Clinical trial results:
Pilot study, single-blind, candesartan versus usual care of peripheral neuropathy development induced by vincristine (PNIV) in patients treated for lymphoma B.

Summary

EudraCT number	2017-000585-30
Trial protocol	FR
Global end of trial date	23 September 2021

Results information

Result version number	v1 (current)
This version publication date	09 November 2023
First version publication date	09 November 2023
Summary attachment (see zip file)	NEUPERSART/Statistical analysis (Rapport d'Analyse Statistique et sécurité NEUPERSART V1.0.pdf)

Trial information

Trial identification

Sponsor protocol code	I16016

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03688633
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CHU de Limoges
Sponsor organisation address	2 avenue Martin Luther King, Limoges, France, 87042
Public contact	Principal Investigator, CHU de Limoges, 33 555051572, laurent.magy@unilim.fr
Scientific contact	Principal Investigator, CHU de Limoges, 33 555051572, laurent.magy@unilim.fr

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	13 October 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 September 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of the clinical study is:
Describing the impact of Candesartan on the occurrence of neuropathy as measured by variation in Total Clinical Neuropathy Score (TNSc) in patients treated for non-Hodgkin's lymphoma type B with multidrugine-containing chemotherapy, evaluating clinical signs Of neuropathy) between baseline (V1) and end of chemotherapy (V4).

Protection of trial subjects:

The trial was carried out in accordance with the regulation, the ICH and the Helsinki declaration. All patients have been informed and have given their consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 October 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	France: 9
Worldwide total number of subjects	9
EEA total number of subjects	9

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)	6
From 65 to 84 years	3

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first inclusion took place on 29/05/2019 and the last on 27/05/2021.
The recruitment took place at the University Hospital of Limoges.

Pre-assignment

Screening details:

Patients with a diagnosis of lymphoma, are recruited in consultation or in hospitalization in the hematologic department
During this interview, the patient will be given information about the study and an information about the benefics and the side effects.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[1]

Blinding implementation details:

The patient is open-label and the primary endpoint is assessed by an investigator blinded to the randomization group.

Arms

Are arms mutually exclusive?	Yes
Arm title	CANDESARTAN

Arm description:

Candesartan (8mg) will then be prescribed and dispensed for a first intake the next day, in addition to the usual treatment (Neurological assessment and neurophysiological exploration).
A prescription is given to the patient for creatinine and kalemia measurement at home after 7 days of treatment.

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

Dosage and administration details:

8 to 16 mg/d daily for 15 weeks
Oral use

Arm title	Usual care

Arm description:

Neurological assessment (EVA, TNSc,EQ-5D) and neurophysiological exploration (ENMG, Sudoscan)

Arm type	No intervention

No investigational medicinal product assigned in this arm

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: The patient is open-label and the primary endpoint is assessed by an investigator blinded to the randomization group

Number of subjects in period 1	CANDESARTAN	Usual care
Started	4	5
Completed	4	5

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	9	9	
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)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	9	9	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
least squares mean	59		
standard deviation	± 9.1	-	
Gender categorical Units: Subjects			
Female	5	5	
Male	4	4	

End points

End points reporting groups

Reporting group title	CANDESARTAN
Reporting group description:	
Candesartan (8mg) will then be prescribed and dispensed for a first intake the next day, in addition to the usual treatment (Neurological assessment and neurophysiological exploration). A prescription is given to the patient for creatinine and kalemia measurement at home after 7 days of treatment.	
Reporting group title	Usual care
Reporting group description:	
Neurological assessment (EVA, TNSc,EQ-5D) and neurophysiological exploration (ENMG, Sudoscan)	

Primary: TNSc score variation

End point title	TNSc score variation[1]
End point description:	
End point type	Primary
End point timeframe:	
19 weeks after the start of treatment	

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: Because of the small number of patients included, no results can be derived from the analysis .
Therefore, the statistical analysis performed on this small number of included subjects is purely descriptive.

End point values	CANDESARTAN	Usual care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	3		
Units: Score variation				
arithmetic mean (standard error)	3 (± 1)	5.7 (± 2.1)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the signing of the consent up to 1 month after the end of the treatment

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	CANDESARTAN
Reporting group description: -	
Reporting group title	Usual care

Reporting group description: -

Serious adverse events	CANDESARTAN	Usual care	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 4 (25.00%)	2 / 5 (40.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Troponin increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pertussis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			

subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	
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: 5 %

Non-serious adverse events	CANDESARTAN	Usual care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	5 / 5 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	2	
Hypotension			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 4 (0.00%)	3 / 5 (60.00%)	
occurrences (all)	0	3	
Chest pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	
occurrences (all)	14	0	
Hyperthermia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			

Heavy menstrual bleeding			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Psychiatric disorders			
Bulimia nervosa			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Investigations			
Blood bilirubin decreased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Blood creatinine decreased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	
occurrences (all)	3	0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Platelet count decreased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Troponin increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Weight decreased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	1 / 4 (25.00%)	2 / 5 (40.00%)	
occurrences (all)	1	2	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Leukopenia			
subjects affected / exposed	3 / 4 (75.00%)	3 / 5 (60.00%)	
occurrences (all)	14	16	
Lymphopenia			
subjects affected / exposed	4 / 4 (100.00%)	5 / 5 (100.00%)	
occurrences (all)	16	25	
Neutropenia			
subjects affected / exposed	3 / 4 (75.00%)	2 / 5 (40.00%)	
occurrences (all)	14	8	
Thrombocytopenia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 5 (20.00%)	
occurrences (all)	3	5	
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 4 (25.00%)	2 / 5 (40.00%)	
occurrences (all)	1	3	
Dyspepsia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	0 / 4 (0.00%)	4 / 5 (80.00%)	
occurrences (all)	0	4	
Vomiting			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 4 (50.00%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			

Cystitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	2	
Pertussis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 February 2020	1- Change in non-inclusion criteria: - Delete "diabetes" - Delete "known previous vitamin deficiency - Delete "patient on anticoagulant or with known blood clotting disorder". 2- Extension of candesartan duration treatment beyond V4 to cover toxicity from last chemotherapy

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
23 September 2021	Reasons for Permanent Discontinuation: -Low accrual rate: 28 months after the enrollment of the first patient, only 9 patients were recruited out of the 40 planned , despite an extension of the inclusion period and modification of the inclusion and non-inclusion criteria. -Overestimation of the inclusion potential Given the very small number of patients, no benefit / risk analysis can be performed. However a full safety analysis is performed as well as a descriptive analysis.	-

Notes:

Limitations and caveats

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

Early termination leading to a small number of subjects analysed; The few data collected does not allow anay analysis.

Notes: