Clinical trial results:
Pilot dose conversion study of extended release tacrolimus, Envarsus from standard twice daily tacrolimus in paediatric renal transplant recipients.

Summary

EudraCT number	2018-003595-13
Trial protocol	GB
Global end of trial date	31 January 2023

Results information

Result version number	v1 (current)
This version publication date	08 February 2024
First version publication date	08 February 2024
Summary attachment (see zip file)	Abstract (Pharmacokinetics of Envarsus in paediatric kidney transplant recipients Abstract EudraCT.pdf)

Trial information

Trial identification

Sponsor protocol code	17CS079

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Nottingham University Hospitals NHS Trust
Sponsor organisation address	Derby Road, Nottingham, United Kingdom, NG7 2UH
Public contact	Dr Jon Jin Kim, Nottingham University Hospitals NHS Trust, jonjin.kim@nuh.nhs.uk
Scientific contact	Dr Jon Jin Kim, Nottingham University Hospitals NHS Trust, jonjin.kim@nuh.nhs.uk

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	20 October 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 January 2023
Global end of trial reached?	Yes
Global end of trial date	31 January 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This pilot study aims to provide dosing guidelines for the conversion of twice daily preparations of tacrolimus to Envarsus. To do this, we will compare pharmacokinetics of Envarsus to standard twice daily tacrolimus. The following values will be obtained:

1) Maximum concentration (Cmax)
2) Time to maximum concentration (Tmax)
3) 24 hour area under the curve (AUC)

Protection of trial subjects:

Participants complied with the study protocol.
Serious adverse events were reported and assessed according to stipulated time frames.
Study was monitored by the data monitoring committee.

Background therapy:

Patients continued all other concomittent medication including other immunosuppression as directed by the medical care team.

Evidence for comparator: -

Actual start date of recruitment	20 January 2020
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	United Kingdom: 5
Worldwide total number of subjects	5
EEA total number of subjects	0

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)	5
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

13 patients were screened and 7 patients consented.
2 patients did not proceed to the trial:
1 patient passed the age of 18 when the trial was paused during COVID-19 pandemic.
1 patient (under 11 years of age) developed unstable kidney function before any trial procedures (other than consenting) and did not start the study.

Pre-assignment

Screening details:

13 patients were screened by the direct care medical team based on review of hospital records.

Period 1

Period 1 title	Twice daily tacrolimus
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Twice daily tacrolimus
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Tacrolimus (immediate release)
Investigational medicinal product code	
Other name	Adoport
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Baseline dose based on current management by direct care team.

Number of subjects in period 1	Twice daily tacrolimus
Started	5
Completed	5

Period 2

Period 2 title	Extended release tacrolimus
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Extended release tacrolimus
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Tacrolimus, prolonged release
Investigational medicinal product code	L04AD02
Other name	Envarsus
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants switched from twice daily tacrolimus to prolonged release tacrolimus based on the total daily dose ratio of 1:0.7 respectively.

Number of subjects in period 2	Extended release tacrolimus
Started	5
Completed	5

Baseline characteristics

Reporting groups	
Reporting group title	Twice daily tacrolimus

Reporting group description: -

Reporting group values	Twice daily tacrolimus	Total	
Number of subjects	5	5	
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			
Age at study entry			
Units: years			
median	15		
full range (min-max)	11 to 17	-	
Gender categorical Units: Subjects			
Female	4	4	
Male	1	1	
Time post-transplant Units: Years			
median	5		
full range (min-max)	1 to 11	-	

End points

End points reporting groups

Reporting group title	Twice daily tacrolimus
Reporting group description: -	
Reporting group title	Extended release tacrolimus
Reporting group description: -	

Primary: Maximum concentration (Cmax)

End point title	Maximum concentration (Cmax)[1]
End point description:	
End point type	Primary
End point timeframe:	
Pharmacokinetic study was performed at baseline on twice daily tacrolimus and after stable drug levels on extended release tacrolimus.	
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: No statistical comparisons were performed (as stated in the protocol) as this was a pilot study.	

End point values	Twice daily tacrolimus	Extended release tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: ng/ml				
geometric mean (geometric coefficient of variation)	14.4 (± 46.9)	9.9 (± 49.3)		

Statistical analyses

No statistical analyses for this end point

Primary: Time to maximum concentration (Tmax)

End point title	Time to maximum concentration (Tmax)[2]
End point description:	
End point type	Primary
End point timeframe:	
As previous	
Notes:	
[2] - 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: No statistical comparisons were performed (as stated in the protocol) as this was a pilot study.	

End point values	Twice daily tacrolimus	Extended release tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: ng/ml				
median (full range (min-max))	1 (1 to 4)	5 (3 to 8)		

Statistical analyses

No statistical analyses for this end point

Primary: Area under the curve (24 hour)

End point title	Area under the curve (24 hour)[3]

End point description:

End point type	Primary

End point timeframe:

As previous

Notes:

[3] - 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: No statistical comparisons were performed (as stated in the protocol) as this was a pilot study.

End point values	Twice daily tacrolimus	Extended release tacrolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: ng/ml				
geometric mean (geometric coefficient of variation)	164 (± 27.8)	141 (± 46.5)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Patients were followed up for 6 months after conversion.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25

Reporting groups

Reporting group title	Post conversion to prolonged release formulation

Reporting group description: -

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No non-serious adverse reports (new or worsening of symptoms) were reported by subjects. There were no episodes of rejection or worsening of kidney function, though these were prespecified in the protocol as not included in the adverse event reporting as they ar part of the secondary study outcomes.

Serious adverse events	Post conversion to prolonged release formulation		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 5 (20.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Renal and urinary disorders			
Paraphimosis	Additional description: Self-admission to hospital for episode of para-phimosis.		
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Post conversion to prolonged release formulation		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)		

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
23 March 2020	Study was paused due to COVID-19.	09 September 2020

Notes:

Limitations and caveats

None reported