Clinical trial results:
A pilot study to assess the safety, tolerability, dose-finding, and efficacy of iadademstat in combination with azacitidine in adult patients with Acute Myeloid Leukemia (AML) in first-line therapy.

Summary

EudraCT number	2018-000482-36
Trial protocol	ES
Global end of trial date	30 September 2022

Results information

Result version number	v1 (current)
This version publication date	16 October 2024
First version publication date	16 October 2024

Trial information

Trial identification

Sponsor protocol code	CL02-ORY-1001AML

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Oryzon Genomics S. A.
Sponsor organisation address	Carrer de Sant Ferran, 74, CORNELLA DE LLOBREGAT, Spain, 08940
Public contact	Douglas V. Faller, Oryzon Genomics S. A., 34 93 515 13 13, dfaller@oryzon.com
Scientific contact	Douglas V. Faller, Oryzon Genomics S. A., 34 93 515 13 13, dfaller@oryzon.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	31 January 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 September 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To asses safety, tolerability and dose finding of ORY-1001 in combination with azacitidine.

Protection of trial subjects:

The protocol and informed consent forms were submitted to an Independent Ethics Committee (IEC) for review and approval before study initiation. All revisions to the informed consent forms (if applicable) after initial IEC approval were submitted to the IEC for review and approval before implementation in accordance with regulatory requirements. This study was conducted in accordance with the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 September 2018
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: 36
Worldwide total number of subjects	36
EEA total number of subjects	36

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)	0
From 65 to 84 years	36
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was an open-label study. Patient enrollment to a particular dose was in accordance with a Patient Allocation and Recruitment Process. The Sponsor was the responsible for allocation of dose cohort and patient numbers.

Pre-assignment

Screening details:

The screening period consisted of 14-day period after the ICF signature. During this screening period study procedures for subject selection were completed (e.g., inclusion/exclusion criteria, disease assessment, medical history, demographics, concomitant medication, vital signs including ECG...)

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	90 mcg/m2/d

Arm description:

Starting dose

Arm type	Experimental
Investigational medicinal product name	Iadademstat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

The dosage of Azacitidine was 75 mg/m2 for 7 days (7 consecutive days or days 1-5, 8, 9). Iadademstat 90 mcg/m2/d orally intake, in a 5 days on/2 day off schedule, 4-weeks cycles

Arm title	60 mcg/m2/d

Arm description:

De-escalation dose

Arm type	Experimental
Investigational medicinal product name	Iadademstat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

The dosage of Azacitidine was 75 mg/m2 for 7 days (7 consecutive days or days 1-5, 8, 9). Iadademstat 60 mcg/m2/d orally intake, in a 5 days on/2 day off schedule, 4-weeks cycles

Number of subjects in period 1	90 mcg/m2/d	60 mcg/m2/d
Started	19	17
Completed	18	16
Not completed	1	1
Protocol deviation	1	1

Baseline characteristics

Reporting groups

Reporting group title	Treatment Period

Reporting group description: -

Reporting group values	Treatment Period	Total	
Number of subjects	36	36	
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)	0	0	
From 65-84 years	36	36	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	18	18	
Male	18	18	

Subject analysis sets

Subject analysis set title	Safety Analysis Set (SAS)
Subject analysis set type	Per protocol

Subject analysis set description:

The SAS is defined as all patients who received at least one dose of the study treatment. SAS was used for all safety analyses.

Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Per protocol

Subject analysis set description:

All patients who met eligibility criteria and have been treated. FAS has been used for sensitivity analyses, including safety analysis and efficacy analysis.

Subject analysis set title	Efficacy Analysis Set (EAS)
Subject analysis set type	Per protocol

Subject analysis set description:

The EAS is defined as all patients who met the eligibility criteria, have been treated, have baseline disease assessment, and have at least 1 available post-baseline efficacy assessment. EAS has been used for the efficacy analyses.

Reporting group values	Safety Analysis Set (SAS)	Full Analysis Set (FAS)	Efficacy Analysis Set (EAS)
Number of subjects	36	34	27

Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	36	34	27
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	18	18	14
Male	18	16	13

End points

End points reporting groups

Reporting group title	90 mcg/m2/d
Reporting group description:	
Starting dose	
Reporting group title	60 mcg/m2/d
Reporting group description:	
De-escalation dose	
Subject analysis set title	Safety Analysis Set (SAS)
Subject analysis set type	Per protocol
Subject analysis set description:	
The SAS is defined as all patients who received at least one dose of the study treatment. SAS was used for all safety analyses.	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients who met eligibility criteria and have been treated. FAS has been used for sensitivity analyses, including safety analysis and efficacy analysis.	
Subject analysis set title	Efficacy Analysis Set (EAS)
Subject analysis set type	Per protocol
Subject analysis set description:	
The EAS is defined as all patients who met the eligibility criteria, have been treated, have baseline disease assessment, and have at least 1 available post-baseline efficacy assessment. EAS has been used for the efficacy analyses.	

Primary: Safety of iadademstat in combination with azacitidine

End point title	Safety of iadademstat in combination with azacitidine
End point description:	
End point type	Primary
End point timeframe:	
Treatment period in both arms of the study	

End point values	90 mcg/m2/d	60 mcg/m2/d	Safety Analysis Set (SAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	19	17	36	
Units: Subjects				
Subjects with AEs	19	17	36	
Subjects with SAEs	18	16	34	
Subjects with AEs ≥G3	19	17	36	
Subjects with AEs leading to drug interrupted	7	5	12	
Subjects with Fatal AEs	8	4	12	
Subjects with ADRs	17	16	33	
Subjects with SADRs	2	1	3	
Subjects with ADRs ≥G3	16	15	31	

Subjects with ADRs leading to drug interrupted	2	0	2	
Subjects with Fatal ADRs	1	0	1	

Statistical analyses

Statistical analysis title	Descriptive statistics
Comparison groups	90 mcg/m2/d v 60 mcg/m2/d
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0 [2]
Method	Descriptive statistics

Notes:

[1] - Descriptive statistics

[2] - Not applicable. Descriptive statistics.

Secondary: Individual Patients Response

End point title	Individual Patients Response

End point description:

Responses per investigator assessment (European LeukemiaNet 2010 criteria) of the 27 patients in the Efficacy Analysis Set

End point type	Secondary

End point timeframe:

Treatment period

End point values	90 mcg/m2/d	60 mcg/m2/d	Efficacy Analysis Set (EAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	14	13	27	
Units: Subjects				
CR	5	4	9	
CRi	4	1	5	
PR	2	6	8	
SD	2	2	4	
PD	1	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:	
ORR: Percentage of subjects archiving complete remission (CR), CR with incomplete recovery (CRi), partial response (PR), confirmed by repeat assessments ≥4 weeks after initial documentation	
End point type	Secondary
End point timeframe:	
Treatment period	

End point values	90 mcg/m2/d	60 mcg/m2/d	Efficacy Analysis Set (EAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	14	13	27	
Units: Subjects				
number (confidence interval 95%)				
Objective response (%; 95% CI)	79 (49 to 95)	85 (55 to 98)	82 (62 to 94)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to response (TTR)

End point title	Time to response (TTR)
End point description:	
TTR defined as time from the start of treatment with iadademstat to the firts objective tumor response observed in terms of number of cycles administrated.	
End point type	Secondary
End point timeframe:	
Treatment period	

End point values	90 mcg/m2/d	60 mcg/m2/d	Efficacy Analysis Set (EAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	14	13	27	
Units: day				
number (confidence interval 95%)				
Time to first response, days (95% CI)	67 (30 to 93)	43 (29 to 80)	64 (32 to 80)	
Time to best response, days (95% CI)	124 (67 to 169)	79 (32 to 283)	105 (67 to 162)	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR: defined as the time from the first occurrence of a documented tumor response to the time of progression or death from any cause, whichever occurs first. (DOR analysis only included responders).

End point type	Secondary

End point timeframe:

Treatment and follow up period

End point values	90 mcg/m2/d	60 mcg/m2/d	Efficacy Analysis Set (EAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	14	13	27	
Units: day				
number (confidence interval 95%)				
CR + CRi + PR, days (95% CI)	282 (16 to 529)	205 (71 to 748)	269 (86 to 529)	

Statistical analyses

No statistical analyses for this end point

Secondary: Event-Free survival (EFS)

End point title	Event-Free survival (EFS)

End point description:

EFS: Time from first study treatment to disease progression or death.

End point type	Secondary

End point timeframe:

Study period

End point values	90 mcg/m2/d	60 mcg/m2/d	Efficacy Analysis Set (EAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	14	13	27	
Units: month				
median (confidence interval 95%)				
EFS (mos) (95% CI)	10.2 (2.0 to 19.4)	7.7 (3.4 to 21.9)	8.9 (3.4 to 11.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS: Time from first study treatment to death from any cause.

End point type	Secondary

End point timeframe:

Study period

End point values	Efficacy Analysis Set (EAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	27			
Units: month				
median (confidence interval 95%)				
OS (mos) (95% CI)	11.1 (4.5 to 29.1)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Throughout the study period

Adverse event reporting additional description:

Any adverse event G3 or more with a frequency threshold of at least 5% and all adverse events G3 or more related to iadademstat (+/- azacitidine)
Any serious adverse event with a frequency threshold of at least 5% and all serious adverse events related to iadademstat (+/- azacitidine)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Safety analysis set

Reporting group description: -

Serious adverse events	Safety analysis set		
Total subjects affected by serious adverse events			
subjects affected / exposed	34 / 36 (94.44%)		
number of deaths (all causes)	12		
number of deaths resulting from adverse events	12		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Differentiation syndrome			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Haemorrhage intracranial			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	1 / 2		
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Blood and lymphatic system disorders			
Febrile neutropenia			

subjects affected / exposed	14 / 36 (38.89%)		
occurrences causally related to treatment / all	1 / 18		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 36 (11.11%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenic colitis			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Infections and infestations			
Pneumonia			
subjects affected / exposed	5 / 36 (13.89%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 2		
COVID-19 pneumonia			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 3		
Sepsis			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

Cellulitis			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Skin infection			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Fungal infection			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

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

Non-serious adverse events	Safety analysis set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 36 (100.00%)		
Investigations			
Platelet count decreased			
subjects affected / exposed	32 / 36 (88.89%)		
occurrences (all)	191		
Neutrophil count decreased			

subjects affected / exposed	24 / 36 (66.67%)		
occurrences (all)	162		
Haemoglobin abnormal			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	5		
White blood cell count decreased			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	5		
White blood cell count abnormal			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	5		
Lymphocyte count decreased			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Lymphocyte count abnormal			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Haemoglobin decreased			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	3		
Weight decreased			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Alanine aminotransferase abnormal			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Aspartate aminotransferase abnormal			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Blood sodium increased			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Differentiation syndrome subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1		
Vascular disorders Hypotension subjects affected / exposed occurrences (all)	3 / 36 (8.33%) 3		
Nervous system disorders Haemorrhage intracranial subjects affected / exposed occurrences (all) Dysgeusia subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2 1 / 36 (2.78%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Febrile neutropenia subjects affected / exposed occurrences (all) Leukocytosis subjects affected / exposed occurrences (all)	24 / 36 (66.67%) 58 17 / 36 (47.22%) 24 2 / 36 (5.56%) 2		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all)	5 / 36 (13.89%) 5 2 / 36 (5.56%) 3		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	3 / 36 (8.33%) 3		
Renal and urinary disorders			

Acute kidney injury subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2		
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 3		
Cellulitis subjects affected / exposed occurrences (all)	4 / 36 (11.11%) 4		
Pneumonia subjects affected / exposed occurrences (all)	5 / 36 (13.89%) 5		
Respiratory tract infection subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2		
COVID-19 pneumonia subjects affected / exposed occurrences (all)	3 / 36 (8.33%) 3		
Sepsis subjects affected / exposed occurrences (all)	3 / 36 (8.33%) 3		
Skin infection subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2		
Septic shock subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2		
Abscess subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1		
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)	3 / 36 (8.33%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 January 2019	Add the determination of minimal residual disease (MRD). Add additional timepoints to peripheral blood smears evaluation. Add 2 more specific biomarkers for the evaluation of gene expression changes: HBA1 and GYPB).
22 October 2019	Add Guide for management of patient's hematological toxicity. Update of participant sites.
06 October 2020	Inclusion criteria 1 and 3 have been amended (and title modified in line with that). To include patients ≥ 18 years unfit for intensive chemotherapy and clarify prior treatments allowed
15 February 2021	Exclusion criteria 10 has been amended. To include the request that all patients should initiate antibacterial, antiviral and antifungal prophylaxis simultaneously with the start of the study treatment and irrespective of the neutrophil count
02 June 2021	Back to initial RP2D of 90 µg/m2/d and recommendation for dose modification in case of neutropenia and/or thrombocytopenia is revised accordingly. To achieve quicker responses after the first cycles of treatment. Provide guidance to modify treatment dosing based on hematological toxicity.
17 May 2022	Set an End of Study date: 30 Sep 2022

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported