Clinical trial results:
Treatment of congenital vascular malformations using Sirolimus: improving quality of Life

Summary

EudraCT number	2016-002157-38
Trial protocol	NL
Global end of trial date	02 December 2021

Results information

Result version number	v1 (current)
This version publication date	25 June 2022
First version publication date	25 June 2022

Trial information

Trial identification

Sponsor protocol code	57911

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03987152
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Radboud university medical center
Sponsor organisation address	Geert Grooteplein Zuid 22, Nijmegen, Netherlands, 6525 GA
Public contact	werkgroep@hecovan.nl, HECOVAN, werkgroep@hecovan.nl
Scientific contact	werkgroep@hecovan.nl, HECOVAN, werkgroep@hecovan.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	26 April 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 September 2021
Global end of trial reached?	Yes
Global end of trial date	02 December 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate whether Sirolimus results in a significant and clinically relevant reduction of pain and an improved quality of life in patients with untreatable vascular malformations.

Protection of trial subjects:

The clinical trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients and/or their parents gave their written informed consent before any study-related procedures were undertaken.
Patients were treated when (increased) pain symptoms occurred with pain relief medication for example. Adverse events were treated.

Background therapy:

Cotrimoxazole as Pneumocystis jirovecii Pneumonia (PJP) prophylaxis.

Evidence for comparator: -

Actual start date of recruitment	18 September 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 74
Worldwide total number of subjects	74
EEA total number of subjects	74

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)	3
Children (2-11 years)	21
Adolescents (12-17 years)	12
Adults (18-64 years)	38
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All patients were enrolled at the Radboudumc between September 2017 and February 2021

Pre-assignment

Screening details:

Inclusion criteria: patients with low flow vascular malformation (venous, lymphatic or combined), aged older than 1 year, with signed informed consent. Patients who are either refractory to standard care. A run-in phase of the first three months of sirolimus use, remaining a total of 68 patients were evaluable for analysis.

Period 1

Period 1 title	Screenings phase
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Screening

Arm description:

Two months period of daily record of pain scores. Pain was recorded using the CHIPPS-scale, (Children and Infants Postoperative Pain Scale) for children aged 0–3 years, visual analogue scale (VAS) clinical pictures for children aged 4–7 years, VAS for patients aged 8–17 years, and numeric pain rating scale (NRS) for adults. No medication is used.

Arm type	Baseline period
Investigational medicinal product name	No product was used
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution in bottle
Routes of administration	Other use

Dosage and administration details:

No product was used

Number of subjects in period 1	Screening
Started	74
Completed	73
Not completed	1
Physician decision	1

Period 2	
Period 2 title	Challenge phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Challenge phase

Arm description:

Six months treatment with sirolimus and co-trimoxazole profylaxis. Open-label single arm.

Arm type	Experimental
Investigational medicinal product name	Sirolimus
Investigational medicinal product code	
Other name	Rapamune
Pharmaceutical forms	Tablet, Oral solution in bottle
Routes of administration	Oral use

Dosage and administration details:

0.8 mg/m2 for children as start dose, 2dd1 mg as start dose for adults. Target trough levels 4-10 ng/mL

Investigational medicinal product name	Cotrimoxazole
Investigational medicinal product code	
Other name	Bactrimel, sulfamethoxazol/trimethoprim
Pharmaceutical forms	Oral suspension, Tablet
Routes of administration	Oral use

Dosage and administration details:

Children: 15/3-25/5 mg/kg/day in 1 dose, 3 times a week on consecutive days.
Adults: 480 mg once per day.

Number of subjects in period 2	Challenge phase
Started	73
Run-in phase completion	67
Completed	67
Not completed	6
On patients request not complete first three month	3
Non-compliance	2
Lost to follow-up	1

Period 3	
Period 3 title	Dechallenge phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms	
Arm title	Dechallenge phase
Arm description:	
Follow-up phase consisting of monthly phone calls	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 3	Dechallenge phase
Started	67
Completion of Challenge phase	67
Completed	67

Period 4	
Period 4 title	Rechallenge phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms	
Arm title	Rechallenge phase
Arm description:	
If patients experienced return of (pain)symptoms due to their vascular malformation during Dechallenge phase, patients restarted with sirolimus using low target levels of 4-10 ng/mL for a period of 12 months (Rechallenge phase).	
Arm type	Experimental
Investigational medicinal product name	Sirolimus
Investigational medicinal product code	
Other name	Rapamune
Pharmaceutical forms	Oral solution in bottle, Tablet
Routes of administration	Oral use
Dosage and administration details:	
0.8 mg/m2 for children as start dose, 2dd1 mg as start dose for adults. Target trough levels 4-10 ng/mL	
Investigational medicinal product name	Cotrimoxazole
Investigational medicinal product code	
Other name	Bactrimel, sulfamethoxazol/trimethoprim
Pharmaceutical forms	Oral suspension, Tablet
Routes of administration	Oral use
Dosage and administration details:	
Children: 15/3-25/5 mg/kg/day in 1 dose, 3 times a week on consecutive days. Adults: 480 mg once per day.	

Number of subjects in period 4[1]	Rechallenge phase
Started	34
Return of symptoms	33
Completed	23
Not completed	12
End of study	12
Joined	1
Turned to age of 1 year during study	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: In total 32 patients did not restarted.

Baseline characteristics

Reporting groups	
Reporting group title	Screenings phase

Reporting group description: -

Reporting group values	Screenings phase	Total	
Number of subjects	74	74	
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)	3	3	
Children (2-11 years)	21	21	
Adolescents (12-17 years)	12	12	
Adults (18-64 years)	38	38	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	23		
standard deviation	± 16.3	-	
Gender categorical Units: Subjects			
Female	49	49	
Male	25	25	
Vascular malformation type Units: Subjects			
Lymphatic malformation	27	27	
Venous malformation	33	33	
Combined malformation	12	12	
Other	2	2	
Mutation type Units: Subjects			
No mutation found	9	9	
Activating PIK3CA mutation	23	23	
Activating TEK mutation	3	3	
Activating PTEN mutation	1	1	
Activating IDH1 mutation	1	1	
Combined activating mutation	1	1	
Measurement failed	2	2	
No DNA diagnostics done	34	34	

Subject analysis sets	
Subject analysis set title	Challenge phase
Subject analysis set type	Full analysis
Subject analysis set description: Amount of patients who completed the Challenge phase.	
Subject analysis set title	Children
Subject analysis set type	Sub-group analysis
Subject analysis set description: To investigate differences in children and adults at Baseline and after Challenge phase.	
Subject analysis set title	Adults
Subject analysis set type	Sub-group analysis
Subject analysis set description: To investigate the characteristics and outcomes in adults	

Reporting group values	Challenge phase	Children	Adults
Number of subjects	67	32	35
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)	3	3	0
Children (2-11 years)	18	18	0
Adolescents (12-17 years)	11	11	0
Adults (18-64 years)	35	0	35
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	23.3	9.5	36
standard deviation	± 16.3	± 4.7	± 12.4
Gender categorical Units: Subjects			
Female	43	23	20
Male	24	9	15
Vascular malformation type Units: Subjects			
Lymphatic malformation	25	16	9
Venous malformation	29	13	16
Combined malformation	11	2	9
Other	2	1	1
Mutation type Units: Subjects			
No mutation found	9	3	6
Activating PIK3CA mutation	20	13	7
Activating TEK mutation	3	1	2
Activating PTEN mutation	1	1	0
Activating IDH1 mutation	1	1	0
Combined activating mutation	1	0	1
Measurement failed	2	2	0

No DNA diagnostics done	30	11	19

End points

End points reporting groups

Reporting group title	Screening
Reporting group description:	
Two months period of daily record of pain scores. Pain was recorded using the CHIPPS-scale, (Children and Infants Postoperative Pain Scale) for children aged 0–3 years, visual analogue scale (VAS) clinical pictures for children aged 4–7 years, VAS for patients aged 8–17 years, and numeric pain rating scale (NRS) for adults. No medication is used.	
Reporting group title	Challenge phase
Reporting group description:	
Six months treatment with sirolimus and co-trimoxazole profylaxis. Open-label single arm.	
Reporting group title	Dechallenge phase
Reporting group description:	
Follow-up phase consisting of monthly phone calls	
Reporting group title	Rechallenge phase
Reporting group description:	
If patients experienced return of (pain)symptoms due to their vascular malformation during Dechallenge phase, patients restarted with sirolimus using low target levels of 4-10 ng/mL for a period of 12 months (Rechallenge phase).	
Subject analysis set title	Challenge phase
Subject analysis set type	Full analysis
Subject analysis set description:	
Amount of patients who completed the Challenge phase.	
Subject analysis set title	Children
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
To investigate differences in children and adults at Baseline and after Challenge phase.	
Subject analysis set title	Adults
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
To investigate the characteristics and outcomes in adults	

Primary: Pain reduction

End point title	Pain reduction
End point description:	
Daily pain scores	
End point type	Primary
End point timeframe:	
In total 8 months: 2 months of Baseline and 6 months Challenge phase	

End point values	Challenge phase	Children	Adults	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	52	32[1]	35[2]	
Units: Number of responders				
Increase of pain	2	0	2	
No change in pain	0	0	0	
Decrease of pain	25	11	14	

No pain due to VM	13	14	17	
No (complete) dairy	12	7	1	

Notes:

[1] - Responded children and completed dairy

[2] - Responded adults and completed dairy

Statistical analyses

Statistical analysis title	Daily pain scores
Comparison groups	Children v Adults
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Mixed models analysis

Secondary: Return of pain(symptoms)

End point title	Return of pain(symptoms)

End point description:

Monthly phone calls, if level of pain or symptoms related to the vascular malformation returned to the level of baseline.

End point type	Secondary

End point timeframe:

During 12 months follow-up visit

End point values	Dechallenge phase	Children	Adults	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	44	25	19	
Units: Number of responded patients				
No recurrence of symptoms	37	3	4	
Recurrence of symtpoms	7	22	15	

Statistical analyses

Statistical analysis title	Recurrence of pain

Statistical analysis description:

Differences between children and adults in terms of recurrence of symptoms.

Comparison groups	Children v Adults

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Chi-squared

Secondary: Reduction of malformation size

End point title	Reduction of malformation size

End point description:

MRI at baseline was compared with MRI at end of Challenge

End point type	Secondary

End point timeframe:

6 months

End point values	Challenge phase	Children	Adults	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	62[3]	32	35	
Units: amount of patients				
Decrease of volume	22	12	10	
No change	38	19	19	
Increase of volume	2	0	2	

Notes:

[3] - In total 5 patients had no MRI

Statistical analyses

Statistical analysis title	Differences in change volume per child/adult
Comparison groups	Children v Adults
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Chi-squared

Secondary: Genetic factors

End point title	Genetic factors

End point description:

During Challenge phase, respons after six months

End point type	Secondary

End point timeframe:

6 months

End point values	Challenge phase	Children	Adults	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	20[4]	13	7	
Units: amount responders with PIK3CA mutation				
Responder	14	11	3	
No responder	6	2	4	

Notes:

[4] - In all patients with a PIK3mutation

Statistical analyses

Statistical analysis title	Differences in PIK3CA mutation and children adults
Comparison groups	Children v Adults
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Chi-squared

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Since start of Challenge phase untill end of study.

Adverse event reporting additional description:

Adverse events were reported and assessed according to the Common Terminology Criteria for Adverse Events 4.03.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	Included patients

Reporting group description: -

Serious adverse events	Included patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 74 (13.51%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Laboratory test abnormal	Additional description: Increased liver enzymes, decreased phosphate		
subjects affected / exposed	4 / 74 (5.41%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Bleeding			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastroenteritis			
subjects affected / exposed	2 / 74 (2.70%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiration abnormal	Additional description: Hypoxic arrest, pneumonia, sinusitis		

subjects affected / exposed	3 / 74 (4.05%)		
occurrences causally related to treatment / all	4 / 5		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infection	Additional description: Sepsis, viral infections, cellulitis		
subjects affected / exposed	4 / 74 (5.41%)		
occurrences causally related to treatment / all	4 / 6		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Included patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	74 / 74 (100.00%)		
Investigations			
Laboratory test abnormal	Additional description: Independed of relationship with sirolimus		
subjects affected / exposed	23 / 74 (31.08%)		
occurrences (all)	31		
Nervous system disorders			
Headache	Additional description: Independed of relationship with sirolimus		
subjects affected / exposed	27 / 74 (36.49%)		
occurrences (all)	45		
Blood and lymphatic system disorders			
Neutropenia	Additional description: Independed of relationship with sirolimus		
subjects affected / exposed	11 / 74 (14.86%)		
occurrences (all)	11		
General disorders and administration site conditions			
Fatigue	Additional description: Independed of relationship with sirolimus		
subjects affected / exposed	26 / 74 (35.14%)		
occurrences (all)	35		
Immune system disorders			
Leukopenia	Additional description: Independed of relationship with sirolimus		
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	6		
Gastrointestinal disorders			

Abdominal pain	Additional description: Independed of relationship with sirolimus		
subjects affected / exposed	10 / 74 (13.51%)		
occurrences (all)	16		
Aphtosous	Additional description: Independent of relationship with sirolimus		
subjects affected / exposed	44 / 74 (59.46%)		
occurrences (all)	64		
Diarrhoea	Additional description: Independent of relationship with sirolimus		
subjects affected / exposed	12 / 74 (16.22%)		
occurrences (all)	14		
Gastroenteritis	Additional description: Independent of relationship with sirolimus		
subjects affected / exposed	18 / 74 (24.32%)		
occurrences (all)	21		
Nausea			
subjects affected / exposed	12 / 74 (16.22%)		
occurrences (all)	12		
Respiratory, thoracic and mediastinal disorders			
Upper respiratory tract infection	Additional description: Independed of relationship with sirolimus		
subjects affected / exposed	40 / 74 (54.05%)		
occurrences (all)	69		
Skin and subcutaneous tissue disorders			
Erythema	Additional description: Erythematous eruption with papules, acnei forme eruption Independed of relationship with sirolimus		
subjects affected / exposed	12 / 74 (16.22%)		
occurrences (all)	18		
Xerosis	Additional description: Independed of relationship with sirolimus		
subjects affected / exposed	8 / 74 (10.81%)		
occurrences (all)	9		
Oedema	Additional description: Independed of relationship with sirolimus		
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	9		
Endocrine disorders			
Menstrual disorder	Additional description: Independed of relationship with sirolimus		
subjects affected / exposed	8 / 74 (10.81%)		
occurrences (all)	11		
Musculoskeletal and connective tissue disorders			

Myalgia	Additional description: Independed of relationship with sirolimus		
subjects affected / exposed	8 / 74 (10.81%)		
occurrences (all)	8		
Infections and infestations			
Infection	Additional description: Independed of relationship with sirolimus		
subjects affected / exposed	50 / 74 (67.57%)		
occurrences (all)	64		
Metabolism and nutrition disorders			
Appetite disorder	Additional description: Decreased appetite - independed of relationship with sirolimus		
subjects affected / exposed	6 / 74 (8.11%)		
occurrences (all)	6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 March 2019	Due to the high quantity of children with low flow malformations, the number of children included will be higher. Instead of 20 children a maximum of 35 children will be inlcuded. Minor changes have been made by the protocol to (correct errors and/or) improve the overall clarity of the original protocol. These adjustments do not affect the safety, exposure or overall study design.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported