



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 | OJMC-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 until 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