potential combination of 2 visits on one calendar day in patients not performing LCI or NPD- Removal of upper limit of body mass index as inclusion criterion- Removal of cystatin C from the set of laboratory parameters |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Based on multiple factors, the design of part 2 is no longer appropriate. Study was terminated at the end of part 1. No safety concerns were identified.

Notes: