Clinical trial results:
Phase 2/3 Study of Monotherapy LY2157299 Monohydrate in Very Low-, Low-, and Intermediate-Risk Patients with Myelodysplastic Syndromes

Summary

EudraCT number	2013-003235-30
Trial protocol	IT DE ES
Global end of trial date	24 September 2017

Results information

Result version number	v1
This version publication date	07 October 2018
First version publication date	07 October 2018

Trial information

Trial identification

Sponsor protocol code	H9H-MC-JBAV

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02008318
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 15242

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, United States, 46285
Public contact	Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 877-CTLilly,
Scientific contact	Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 877-285-4559,

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	24 September 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to investigate the effect of the study drug known as galunisertib in participants with myelodysplastic syndromes (MDS). Participants with different degrees of disease (very low, low, and intermediate risk) will be studied. The study treatment is expected to last about 6 months for each participant.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 March 2014
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	Spain: 12
Country: Number of subjects enrolled	Germany: 23
Country: Number of subjects enrolled	Italy: 8
Worldwide total number of subjects	43
EEA total number of subjects	43

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)	9

From 65 to 84 years	34
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This is a single-arm study (Galunisertib at 150 milligram [mg]); the Galunisertib at 80 mg was considered exploratory and only conducted in parallel with the main study, at one site in Spain.

Pre-assignment

Screening details:

No text.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Galunisertib at 150 mg

Arm description:

Galunisertib at 150 mg given orally twice daily (BID) for 14 days followed by 14 days with no study drug (28 day cycles). Completed participants completed at least 6 cycles.

Arm type	Experimental
Investigational medicinal product name	Galunisertib
Investigational medicinal product code	
Other name	LY2157299
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Galunisertib at 150 mg given orally twice daily (BID) for 14 days followed by 14 days with no study drug (28 day cycles).

Arm title	Galunisertib at 80 mg

Arm description:

Exploratory arm: Galunisertib at 80 mg given orally twice daily (BID) for 14 days followed by 14 days with no study drug (28 day cycles). Completed participants completed at least 6 cycles.

Arm type	Exploratory
Investigational medicinal product name	Galunisertib
Investigational medicinal product code	
Other name	LY2157299
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Galunisertib at 80 mg given orally twice daily (BID) for 14 days followed by 14 days with no study drug (28 day cycles).

Number of subjects in period 1	Galunisertib at 150 mg	Galunisertib at 80 mg
Started	41	2
Received At Least 1 Dose of Study Drug	41	2
Completed	29	1
Not completed	12	1
Physician decision	2	-
Consent withdrawn by subject	3	-
Adverse event, non-fatal	4	-
Progressive Disease	2	-
Protocol deviation	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Galunisertib at 150 mg
Reporting group description:	
Galunisertib at 150 mg given orally twice daily (BID) for 14 days followed by 14 days with no study drug (28 day cycles). Completed participants completed at least 6 cycles.	
Reporting group title	Galunisertib at 80 mg
Reporting group description:	
Exploratory arm: Galunisertib at 80 mg given orally twice daily (BID) for 14 days followed by 14 days with no study drug (28 day cycles). Completed participants completed at least 6 cycles.	

Reporting group values	Galunisertib at 150 mg	Galunisertib at 80 mg	Total
Number of subjects	41	2	43
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	70.49	62.50	
standard deviation	± 7.65	± 10.61	-
Gender categorical			
Units: Subjects			
Female	15	1	16
Male	26	1	27
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	5	0	5
Not Hispanic or Latino	32	2	34
Unknown or Not Reported	4	0	4
Race (NIH/OMB)			
Units: Subjects			
White	41	2	43
IPSS-R Prognostic Risk Score			
Measure Description: Revised International Prognostic Scoring System (IPSS-R) is a screening tool used for MDS risk assessment. IPSS-R gives great weight to cytogenetic abnormalities and severity of cytopaenias, while reassigning the weighting for blast percentages. Score Categories: ≤1.5 Very Low, >1.5 - 3 Low, >3 - 4.5 Intermediate, >4.5 - 6 High, >6 Very High. The MDS Foundation website provides a calculator for determining IPSS-R scoring.			
Units: Subjects			
Very Low= (≤1.5)	2	0	2
Low= (>1.5 - 3)	30	1	31
Intermediate= (>3 - 4.5)	9	1	10

End points

End points reporting groups

Reporting group title	Galunisertib at 150 mg
Reporting group description:	
Galunisertib at 150 mg given orally twice daily (BID) for 14 days followed by 14 days with no study drug (28 day cycles). Completed participants completed at least 6 cycles.	
Reporting group title	Galunisertib at 80 mg
Reporting group description:	
Exploratory arm: Galunisertib at 80 mg given orally twice daily (BID) for 14 days followed by 14 days with no study drug (28 day cycles). Completed participants completed at least 6 cycles.	
Subject analysis set title	Galunisertib
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All participants who received study drug, regardless of dose.	

Primary: Percentage of Participants with Hematological Improvement (HI)

End point title	Percentage of Participants with Hematological Improvement (HI)
End point description:	
Percentage of participants with hematological improvement (HI) based on International Working Group (IWG) 2006 criteria in participants with very low, low, and intermediate-risk myelodysplastic syndromes treated with Galunisertib plus best supportive care, as assessed by the International Prognostic Scoring System (IPSS-R). To be classified as an HI responder, the HI response must have lasted at least 8 weeks (56 days). Analysis Population Description: participants who received at least one dose of study drug.	
End point type	Primary
End point timeframe:	
Baseline through end of study treatment (24 weeks)	

End point values	Galunisertib at 150 mg	Galunisertib at 80 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	2		
Units: percentage of participants				
number (confidence interval 95%)	31.7 (18.1 to 48.1)	0.0 (0.0 to 84.2)		

Statistical analyses

Statistical analysis title	Overall HI Response Rate Statisical Analysis
Comparison groups	Galunisertib at 150 mg v Galunisertib at 80 mg

Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Clopper-Pearson Method

Primary: Percentage of Participants who are Transfusion-free or have Hemoglobin (Hb) Increase ≥1.5 Grams/Deciliter Maintained for 8 Weeks During Phase 3

End point title	Percentage of Participants who are Transfusion-free or have Hemoglobin (Hb) Increase ≥1.5 Grams/Deciliter Maintained for 8 Weeks During Phase 3[1]

End point description:

Comparison of the percentage of participants with very low-, low-,and intermediate-risk MDS who were transfusion-free or had an increase ≥1.5 g/dL in hemoglobin (Hb) maintained for at least 8 weeks within the first 24 weeks of treatment with galunisertib plus best supportive care or placebo plus best supportive care and assessed by IPSS-R.

The Phase 3 portion of this study was not conducted because efficacy level required in phase 2 to move forward to phase 3 was not achieved.

Analysis Population Description: participants who received at least one dose of study drug during Phase 3.

End point type	Primary

End point timeframe:

Baseline through end of study treatment (24 weeks)

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: The Phase 3 portion of this study was not conducted because efficacy level required in phase 2 to move forward to phase 3 was not achieved. No statistical analysis completed for this end point.

End point values	Galunisertib at 150 mg	Galunisertib at 80 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: percentage of participants				
number (confidence interval 95%)	(to)	(to)		

Notes:

[2] - Efficacy level required in phase 2 to move forward to phase 3 was not achieved.

[3] - Efficacy level required in phase 2 to move forward to phase 3 was not achieved.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Brief Fatigue Inventory (BFI)

End point title	Change from Baseline in Brief Fatigue Inventory (BFI)

End point description:

The Brief Fatigue Inventory (BFI) is a brief participant-reported questionnaire that measures the severity of fatigue based on the worst fatigue experienced during the past 24-hours. The severity of fatigue is assessed using an 11-point numeric scale, with 0 = no fatigue and 10 = fatigue as bad as you can imagine.

Population Analysis Description: participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline, Follow up (final visit up to 24 months)

End point values	Galunisertib at 150 mg	Galunisertib at 80 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	2		
Units: units on a scale				
least squares mean (standard error)				
Current Fatigue at Follow-up	0.818 (± 0.42)	-1.005 (± 2.08)		
Usual Fatigue at Follow-up	-0.017 (± 0.37)	-0.157 (± 1.87)		
Worst Fatigue at Follow-up	-0.191 (± 0.38)	-0.063 (± 1.93)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in EuroQol 5-Dimension 5 Level Instrument

End point title	Change from Baseline in EuroQol 5-Dimension 5 Level Instrument

End point description:

EuroQol 5-Dimension 5 Level Instrument (EQ-5D-5L) was not conducted, trial terminated prior to Phase 3. No data collected.

Analysis Population Description: participants who received at least one dose of study drug during Phase 3.

End point type	Secondary

End point timeframe:

Phase 3: Baseline, Cycle 2, Cycle 4, Cycle 6 (Cycle = 28 days)

End point values	Galunisertib at 150 mg	Galunisertib at 80 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: Units on a scale				

Notes:

[4] - EQ-5D-5L was not conducted, trial terminated prior to Phase 3. No data collected.

[5] - EQ-5D-5L was not conducted, trial terminated prior to Phase 3. No data collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Cytogenetic Response

End point title	Percentage of Participants with Cytogenetic Response

End point description:

Percentage of Participants with Cytogenetic Response with either complete or partial response. Complete cytogenetic response is the disappearance of the chromosomal abnormality without appearance of new ones. Partial cytogenetic response is at least 50% reduction of the chromosomal abnormality.

Analysis Population Description: participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline, Cycle 3, Cycle 6 (Cycle = 28 days)

End point values	Galunisertib at 150 mg	Galunisertib at 80 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	2		
Units: percentage of participants				
number (confidence interval 95%)	2.4 (0.1 to 12.9)	0 (0 to 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who are Hospitalized (Resource Utilization)

End point title	Percentage of Participants who are Hospitalized (Resource Utilization)

End point description:

Percentage of any participant with a hospitalization admission and discharge date on the same day are counted as a half-day in the duration of hospitalization.

Analysis Population Description: participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline through end of study treatment (24 weeks)

End point values	Galunisertib at 150 mg	Galunisertib at 80 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	2		
Units: percentage of participants				
number (not applicable)	24.3	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Population Pharmacokinetics (PK): Median Population Clearance of Galunisertib

End point title	Population Pharmacokinetics (PK): Median Population Clearance of Galunisertib

End point description:

Population mean (between-participant coefficient variation [CV%]) apparent clearance.

Analysis Population Description: participants who received at least one dose of study drug with evaluable PK data.

End point type	Secondary

End point timeframe:

Day 1 pre-dose & 0.5 between2 hours post dose; Day 14 pre-dose, 0.5 between 2 & 3 between 5 hours post dose; Days 15 & 16 (if logistically possible) 0.5 between 2 hours post dose

End point values	Galunisertib			
Subject group type	Subject analysis set			
Number of subjects analysed	43			
Units: Liter per hour (L/h)				
geometric mean (geometric coefficient of variation)	32 (± 52)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)[6]

End point description:

Overall survival is defined as the time from the date of first dose to the date of death from any cause.

Analysis Population Description: participants who received at least one dose of study drug excluding the exploratory participants.

End point type	Secondary

End point timeframe:

Baseline to date of death from any cause (Up to 2 years)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The galunisertib at 80 mg arm was considered exploratory and only conducted in parallel with the main study, at one site in Spain. The Overall Survival for the exploratory arm was not included in the analysis.

End point values	Galunisertib at 150 mg			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Median				
median (full range (min-max))	679 (29 to 729)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Bone Marrow Fibrosis

End point title	Change From Baseline in Bone Marrow Fibrosis[7]

End point description:

Change from baseline in bone marrow fibrosis measured the number of participants with a change in bone marrow fibrosis grading (negative, mild, moderate, and severe).

Analysis Population Description: participants who received at least one dose of study drug and had both a baseline and postbaseline assessment excluding the exploratory participants.

End point type	Secondary

End point timeframe:

Baseline, Cycle 3, Cycle 6 (Cycle = 28 days)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The galunisertib at 80 mg arm was considered exploratory and only conducted in parallel with the main study, at one site in Spain. The change from baseline in bone marrow fibrosis for the exploratory arm was not included in the analysis.

End point values	Galunisertib at 150 mg			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: participants				
number (not applicable)	11			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline through end of study treatment or death from any cause (Up to 2 years)	
Adverse event reporting additional description:	
H9H-MC-JBAV	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups	
Reporting group title	Galunisertib at 150 mg
Reporting group description:	
Galunisertib at 150 mg given orally twice daily (BID) for 14 days followed by 14 days with no study drug (28 day cycles). Participants will receive best supportive care (BSC) according to institutional guidelines.	
Reporting group title	Galunisertib at 80 mg
Reporting group description:	
Exploratory arm: Galunisertib at 80 mg given orally twice daily (BID) for 14 days followed by 14... more days with no study drug (28 day cycles). Completed participants completed at least 6 cycles.	

Serious adverse events	Galunisertib at 150 mg	Galunisertib at 80 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 41 (19.51%)	0 / 2 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
cardiac failure			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	2 / 41 (4.88%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
febrile neutropenia			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	1 / 41 (2.44%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
lymphadenopathy			
alternative dictionary used: MedDRA 20.1			

subjects affected / exposed	1 / 41 (2.44%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
crohn's disease			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	1 / 41 (2.44%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
retroperitoneal haemorrhage			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	1 / 41 (2.44%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
respiratory failure			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	2 / 41 (4.88%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infections and infestations			
pneumonia			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	1 / 41 (2.44%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
respiratory syncytial virus infection			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	1 / 41 (2.44%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
tongue abscess			
alternative dictionary used: MedDRA 20.1			

subjects affected / exposed	1 / 41 (2.44%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Galunisertib at 150 mg	Galunisertib at 80 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 41 (80.49%)	2 / 2 (100.00%)	
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	3 / 41 (7.32%)	0 / 2 (0.00%)	
occurrences (all)	3	0	
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	3 / 41 (7.32%)	0 / 2 (0.00%)	
occurrences (all)	18	0	
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	5 / 41 (12.20%)	1 / 2 (50.00%)	
occurrences (all)	13	1	
fatigue			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	4 / 41 (9.76%)	0 / 2 (0.00%)	
occurrences (all)	4	0	
oedema peripheral			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	3 / 41 (7.32%)	0 / 2 (0.00%)	
occurrences (all)	3	0	
pyrexia			
alternative dictionary used: MedDRA 20.1			

subjects affected / exposed	5 / 41 (12.20%)	0 / 2 (0.00%)	
occurrences (all)	8	0	
Gastrointestinal disorders			
diarrhoea			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	7 / 41 (17.07%)	0 / 2 (0.00%)	
occurrences (all)	8	0	
nausea			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	3 / 41 (7.32%)	0 / 2 (0.00%)	
occurrences (all)	4	0	
vomiting			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	5 / 41 (12.20%)	0 / 2 (0.00%)	
occurrences (all)	6	0	
Respiratory, thoracic and mediastinal disorders			
cough			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	0 / 41 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	1	
rhinorrhoea			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	0 / 41 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
back pain			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	3 / 41 (7.32%)	0 / 2 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			
nasopharyngitis			
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	4 / 41 (9.76%)	0 / 2 (0.00%)	
occurrences (all)	4	0	

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

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

The response rate at interim analysis did not meet the predefined rate. The Phase 3 portion was not initiated and the sponsor decided on early discontinuation of the study at the conclusion of Phase 2.

Notes: