

**Clinical trial results:****A Multi-centre, Flexible Dose, Parallel Group, Open-label, Active Control (Calcium-based Phosphate Binder), Long-term Extension Study Evaluating the Efficacy, Safety and Tolerability of Colestilan (MCI-196) in Paediatric Subjects With Hyperphosphataemia and With Either Chronic Kidney Disease Stage 5 on Dialysis or Chronic Kidney Disease Stages 3b to 5 Not on Dialysis****Summary**

EudraCT number	2012-002583-27
Trial protocol	DE
Global end of trial date	14 January 2015

Results information

Result version number	v1 (current)
This version publication date	09 March 2016
First version publication date	09 March 2016

Trial information**Trial identification**

Sponsor protocol code	MCI-196-E15
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01814917
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 (MTPE), regulatory@mt-pharma-eu.com
Scientific contact	General Information, Mitsubishi Tanabe Pharma Europe Ltd (MTPE), 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)	EMEA-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	23 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 primary objectives of the study were to assess the long-term efficacy and safety of treatment with colestilan (including combination therapy).

Protection of trial subjects:

1. 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 if they could safely provide 8 ml of blood at each visit, this is specified in exclusion criteria 2.
2. When investigating new drugs there is always a risk of unexpected side effects and occasionally allergic reactions. Subjects were closely monitored during the study.
3. Rescue treatment for hyperphosphataemia with CBPB, in addition to the allocated fixed dose of colestilan (MCI196) or CBPB, is allowable as clinically indicated. The appropriate dose was decided by the Investigator based on his/her clinical experience.
4. Rescue treatment for hypocalcaemia with calcium supplements was allowed as clinically indicated. Adjustment of dosing of Vitamin D /analogues was permitted during the study to correct hypocalcaemia. The appropriate dose was to be 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. The flipchart was used as a tool to help explain/discuss aspects of the study in more detail, the study staff were able to answers all questions the subject/parent/caregiver may have.
6. Tablet intake - it is known that tablets can be difficult to swallow, especially for very young children. The IMP was made available also in granule formulation.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 August 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	Turkey: 1
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Germany: 3
Worldwide total number of subjects	6
EEA total number of subjects	5

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)	2
Adolescents (12-17 years)	4
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 who have either completed the MCI-196-E14 or MCI-196-E16 studies, or who were withdrawn from MCI-196-E14 to receive flexible dosing in this study.

Pre-assignment

Screening details:

Subjects were recruited from those who have either completed the MCI-196-E14 (EudraCT number 2012-002581-12) or MCI-196-E16 (EudraCT number 2012-002582-35) studies, or who have been withdrawn from MCI-196-E14.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
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Arm title	MCI-196
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Arm description:

Colestilan

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

Dosage and administration details:

1g tablets and granules of approx 20mg packaged in 2g or 3g sachets.

Arm title	Combination
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Arm description:

Colestilan and CBPB

Arm type	Experimental
Investigational medicinal product name	CBPB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

As per physician's guidance.

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:

1g tablets and granules of approx 20mg packaged in 2g or 3g sachets.

Number of subjects in period 1	MCI-196	Combination
Started	4	2
Completed	1	1
Not completed	3	1
Renal Transplant	1	-
Hyperphosphataemia	1	-
Early withdrawal	1	1

Baseline characteristics

Reporting groups

Reporting group title	MCI-196
Reporting group description: Colestilan	
Reporting group title	Combination
Reporting group description: Colestilan and CBPB	

Reporting group values	MCI-196	Combination	Total
Number of subjects	4	2	6
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)	2	0	2
Adolescents (12-17 years)	2	2	4
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	11.8	17	
standard deviation	± 3.9	± 0	-
Gender categorical			
Units: Subjects			
Female	2	1	3
Male	2	1	3

End points

End points reporting groups

Reporting group title	MCI-196
Reporting group description:	
Colestilan	
Reporting group title	Combination
Reporting group description:	
Colestilan and CBPB	

Primary: Proportion of responders

End point title	Proportion of responders ^[1]
End point description:	
End point type	Primary
End point timeframe:	
At week 52 or LOCF	

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 prematurely terminated. The available data was very limited and highly variable. No consistent reductions (>0.5 mmol/L) from baseline in phosphorus levels were observed for any subject after dosing with MCI-196 alone or combination therapy.

End point values	MCI-196	Combination		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[2]	0 ^[3]		
Units: Percentage				

Notes:

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

[3] - 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 AEs that occur from the time written informed consent and/or assent was obtained to the End Of Study visit were recorded in the source documentation 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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18
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Reporting groups

Reporting group title	MCI-196
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Reporting group description:

Colestilan

Reporting group title	Combination
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Reporting group description:

Colestilan and CBPB

Serious adverse events	MCI-196	Combination	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 4 (25.00%)	0 / 2 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Social circumstances			
Social stay hospitalisation			
subjects affected / exposed	1 / 4 (25.00%)	0 / 2 (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: 1 %

Non-serious adverse events	MCI-196	Combination	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 4 (75.00%)	1 / 2 (50.00%)	
Surgical and medical procedures			
Tonsillectomy			

subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 2 (50.00%) 1	
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 2	0 / 2 (0.00%) 0	
Fatigue subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 2 (0.00%) 0	
Social circumstances Social stay hospitalisation subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 2 (0.00%) 0	
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 2 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Oropharyngeal Pain subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 2	0 / 2 (0.00%) 0	
Investigations Blood Parathyroid Hormone Increased subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 2	0 / 2 (0.00%) 0	
Blood Biocarbonate Decreased subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 2 (0.00%) 0	
Blood phosphorus increased subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 2 (0.00%) 0	
Blood potassium increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 2 (50.00%) 1	
Injury, poisoning and procedural complications			

Fall subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 2 (0.00%) 0	
Gastrostomy Tube Site Complication subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 2 (0.00%) 0	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 2 (0.00%) 0	
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 2 (0.00%) 0	
Eye disorders Visual impairment subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 2 (0.00%) 0	
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 3	0 / 2 (0.00%) 0	
Nausea subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 2	0 / 2 (0.00%) 0	
Vomiting subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 6	0 / 2 (0.00%) 0	
Abdominal distension subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 2 (0.00%) 0	
Abdominal pain subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 2 (0.00%) 0	
Diarrhoea subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 2 (0.00%) 0	

Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Neck pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 4 (50.00%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Oral Herpes			
subjects affected / exposed	1 / 4 (25.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Rhinitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 2 (0.00%)	
occurrences (all)	3	0	
Urinary Tract Infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Folate Deficiency			
subjects affected / exposed	1 / 4 (25.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Hypercalcaemia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Hyperphosphataemia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	

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.

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.

Notes: