

**Clinical trial results:**

**A PILOT, PHASE II STUDY WITH A PROSPECTIVE, RANDOMIZED, CROSS-OVER, PLACEBO-CONTROLLED, DOUBLE-BLIND DESIGN TO ASSESS THE SHORT-TERM EFFECTS OF TOLVAPTAN PLUS PLACEBO VS TOLVAPTAN PLUS OCTREOTIDE LAR COMBINATION THERAPY IN ADPKD PATIENTS WITH NORMAL KIDNEY FUNCTION OR HYPERFILTRATION**

**Summary**

EudraCT number	2017-004701-40
Trial protocol	IT
Global end of trial date	08 April 2022

**Results information**

Result version number	v1 (current)
This version publication date	04 June 2023
First version publication date	04 June 2023
Summary attachment (see zip file)	Article (TOOL_Study.pdf) Supplemental material (TOOL_Supplemental material.pdf)

**Trial information****Trial identification**

Sponsor protocol code	TOOL
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**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03541447
WHO universal trial number (UTN)	-

Notes:

**Sponsors**

Sponsor organisation name	Istituto di Ricerche Farmacologiche Mario Negri IRCCS
Sponsor organisation address	Via G.B. Camozzi 3, Ranica, Italy,
Public contact	UOC Regulatory, Ethical and Legal Affairs, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, 035 0354535308, nadia.rubis@marionegri.it
Scientific contact	UOC Regulatory, Ethical and Legal Affairs, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, +39 0354535308, nadia.rubis@marionegri.it

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 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 April 2022
Global end of trial reached?	Yes
Global end of trial date	08 April 2022
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the effect of 4-week Tolvaptan and Octreotide LAR combination therapy as compared to Tolvaptan and Placebo combination therapy on GFR, as assessed by the Iohexol Plasma Clearance Technique, in 20 ADPKD patients with normal kidney function (GFR: >80 and <120 ml/min/1.73m<sup>2</sup>) or hyperfiltration (GFR >120 ml/min/1.73m<sup>2</sup>).

Protection of trial subjects:

This study was conducted in conformance with the Declaration of Helsinki, Good Clinical Practice standards, and applicable country regulations regarding ethical committee review, informed consent, protection of human subjects participating in biomedical research, and privacy.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2018
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	Italy: 19
Worldwide total number of subjects	19
EEA total number of subjects	19

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)	19

From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

#### Recruitment details:

Overall, 75 potentially eligible patients were identified and referred to the Clinical Research Center: 34 signed the written informed consent to study participation. Then, 22 eligible patients entered the run-in phase between January 22, 2019, and July 2, 2021 and 20 were finally randomized: ten to each treatment sequence.

### Pre-assignment

#### Screening details:

Potentially eligible patients were identified from the database of the ADPKD Outpatient Clinics of the Unit of Nephrology of the ASST and were referred to the Clinical Research Center for Rare Diseases Aldo e Cele Daccò of the Istituto di Ricerche Farmacologiche Mario Negri IRCCS in Ranica (Italy).

### Period 1

Period 1 title	First treatment period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

### Arms

Arm title	Tolvaptan-Placebo
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#### Arm description:

All patients received a first 4-week treatment period with tolvaptan. Tolvaptan was started at the dose of 45 mg in the morning and 15 mg in the afternoon. Then, morning and afternoon doses were up-titrated every 2 days to 60 and 30 mg and then to 90 and 30 mg, respectively, according to tolerability. By completion of this 4-week titration period, participants were randomly allocated using a 1:1 randomization ratio to 4-week treatment periods with tolvaptan. During these two treatment periods, tolvaptan was administered at the maintenance dose achieved at the end of the titration period. According to the randomization plan, at the start of one of the two treatment periods, tolvaptan was combined with two 20-mg i.m. injections of octreotide- LAR, whereas at the start of the other treatment period, tolvaptan was combined with two i.m. injections of 0.9% NaCl solution (placebo for octreotide-LAR).

Arm type	Placebo
Investigational medicinal product name	0.9% NaCl
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

#### Dosage and administration details:

Two i.m. injections of 0.9% NaCl solution (placebo for octreotide-LAR).

Investigational medicinal product name	Tolvaptan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

#### Dosage and administration details:

All patients received a first 4-week treatment period with tolvaptan. Tolvaptan was started at the dose of 45 mg in the morning and 15 mg in the afternoon. Then, morning and afternoon doses were up-titrated every 2 days to 60 and 30 mg and then to 90 and 30 mg, respectively, according to tolerability.

<b>Number of subjects in period 1</b>	Tolvaptan-Placebo
Started	19
Completed	19

## Period 2

Period 2 title	Second treatment period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

## Arms

<b>Arm title</b>	Tolvaptan-Octreotide LAR
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### Arm description:

All patients received a first 4-week treatment period with tolvaptan. Tolvaptan was started at the dose of 45 mg in the morning and 15 mg in the afternoon. Then, morning and afternoon doses were up-titrated every 2 days to 60 and 30 mg and then to 90 and 30 mg, respectively, according to tolerability. By completion of this 4-week titration period, participants were randomly allocated using a 1:1 randomization ratio to 4-week treatment periods with tolvaptan. During these two treatment periods, tolvaptan was administered at the maintenance dose achieved at the end of the titration period. According to the randomization plan, at the start of one of the two treatment periods, tolvaptan was combined with two 20-mg i.m. injections of octreotide-LAR, whereas at the start of the other treatment period, tolvaptan was combined with two i.m. injections of 0.9% NaCl solution (placebo for octreotide-LAR).

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

### Dosage and administration details:

All patients received a first 4-week treatment period with tolvaptan. Tolvaptan was started at the dose of 45 mg in the morning and 15 mg in the afternoon. Then, morning and afternoon doses were up-titrated every 2 days to 60 and 30 mg and then to 90 and 30 mg, respectively, according to tolerability.

Investigational medicinal product name	Octreotide LAR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intramuscular use

### Dosage and administration details:

Two 20-mg i.m. injections of octreotide-LAR

<b>Number of subjects in period 2</b>	Tolvaptan- Octreotide LAR
Started	19
Completed	19

## Baseline characteristics

### Reporting groups

Reporting group title	First treatment period
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Reporting group description: -

Reporting group values	First treatment period	Total	
Number of subjects	19	19	
Age categorical			
Units: Subjects			
Adults (18-64 years)	19	19	
Age continuous			
Units: years			
arithmetic mean	41		
standard deviation	± 12	-	
Gender categorical			
Units: Subjects			
Female	9	9	
Male	10	10	
Diabetes			
Units: Subjects			
Diabetes	7	7	
Non diabetes	12	12	
Smoke			
Units: Subjects			
Current smokers	8	8	
Never smoked	7	7	
Former smokers	4	4	
Mayo class			
Units: Subjects			
1A	2	2	
1B	4	4	
1C	5	5	
1D	7	7	
1E	1	1	
BMI			
Units: kg/m2			
arithmetic mean	24.2		
standard deviation	± 3.6	-	
Systolic BP			
Units: mm Hg			
arithmetic mean	128		
standard deviation	± 8	-	
Diastolic BP			
Units: mm Hg			
arithmetic mean	82		
standard deviation	± 7	-	
Heart rate			

Units: bpm arithmetic mean standard deviation	67 ± 11	-	
Creatinine Units: md/dl arithmetic mean standard deviation	0.9 ± 0.1	-	
Glomerular Filtration rate			
By Iohexol plasma clearance			
Units: ml/min/1.73m2 arithmetic mean standard deviation	85.13 ± 13	-	
Renal blood flow Units: ml/min/1.73m2 arithmetic mean standard deviation	707 ± 211	-	
Renal plasmna flow Units: ml/min/1.73m2 arithmetic mean standard deviation	431 ± 110	-	
Renal vascular resistance Units: dynXs/cm5 median inter-quartile range (Q1-Q3)	11.675 9.967 to 14.621	-	
Total Kidney Volume Units: ml median inter-quartile range (Q1-Q3)	1142 850 to 1859	-	
Cystic kidney volume Units: ml median inter-quartile range (Q1-Q3)	738 407 to 1413	-	
24 H urine protein Units: g/24H median inter-quartile range (Q1-Q3)	0.1 0.06 to 0.13	-	
24H Urine albumin Units: ug/min median inter-quartile range (Q1-Q3)	14 6 to 24	-	
24 H Urine sodium Units: mEq/24H arithmetic mean standard deviation	149 ± 57	-	
24H Urine potassium Units: mEq/24H arithmetic mean standard deviation	62 ± 21	-	
24H Urine urea Units: g/24H arithmetic mean standard deviation	25 ± 8	-	

24H Urine creatinine Units: mg/24H arithmetic mean standard deviation	1540 ± 423	-	
Phospahte Units: mg/dl arithmetic mean standard deviation	3.2 ± 0.4	-	
Calcium Units: mg/dl arithmetic mean standard deviation	9 ± 0.2	-	
Sodium Units: mEq/dl arithmetic mean standard deviation	139 ± 2	-	
Potassium Units: mEq/dl arithmetic mean standard deviation	3.8 ± 0.3	-	
Glucose Units: mg/dl arithmetic mean standard deviation	88 ± 7	-	
Protein Units: g/dl arithmetic mean standard deviation	6.6 ± 0.4	-	
Total cholesterol Units: mg/dl arithmetic mean standard deviation	176 ± 33	-	
LDL Units: mg/dl arithmetic mean standard deviation	113 ± 30	-	
HDL Units: mg/dl arithmetic mean standard deviation	50 ± 13	-	
Triglycerides Units: mg/dl arithmetic mean standard deviation	80 ± 41	-	
Albumin Units: g/dl arithmetic mean standard deviation	3.8 ± 0.2	-	
Hemoglobin Units: g/dl arithmetic mean standard deviation	12.7 ± 1.4	-	



## End points

### End points reporting groups

Reporting group title	Tolvaptan-Placebo
Reporting group description:	
All patients received a first 4-week treatment period with tolvaptan. Tolvaptan was started at the dose of 45 mg in the morning and 15 mg in the afternoon. Then, morning and afternoon doses were up-titrated every 2 days to 60 and 30 mg and then to 90 and 30 mg, respectively, according to tolerability. By completion of this 4-week titration period, participants were randomly allocated using a 1:1 randomization ratio to 4-week treatment periods with tolvaptan. During these two treatment periods, tolvaptan was administered at the maintenance dose achieved at the end of the titration period. According to the randomization plan, at the start of one of the two treatment periods, tolvaptan was combined with two 20-mg i.m. injections of octreotide- LAR, whereas at the start of the other treatment period, tolvaptan was combined with two i.m. injections of 0.9% NaCl solution (placebo for octreotide-LAR).	
Reporting group title	Tolvaptan-Octreotide LAR
Reporting group description:	
All patients received a first 4-week treatment period with tolvaptan. Tolvaptan was started at the dose of 45 mg in the morning and 15 mg in the afternoon. Then, morning and afternoon doses were up-titrated every 2 days to 60 and 30 mg and then to 90 and 30 mg, respectively, according to tolerability. By completion of this 4-week titration period, participants were randomly allocated using a 1:1 randomization ratio to 4-week treatment periods with tolvaptan. During these two treatment periods, tolvaptan was administered at the maintenance dose achieved at the end of the titration period. According to the randomization plan, at the start of one of the two treatment periods, tolvaptan was combined with two 20-mg i.m. injections of octreotide-LAR, whereas at the start of the other treatment period, tolvaptan was combined with two i.m. injections of 0.9% NaCl solution (placebo for octreotide-LAR).	

### Primary: Primary Comparison GFR

End point title	Primary Comparison GFR
End point description:	
The GFR was stable (Delta GFR: 0 [25 to 4] ml/min per 1.73 m <sup>2</sup> ) during the 1-month run-in period whereas it significantly decreased by 3 (21 to 5) ml/min per 1.73 m <sup>2</sup> during the 1-month tolvaptan and placebo treatment period (P=0.01) and by 7 (3–14) ml/min per 1.73 m <sup>2</sup> during the 1-month dual treatment period (P=0.03). GFR changes during the two treatment periods differed by 2 (25 to 14) ml/min per 1.73 m <sup>2</sup> . The difference, however, was not significant (P=0.28).	
End point type	Primary
End point timeframe:	
Baseline compared to 1 month after Tolvaptan and Octreotide–Long-Acting Release and Tolvaptan and Placebo	

End point values	Tolvaptan-Placebo	Tolvaptan-Octreotide LAR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: ml/min per 1.73m <sup>2</sup>				
arithmetic mean (standard deviation)				
Pre	83 (± 13)	85 (± 15)		
Post	79 (± 14)	78 (± 12)		

## Statistical analyses

<b>Statistical analysis title</b>	Primary comparisons endpoint
Statistical analysis description: The primary and secondary efficacy variables of this cross-over study were analyzed by paired t test (or Wilcoxon signed-rank test, in case of departure from normality assumptions) and, in a multivariable, exploratory approach, by using a linear mixed model for repeated measures (PROC MIXED, SAS version 9.2; SAS Institute Inc., Cary, NC), with sequence, period, and treatment as fixed effects and participant as random effect.	
Comparison groups	Tolvaptan-Placebo v Tolvaptan-Octreotide LAR
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.28 <sup>[1]</sup>
Method	unpaired t-test

Notes:

[1] -  $H_0 : \text{diff} = 0$

where  $\text{diff} = \text{delta1} - \text{delta2}$ ,

$\text{delta1} = \text{GFR 1 month octreotide} - \text{GFR baseline octreotide}$

$\text{delta2} = \text{GFR 1 month placebo} - \text{GFR baseline placebo}$ .

## Primary: Coprimary Comparisons GFR

End point title	Coprimary Comparisons GFR
End point description: During the first week treatment period, the GFR significantly decreased by 3 (0–7) ml/min per 1.73 m <sup>2</sup> with tolvaptan and placebo therapy (P=0.006) and by 10 (26 to 16) ml/min per 1.73 m <sup>2</sup> with dual therapy (P,0.001). Both changes significantly differed from the GFR changes were observed during the run-in period (P=0.03 and P=0.001, respectively). Notably, the GFR reduction achieved by tolvaptan and octreotide-LAR add-on therapy exceeded the reduction achieved by tolvaptan and placebo by 3 (0–12) ml/min per 1.73 m <sup>2</sup> (Figure 1B), and the excess reduction was statistically significant (P=0.01).	
End point type	Primary
End point timeframe: Baseline compared to 1 week after Tolvaptan and Octreotide–Long-Acting Release and Tolvaptan and Placebo	

End point values	Tolvaptan-Placebo	Tolvaptan-Octreotide LAR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: ml/min per 1.73m <sup>2</sup>				
arithmetic mean (standard deviation)				
Pre	83 (± 13)	85 (± 13)		
Post	78 (± 13)	75 (± 11)		

## Statistical analyses

<b>Statistical analysis title</b>	Coprimary comparisons endpoint
Comparison groups	Tolvaptan-Octreotide LAR v Tolvaptan-Placebo

Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01 <sup>[2]</sup>
Method	unpaired t-test

Notes:

[2] - H0 : diff = 0

where diff = delta1-delta2,

delta1 = GFR 1 week octreotide - GFR baseline octreotide

delta2 = GFR 1 week placebo - GFR baseline placebo.

## Secondary: Total Kidney Volume TKV

End point title	Total Kidney Volume TKV
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End point description:

TKV nonsignificantly decreased by 4 (-23 to 48) ml during the 1-month tolvaptan and placebo treatment period (P50.73), whereas it decreased significantly by 41 (25-77) ml during the 1-month treatment period with tolvaptan and octreotide-LAR (P <.001). TKV changes during the two treatment periods differed by 39.1613.3 ml, and the difference was statistically significant (P=0.01). Similar results were obtained by measuring height-adjusted TKV (data not shown). Changes in cystic kidney volume paralleled changes in TKV.

End point type	Secondary
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End point timeframe:

Baseline compared to 1 week after Tolvaptan and Octreotide-Long-Acting Release and Tolvaptan and Placebo

End point values	Tolvaptan- Placebo	Tolvaptan- Octreotide LAR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: ml				
arithmetic mean (standard deviation)				
Pre	1318 (± 623)	1295 (± 623)		
Post	1313 (± 625)	1185 (± 519)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Cystics Kidney Volume (CKV)

End point title	Cystics Kidney Volume (CKV)
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End point description:

End point type	Secondary
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End point timeframe:

Baseline compared to 1 week after Tolvaptan and Octreotide-Long-Acting Release and Tolvaptan and Placebo

<b>End point values</b>	Tolvaptan- Placebo	Tolvaptan- Octreotide LAR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: ml				
arithmetic mean (standard deviation)				
Pre	889 (± 557)	836 (± 505)		
Post	883 (± 545)	737 (± 452)		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

The adverse events will be reported during whole study up to 30 days after last dose of study drug.

Adverse event reporting additional description:

Regarding the non-serious adverse event please refer to table 3 of the article attached

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.1
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### Reporting groups

Reporting group title	Overall
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Reporting group description: -

Serious adverse events	Overall		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 19 (15.79%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Elevated transaminase levels			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Elevated CPK levels			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 19 (5.26%)		
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 %

<b>Non-serious adverse events</b>	Overall		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 19 (100.00%)		
Renal and urinary disorders			
Polyuria			
subjects affected / exposed	19 / 19 (100.00%)		
occurrences (all)	19		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 November 2020	Changing in inclusion/exclusion criteria due to recruitment slow rate

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/36754009>