Clinical trial results:
A phase I study of Human Pharmacokinetics and Safety of ORY-1001, and LSD1 inhibitor, in relapsed or refractory acute leukaemia (AL)

Summary

EudraCT number	2013-002447-29
Trial protocol	ES GB
Global end of trial date	01 September 2016

Results information

Result version number	v1 (current)
This version publication date	26 June 2020
First version publication date	26 June 2020

Trial information

Trial identification

Sponsor protocol code	CL01-ORY-1001

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	c/Sant Ferran 74, Cornella de LLobregat, Spain, 08940
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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	01 September 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 September 2016
Global end of trial reached?	Yes
Global end of trial date	01 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the safety (haematological and non-haematological toxicities) and tolerability of ORY-1001 in patients with relapsed/refractory AL.
The secondary objectives were to:
- Characterise the PK of orally administered ORY-1001 in patients with relapsed/refractory AL
- Characterise the PD of orally administered ORY-1001 in patients with relapsed/refractory AL.
- Assess remission rate (CR/CRi, PR) of ORY-1001 in patients with relapsed/refractory AL, particularly in those with rMLL gene, TAL1/LMO overexpression or Notch1 activation, as the drug shows more benefit in vitro or in animal models of AL.

Protection of trial subjects:

A Safety Monitoring Committee was responsible for the decisions related with dose escalation. Additionally, the committee was responsible for decisions of stopping the trial in case of unacceptable toxicities. The committee was formed by representatives of the sponsor and the investigators from all participating sites and reviewed safety data on an ongoing basis.

Background therapy:

As previously mentioned, relapsed/refractory AL has very poor prognosis, the only curative strategy is hematopoietic allotransplant but up to 50% of patients won't be suitable candidates for this procedure (not achieving CR/CRi, early relapse, and unacceptable co-morbidity index) or will relapse after this procedure. Relapse has been associated with the inability of current treatment to eradicate leukemic stem cells. Investigation of new therapeutic drugs is imperative.

ORY-1001 has demonstrated to be safe and effective to treat AL in animal models, and it seems that rMLL AL, TAL1 or LMO complex over-expressing or Notch1 activated AL and promyelocytic leukaemia, may particularly benefit from this drug

Evidence for comparator: -

Actual start date of recruitment	30 January 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Scientific research
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 23
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	France: 10
Worldwide total number of subjects	41
EEA total number of subjects	41

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)	17
From 65 to 84 years	24
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was performed in 10 sites: Spain(5), UK(2), France(3). 43 pats were screened: 1 was screening failure and 1 died prior to treatment. 41 pats received study medication: 27 pats entered in dose escalation cohorts, 12 completed the study and 15 discontinued. 14 pats entered in the expansion cohort: 3 completed the study and 11 discontinued

Pre-assignment

Screening details:

Patients aged 16 and above , must have relapsed or refractory AL (excluding promyelocytic leukaemia) considered by the investigator ineligible for intensive chemotherapy regimen at that time and must have ECOG Performance Status (PS) of 0-2 .

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	COHORT 1 - ORY 1001 - 5 µg/m2/d

Arm description:

Cohort 1 - ORY 1001 - 5 µg/m2/d

Arm type	Experimental
Investigational medicinal product name	ORY1001
Investigational medicinal product code	
Other name	Iadademstat
Pharmaceutical forms	Oral suspension in pre-filled oral applicator
Routes of administration	Oral use

Dosage and administration details:

ORY-1001 for oral intake once daily during 5 consecutive days with 2 days of rest during 28-days cycles.

Arm title	COHORT 2 - ORY 1001 - 15 µg/m2/d

Arm description:

Cohort 2 - ORY 1001 - 15 µg/m2/d

Arm type	Experimental
Investigational medicinal product name	ORY1001
Investigational medicinal product code	
Other name	Iadademstat
Pharmaceutical forms	Oral suspension in pre-filled oral applicator
Routes of administration	Oral use

Dosage and administration details:

ORY-1001 for oral intake once daily during 5 consecutive days with 2 days of rest during 28-days cycles.

Arm title	COHORT 3 - ORY 1001 - 30 µg/m2/d

Arm description:

Cohort 3 - ORY 1001 - 30 µg/m2/d

Arm type	Experimental

Investigational medicinal product name	ORY1001
Investigational medicinal product code	
Other name	Iadademstat
Pharmaceutical forms	Oral suspension in pre-filled oral applicator
Routes of administration	Oral use

Dosage and administration details:

ORY-1001 for oral intake once daily during 5 consecutive days with 2 days of rest during 28-days cycles.

Arm title	COHORT 4 - ORY 1001 - 45 µg/m2/d

Arm description:

Cohort 4 - ORY 1001 - 45 µg/m2/d

Arm type	Experimental
Investigational medicinal product name	ORY1001
Investigational medicinal product code	
Other name	Iadademstat
Pharmaceutical forms	Oral suspension in pre-filled oral applicator
Routes of administration	Oral use

Dosage and administration details:

ORY-1001 for oral intake once daily during 5 consecutive days with 2 days of rest during 28-day cycles.

Arm title	COHORT 5 - ORY 1001 - 60 µg/m2/d

Arm description:

Cohort 5 - ORY 1001 - 60 µg/m2/d

Arm type	Experimental
Investigational medicinal product name	ORY1001
Investigational medicinal product code	
Other name	Iadademstat
Pharmaceutical forms	Oral suspension in pre-filled oral applicator
Routes of administration	Oral use

Dosage and administration details:

ORY-1001 for oral intake once daily during 5 consecutive days with 2 days of rest during 28-day cycles.

Arm title	COHORT 6 - ORY 1001 - 80 µg/m2/d

Arm description:

Cohort 6 - ORY 1001 - 80 µg/m2/d

Arm type	Experimental
Investigational medicinal product name	ORY1001
Investigational medicinal product code	
Other name	Iadademstat
Pharmaceutical forms	Oral suspension in pre-filled oral applicator
Routes of administration	Oral use

Dosage and administration details:

ORY-1001 for oral intake once daily during 5 consecutive days with 2 days of rest during 28-day cycles.

Arm title	COHORT 7- ORY 1001 - 140 µg/m2/d

Arm description:

Cohort 7 - ORY 1001 - 140 µg/m2/d

Arm type	Experimental
Investigational medicinal product name	ORY1001
Investigational medicinal product code	
Other name	Iadademstat
Pharmaceutical forms	Oral suspension in pre-filled oral applicator
Routes of administration	Oral use

Dosage and administration details:

ORY-1001 for oral intake once daily during 5 consecutive days with 2 days of rest for 4 blocks during 28-days cycles.

Arm title	COHORT 8 - ORY 1001 - 220 µg/m2/d

Arm description:

Cohort 8 - ORY 1001 - 220 µg/m2/d

Arm type	Experimental
Investigational medicinal product name	ORY1001
Investigational medicinal product code	
Other name	Iadademstat
Pharmaceutical forms	Oral suspension in pre-filled oral applicator
Routes of administration	Oral use

Dosage and administration details:

ORY-1001 for oral intake once daily during 5 consecutive days with 2 days of rest for 4 blocks during 28-days cycles.

Arm title	EXPANSION COHORT - ORY1001 -140 µg/m2/d

Arm description:

Extension Cohort, 140 µg/m2/d, as agreed by SMC

Arm type	Experimental
Investigational medicinal product name	ORY1001
Investigational medicinal product code	
Other name	Iadademstat
Pharmaceutical forms	Oral suspension in pre-filled oral applicator
Routes of administration	Oral use

Dosage and administration details:

ORY-1001 for oral intake once daily during 5 consecutive days with 2 days of rest during 28-days cycles.

Number of subjects in period 1	COHORT 1 - ORY 1001 - 5 µg/m2/d	COHORT 2 - ORY 1001 - 15 µg/m2/d	COHORT 3 - ORY 1001 - 30 µg/m2/d
Started	3	3	3
Completed	2	2	3
Not completed	1	1	0
UNACEPTABLE TOXICITY	-	-	-
Consent withdrawn by subject	-	-	-
DEATH	-	1	-
DEPRESSED LEVEL OF CONSCIUSNESS	-	-	-
INTERCURRENT ILLNES	-	-	-
DISEASE PROGRESSION	1	-	-
DEATH DUE TO SEPSIS	-	-	-

Number of subjects in period 1	COHORT 4 - ORY 1001 - 45 µg/m2/d	COHORT 5 - ORY 1001 - 60 µg/m2/d	COHORT 6 - ORY 1001 - 80 µg/m2/d
Started	3	4	3

Completed	1	1	1
Not completed	2	3	2
UNACEPTABLE TOXICITY	-	-	-
Consent withdrawn by subject	-	-	-
DEATH	-	-	-
DEPRESSED LEVEL OF CONSCIUSNESS	-	1	-
INTERCURRENT ILLNES	-	-	1
DISEASE PROGRESSION	2	1	1
DEATH DUE TO SEPSIS	-	1	-

Number of subjects in period 1	COHORT 7- ORY 1001 - 140 µg/m2/d	COHORT 8 - ORY 1001 - 220 µg/m2/d	EXPANSION COHORT - ORY1001 -140 µg/m2/d
Started	3	5	14
Completed	1	1	3
Not completed	2	4	11
UNACEPTABLE TOXICITY	-	1	-
Consent withdrawn by subject	-	1	1
DEATH	2	1	2
DEPRESSED LEVEL OF CONSCIUSNESS	-	-	-
INTERCURRENT ILLNES	-	-	-
DISEASE PROGRESSION	-	1	8
DEATH DUE TO SEPSIS	-	-	-

Baseline characteristics

Reporting groups	
Reporting group title	COHORT 1 - ORY 1001 - 5 µg/m2/d
Reporting group description: Cohort 1 - ORY 1001 - 5 µg/m2/d	
Reporting group title	COHORT 2 - ORY 1001 - 15 µg/m2/d
Reporting group description: Cohort 2 - ORY 1001 - 15 µg/m2/d	
Reporting group title	COHORT 3 - ORY 1001 - 30 µg/m2/d
Reporting group description: Cohort 3 - ORY 1001 - 30 µg/m2/d	
Reporting group title	COHORT 4 - ORY 1001 - 45 µg/m2/d
Reporting group description: Cohort 4 - ORY 1001 - 45 µg/m2/d	
Reporting group title	COHORT 5 - ORY 1001 - 60 µg/m2/d
Reporting group description: Cohort 5 - ORY 1001 - 60 µg/m2/d	
Reporting group title	COHORT 6 - ORY 1001 - 80 µg/m2/d
Reporting group description: Cohort 6 - ORY 1001 - 80 µg/m2/d	
Reporting group title	COHORT 7- ORY 1001 - 140 µg/m2/d
Reporting group description: Cohort 7 - ORY 1001 - 140 µg/m2/d	
Reporting group title	COHORT 8 - ORY 1001 - 220 µg/m2/d
Reporting group description: Cohort 8 - ORY 1001 - 220 µg/m2/d	
Reporting group title	EXPANSION COHORT - ORY1001 -140 µg/m2/d
Reporting group description: Extension Cohort, 140 µg/m2/d, as agreed by SMC	

Reporting group values	COHORT 1 - ORY 1001 - 5 µg/m2/d	COHORT 2 - ORY 1001 - 15 µg/m2/d	COHORT 3 - ORY 1001 - 30 µg/m2/d
Number of subjects	3	3	3
Age categorical Units: Subjects			
Adults (18-64 years)	0	3	1
From 65-84 years	3	0	2
Gender categorical Units: Subjects			
Female	0	0	1
Male	3	3	2

Reporting group values	COHORT 4 - ORY 1001 - 45 µg/m2/d	COHORT 5 - ORY 1001 - 60 µg/m2/d	COHORT 6 - ORY 1001 - 80 µg/m2/d
Number of subjects	3	4	3
Age categorical Units: Subjects			
Adults (18-64 years)	1	1	0
From 65-84 years	2	3	3

Gender categorical Units: Subjects			
Female	2	2	1
Male	1	2	2

Reporting group values	COHORT 7- ORY 1001 - 140 µg/m2/d	COHORT 8 - ORY 1001 - 220 µg/m2/d	EXPANSION COHORT - ORY1001 -140 µg/m2/d
Number of subjects	3	5	14
Age categorical Units: Subjects			
Adults (18-64 years)	2	1	8
From 65-84 years	1	4	6
Gender categorical Units: Subjects			
Female	1	1	5
Male	2	4	9

Reporting group values	Total		
Number of subjects	41		
Age categorical Units: Subjects			
Adults (18-64 years)	17		
From 65-84 years	24		
Gender categorical Units: Subjects			
Female	13		
Male	28		

Subject analysis sets

Subject analysis set title	Safety analysis (SA) set
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who received any amount of ORY-1001 were included in the data summaries for safety (Safety Population).

Subject analysis set title	Full analysis (FA) set
Subject analysis set type	Full analysis

Subject analysis set description:

All patients who received any amount of ORY-1001 and had protocol evaluations performed in concordance with the time points defined in the protocol, irrespective of whether they completed the schedule or not, were included in data summaries for analysis. Baseline was the date of the first dose of ORY-1001. Patients who had received any amount of ORY-1001, and had any post-baseline efficacy assessment were analysed for efficacy parameters (Treated Population).

Reporting group values	Safety analysis (SA) set	Full analysis (FA) set	
Number of subjects	41	41	
Age categorical Units: Subjects			
Adults (18-64 years)	17	17	
From 65-84 years	24	24	

Gender categorical Units: Subjects			
Female	13	13	
Male	28	28	

End points

End points reporting groups

Reporting group title	COHORT 1 - ORY 1001 - 5 µg/m2/d
Reporting group description: Cohort 1 - ORY 1001 - 5 µg/m2/d	
Reporting group title	COHORT 2 - ORY 1001 - 15 µg/m2/d
Reporting group description: Cohort 2 - ORY 1001 - 15 µg/m2/d	
Reporting group title	COHORT 3 - ORY 1001 - 30 µg/m2/d
Reporting group description: Cohort 3 - ORY 1001 - 30 µg/m2/d	
Reporting group title	COHORT 4 - ORY 1001 - 45 µg/m2/d
Reporting group description: Cohort 4 - ORY 1001 - 45 µg/m2/d	
Reporting group title	COHORT 5 - ORY 1001 - 60 µg/m2/d
Reporting group description: Cohort 5 - ORY 1001 - 60 µg/m2/d	
Reporting group title	COHORT 6 - ORY 1001 - 80 µg/m2/d
Reporting group description: Cohort 6 - ORY 1001 - 80 µg/m2/d	
Reporting group title	COHORT 7- ORY 1001 - 140 µg/m2/d
Reporting group description: Cohort 7 - ORY 1001 - 140 µg/m2/d	
Reporting group title	COHORT 8 - ORY 1001 - 220 µg/m2/d
Reporting group description: Cohort 8 - ORY 1001 - 220 µg/m2/d	
Reporting group title	EXPANSION COHORT - ORY1001 -140 µg/m2/d
Reporting group description: Extension Cohort, 140 µg/m2/d, as agreed by SMC	
Subject analysis set title	Safety analysis (SA) set
Subject analysis set type	Safety analysis
Subject analysis set description: All patients who received any amount of ORY-1001 were included in the data summaries for safety (Safety Population).	
Subject analysis set title	Full analysis (FA) set
Subject analysis set type	Full analysis
Subject analysis set description: All patients who received any amount of ORY-1001 and had protocol evaluations performed in concordance with the time points defined in the protocol, irrespective of whether they completed the schedule or not, were included in data summaries for analysis. Baseline was the date of the first dose of ORY-1001. Patients who had received any amount of ORY-1001, and had any post-baseline efficacy assessment were analysed for efficacy parameters (Treated Population).	

Primary: Tolerability

End point title	Tolerability
End point description:	
End point type	Primary
End point timeframe: Evaluate the tolerability of ORY-1001 along of cycle of treatment	

End point values	COHORT 1 - ORY 1001 - 5 µg/m2/d	COHORT 2 - ORY 1001 - 15 µg/m2/d	COHORT 3 - ORY 1001 - 30 µg/m2/d	COHORT 4 - ORY 1001 - 45 µg/m2/d
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	3
Units: Patients				
Dose limiting toxicities	0	0	0	0

End point values	COHORT 5 - ORY 1001 - 60 µg/m2/d	COHORT 6 - ORY 1001 - 80 µg/m2/d	COHORT 7- ORY 1001 - 140 µg/m2/d	COHORT 8 - ORY 1001 - 220 µg/m2/d
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	3	5
Units: Patients				
Dose limiting toxicities	0	0	0	2

End point values	EXPANSION COHORT - ORY1001 -140 µg/m2/d	Full analysis (FA) set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	14	41		
Units: Patients				
Dose limiting toxicities	0	2		

Statistical analyses

Statistical analysis title	Dose limiting toxicities

Statistical analysis description:

Escalation has been proceed according to a standard Phase I design in which cohorts of 3-6 patients were treated per dose level (Simon et al., 1997); dose increases had been applied according to a modified Fibonacci scheme (Cohorts 1 to 6) and then by a genuine Fibonacci scheme for Cohorts 7 and 8.

Comparison groups	COHORT 1 - ORY 1001 - 5 µg/m2/d v COHORT 2 - ORY 1001 - 15 µg/m2/d v COHORT 3 - ORY 1001 - 30 µg/m2/d v COHORT 4 - ORY 1001 - 45 µg/m2/d v COHORT 5 - ORY 1001 - 60 µg/m2/d v COHORT 6 - ORY 1001 - 80 µg/m2/d v COHORT 7- ORY 1001 - 140 µg/m2/d v COHORT 8 - ORY 1001 - 220 µg/m2/d v EXPANSION COHORT - ORY1001 -140 µg/m2/d

Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0
Method	NA
Parameter estimate	NA
Point estimate	0.5
Confidence interval	
level	Other: 0 %
sides	1-sided
upper limit	1

Notes:

[1] - Maximum Tolerated Dose: the highest dose for which no more than 1 of the 6 treated patients exhibits DLT. The Maximum Tolerated Dose and Dose Limiting Toxicities were assessed in a dose escalation cohort, and an extension cohort was treated at the Maximum Tolerated Dose.

Secondary: Efficacy

End point title	Efficacy

End point description:

CRi: Morphologic Complete remission but with incomplete blood count recovery
Resistant disease (RD): Failure to achieve CR or CRi, or failure to achieve CR, CRi or PR; only includes patients surviving > 7d following completion of initial treatment, with evidence of persistent leukaemia by blood and/or BM examination.
Death in aplasia (DA): Deaths occurring > 7d following completion of initial treatment while cytopenic; with an aplastic or hypoplastic BM maintained within 7d of death, without evidence of persistent leukaemia.
Death from indeterminate cause (DI) Deaths occurring before completion of therapy, or <7d following its completion; or deaths occurring >7d following completion of initial therapy with no blasts in the blood, but no BM examination available
Relapse: BM blasts > 5%; or reappearance of blasts in the blood; or development of extramedullary disease.

End point type	Secondary

End point timeframe:

Bone marrow aspirate had been analyzed on basal and after each cycle (+/-3d)

End point values	COHORT 1 - ORY 1001 - 5 µg/m2/d	COHORT 2 - ORY 1001 - 15 µg/m2/d	COHORT 3 - ORY 1001 - 30 µg/m2/d	COHORT 4 - ORY 1001 - 45 µg/m2/d
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	3
Units: Patients				
CRi	0	0	0	0
RD	3	3	2	3
DA	0	0	0	0
DI	0	0	0	0
Relapse	0	0	1	0

End point values	COHORT 5 - ORY 1001 - 60 µg/m2/d	COHORT 6 - ORY 1001 - 80 µg/m2/d	COHORT 7- ORY 1001 - 140 µg/m2/d	COHORT 8 - ORY 1001 - 220 µg/m2/d

Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	3	4
Units: Patients				
CRi	1	0	0	0
RD	1	3	2	4
DA	2	0	1	0
DI	0	0	0	0
Relapse	0	0	0	0

End point values	EXPANSION COHORT - ORY1001 -140 µg/m2/d	Full analysis (FA) set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	12	38		
Units: Patients				
CRi	0	1		
RD	9	30		
DA	2	5		
DI	0	0		
Relapse	1	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Time frame defined as the period from the administration of the first dose of ORY-1001 until the final visit, planned approximately 30 days after receiving the last dose.

Adverse event reporting additional description:

An AE should preferably be documented in terms of one single medical term (diagnosis). Only when this is not feasible, an AE may be documented in terms of the predominant signs and/or symptoms observed by the investigator or reported by the patient at each study visit. If possible, the terminology should adhere to the one used in CTCA 4.0

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Safety population

Reporting group description:

All patients who received any amount of ORY-1001 were included in the data summaries for safety (Safety Population).

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	35 / 41 (85.37%)		
number of deaths (all causes)	26		
number of deaths resulting from adverse events	26		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Leukaemia cutis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Disease progression			

subjects affected / exposed	5 / 41 (12.20%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 5			
Pyrexia				
subjects affected / exposed	2 / 41 (4.88%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Graft versus host disease in liver				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Respiratory failure				
subjects affected / exposed	3 / 41 (7.32%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 3			
Differentiation syndrome				
subjects affected / exposed	2 / 41 (4.88%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	2 / 2			
Interstitial lung disease				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Investigations				
White blood cell count increased				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			

Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pericarditis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Supraventricular tachycardia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Haemorrhage intracranial			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Depressed level of consciousness			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Haemorrhagic stroke			
subjects affected / exposed	1 / 41 (2.44%)		
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	12 / 41 (29.27%)		
occurrences causally related to treatment / all	4 / 14		
deaths causally related to treatment / all	0 / 2		
Leukocytosis			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Lung infection			
subjects affected / exposed	5 / 41 (12.20%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	0 / 3		
Sepsis			
subjects affected / exposed	4 / 41 (9.76%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Cellulitis			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	1 / 1		

Pneumonia			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 3		
Anal abscess			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary sepsis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory tract infection			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Septic shock			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinusitis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Skin infection			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 41 (100.00%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	5		
Haematoma			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Phlebitis			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	6 / 41 (14.63%)		
occurrences (all)	6		
Headache			
subjects affected / exposed	6 / 41 (14.63%)		
occurrences (all)	10		
Haemorrhage intracranial			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	16 / 41 (39.02%)		
occurrences (all)	24		
Pyrexia			
subjects affected / exposed	12 / 41 (29.27%)		
occurrences (all)	14		
Oedema peripheral			
subjects affected / exposed	8 / 41 (19.51%)		
occurrences (all)	11		
Fatigue			

subjects affected / exposed	7 / 41 (17.07%)		
occurrences (all)	9		
Disease progression			
subjects affected / exposed	5 / 41 (12.20%)		
occurrences (all)	5		
Chest pain			
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	4		
Mucosal inflammation			
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	4		
Oedema			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	22 / 41 (53.66%)		
occurrences (all)	27		
Thrombocytopenia			
subjects affected / exposed	8 / 41 (19.51%)		
occurrences (all)	11		
Leukocytosis			
subjects affected / exposed	6 / 41 (14.63%)		
occurrences (all)	6		
Neutropenia			
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	4		
Anaemia			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	17 / 41 (41.46%)		
occurrences (all)	23		
Constipation			

subjects affected / exposed	11 / 41 (26.83%)		
occurrences (all)	14		
Nausea			
subjects affected / exposed	11 / 41 (26.83%)		
occurrences (all)	13		
Vomiting			
subjects affected / exposed	7 / 41 (17.07%)		
occurrences (all)	7		
Dry mouth			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Haemorrhoids			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 41 (12.20%)		
occurrences (all)	5		
Epistaxis			
subjects affected / exposed	5 / 41 (12.20%)		
occurrences (all)	5		
Respiratory failure			
subjects affected / exposed	5 / 41 (12.20%)		
occurrences (all)	5		
Productive cough			
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	4		
Oropharyngeal pain			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Pleural effusion			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Rhinorrhoea			

subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 3		
Skin and subcutaneous tissue disorders Petechiae subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Rash maculo-papular subjects affected / exposed occurrences (all)	 5 / 41 (12.20%) 9 3 / 41 (7.32%) 3 3 / 41 (7.32%) 3		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 3 / 41 (7.32%) 5		
Musculoskeletal and connective tissue disorders Bone pain subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all)	 4 / 41 (9.76%) 4 3 / 41 (7.32%) 4		
Infections and infestations Cellulitis subjects affected / exposed occurrences (all) Lung infection subjects affected / exposed occurrences (all) Sepsis subjects affected / exposed occurrences (all) Oral candidiasis subjects affected / exposed occurrences (all)	 5 / 41 (12.20%) 6 5 / 41 (12.20%) 6 5 / 41 (12.20%) 5 4 / 41 (9.76%) 4		

Oral herpes subjects affected / exposed occurrences (all) Pneumonia subjects affected / exposed occurrences (all)	 4 / 41 (9.76%) 4 4 / 41 (9.76%) 5		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all) Hypocalcaemia subjects affected / exposed occurrences (all)	 9 / 41 (21.95%) 11 4 / 41 (9.76%) 9 3 / 41 (7.32%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 October 2013	Protocol version 3 date 16 October 2013 was amended to update the times of collection PK/PD samples.
26 September 2014	Protocol version 7 date 26 September 2014 was amended - to include nucleic acid sequencing on study samples - to modify or to extend dose escalation - to shorten the accrual interval between patients enrolled in a given dose cohort. Patients were included consecutively in each dose level with a minimum time interval of one week to allow for detection of serious and/or unexpected AEs before further patients were treated. -to assess ORY1001 PK parameters in whole blood
28 January 2015	Protocol version 7.1 date 28 January 2015 .At the request of the Medicines and Healthcare Products Regulatory Authority, UK, a maximum dose of ORY-1001 was included in the protocol. A maximum dose of 580 µg/m2/day was chosen (unless DLT are identified at a lower dose) based on the initial maximal dose (141 µg/m2) corrected by the factor for pre-clinical (dog) to human exposure (< 4.5 X 141 µg/m2=630 µg/m2) and 2 new cohorts, with
06 March 2015	Protocol version 8.0 date 06 March 2015 The change in maximum dose of ORY-1001 requested by the Medicines and Healthcare Products Regulatory Authority, UK, and included in Protocol version 7.1 date 28 January 2015 was included in the global protocol. -The planned number of sites was increased to include 3 sites in France, and 1 more site in the UK. -The time frame of the study was prolonged; study end was planned for the 2nd quarter 2016. -An interim analysis was planned when the MTD was reached. After the Interim Report the Safety Monitoring Committee decided the priority subtypes of AML to be included in the extension arm, dosing regimen and total number of patients in the extension. For clarification of the definition of the analysis population to be used for the safety analysis the following statement of the protocol was ignored: "Patients who are treated with ORY-1001, but have no follow up for safety, will not be included in safety analyses, because their inclusion would dilute percentages of patients with AEs or laboratory toxicities." (see protocol section. 10.6. Procedures for handling missing, unused and spurious data). This was contradictory to the definition of the safety set given in the former sections of the protocol. Instead all patients who received any amount of ORY-1001 were included in data summaries for safety

12 October 2015	Protocol version 9.0 date 12 October 2015 -PD-LSD1 target engagement analysis was added to the PD assessments to assess the pharmacokinetic/pharmacodynamic (PK/PD) relationship and dose response to LSD1 inhibitors in clinical samples. -To improve recruitment, the number of sites was increased to 5 hospitals in Spain, 2 in UK and 3 in France. -Changes to the planned analyses Transfusions can interfere with PK/PD measurements, it was therefore planned that if the patient required a transfusion during the 5 day treatment block, the PK/PD readouts following the transfusion would be recorded but omitted from analysis. This was not done because the PD responses measured over 24 hours on Days 1, 5 and 26 were expected to be relatively independent of these factors. Additional analyses -The Medical Statistics Core Facility at IDIBAPS (Institute d'investigacions Biomèdiques August Pi i Sunyer), Barcelona, Spain performed an additional analysis of the peripheral blasts. - A population pharmacokinetic/ pharmacodynamic model was developed to identify and quantify the impact of intrinsic and extrinsic factors on the pharmacokinetics of ORY1001 and to evaluate the relationship between exposure and effect (changes on blasts counts). Marta Valle, PharmD, PhD was responsible for the PKPD modeling and simulation at the Institut de Recerca de l'HSCSP, Hospital de la Santa Creu i Sant Pau, Spain. The complete report is included in Section 16.1.14.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported