Clinical trial results:
Relative bioavailability and comparative pharmacokinetics of 13-CRA oral liquid and extracted capsule formulations: a randomised, open label, multi-dose, cross-over clinical trial in patients requiring treatment cycles of 13-CRA.

Summary

EudraCT number	2016-005104-25
Trial protocol	GB
Global end of trial date	13 September 2019

Results information

Result version number	v1 (current)
This version publication date	30 December 2020
First version publication date	30 December 2020
Summary attachment (see zip file)	Medical Journal Manuscript (Medical Journal Manuscript (1).pdf) Supplement file 1 (Supplemental File 1 (1).pdf) Supplement file 2 (Supplemental File 2 (1).pdf)

Trial information

Trial identification

Sponsor protocol code	INV500

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03291080
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Nova Labs Ltd
Sponsor organisation address	Gloucester Crescent, Leicester, United Kingdom, LE184YL
Public contact	Project Manager / Head of Clinical , Nova BioPharma Limited, 44 0116 2230100, hussain.mulla@novalabs.co.uk
Scientific contact	Project Manager / Head of Clinical , Nova BioPharma Limited, 44 0116 2230100, hussain.mulla@novalabs.co.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	31 January 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 September 2019
Global end of trial reached?	Yes
Global end of trial date	13 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine how 13-CRA is absorbed into the body, to what extent, and how it is handled in the body, when it is administered using the new liquid formulation and the current 'extract from capsule' method.

Protection of trial subjects:

This was a low intervention study requiring only blood samples for measurement of pharmacokinetics.

Background therapy:

Neuroblastoma treatment protocols involve multiple chemotherapy agents. IN the maintenance phase, 13-CRA is administered with immunotherapy (anti-GD2 monoclonal antobodies) e.g. Dinutuximab

Evidence for comparator:

This was a relative bioavialbility and PK study to evaluate a new liquid formulation of oral 13-CRA. The appropriate comparator was 13-CRA capsule (isotretinoin) which is approved in the community.

Actual start date of recruitment	01 January 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	United Kingdom: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

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)	2
Children (2-11 years)	18
Adolescents (12-17 years)	0
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All children recruited in UK hospitals.
Date of first consent: 07 June 2018
Date of firs enrolment: 09 July 2018
Date of last completed: 13 Sept 2019

Pre-assignment

Screening details:

When the patient attended the hospital clinic for initiation fo 13-CRA treatment, the parents/legal guardians of the patient was approached to discuss the possibility of the child's entry into the trial.

Pre-assignment period milestones

Number of subjects started	20
Number of subjects completed	20

Period 1

Period 1 title	Cycle 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Test oral liquid

Arm description:

Dosing with oral liquid 13-CRA

Arm type	Experimental
Investigational medicinal product name	13-cis-retinoic acid
Investigational medicinal product code	
Other name	isotretinoin
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

160mg/m2/ per day in two divided doses (morning and evening)

Number of subjects in period 1	Test oral liquid
Started	20
Completed	20

Period 2	
Period 2 title	Cycle 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Oral 13-CRA capsule

Arm description:

Reference 13-CRA capsule

Arm type	Active comparator
Investigational medicinal product name	13-cis retinoic acid
Investigational medicinal product code	
Other name	isotretinoin
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

160mg/m2/day in two divided doses (morning and evening)

Number of subjects in period 2	Oral 13-CRA capsule
Started	20
Completed	20

Baseline characteristics

Reporting groups	
Reporting group title	Test oral liquid
Reporting group description:	
Dosing with oral liquid 13-CRA	

Reporting group values	Test oral liquid	Total	
Number of subjects	20	20	
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)	2	2	
Children (2-11 years)	18	18	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	5	5	
Male	15	15	

End points

End points reporting groups	
Reporting group title	Test oral liquid
Reporting group description: Dosing with oral liquid 13-CRA	
Reporting group title	Oral 13-CRA capsule
Reporting group description: Reference 13-CRA capsule	

Primary: Pharmacokinetics	
End point title	Pharmacokinetics
End point description:	
End point type	Primary
End point timeframe: PK parameters estimated at the end of the study once all patients had completed treatment.	

End point values	Test oral liquid	Oral 13-CRA capsule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20[1]		
Units: Relative bioavailability				
geometric mean (confidence interval 95%)	65 (54 to 77)	0 (0 to 0)		

Notes:

[1] - cross-over pooled analysis

Statistical analyses

Statistical analysis title	Mean difference in AUC
Statistical analysis description: Difference in the mean AUC between the formulations (oral liquid and capsule)	
Comparison groups	Test oral liquid v Oral 13-CRA capsule
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.01
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	3933
Confidence interval	
level	95 %
sides	2-sided
lower limit	2020
upper limit	5846

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE was collected in the clinic, for the 14 days that the patient received the medication at home, for 14 (+7) days between dosing cycles and for the 14 days from the time of the last dose after cycle 2.

Adverse event reporting additional description:

Trial site personnel reported any AE, whether observed by the research staff or reported by the patient or recorded in the diary card.
Oropharyngeal tolerability was assessed at baseline and following dosing until the patient completed the trial. Any local clinically relevant changes were recorded as adverse events.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	All subjects

Reporting group description: -

Serious adverse events	All subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 20 (5.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Gastrointestinal disorders			
Haematemesis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 20 (90.00%)		
Gastrointestinal disorders			
Chapped lips			
subjects affected / exposed	18 / 20 (90.00%)		
occurrences (all)	85		

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? No

Limitations and caveats

None reported