



Clinical trial results:

A Phase I/IIA, Multi-Centre, Open-Label, Dose-Escalation Study with Expansion Arms to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of CB-103 Administered Orally in Adult Patients with Advanced or Metastatic Solid Tumours and Haematological Malignancies Characterised by Alterations of the NOTCH Signalling Pathway

Summary

EudraCT number	2017-001491-35
Trial protocol	ES NL DE
Global end of trial date	11 November 2022

Results information

Result version number	v1 (current)
This version publication date	26 November 2023
First version publication date	26 November 2023
Summary attachment (see zip file)	A Phase I Study of the Pan-Notch Inhibitor CB-103 for Patients with Advanced Adenoid Cystic Carcinoma and Other Tumors (crc-23-0333.pdf)

Trial information

Trial identification

Sponsor protocol code	CB103-C-101
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Cellestia Biotech AG
Sponsor organisation address	Tech Park Hochbergerstrasse 60C, Basel, Switzerland, 4057
Public contact	Chief Development Officer, Cellestia Biotech AG, maria.bobadilla@cellestia.com
Scientific contact	Chief Development Officer, Cellestia Biotech AG, maria.bobadilla@cellestia.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	11 November 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 November 2022
Global end of trial reached?	Yes
Global end of trial date	11 November 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase I, Part A - Dose Escalation

- determine the MTD or RP2D of CB-103 as a single agent when administered orally and with repeat dosing to adult patients with advanced or metastatic solid tumours and haematological malignancies, who have progressed despite curative therapy or for whom no curative therapy exists

Phase IIA, Part B - Expansion

- assess preliminary anti-tumour activity of single agent CB-103 when administered orally and with repeat dosing in the different expansion arms across the different indications

Protection of trial subjects:

The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure (IB), and other relevant supporting information were submitted to an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) by the investigator or by CRO delegated by Sponsor (as required) and reviewed and approved by the IRB/IEC before the study was initiated. This study was conducted in full compliance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines; the principles of the "Declaration of Helsinki"; applicable laws and regulations. Overall conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH GCP guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies, and all other applicable local regulations. The Investigator or his/her representative explained the nature of the study to the participant or his/her legally authorized representative and answered all questions regarding the study. Participants were informed that their participation was voluntary. Participants or their legally authorized representative were required to sign a statement of informed consent that meets the local regulations, ICH guidelines, and the IRB/IEC or study site requirements.

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	Spain: 37
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	United States: 13
Country: Number of subjects enrolled	Korea, Republic of: 9
Country: Number of subjects enrolled	Switzerland: 15

Worldwide total number of subjects	79
EEA total number of subjects	42

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)	55
From 65 to 84 years	24
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study enrolled adults with histologically confirmed, locally advanced and/or metastatic solid tumors who had progressed on at least one line of prior systemic therapy (except for ACC) and relapsed/refractory T-ALL/LBL for whom no standard therapy was available.

Pre-assignment

Screening details:

Key eligibility criteria included subjects ≥ 18 years of age. In dose escalation, subjects with solid tumors with known or frequent Notch pathway-activating mutations were eligible, while the confirmatory cohort enrolled subjects with selected tumor types (incl. T-ALL/LBL) and confirmed Notch pathway activation.

Period 1

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

Blinding implementation details:

Not applicable

Arms

Arm title	CB-103 orally for 28 days
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Arm description:

CB-103 will be administered orally in treatment cycles of 28-days each. Aim of the expansion Phase IIA, Part B of the study will be to collect preliminary evidence of anti-tumour activity.

Arm type	Experimental
Investigational medicinal product name	CB-103
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

CB-103 will be administered orally in treatment cycles of 28-days each.

Number of subjects in period 1	CB-103 orally for 28 days
Started	79
Completed	79

Baseline characteristics

Reporting groups

Reporting group title

Overall trial

Reporting group description:

CB-103 capsules will be administered orally in treatment cycles of 28-days each.

Reporting group values	Overall trial	Total	
Number of subjects	79	79	
Age categorical			
patients ≥18 years of age with evaluable disease, Eastern Cooperative Oncology Group (ECOG) performance status 0–1, able to swallow capsules, and adequate organ function.			
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)	55	55	
From 65-84 years	24	24	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	34	34	
Male	45	45	

End points

End points reporting groups

Reporting group title	CB-103 orally for 28 days
Reporting group description: CB-103 will be administered orally in treatment cycles of 28-days each. Aim of the expansion Phase IIA, Part B of the study will be to collect preliminary evidence of anti-tumour activity.	

Primary: For dose escalation: Number of subjects experiencing DLT during the first 28-day cycle. In the confirmatory phase, the incidence rate, severity, and relationship of AEs to CB-103

End point title	For dose escalation: Number of subjects experiencing DLT during the first 28-day cycle. In the confirmatory phase, the incidence rate, severity, and relationship of AEs to CB-103 ^[1]
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End point description:

End point type	Primary
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End point timeframe:

The first 28-days cycle.

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: This trial is a single arm trial. There is no comparison arm.

End point values	CB-103 orally for 28 days			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: 1	79			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Cycle 1 Day 1 through Safety Follow-Up.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.1
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Reporting groups

Reporting group title	Overall Trial
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Reporting group description: -

Serious adverse events	Overall Trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 79 (3.80%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Liver function test increased			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Drug Induced Liver Injury			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Stevens-Johnson syndrome			
subjects affected / exposed	1 / 79 (1.27%)		
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	Overall Trial		
Total subjects affected by non-serious adverse events subjects affected / exposed	76 / 79 (96.20%)		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	13 / 79 (16.46%) 39		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	9 / 79 (11.39%) 10		
Eye disorders Dyschromatopsia subjects affected / exposed occurrences (all) Vision blurred subjects affected / exposed occurrences (all)	15 / 79 (18.99%) 18 12 / 79 (15.19%) 13		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	17 / 79 (21.52%) 21 10 / 79 (12.66%) 14 10 / 79 (12.66%) 10 9 / 79 (11.39%) 12		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 September 2018	The changes are aimed to simplify and clean the protocol besides addressing few main changes. Due to strategic considerations and to further focus on CB-103 development, a set of indications have been excluded at this point in time to emphasize those ones with a distinct oncogenic role of NOTCH pathway activation as well as on those which are currently included in the development plan for CB-103. Consequently, several sections of the protocol, including the exclusion/inclusion criteria, have been revised accordingly. Other inclusion/exclusion criteria have been revised for further clarity. Three more blood samples have been introduced for genotyping patients for polymorphisms of metabolizing enzymes to understand its impact on the clinical PK of CB-103. Concerning the other pre-existing specimens' sampling, more precise time-point windows have been defined. On a case-by-case basis, intra-patient dose escalation is being considered and the circumstances under which this is allowed have been introduced. Finally, a number of other administrative or editorial changes and corrections are made throughout the protocol.
16 October 2019	Based on incoming competitive data in the field, the solid tumour indications have been streamlined while the hematological malignancies have been excluded from the protocol at this point in time. Consequently, several sections of the protocol, including the exclusion/inclusion criteria, have been revised accordingly. Other inclusion/exclusion criteria have been modified for further clarity. Notch-dependant patient enrichment is implemented in the MTD/RP2D final cohort of the Part A of the study, hence enhancing the chances of enrolled patients to benefit from the treatment. For these patients the fresh biopsy at pre-dose and on-treatment have been made mandatory. Based on incoming clinical and pre-clinical data, this final cohort of the Part A of the study is limited to the enrolment of Adenoid Cystic Carcinoma (ACC) and Breast Cancer patients. Some blood sampling has been reduced or removed, whereas a 24-hr urine sample collection and one stool sample have been added to explore the metabolite profile of CB-103 in such matrices. In case of twice daily intake of CB-103 it has been clarified the PK sampling and ECG scheme to apply. Other exploratory biomarkers analyses have been introduced. The PK sub-study is made mandatory. In addition to the major changes above, minor edits have been made throughout the protocol to correct for typographical, formatting and other minor errors.

22 September 2020	T-cell acute lymphoblastic leukemia (T-ALL) / T-cell lymphoblastic lymphoma (T-LBL) are being added as target disease because approximately 80% of cases have Notch pathway activation. Other Notch inhibitors have shown promising response data in this disease but could not further advance in the clinic due to toxicity issues observed with those compounds. It is believed that CB-103 has a better safety profile and can be a novel treatment for T-ALL/T-LBL patients. It will also be possible to enroll patients with any cancer (histology agnostic) that has Notch pathway activation, since these patients may benefit from treatment that targets the causal pathway. The sample size of the escalation phase has been increased because the 8 dose levels have been completed and the MTD was not reached. Optimization of the schedule (twice daily dosing of CB-103) with potential further dose escalation is being explored. Given the additional indications, and a planned expansion of the study into Asian countries, the sample size of the dose confirmation cohort was increased. The exploratory endpoints have been updated to match the clinical indications covered in the study and modified to investigate differences between indications and ethnic groups. The goal is to confirm the dose of CB-103 is safe in patients across indications and ethnicities. The MTD/RP2D cohort (previously referred to as the "final" MTD/RP2D cohort) is now referred to as the "confirmatory" cohort as it was felt that this is a better designation for this particular cohort.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported