



## Clinical trial results:

### Treat\_CCM Clinical Trial. A multicenter randomized clinical trial on Propranolol in familial Cerebral Cavernous Malformation

#### Summary

EudraCT number	2017-003595-30
Trial protocol	IT
Global end of trial date	31 December 2021

#### Results information

Result version number	v1 (current)
This version publication date	21 December 2022
First version publication date	21 December 2022
Summary attachment (see zip file)	SUMMARY (Abstract_TREAT_CCM.pdf)

#### Trial information

##### Trial identification

Sponsor protocol code	IRFMN-7358
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##### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	IFOM
Sponsor organisation address	Via Adamello 16, Milan, Italy, 20139
Public contact	DIPARTIMENTO DI MEDICINA CARDIOVASCOLARE, IRCCS ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI, roberto.latini@marionegri.it
Scientific contact	DIPARTIMENTO DI MEDICINA CARDIOVASCOLARE, IRCCS ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI, roberto.latini@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	02 May 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2021
Global end of trial reached?	Yes
Global end of trial date	31 December 2021
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

Test whether a chronic treatment with propranolol will reduce the burden of cerebrovascular lesions, of clinical events and symptoms in patients with familial CCM.

Protection of trial subjects:

DSMB convened every 6 months to assess events, patient reported side effects and patient ECG to safeguard the patient's safety.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 2018
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	Italy: 83
Worldwide total number of subjects	83
EEA total number of subjects	83

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)	72
From 65 to 84 years	11
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Patients were recruited in 6 Italian centers: Policlinico Milano, Istituto Neurologico Carlo Besta Milano, Ospedale Niguarda Milano, Policlinico Gemelli Roma, Casa Sollievo della Sofferenza San Giovanni Rotondo, Ospedale Bonino Pulejo Messina.

### Pre-assignment

Screening details:

In total, 95 patients were screened. Of these 4 met excluded criteria and 8 declined participation. Therefore, 83 patients were randomized into the trial.

### Pre-assignment period milestones

Number of subjects started	83
Number of subjects completed	83

### Period 1

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

Blinding implementation details:

Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Propranolol

Arm description:

one group received propranolol (recommended initial dose is 40 mg bid, to be uptitrated to 80 mg bid, however, doses as low as 10 mg bid and up to 160 mg bid, 20 to 320mg daily, are acceptable according to tolerability) on the top of recommended standard care.

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

Dosage and administration details:

Initial oral dose 40 mg bid, uptitrated to 80mg bid doses as low as 10 mg bid and up to 160 mg bid, 20 to 320mg daily, are acceptable according to tolerability.

<b>Arm title</b>	Standard of care
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Arm description:

Standard of care

Arm type	No intervention
No investigational medicinal product assigned in this arm	

<b>Number of subjects in period 1</b>	Propranolol	Standard of care
Started	57	26
Completed	54	26
Not completed	3	0
side effects: 2 hypotension & 1 weakness	3	-

## Baseline characteristics

### Reporting groups

Reporting group title	Propranolol
Reporting group description: one group received propranolol (recommended initial dose is 40 mg bid, to be uptitrated to 80 mg bid, however, doses as low as 10 mg bid and up to 160 mg bid, 20 to 320mg daily, are acceptable according to tolerability) on the top of recommended standard care.	
Reporting group title	Standard of care
Reporting group description: Standard of care	

Reporting group values	Propranolol	Standard of care	Total
Number of subjects	57	26	83
Age categorical			
Categorical breakdown of age for patients included in trial			
Units: Subjects			
Adults (18-64 years)	52	20	72
From 65-84 years	5	6	11
Gender categorical			
Units: Subjects			
Female	34	14	48
Male	23	12	35

## End points

### End points reporting groups

Reporting group title	Propranolol
Reporting group description: one group received propranolol (recommended initial dose is 40 mg bid, to be uptitrated to 80 mg bid, however, doses as low as 10 mg bid and up to 160 mg bid, 20 to 320mg daily, are acceptable according to tolerability) on the top of recommended standard care.	
Reporting group title	Standard of care
Reporting group description: Standard of care	

### Primary: The occurrence of new clinically symptomatic intra-cerebral haemorrhage or focal neurological deficit attributable to CCM over 24 months

End point title	The occurrence of new clinically symptomatic intra-cerebral haemorrhage or focal neurological deficit attributable to CCM over 24 months
End point description: The primary outcome was the occurrence of new clinically symptomatic intra-cerebral haemorrhage or focal neurological deficit attributable to CCM over 24 months.	
End point type	Primary
End point timeframe: 24 MONTHS	

End point values	Propranolol	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57 <sup>[1]</sup>	26 <sup>[2]</sup>		
Units: EVENTS	2	2		

Notes:

[1] - Propranolol

[2] - Standard care

### Statistical analyses

Statistical analysis title	Primary endpoint
Statistical analysis description: If the 80% CI did not include 1·0 (equivalence), the results would be considered as showing a signal of efficacy.	
Comparison groups	Propranolol v Standard of care
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	other <sup>[3]</sup>
P-value	< 0.05 <sup>[4]</sup>
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.43

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.18
upper limit	0.98
Variability estimate	Standard error of the mean

Notes:

[3] - If the 80% CI did not include 1·0 (equivalence), the results would be considered as showing a signal of efficacy.

[4] - The primary endpoint occurred in 4% in propranolol (incidence 1·7 cases [95% CI 1·4–2·0] per 100 person-years) and 8% in standard care group (3·9 [3·1–4·7] per 100 person-years); univariable HR 0·43 [80% CI 0·18–0·98];

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events during the course of 24 months follow-up.

Adverse event reporting additional description:

Collected by the treating physician in eCRF

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	24
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### Reporting groups

Reporting group title	Propranolol
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Reporting group description:

patients randomized to propranolol

Reporting group title	standard care
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Reporting group description:

patients randomized to standard care

Serious adverse events	Propranolol	standard care	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 57 (12.28%)	4 / 26 (15.38%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Subarachnoid haemorrhage	Additional description: POST-TRAUMATIC		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 57 (1.75%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 57 (1.75%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Epilepsy			
alternative assessment type: Non-systematic			

subjects affected / exposed	2 / 57 (3.51%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage	Additional description: Spinal haemorrhage		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 57 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
intra cerebral hemorrhage			
subjects affected / exposed	1 / 57 (1.75%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
10034907	Additional description: PHLEGMON		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 57 (1.75%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis	Additional description: one patient		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 57 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Endocarditis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 57 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metabolism and nutrition disorders			
Hyponatraemia	Additional description: Iatrogenic hyponatraemia		
subjects affected / exposed	0 / 57 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Propranolol	standard care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 57 (19.30%)	1 / 26 (3.85%)	
Cardiac disorders			
Tachycardia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 57 (1.75%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Atrial fibrillation			
subjects affected / exposed	1 / 57 (1.75%)	0 / 26 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 57 (7.02%)	0 / 26 (0.00%)	
occurrences (all)	4	0	
Paraesthesia			
subjects affected / exposed	2 / 57 (3.51%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Eye disorders			
10047555	Additional description: SCOTOMA		
subjects affected / exposed	1 / 57 (1.75%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Squamous cell carcinoma of the cervix			
subjects affected / exposed	0 / 57 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Renal and urinary disorders			

Kidney congestion subjects affected / exposed occurrences (all)	Additional description: KIDNEY STONE		
	1 / 57 (1.75%) 1	0 / 26 (0.00%) 0	
Musculoskeletal and connective tissue disorders Fracture subjects affected / exposed occurrences (all)			
	Additional description: TIBIA		
	1 / 57 (1.75%) 1	0 / 26 (0.00%) 0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 June 2018	La richiesta di ES riguarda la partecipazione / apertura di 1 nuovo centro per la sperimentazione Treat_CCM IRCCS CASA SOLLIEVO DELLA SOFFERENZA DIVISIONE DI GENETICA MEDICA UOC REFERENTE: DOTT. MARCO CASTORI e-mail: m.castori@operapadrepio.it
30 November 2018	<p>Modifiche sulla composizione: Steering Committee, Data Safety &amp; Monitoring Board, Clinical Event Committee</p> <p>Dopo varie verifiche si segnala la nuova composizione.</p> <ul style="list-style-type: none"><li>• Dosaggio farmaco in studio, propranololo</li></ul> <p>La decisione di allargare l'intervallo del dosaggio del farmaco in studio (propranololo) è fondata sulle segnalazioni da parte dei diversi clinici che hanno dovuto ridurre i dosaggi rispetto a quelli prestabiliti causa ipotensione e/o bradicardia marcata.</p> <p>L'inclusione del dosaggio più alto (160 mg ogni 12 ore), in pazienti che lo tollerano è motivata dalla necessità di utilizzare la dose massima tollerata in una patologia di cui non si conoscono esattamente i meccanismi (Ved. RCP del farmaco Inderal).</p> <ul style="list-style-type: none"><li>• Inclusione della raccolta Microbioma</li></ul> <p>Sono stati recentemente scoperte delle relazioni tra presenza di alcuni ceppi batterici nell'intestino e rischio di sanguinamento degli angiomi cerebrali (Tang AT et al, Nature, 2017). A tal proposito abbiamo incluso la raccolta delle feci a 0,12 e 24 mesi per analizzare il microbioma. Per ottenere il consenso alla raccolta delle feci dai pazienti già inclusi nello studio, è stato predisposto un Foglio Informativo e Modulo di Consenso per la raccolta dei campioni dello Studio Microbioma (vedi allegato 7)</p> <ul style="list-style-type: none"><li>• Modifica dell'endpoint primario: crisi convulsive</li></ul> <p>Insorgenza di nuove crisi comiziali nel corso dello studio puo' essere dovuta non solo ad un aggravamento della malattia (sanguinamento di un angioma) ma anche da un' insufficiente copertura con farmaci anticonvulsivanti, assunti da circa la metà dei pazienti finora inclusi nello studio.</p> <p>Pertanto, vista la possibile ambiguità nell'interpretazione nelle nuove crisi comiziali, queste vengono spostate dall'endpoint primario all'endpoint secondario.</p> <ul style="list-style-type: none"><li>• Analisi statistica</li></ul> <p>La sezione statistica è stata ampiamente ridotta rendendola più chiara, anche se non è stato alterato il disegno.</p> <ul style="list-style-type: none"><li>• Tempistiche studio</li></ul> <p>Le Tempistiche sono state aggiornate in base all'effettivo</p>

10 December 2019	<p><b>Modifica Time Scale</b>  La durata della randomizzazione è stata estesa dai 12 mesi previsti a 19 mesi, per permettere di includere nello studio un maggior numero di pazienti in modo da soddisfare le richieste che ci provenivano da tutta Italia. L'ultimo paziente è stato incluso 4/12/2019 presso il centro di San Giovanni Rotondo: di conseguenza la fine del follow-up è prevista per dicembre 2021.</p> <p><b>Aggiunta referenza</b>  E' stata aggiunta una referenza recente rilevante per la comprensione della patologia in esame (Malinverno M, Maderna C, Abu Taha A, et al. Endothelial cell clonal expansion in the development of cerebral cavernous malformations. Nat Commun. 2019;10(1):2761. Published 2019 Jun 24. doi:10.1038/s41467-019-10707-x)</p> <p><b>Aggiunta paragrafo Background and rationale</b>  E' stato aggiunto un paragrafo sulla importanza di studiare il microbioma nei pazienti con CCM, basandoci sulla evidenza sperimentale pubblicata da Tang et al, 2017 (Tang AT, Choi JP, Kotzin JJ, Yang Y, Hong CC, Hobson N, Girard R, Zeineddine HA, Lightle R, Moore T, Cao Y, Shenkar R, Chen M, Mericko P, Yang J, Li L, Tanes C, Kobuley D, Vösa U, Whitehead KJ, Li DY, Franke L, Hart B, Schwaninger M, Henao-Mejia J, Morrison L, Kim H, Awad IA, Zheng X, Kahn ML. Endothelial TLR4 and the microbiome drive cerebral cavernous malformations. 2017 Nature 18;545(7654):305-310</p> <p><b>Questionari</b>  E' stato aggiunto un paragrafo in cui vengono descritti i questionari sullo stato di salute (SF-36) depressione (Beck Depression Inventory – BDI) e ansia (STAI X-1, STAI X-2), che vengono somministrati ai pazienti all'ingresso, 12, 24 mesi. Ai soggetti che aderiranno allo studio del microbioma verrà anche richiesta la compilazione di un questionario sulle abitudini alimentari.</p>
26 June 2020	<p><b>CAMBIO PROMOTORE</b>  In ottemperanza alla richiesta dell'Ufficio Ricerca Indipendente AIFA, il Promotore è diventato IFOM, mentre il Mario Negri coordina il trial come CRO</p> <p><b>STUDIO OSSERVAZIONALE</b>  Lo studio Treat_CCM, di cui il primo paziente è stato arruolato in aprile 2018, è basato su una collaborazione del Promotore, IFOM, con il Mario Negri, che coordina i 6 centri neurologici italiani.  La inclusione dei 71 pazienti si è conclusa nel dicembre 2019. Attualmente i primi pazienti stanno concludendo il follow-up di 2 anni, previsto dal protocollo; l'ultimo paziente concluderà il follow-up nel dicembre 2021.  Considerata la difficoltà di costituire un campione ben selezionato di pazienti affetti da una rara come i cavernomi cerebrali familiari (CCM), in accordo con i Responsabili delle 6 Unità Operative, si vuole offrire ai pazienti la possibilità di continuare a essere seguiti, ciascuno nei rispettivi centri di riferimento.  Lo studio osservazionale avrà una durata variabile fino a un massimo di 18 mesi. In questo modo si otterranno dati sia clinici che di imaging e biochimici in un arco di tempo prolungato, non disponibili ad oggi in letteratura.  Alla fine di questo studio osservazionale verranno valutati i risultati e si deciderà se passare alla seconda fase, prevista dal protocollo (Protocol version 4.0, pag. 22), uno studio di Fase 2 a singolo braccio con propranololo.</p> <p><b>TIME SCALE</b>  19 mesi è il tempo richiesto per includere gli 83 pazienti. Questo fa sì che la durata totale dello studio clinico dal primo paziente incluso all'ultima visita dell'ultimo paziente è di 43 mesi. Mentre la durata dell'intero progetto, comprensiva di 3 mesi emergenza COVID, analisi dati dello studio osservazionale e del trial, sarà di 48 mesi.</p>

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Notes:

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## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This study has some limitations. First, Treat_CCM recruited more than its target sample size. The Steering Committee decided to include as many patients as possible within the 18-month inclusion period, given the expected low incidence of endpoint cl
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Notes:

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## **Online references**

<http://www.ncbi.nlm.nih.gov/pubmed/36403580>