Clinical trial results:
The TEAM Study (Thiopurine EnhAnced Maintenance therapy)
A Phase 1-2 Study of 6-Thioguanine in Combination with Methotrexate and 6-Mercaptopurine During Maintenance Therapy of Childhood, Adolescent, and Adult Lymphoblastic Non-Hodgkin's Lymphoma and Acute Lymphoblastic Leukemia

Summary

EudraCT number	2014-002248-42
Trial protocol	DK FI
Global end of trial date	12 March 2020

Results information

Result version number	v1 (current)
This version publication date	21 March 2021
First version publication date	21 March 2021

Trial information

Trial identification

Sponsor protocol code	0JMC-2014-6TG/6MP

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02912676
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bonkolab, Rigshospitalet
Sponsor organisation address	Blegdamsvej 9, Copenhagen Ø, Denmark, DK-21000
Public contact	Bonkolab, Rigshospitalet, Bonkolab, +45 35454652, Kjeld.Schmiegelow@regionh.dk
Scientific contact	Bonkolab, Rigshospitalet, Bonkolab, +45 35454652, Kjeld.Schmiegelow@regionh.dk

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 August 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 March 2020
Global end of trial reached?	Yes
Global end of trial date	12 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To explore the feasibility of 6TG as a supplement to maintenance therapy of Acute Lymphoblastic Leukemia and Lymphoblastic Non-Hodgkin's Lymphoma in order to improve the existing dose adjustment strategies. We hypothesize that MTX/6MP/6TG combination therapy will achieve a higher DNA-TGN level and enhance the effect of 6MP. We will describe toxicities, hematology and thiopurine metabolite levels during MTX/6MP/6TG combination therapy.
This study will be the first to assess the applicability of 6TG in combination with standard MTX/6MP maintenance therapy.

Protection of trial subjects:

During 6TG therapy the frequency of controls was increased from biweekly to every week in order to note any toxicities early. In case of myelo-/hepatotoxicity or infection the recommendations in the NOPHO therapy guidelines were followed with regards to the dosing of 6MP and MTX. In case of toxicity the administration of 6TG was either withheld or reduced depending on the toxicity.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 August 2016
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	Denmark: 33
Country: Number of subjects enrolled	Finland: 1
Worldwide total number of subjects	34
EEA total number of subjects	34

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)	3
Children (2-11 years)	22

Adolescents (12-17 years)	4
Adults (18-64 years)	5
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Eligible patients were included, when they reached maintenance therapy phase II (maintenance-II). Patients were included during the entire course of maintenance-II but had to have at least 3 months of remaining therapy upon first visit. Inclusion was completed in December 2018, and the last TEAM patient finished therapy in March 2020.

Pre-assignment

Screening details:

Patients aged 1–45 years with non-high risk ALL (i.e. standard and intermediate risk) and treated according to the NOPHO ALL2008 protocol were eligible for the study.
Eligible patients were included, when they reached maintenance therapy phase II. Patients had to have at least three months of remaining therapy upon first visit.

Period 1

Period 1 title	Before TEAM
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Before TEAM

Arm description:

TEAM-patients before TEAM.
Time period before TEAM was defined as two months prior to initiation of 6TG treatment.

Arm type	Active comparator
Investigational medicinal product name	6-mercaptopurine
Investigational medicinal product code	
Other name	Xaluprine, Puri-nethol
Pharmaceutical forms	Tablet, Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Dosing of daily oral 6MP is targeted to a WBC level of 1.5–3.0 x109/L. Therapy was discontinued 2.5 years from diagnosis.

Investigational medicinal product name	Methotrexat
Investigational medicinal product code	
Other name	MTX
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dosing of weekly oral MTX is targeted to a WBC level of 1.5–3.0 x109/L. Therapy was discontinued 2.5 years from diagnosis.

Number of subjects in period 1	Before TEAM
Started	34
Completed	32
Not completed	2
Consent withdrawn by subject	2

Period 2

Period 2 title	TEAM
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	TEAM

Arm description:

TEAM patients. Time period before TEAM was defined as two months prior to initiation of 6TG treatment.

Arm type	Experimental
Investigational medicinal product name	6-Thioguanine
Investigational medicinal product code	
Other name	6TG
Pharmaceutical forms	Oral solution, Tablet
Routes of administration	Oral use

Dosage and administration details:

Incremental 6TG doses were added to standard MTX/6MP maintenance therapy at a dose of 2.5 mg/m2/day and increased by 2.5 mg/m2/day biweekly until reaching maximum 6TG dose of 12.5 mg/m2/day. DNA-TG target level was DNA-TG above 500 fmol/µg DNA (approximate mean DNA-TG at end of MTX/6MP based maintenance therapy). TEAM patients followed the same WBC target of 1.5–3.0 x109/L. If DNA-TG and/or WBC targets were not reached at maximum 6TG doses (i.e. 12.5 mg/m2/day) 6MP and/or MTX dosages were adjusted.

Investigational medicinal product name	6-mercaptopurine
Investigational medicinal product code	
Other name	Xaluprine, Puri-nethol
Pharmaceutical forms	Oral suspension, Tablet
Routes of administration	Oral use

Dosage and administration details:

Dosing of daily oral 6MP is targeted to a WBC level of 1.5–3.0 x109/L. Therapy was discontinued 2.5 years from diagnosis.

Investigational medicinal product name	Methotrexat
Investigational medicinal product code	
Other name	MTX
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dosing of weekly oral MTX is targeted to a WBC level of 1.5–3.0 x109/L. Therapy was discontinued 2.5 years from diagnosis.

Number of subjects in period 2	TEAM
Started	32
Completed	30
Not completed	2
Consent withdrawn by subject	1

On-therapy leukemic relaps	1

Baseline characteristics

Reporting groups	
Reporting group title	Before TEAM

Reporting group description: -

Reporting group values	Before TEAM	Total	
Number of subjects	34	34	
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	3	3	
Children (2-11 years)	22	22	
Adolescents (12-17 years)	4	4	
Adults (18-64 years)	5	5	
Gender categorical Units: Subjects			
Female	12	12	
Male	22	22	

End points

End points reporting groups

Reporting group title	Before TEAM
Reporting group description:	
TEAM-patients before TEAM. Time period before TEAM was defined as two months prior to initiation of 6TG treatment.	
Reporting group title	TEAM
Reporting group description:	
TEAM patients. Time period before TEAM was defined as two months prior to initiation of 6TG treatment.	

Primary: DNA-TG

End point title	DNA-TG
End point description:	
End point type	Primary
End point timeframe:	
DNA-TG was measured weekly or biweekly during the time period from initiation of 6TG until discontinuation of all therapy	

End point values	Before TEAM	TEAM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	32		
Units: fmol/µg				
arithmetic mean (full range (min-max))	530 (157 to 1279)	764 (273 to 1402)		

Statistical analyses

Statistical analysis title	Mean difference
Comparison groups	Before TEAM v TEAM
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.0001
Method	Welch´s t-test
Parameter estimate	Mean difference (final values)
Point estimate	251
Confidence interval	
level	95 %
sides	2-sided
lower limit	160
upper limit	341

Variability estimate	Standard error of the mean

Notes:

[1] - Paired t-test

Secondary: Ery-TGN

End point title	Ery-TGN

End point description:

End point type	Secondary

End point timeframe:

Ery-TGN was measured weekly or biweekly during the time period from initiation of 6TG until discontinuation of all therapy

End point values	Before TEAM	TEAM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	32		
Units: nmol/mmol hbg				
arithmetic mean (full range (min-max))	240 (100 to 485)	721 (339 to 1396)		

Statistical analyses

Statistical analysis title	Mean difference
Comparison groups	Before TEAM v TEAM
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	< 0.0001
Method	Welch´s t-test
Parameter estimate	Mean difference (final values)
Point estimate	470
Confidence interval	
level	95 %
sides	2-sided
lower limit	349
upper limit	590
Variability estimate	Standard error of the mean

Notes:

[2] - Paired t-test

Secondary: 6MP dose

End point title	6MP dose

End point description:

End point type	Secondary

End point timeframe:

6MP dose was adjusted weekly or biweekly during the time period from initiation of 6TG until discontinuation of all therapy

End point values	Before TEAM	TEAM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	32		
Units: mg/m2/day				
arithmetic mean (full range (min-max))	53 (6 to 121)	45 (7 to 79)		

Statistical analyses

Statistical analysis title	Mean difference
Comparison groups	Before TEAM v TEAM
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.09
Method	Welch´s t-test
Parameter estimate	Mean difference (final values)
Point estimate	-9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19
upper limit	1
Variability estimate	Standard error of the mean

Notes:

[3] - Paired t-test

Secondary: MTX dose

End point title	MTX dose

End point description:

End point type	Secondary

End point timeframe:

measured weekly during the time period from initiation of 6TG until discontinuation of all therapy

End point values	Before TEAM	TEAM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	32		
Units: mg/m2/day				
arithmetic mean (full range (min-max))	19 (4 to 41)	19 (5 to 38)		

Statistical analyses

Statistical analysis title	Mean difference
Comparison groups	Before TEAM v TEAM
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.99
Method	Welch´s t-test
Parameter estimate	Mean difference (final values)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.8
upper limit	2.7
Variability estimate	Standard error of the mean

Notes:

[4] - Paired t-test

Secondary: Ery-MeMP

End point title	Ery-MeMP

End point description:

End point type	Secondary

End point timeframe:

Measured weekly during the time period from initiation of 6TG until discontinuation of all therapy

End point values	Before TEAM	TEAM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	32		
Units: nmol/mmol hgb				
arithmetic mean (full range (min-max))	8462 (177 to 21520)	5931 (142 to 14385)		

Statistical analyses

Statistical analysis title	Mean difference
Comparison groups	Before TEAM v TEAM
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.06
Method	Welch´s t-test
Parameter estimate	Mean difference (final values)
Point estimate	-1.948
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.011
upper limit	115
Variability estimate	Standard error of the mean

Notes:

[5] - Paired t-test

Secondary: WBC

End point title	WBC

End point description:

End point type	Secondary

End point timeframe:

Measured weekly or biweekly during the time period from initiation of 6TG until discontinuation of all therapy

End point values	Before TEAM	TEAM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	32		
Units: billion cells per litre				
arithmetic mean (full range (min-max))	3.1 (1.9 to 5.7)	3.2 (2.2 to 5.5)		

Statistical analyses

Statistical analysis title	Mean difference
Comparison groups	Before TEAM v TEAM
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.78
Method	Welch´s t-test
Parameter estimate	Mean difference (final values)
Point estimate	0.05

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	0.41
Variability estimate	Standard error of the mean

Notes:

[6] - Paired t-test

Secondary: ANC

End point title	ANC

End point description:

End point type	Secondary

End point timeframe:

Measured weekly or biweekly during the time period from initiation of 6TG until discontinuation of all therapy

End point values	Before TEAM	TEAM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	32		
Units: Billion cells per litre				
arithmetic mean (full range (min-max))	1.8 (0.7 to 3.7)	1.9 (1.0 to 3.7)		

Statistical analyses

Statistical analysis title	Mean difference
Comparison groups	Before TEAM v TEAM
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.4
Method	Welch´s t-test
Parameter estimate	Mean difference (final values)
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.19
upper limit	0.45
Variability estimate	Standard error of the mean

Notes:

[7] - Paired-t-test

Secondary: TBC

End point title	TBC

End point description:

End point type	Secondary

End point timeframe:

Measured weekly or biweekly during the time period from initiation of 6TG until discontinuation of all therapy

End point values	Before TEAM	TEAM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	32		
Units: Billion cells per litre				
arithmetic mean (full range (min-max))	247 (108 to 371)	261 (56 to 383)		

Statistical analyses

Statistical analysis title	Mean difference
Comparison groups	Before TEAM v TEAM
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.02
Method	Welch´s t-test
Parameter estimate	Mean difference (final values)
Point estimate	19
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.7
upper limit	35
Variability estimate	Standard error of the mean

Notes:

[8] - Paired-t-test

Secondary: Hgb

End point title	Hgb

End point description:

End point type	Secondary

End point timeframe:

Measured weekly or biweekly during the time period from initiation of 6TG until discontinuation of all therapy

End point values	Before TEAM	TEAM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	32		
Units: mmol/L				
arithmetic mean (full range (min-max))	7.6 (6.3 to 9.3)	7.7 (6.3 to 9.0)		

Statistical analyses

Statistical analysis title	Mean difference
Comparison groups	Before TEAM v TEAM
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.1
Method	Welch´s t-test
Parameter estimate	Mean difference (final values)
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.4
Variability estimate	Standard error of the mean

Notes:

[9] - Paired t-test

Secondary: ALAT

End point title	ALAT

End point description:

End point type	Secondary

End point timeframe:

Measured weekly or biweekly during the time period from initiation of 6TG until discontinuation of all therapy

End point values	Before TEAM	TEAM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	32		
Units: U/L				
arithmetic mean (full range (min-max))	139 (26 to 373)	118 (20 to 265)		

Statistical analyses

Statistical analysis title	Mean difference
Comparison groups	Before TEAM v TEAM
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.23
Method	Welch´s t-test
Parameter estimate	Mean difference (final values)
Point estimate	-13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-35
upper limit	9
Variability estimate	Standard error of the mean

Notes:

[10] - Paired t-test

Secondary: Coagulation factors II-VII-X

End point title	Coagulation factors II-VII-X

End point description:

End point type	Secondary

End point timeframe:

Measured weekly or biweekly during the time period from initiation of 6TG until discontinuation of all therapy

End point values	Before TEAM	TEAM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	32		
Units: IU/L				
arithmetic mean (full range (min-max))	0.7 (0.4 to 0.9)	0.7 (0.5 to 0.9)		

Statistical analyses

Statistical analysis title	Mean difference
Comparison groups	Before TEAM v TEAM
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.42
Method	Welch´s t-test
Parameter estimate	Mean difference (final values)
Point estimate	0.02

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.08
Variability estimate	Standard error of the mean

Notes:
[11] - Paired t-test

Secondary: INR

End point title	INR

End point description:

End point type	Secondary

End point timeframe:
Measured weekly during the time period from initiation of 6TG until discontinuation of all therapy

End point values	Before TEAM	TEAM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	32		
Units: No unit for INR				
arithmetic mean (full range (min-max))	1.2 (1.0 to 1.6)	1.2 (1.1 to 1.3)		

Statistical analyses

Statistical analysis title	Mean difference
Comparison groups	Before TEAM v TEAM
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.06
Method	Welch´s t-test
Parameter estimate	Mean difference (final values)
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0.002
Variability estimate	Standard error of the mean

Notes:
[12] - Paired t-test

Secondary: Bilirubin

End point title	Bilirubin

End point description:

End point type	Secondary

End point timeframe:

Measured weekly or biweekly during the time period from initiation of 6TG until discontinuation of all therapy

End point values	Before TEAM	TEAM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	32		
Units: micromole(s)/litre				
arithmetic mean (full range (min-max))	11 (4 to 32)	12 (5 to 29)		

Statistical analyses

Statistical analysis title	Mean difference
Comparison groups	Before TEAM v TEAM
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.95
Method	Welch´s t-test
Parameter estimate	Mean difference (final values)
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	1.9
Variability estimate	Standard error of the mean

Notes:

[13] - Paired t-test

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From inclusion untill 24 hours after the last 6TG dose.
Follow-up for 5 years - off-study.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	All subjects

Reporting group description: -

Serious adverse events	All subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 34 (14.71%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Blood and lymphatic system disorders			
Leukemic relaps			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteonecrosis			
subjects affected / exposed	4 / 34 (11.76%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	All subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 34 (97.06%)		
Ear and labyrinth disorders			

Acute Otitis Media subjects affected / exposed occurrences (all)	5 / 34 (14.71%) 5		
Eye disorders Herpes ophthalmic subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	20 / 34 (58.82%) 20		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) Molluscum contagiosum subjects affected / exposed occurrences (all)	10 / 34 (29.41%) 10 1 / 34 (2.94%) 1		
Infections and infestations Fever subjects affected / exposed occurrences (all)	20 / 34 (58.82%) 20		

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

None reported