Clinical trial results:
A Double-Blind, Placebo-Controlled, Randomized, Phase Ib/IIa Clinical Study of ApTOLL for the Treatment of Acute Ischemic Stroke

Summary

EudraCT number	2020-002059-38
Trial protocol	FR DE PT
Global end of trial date	22 July 2022

Results information

Result version number	v1 (current)
This version publication date	08 October 2023
First version publication date	08 October 2023

Trial information

Trial identification

Sponsor protocol code	APRIL

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04734548
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AptaTargets S.L.
Sponsor organisation address	Av. Cardenal Herrera Oria 298, Madrid, Spain, 28035
Public contact	CFO and Legal Manager, AptaTargets S.L, 34 34910568359, m.zarabozo@aptatargets.com
Scientific contact	Associate Professor, AptaTargets S.L, 34 910568359, m.hernandez@aptatargets.com

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	22 July 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 July 2022
Global end of trial reached?	Yes
Global end of trial date	22 July 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate if administering ApTOLL intravenously (IV) at ascending doses is safe and well tolerated compared to placebo when administered with endovascular therapy (EVT) ± IV recombinant tissue Plasminogen Activator (rt-PA) in the acute ischemic stroke (AIS) target population.

Protection of trial subjects:

Prior to the dosing, patients and/or legal representatives must receive oral and written information concerning the study. If they subsequently agree to participate, they or their legal representatives must sign the informed consent form, under the awareness of their ability to withdraw from the study at any time and for any reason.
The subjects will receive instructions from the investigators which must be followed strictly. Informed consent must be signed by the patient or their authorized legal representative before any study specific treatment is performed.
Patients will receive standard ESO guidelines directed medical therapy, which can include IV rt-PA infusion in patients presenting within the first 4.5 hours from last-seen-normal and meeting other ESO label criteria. Post-tPA patients will be treated based on standard study site protocols for these patients.
In all patients, endovascular thrombectomy will be initiated (groin puncture) after randomization and administration of the study drug. EVT should be initiated within 8 hours from symptoms onset.
Individual investigators may use any approved device or any combination of devices to remove thrombus. If there is severe stenosis of the common carotid artery or the proximal internal carotid artery, investigators may also use devices for angioplasty or for stenting of the carotid artery as deemed appropriate.
The study will be conducted in accordance with legal normative and regulations, and with the general principles outlined in the International Ethical Guidelines for Biomedical research in humans. In addition, the study will be performed according to the protocol, GCP guideline and the ICH requirements and applicable local laws.
Any individual patient or family member complaints regarding adverse events or morbidity will be handled locally by each institution’s patient safety centre.

Background therapy:

EVT ± IV recombinant tissue Plasminogen Activator (rt-PA)

Evidence for comparator:

Standard of Care

Actual start date of recruitment	07 November 2020
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	Spain: 143
Country: Number of subjects enrolled	France: 8
Worldwide total number of subjects	151
EEA total number of subjects	151

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)	44
From 65 to 84 years	86
85 years and over	21

Subject disposition

Recruitment

Recruitment details:

The first patient was included in the study on November 7, 2020. The last patient was included on April 22, 2022. The last patient last visit was completed on July 22, 2022.

Pre-assignment

Screening details:

Men and non-pregnant women with confirmed Acute Ischemic Stroke with Large Vessel Occlusion in the anterior circulation, defined as per EU-US guidelines, with a <6h window from onset of symptoms to drug administration, who were candidates to receive EVT treatment.

Period 1

Period 1 title	Phase Ib & IIa (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

In Phase Ib, four dose levels were performed, and eligible patients were randomized into ApTOLL plus EVT vs. Placebo plus EVT at 3:1 ratio, at every dose level.
In Phase IIa the randomization algorithm followed the Dunnet's random allocation procedure of square root (number of groups - 1), which assigns patients with the following frequency to placebo, active A and active B: √2 :1:1, which, in turn, yields a probability of assignment of 0.41, 0.29 and 0.29, respectively.

Arms

Are arms mutually exclusive?	Yes
Arm title	ApTOLL

Arm description:

Phase Ib: ApTOLL (0.025 – 0.2 mg/Kg) 30min IV infusion.
Phase IIa: ApTOLL (0.05 mg/Kg [Dose A] and 0.2 mg/Kg [Dose B]) 30min IV infusion.

Arm type	Experimental
Investigational medicinal product name	ApTOLL
Investigational medicinal product code	PRD10291571
Other name	Aptamer 4FT
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

One single 30 min IV infusion prior to thrombectomy.

Arm title	Placebo

Arm description:

Phase Ib & IIa: Placebo 30min IV infusion.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intracavernous use

Dosage and administration details:

One single 30 min IV infusion prior to thrombectomy.

Number of subjects in period 1	ApTOLL	Placebo
Started	96	55
Completed	83	43
Not completed	13	12
Adverse event, serious fatal	13	10
Consent withdrawn by subject	-	2

Baseline characteristics

Reporting groups	
Reporting group title	ApTOLL
Reporting group description:	
Phase Ib: ApTOLL (0.025 – 0.2 mg/Kg) 30min IV infusion. Phase IIa: ApTOLL (0.05 mg/Kg [Dose A] and 0.2 mg/Kg [Dose B]) 30min IV infusion.	

Reporting group title	Placebo
Reporting group description:	
Phase Ib & IIa: Placebo 30min IV infusion.	

Reporting group values	ApTOLL	Placebo	Total
Number of subjects	96	55	151
Age categorical Units: Subjects			
Adults (18-69 years)	40	20	60
70 years and over	56	35	91
Age continuous Units: years			
median	74	75	
inter-quartile range (Q1-Q3)	67 to 81	60 to 82	-
Gender categorical Units: Subjects			
Female	41	22	63
Male	55	33	88

End points

End points reporting groups

Reporting group title	ApTOLL
Reporting group description:	
Phase Ib: ApTOLL (0.025 – 0.2 mg/Kg) 30min IV infusion. Phase IIa: ApTOLL (0.05 mg/Kg [Dose A] and 0.2 mg/Kg [Dose B]) 30min IV infusion.	

Reporting group title	Placebo
Reporting group description:	
Phase Ib & IIa: Placebo 30min IV infusion.	

Primary: Death

End point title	Death
End point description:	

End point type	Primary
End point timeframe:	
Baseline-Day 90	

End point values	ApTOLL	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	55		
Units: percentage	13	10		

Statistical analyses

Statistical analysis title	ApTOLL vs Placebo
Comparison groups	ApTOLL v Placebo
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided

Primary: All AEs

End point title	All AEs
End point description:	

End point type	Primary

End point timeframe:
Baseline-Day 90

End point values	ApTOLL	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	55		
Units: percentage	89	51		

Statistical analyses

Statistical analysis title	ApTOLL vs Placebo
Comparison groups	ApTOLL v Placebo
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Day 1 to Day 90	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0
Reporting groups	
Reporting group title	ApTOLL
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	ApTOLL	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	30 / 96 (31.25%)	20 / 53 (37.74%)	
number of deaths (all causes)	13	10	
number of deaths resulting from adverse events			
Vascular disorders			
Vascular disorders			
subjects affected / exposed	3 / 96 (3.13%)	3 / 53 (5.66%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Nervous system disorder			
subjects affected / exposed	28 / 96 (29.17%)	17 / 53 (32.08%)	
occurrences causally related to treatment / all	0 / 28	0 / 17	
deaths causally related to treatment / all	0 / 13	0 / 10	
Infections and infestations			
Infections and infestations			
subjects affected / exposed	6 / 96 (6.25%)	3 / 53 (5.66%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 13	0 / 10	

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

Non-serious adverse events	ApTOLL	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	88 / 96 (91.67%)	51 / 53 (96.23%)	
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	55 / 96 (57.29%)	34 / 53 (64.15%)	
occurrences (all)	55	34	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	5 / 96 (5.21%)	1 / 53 (1.89%)	
occurrences (all)	5	1	
Eye disorders			
Eye disorders			
subjects affected / exposed	0 / 96 (0.00%)	3 / 53 (5.66%)	
occurrences (all)	0	3	
Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed	27 / 96 (28.13%)	16 / 53 (30.19%)	
occurrences (all)	27	16	
Infections and infestations			
Infections and infestations			
subjects affected / exposed	71 / 96 (73.96%)	47 / 53 (88.68%)	
occurrences (all)	71	47	
Metabolism and nutrition disorders			
Metabolism and nutrition disorders			
subjects affected / exposed	20 / 96 (20.83%)	20 / 53 (37.74%)	
occurrences (all)	20	20	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 October 2020	To include the NIHSS determination at Day 5 after randomization.
22 January 2021	v3.0 (France) To update the Stopping Rules of the trial after updating the DSMB charter.
23 February 2021	v2.1 (Germany) To update the Stopping Rules of the trial after updating the DSMB charter.
21 May 2021	v4.0 (Spain): To update the Stopping Rules of the trial after updating the DSMB charter.
21 May 2021	v4.0 (Spain) To define the times to obtain samples for biomarker determination in Phase IIa. To add an image substudy in some sites at Day 90 after randomization. To add a new subestudy to determine biomarkers in some sites. To modify exclusion criterium 9: Subjects with identifiable intracerebral tumors (meningioma is considered extracerebral tumor, so it is not included in this exclusion criterium).
01 June 2021	v3.2 (France) To define the times to obtain samples for biomarker determination in Phase IIa. To add an image substudy in some sites at Day 90 after randomization. To add a new subestudy to determine biomarkers in some sites. To modify exclusion criterium 9: Subjects with identifiable intracerebral tumors (meningioma is considered extracerebral tumor, so it is not included in this exclusion criterium).
21 June 2021	v3.0 (Germany) To define the times to obtain samples for biomarker determination in Phase IIa. To add an image substudy in some sites at Day 90 after randomization. To add a new subestudy to determine biomarkers in some sites. To modify exclusion criterium 9: Subjects with identifiable intracerebral tumors (meningioma is considered extracerebral tumor, so it is not included in this exclusion criterium).
06 October 2021	v3.0 (Portugal): To update the Stopping Rules of the trial after updating the DSMB charter. To define the times to obtain samples for biomarker determination in Phase IIa. To add an image substudy in some sites at Day 90 after randomization. To add a new subestudy to determine biomarkers in some sites. To modify exclusion criterium 9: Subjects with identifiable intracerebral tumors (meningioma is considered extracerebral tumor, so it is not included in this exclusion criterium).
11 October 2021	v4.0 (France): To modify the inclusion criterium 1: Age ≥18 and ≤85 years to Age ≥18 and ≤90 years. To define the timing to include patients with wake-up strokes
11 October 2021	v4.0 (Germany): To modify the inclusion criterium 1: Age ≥18 and ≤85 years to Age ≥18 and ≤90 years. To define the timing to include patients with wake-up strokes
11 October 2021	v5.0 (Spain): To modify the inclusion criterium 1: Age ≥18 and ≤85 years to Age ≥18 and ≤90 years. To define the timing to include patients with wake-up strokes

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported