



## Clinical trial results: Phase Ib/IIa study of palbociclib in MLL-rearranged acute leukemias

### Summary

EudraCT number	2014-003647-34
Trial protocol	DE
Global end of trial date	03 June 2020

### Results information

Result version number	v1 (current)
This version publication date	20 June 2021
First version publication date	20 June 2021

### Trial information

#### Trial identification

Sponsor protocol code	AMLSG23-14/Palbo-AL-1
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02310243
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	University Hospital Ulm
Sponsor organisation address	Albert-Einstein-Allee 23, Ulm, Germany, 89081
Public contact	AMLSG Clinical trials office, University Hospital Ulm, 0049 73150056071, aml.sekretariat@uniklinik-ulm.de
Scientific contact	AMLSG Clinical trials office, University Hospital Ulm, 0049 73150056071, aml.sekretariat@uniklinik-ulm.de

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	25 May 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	03 June 2020
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

Primary Efficacy Objective

Evaluation of best response to palbociclib including complete remission (CR) and complete remission with incomplete hematologic recovery (CRi), partial remission (PR) and anti-leukemic efficacy (ALE).

Phase Ib:

Evaluation of tolerability and safety of palbociclib in patients with MLL-rearranged leukemia.

Phase IIa:

Assessment of overall response rate to palbociclib including CR, CRi, PR and ALE.

Secondary Efficacy Objective

To evaluate the impact of palbociclib on relapse-free (RFS) and overall survival (OS) in adult patients with MLL-rearranged leukemia.

To evaluate the target (CDK6) inhibition of palbociclib by CDK6 activity in circulating blast cells.

Safety and QoL Objectives

Incidence and intensity of adverse events (AEs) with the addition of palbociclib as assessed according to NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

Quality of life was assessed by the EORTC Quality of Life Core Questionnaire (QLQ-C30).

Protection of trial subjects:

In this study, safety was assessed by evaluating the following: reported adverse events, clinical laboratory test results, vital signs measurements, ECG findings, echo scan, physical examination findings, monitoring of concomitant therapy. For each safety parameter, all findings (whether normal or abnormal) were recorded in the eCRF.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 July 2015
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	Germany: 18
Worldwide total number of subjects	18
EEA total number of subjects	18

Notes:

<b>Subjects enrolled per age group</b>	
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	9
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

First patient in: 30.07.2015

Last patient last visit: 17.10.2019

Accrual to the trial was stopped after eighteen patients during phase II. The recruitment of the trial was very slow, during 2018 and 2019 only 5 patients were recruited, in the last 10 months before the trial was terminated prematurely no patient was recruited.

### Pre-assignment

Screening details:

Cyto- and Molecular genetics characterization (central AMLSG reference lab) of blood and bone marrow was performed at baseline to make an enrollment possible.

### Period 1

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

### Arms

Arm title	Study treatment
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Palbociclib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

palbociclib 125 mg was taken once daily for 21 days, followed by a 7-day wash-out period, up to 6 cycles.

Number of subjects in period 1	Study treatment
Started	18
Completed	1
Not completed	17
Adverse event, serious fatal	2
Consent withdrawn by subject	1
Physician decision	1
death before treatment	2
PBSCT	1
Lack of efficacy	10



## Baseline characteristics

### Reporting groups

Reporting group title	Overall trial period
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Reporting group description: -

Reporting group values	Overall trial period	Total	
Number of subjects	18	18	
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)	9	9	
From 65-84 years	9	9	
85 years and over	0	0	
Age continuous			
Units: years			
median	64		
full range (min-max)	21 to 79	-	
Gender categorical			
Units: Subjects			
Female	11	11	
Male	7	7	
Type of leukemia			
Units: Subjects			
AML	15	15	
ALL	3	3	
Ethnicity			
Units: Subjects			
Caucasian	17	17	
Asian	0	0	
North African / Arabian / Turk	1	1	
Other African	0	0	
Other (South American)	0	0	
Status of disease			
Units: Subjects			
Newly diagnosed disease	3	3	
Refractory disease	1	1	
Relapsed disease	14	14	
Type of AML			
Units: Subjects			
De novo AML	9	9	
Secondary AML after MDS/MPS	5	5	

Treatment-related AML	1	1	
Missing	3	3	
WHO ECOG performance status			
Units: Subjects			
ECOG 0	3	3	
ECOG 1	10	10	
ECOG 2	5	5	
Karyotype			
Units: Subjects			
t(4;11)(q21;q23) / AFF1-MLL (AF4-MLL)	3	3	
t(6;11)(q27;q23) / MLLT4-MLL (AF6-MLL)	2	2	
t(9;11)(p22;q23) / MLLT3-MLL (AF9-MLL)	7	7	
t(10;11)(p13;q23) / MLLT10-MLL (AF10-MLL)	0	0	
t(11;17)(q23;q25) / MLL-SEPT9	1	1	
t(11;19)(q23;p13.1) / MLL-ELL	0	0	
t(11;19)(q23;p13.3) / MLL-MLLT1 (MLL-ENL)	3	3	
Other MLL rearrangement (t(1;11))	2	2	
HCTCI score			
Units: Points			
median	1		
full range (min-max)	0 to 4	-	
Hemoglobin			
Units: g/dl			
median	10.8		
full range (min-max)	7.1 to 13.5	-	
Platelets			
Units: G/l			
median	56		
full range (min-max)	14 to 284	-	
White blood count			
Units: G/l			
median	7.6		
full range (min-max)	1 to 143.6	-	
Bone marrow blast			
Units: percent			
median	70		
full range (min-max)	7 to 95	-	
Peripheral blood blast			
Units: percent			
median	19		
full range (min-max)	0 to 84	-	

## End points

### End points reporting groups

Reporting group title	Study treatment
Reporting group description: -	
Subject analysis set title	Safety-run-in population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients who were treated within the safety run-in phase	

### Primary: Best response including complete remission (CR)/complete remission with incomplete hematologic recovery (CRi)/partial remission (PR) and anti-leukemic efficacy (ALE)

End point title	Best response including complete remission (CR)/complete remission with incomplete hematologic recovery (CRi)/partial remission (PR) and anti-leukemic efficacy (ALE) <sup>[1]</sup>
End point description:	
End point type	Primary
End point timeframe:	
overall treatment period	

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: Primary and secondary efficacy variables were not analyzed due to premature termination of the trial.

End point values	Study treatment			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: responses				
CR	0			
CRi	1			
PR	1			
ALE	0			
Missing	2			
PD	6			
SD	8			

### Statistical analyses

No statistical analyses for this end point

### Primary: Assessment overall response rate including CR, CRi, PR and ALE

End point title	Assessment overall response rate including CR, CRi, PR and ALE <sup>[2]</sup>
End point description:	
End point type	Primary



End point timeframe:  
overall treatment period

Notes:

[2] - 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: Primary and secondary efficacy variables were not analyzed due to premature termination of the trial.

End point values	Study treatment			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: responses				
CR / CRi / PR / ALE	2			
No response	14			
Missing	2			

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Rate of Dose-limiting toxicity

End point title	Rate of Dose-limiting toxicity
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End point description:

End point type	Other pre-specified
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End point timeframe:

phase Ib of the study, first treatment cycle (28 days)

End point values	Safety-run-in population			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: Patients with DLT				
DLT	0			
No DLT	6			

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

The AE reporting period for this trial begins upon start of treatment and ends 28 days after the last treatment administration or when all drug-related toxicities are resolved, or when the investigator assesses AEs as "chronic" or "stable".

Assessment type	Systematic
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### Dictionary used

Dictionary name	CTCAE
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Dictionary version	4.03
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### Reporting groups

Reporting group title	Overall treatment period
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Reporting group description: -

Serious adverse events	Overall treatment period		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 16 (62.50%)		
number of deaths (all causes)	16		
number of deaths resulting from adverse events	7		
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Blood and lymphatic system disorders			
Blood and lymphatic system disorders - Other			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Death NOS			

subjects affected / exposed	3 / 16 (18.75%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 3		
Fever			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions - Other			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	1 / 2		
Gastrointestinal disorders			
Gastrointestinal disorders - Other			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Infections and infestations			
Catheter related infection			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations - Other			

subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Lung infection			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Pharyngitis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 16 (6.25%)		
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 %

<b>Non-serious adverse events</b>	Overall treatment period		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 16 (93.75%)		
Vascular disorders			
Hematoma			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	3		
Thromboembolic event			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Vascular disorders - Other			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Vasculitis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
General disorders and administration			

site conditions			
Chills			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Edema limbs			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	5		
Fatigue			
subjects affected / exposed	4 / 16 (25.00%)		
occurrences (all)	5		
Fever			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Pain			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	3		
Reproductive system and breast disorders			
Reproductive system and breast disorders - Other			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	5 / 16 (31.25%)		
occurrences (all)	7		
Pleural effusion			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders - Other			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Psychiatric disorders			

Anorgasmia subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 2		
Anxiety subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Confusion subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Insomnia subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Investigations			
Activated partial thromboplastin time prolonged subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 3		
Alkaline phosphatase increased subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Blood bilirubin increased subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Creatinine increased subjects affected / exposed occurrences (all)	3 / 16 (18.75%) 5		
Electrocardiogram QT corrected interval prolonged subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2		
Hemoglobin increased subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
INR increased			

subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 2		
Investigations - Other subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 4		
Lymphocyte count decreased subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 2		
Lymphocyte count increased subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 4		
Neutrophil count decreased subjects affected / exposed occurrences (all)	9 / 16 (56.25%) 27		
Platelet count decreased subjects affected / exposed occurrences (all)	10 / 16 (62.50%) 26		
White blood cell decreased subjects affected / exposed occurrences (all)	9 / 16 (56.25%) 22		
Injury, poisoning and procedural complications Ankle fracture subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Wound complication subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Cardiac disorders Cardiac disorders - Other subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2		
Sinus bradycardia subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Sinus tachycardia			

subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Ventricular arrhythmia			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	2		
Nervous system disorders			
Concentration impairment			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	4 / 16 (25.00%)		
occurrences (all)	4		
Facial nerve disorder			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Nervous system disorders - Other			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Paresthesia			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Peripheral motor neuropathy			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Syncope			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	12 / 16 (75.00%)		
occurrences (all)	29		
Blood and lymphatic system disorders - Other			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	2		
Febrile neutropenia			



<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Leukocytosis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>3 / 16 (18.75%)</p> <p>3</p> <p>4 / 16 (25.00%)</p> <p>4</p>		
<p>Ear and labyrinth disorders</p> <p>Tinnitus</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 16 (6.25%)</p> <p>1</p>		
<p>Eye disorders</p> <p>Blurred vision</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dry eye</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 16 (6.25%)</p> <p>2</p> <p>1 / 16 (6.25%)</p> <p>2</p>		
<p>Gastrointestinal disorders</p> <p>Abdominal pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Anal necrosis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Constipation</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dental caries</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Diarrhea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dyspepsia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Gastroesophageal reflux disease</p>	<p>1 / 16 (6.25%)</p> <p>1</p> <p>1 / 16 (6.25%)</p> <p>2</p> <p>2 / 16 (12.50%)</p> <p>2</p> <p>1 / 16 (6.25%)</p> <p>1</p> <p>2 / 16 (12.50%)</p> <p>3</p> <p>1 / 16 (6.25%)</p> <p>1</p>		

subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Gastrointestinal disorders - Other			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Mucositis oral			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	4		
Oral dysesthesia			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Oral hemorrhage			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Oral pain			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Tooth development disorder			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Rash maculo-papular			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders - Other			

subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 3		
Renal and urinary disorders Bladder perforation subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2		
Musculoskeletal and connective tissue disorders Bone pain subjects affected / exposed occurrences (all)  Musculoskeletal and connective tissue disorder - Other subjects affected / exposed occurrences (all)  Pain in extremity subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1  3 / 16 (18.75%) 4  1 / 16 (6.25%) 1		
Infections and infestations Biliary tract infection subjects affected / exposed occurrences (all)  Catheter related infection subjects affected / exposed occurrences (all)  Infections and infestations - Other subjects affected / exposed occurrences (all)  Upper respiratory infection subjects affected / exposed occurrences (all)  Urinary tract infection subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1  1 / 16 (6.25%) 1  2 / 16 (12.50%) 4  2 / 16 (12.50%) 2  1 / 16 (6.25%) 2		
Metabolism and nutrition disorders Hyperkalemia subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2		

Hypoalbuminemia			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Hypokalemia			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Hypomagnesemia			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	3		
Metabolism and nutrition disorders - Other			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	5		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 July 2015	Main changes were: <ul style="list-style-type: none"><li>- Integration of updated information regarding the IMP</li><li>- Correction of permitted concomitant medication</li></ul>
30 December 2016	Main changes were: <ul style="list-style-type: none"><li>- Integration of new knowledge and update of the information related to the IMP</li><li>- Update of the phase Ib for patients with MLL-rearranged leukemia</li><li>- Update the list of expected leukemia-associated adverse events and implementation of the adverse events of special interest (AESI)</li><li>- Update of the people involved</li><li>- Include some minor administrative-type changes</li></ul>
04 December 2017	Main changes were: <ul style="list-style-type: none"><li>- Update of the supply of Palbociclib</li></ul>

Notes:

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### 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.

On June 3rd 2020 the study was early terminated. The recruitment of the trial was very slow, during 2018 and 2019 only 5 patients were recruited, in the last 10 months before the trial was terminated prematurely no patient was recruited.

Notes: