



Clinical trial results:

A Multi-centre, Open-label Study Evaluating the Safety and Tolerability of Colestilan (MCI-196) in Paediatric Subjects with Chronic Kidney Disease Stages 3b to 5 and with Hyperphosphataemia not on Dialysis Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2012-002582-35 |
| Trial protocol | GB DE |
| Global end of trial date | 14 January 2015 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 19 February 2016 |
| First version publication date | 19 February 2016 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | MCI-196-E16 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01818687 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|-------------------------------------------------------------------------------------------|
| Sponsor organisation name | Mitsubishi Tanabe Pharma Corporation |
| Sponsor organisation address | 17-10, Nihonbashi-Koamicho, Chuo-ku, Tokyo, Japan, 103-8405 |
| Public contact | General Information, Mitsubishi Tanabe Pharma Europe Ltd , regulatory@mt-pharma-eu.com |
| Scientific contact | General Information, Mitsubishi Tanabe Pharma Europe Ltd, regulatory@mt-pharma-eu.com |

Notes:

Paediatric regulatory details

| | |
|----------------------------------------------------------------------|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-000878-PIP02-11 |
| 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? | Yes |

Notes:

Results analysis stage

| | |
|------------------------------------------------------|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 18 May 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 03 December 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 14 January 2015 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The objective of this study was to assess safety and tolerability of colestilan in paediatric subjects (aged 2 years to <18 years) with CKD Stages 3b to 5, diagnosed with hyperphosphataemia, who were not on dialysis.

Protection of trial subjects:

1 For subjects on phosphate binders: during the wash-out period, a max of 4 weeks, subjects stopped their current phosphate binder treatment, which was likely to cause a rise in P levels. The increase in P was not dangerous for a short period of time and once the required P level was reached, the subject was randomised and treated with Colestilan (MCI-196). The level to which the P is required to rise was specified in inclusion criteria 6 and 7.

2 When specifying the amount of blood to be drawn the following guidelines were used: trial-related blood loss (including loss in the procedure) should not exceed 3% of total blood volume during a period of 4 weeks and should not exceed 1% total blood volume at any single time.

Subjects were enrolled to the study only if they could safely provide 8 ml of blood at each visit.

3 When investigating new drugs there is always a risk of unexpected side effects and occasionally allergic reactions. Subjects were closely monitored during the study.

4 Rescue treatment: Hyperphosphataemia, after the max dose of Colestilan (MCI-196) (BSAeq of 15 g/day) was reached, the subject was either withdrawn from the study or the Investigator added CBPB as rescue medication, in addition to the max dose of Colestilan (MCI-196). Adjustment of dosing of vitamin D/analogues was permitted during the study to correct hypocalcaemia. The appropriate doses of rescue treatment were decided by the Investigator based on his/her clinical experience.

5 Consent/assent process: Enough time was provided to the subject/parent/caregiver to consider participation in the study. In addition to the patient information sheet and consent/assent forms, a study flipchart was provided to all sites, which was used as a tool to help explain/discuss aspects of the study in more detail.

6 Tablet intake - it is known that tablets can be difficult to swallow, especially by very young children. The IMP was made available also in granule formulation.

Background therapy: -

Evidence for comparator: -

| | |
|-----------------------------------------------------------|--------------|
| Actual start date of recruitment | 24 June 2013 |
| 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 | Germany: 2 |
| Country: Number of subjects enrolled | United Kingdom: 2 |
| Worldwide total number of subjects | 4 |
| EEA total number of subjects | 4 |

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) | 3 |
| Adolescents (12-17 years) | 1 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from those patients with hyperphosphataemia who were already attending the clinics for the treatment of CKD stages 3b to 5.

Pre-assignment

Screening details:

The study comprised of a screening period (1 to 4 weeks) and a wash-out period (1 to 4 weeks). A total of 14 subjects were screened. 10 subjects were withdrawn before randomisation (screen failed).

Period 1

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

Arms

| | |
|-----------|------------------------|
| Arm title | MCI-196 (All Subjects) |
|-----------|------------------------|

Arm description:

All study subjects were treated for 17 weeks. The starting daily doses of colestilan (MCI-196) was the body surface area equivalent (BSAeq) of 6 g/day in adults, (i.e., 3.47 g/m²/day), oral, divided doses with food. The colestilan dose was titrated up within 3 days of the visit, based on the serum P level and/or the judgement of the Investigator, whichever was more suitable for the best care of the subject.

| | |
|----------------------------------------|------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Colestilan |
| Investigational medicinal product code | MCI-196 |
| Other name | |
| Pharmaceutical forms | Granules, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

1 gram tablets and granules of approximately 20 mg packaged in 2 g or 3 g sachets

| | |
|---------------------------------------|------------------------|
| Number of subjects in period 1 | MCI-196 (All Subjects) |
| Started | 4 |
| Completed | 4 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------------------|
| Reporting group title | MCI-196 (All Subjects) |
|-----------------------|------------------------|

Reporting group description:

All study subjects were treated for 17 weeks. The starting daily doses of colestilan (MCI-196) was the body surface area equivalent (BSAeq) of 6 g/day in adults, (i.e., 3.47 g/m²/day), oral, divided doses with food. The colestilan dose was titrated up within 3 days of the visit, based on the serum P level and/or the judgement of the Investigator, whichever was more suitable for the best care of the subject.

| Reporting group values | MCI-196 (All Subjects) | Total | |
|----------------------------------------------------|------------------------|-------|--|
| Number of subjects | 4 | 4 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 3 | 3 | |
| Adolescents (12-17 years) | 1 | 1 | |
| Adults (18-64 years) | 0 | 0 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 10.3 | | |
| standard deviation | ± 2.6 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 1 | 1 | |
| Male | 3 | 3 | |

End points

End points reporting groups

| | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| Reporting group title | MCI-196 (All Subjects) |
| Reporting group description: All study subjects were treated for 17 weeks. The starting daily doses of colestilan (MCI-196) was the body surface area equivalent (BSAeq) of 6 g/day in adults, (i.e., 3.47 g/m ² /day), oral, divided doses with food. The colestilan dose was titrated up within 3 days of the visit, based on the serum P level and/or the judgement of the Investigator, whichever was more suitable for the best care of the subject. | |

Primary: Percentage of subjects who, due to hyperphosphataemia, require rescue treatment and/or discontinuation of therapy with colestilan (MCI-196)

| | |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of subjects who, due to hyperphosphataemia, require rescue treatment and/or discontinuation of therapy with colestilan (MCI-196) ^[1] |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline to Week 17

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: This study was terminated prematurely. From the limited data collected in this study, due to small sample size, no analysis of the data was conducted nor can any reasonable conclusions be made.

| End point values | MCI-196 (All Subjects) | | | |
|-----------------------------|------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 4 ^[2] | | | |
| Units: Percentage | 0 | | | |

Notes:

[2] - This study was prematurely terminated. No statistical analyses were completed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events (AE) that occurred from the time written informed consent/assent was taken until the end of study or discontinuation were recorded in the source documents and reported in the CRF.

Adverse event reporting additional description:

AEs were classified as 'treatment emergent' (i.e. TEAEs or serious TEAEs) if they occurred following administration of IMP. All events reported in this database are treatment emergent.

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

Dictionary used

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

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|--------------------|----|
| Dictionary version | 18 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|------------------------|
| Reporting group title | MCI-196 (All subjects) |
|-----------------------|------------------------|

Reporting group description:

All study subjects were treated for 17 weeks. The starting daily doses of colestilan (MCI-196) was the body surface area equivalent (BSAeq) of 6 g/day in adults, (i.e., 3.47 g/m²/day), oral, divided doses with food. The colestilan dose was titrated up within 3 days of the visit, based on the serum P level and/or the judgement of the Investigator, whichever was more suitable for the best care of the subject.

| Serious adverse events | MCI-196 (All subjects) | | |
|---------------------------------------------------|------------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |

Frequency threshold for reporting non-serious adverse events: 1 %

| Non-serious adverse events | MCI-196 (All subjects) | | |
|-------------------------------------------------------|------------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 4 / 4 (100.00%) | | |
| Investigations | | | |
| Blood sodium increased | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |
| Blood thyroid stimulating hormone increased | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |
| Calcium ionised decreased | | | |

| | | | |
|------------------------------------------------------|----------------|--|--|
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |
| Fibroblast growth factor 23 increased | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 3 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | | |
| occurrences (all) | 2 | | |
| General disorders and administration site conditions | | | |
| Drug interaction | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |
| Granuloma | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 3 / 4 (75.00%) | | |
| occurrences (all) | 6 | | |
| Nausea | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | | |
| occurrences (all) | 4 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |
| Abdominal pain upper | | | |

| | | | |
|-------------------------------------------------|----------------|--|--|
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 2 | | |
| Constipation | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 2 | | |
| Lip dry | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |
| Skin and subcutaneous tissue disorders | | | |
| Miliaria | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |
| Skin irritation | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |
| Endocrine disorders | | | |
| Hyperparathyroidism | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | | |
| occurrences (all) | 1 | | |
| Metabolism and nutrition disorders | | | |
| Hyperphosphataemia | | | |

| | | | |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 2 / 4 (50.00%) | | |
| occurrences (all) | 3 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|-----------------|-------------------------|--------------|
| 14 January 2015 | Study early termination | - |

Notes:

Limitations and caveats

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

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|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| There were significant challenges to recruitment in all age groups and in this patient population. The study was terminated early due to the withdrawal of the MAA. |
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Notes: