



Clinical trial results:

A phase I/II open label clinical trial assessing safety and efficacy of intravesical instillation of VPM1002BC in patients with recurrent non-muscle invasive bladder cancer after standard BCG therapy

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2014-005330-58 |
| Trial protocol | DE NL |
| Global end of trial date | 07 March 2023 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 30 July 2023 |
| First version publication date | 30 July 2023 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | SAKK06/14 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02371447 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Swiss Group for Clinical Cancer Research (SAKK) |
| Sponsor organisation address | Effingerstrasse 33, Bern, Switzerland, 3008 |
| Public contact | Head Regulatory Affairs, Swiss Group for Clinical Cancer Research (SAKK), +41 31389 91 91, sakkcc@sak.ch |
| Scientific contact | Head Regulatory Affairs, Swiss Group for Clinical Cancer Research (SAKK), +41 31389 91 91, sakkcc@sak.ch |

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 | 06 June 2023 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|---------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 07 March 2023 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Phase I: To determine safety, tolerability and the recommended phase II dose (RP2D) of intravesical VPM1002BC instillations in patients with recurrence of non-muscle-invasive bladder cancer after transurethral resection of the bladder (TURB) and standard Bacille Calmette Guérin (BCG) therapy.

Phase II: To investigate the efficacy, safety, tolerability and immunogenicity of intravesical VPM1002BC instillations in patients with recurrence of non-muscle-invasive bladder cancer after TURB and standard BCG therapy.

Protection of trial subjects:

Protection of trial subjects was ensured by Safety Monitoring, i.e. assessment of adverse events, serious adverse events, adverse drug reactions, and the continuous assessment of laboratory values and vital signs.

Background therapy:

none

Evidence for comparator:

not applicable

| | |
|---|-------------------|
| Actual start date of recruitment | 08 September 2015 |
| 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 | Germany: 8 |
| Country: Number of subjects enrolled | Switzerland: 34 |
| Worldwide total number of subjects | 42 |
| EEA total number of subjects | 8 |

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) | 8 |
| From 65 to 84 years | 34 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

42 patients at 14 sites in Switzerland (9 sites, 34 patients) and Germany (5 sites, 8 patients) have been enrolled from September 2015 to April 2018.

Pre-assignment

Screening details:

Eligibility criteria of a patient were checked by the investigator. Once a patient fulfils all inclusion criteria and not any of the exclusion criteria, he/she was enrolled.

Period 1

| | |
|------------------------------|---------------------------|
| Period 1 title | Phase I - Induction Phase |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|-----------|-----------|
| Arm title | VPM1002BC |
|-----------|-----------|

Arm description:

Phase I: Dose finding.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | VPM1002BC |
| Investigational medicinal product code | |
| Other name | Mycobacterium bovis BCGΔureC::Hly+ for immunotherapy |
| Pharmaceutical forms | Intravesical suspension |
| Routes of administration | Instillation |

Dosage and administration details:

Dose level 1: 1-19.2x10E8 CFUs/50ml (CFU= colony forming units) per instillation (or dose level -1: 1-19.2x10E7 CFUs/46.4ml per instillation [not applied])

Induction: 6 instillations at weekly intervals (within 6 to 12 weeks). First instillation has to be done within 14 days after registration and corresponds to day 1 of the trial treatment schedule (= treatment start).

After sterile transurethral insertion of a self-lubricating Charrière 12-16 catheter and after re-suspension of the dose of VPM1002BC in 50 ml of diluent, the dispersion is applied into the bladder without pressure.

| | |
|---------------------------------------|-----------|
| Number of subjects in period 1 | VPM1002BC |
| Started | 6 |
| End of Phase I Induction | 6 |
| Completed | 42 |

| | |
|----------------------|----|
| Joined | 36 |
| Phase II recruitment | 36 |

Period 2

| | |
|------------------------------|-------------------------------------|
| Period 2 title | Phase II - Baseline/Treatment Phase |
| Is this the baseline period? | Yes ^[1] |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|--|--|
| Arm title | VPM1002BC |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | VPM1002BC |
| Investigational medicinal product code | |
| Other name | Mycobacterium bovis BCGΔureC::Hly+ for immunotherapy |
| Pharmaceutical forms | Intravesical suspension |
| Routes of administration | Instillation |

Dosage and administration details:

Dose level 1: 1-19.2x10E8 CFUs/50ml (CFU= colony forming units) per instillation

Induction: 6 instillations at weekly intervals (within 6 to 12 weeks). First instillation has to be done within 14 days after registration and corresponds to day 1 of the trial treatment schedule (= treatment start).

Maintenance: 3 instillations at weekly intervals starting at week 13 from day 1 followed by 3 instillations at weekly intervals starting at week 25 from day 1, followed by 3 instillations at weekly intervals starting at week 49 from day 1.

After sterile transurethral insertion of a self-lubricating Charrière 12-16 catheter and after re-suspension of the dose of VPM1002BC in 50 ml of diluent, the dispersion is applied into the bladder without pressure.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: This was a combined Phase I/II study. Period 1 refers to Phase I induction phase (dose finding), and Period 2 to Phase II baseline/treatment phase.

| | |
|---------------------------------------|-----------|
| Number of subjects in period 2 | VPM1002BC |
| Started | 42 |
| Completed | 42 |

Period 3

| | |
|------------------------------|----------------------------|
| Period 3 title | Phase II - Follow-up Phase |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|---|-----------------|
| Arm title | Follow-up |
| Arm description: - | |
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 3 | Follow-up |
|---------------------------------------|-----------|
| Started | 42 |
| Completed | 19 |
| Not completed | 23 |
| Death | 12 |
| Lost to follow-up | 11 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | VPM1002BC |
|-----------------------|-----------|

Reporting group description: -

| Reporting group values | VPM1002BC | Total | |
|------------------------|-----------|-------|--|
| Number of subjects | 42 | 42 | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 8 | 8 | |
| From 65-84 years | 34 | 34 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 4 | 4 | |
| Male | 38 | 38 | |

End points

End points reporting groups

| | |
|---|---------------|
| Reporting group title | VPM1002BC |
| Reporting group description: Phase I: Dose finding. | |
| Reporting group title | VPM1002BC |
| Reporting group description: - | |
| Reporting group title | Follow-up |
| Reporting group description: - | |
| Subject analysis set title | FAS |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Full analysis ste including all registered patients, exluding two patients failing to satisfy major eligibilty criteria. | |
| Subject analysis set title | PPS |
| Subject analysis set type | Per protocol |
| Subject analysis set description: PPS including all patients in the FAS and excluding 15 patients with serious protocol deviations. | |

Primary: PE | Recurrence-free rate (90%CI)

| | |
|--|--|
| End point title | PE Recurrence-free rate (90%CI) ^[1] |
| End point description: The primary endpoint (PE) was analyzed using a test statistic based on the Kaplan-Meier (KM) estimator of the cumulative hazard function. The KM estimator was evaluated at 62 weeks as we allowed 2 weeks delay in the last assessment. The recurrence-free rate at 60 weeks together with a one-sided 90% as well a two-sided 95% confidence interval (CI) estimated using the KM estimator are shown. Note: Dummy data ("9999") entered for upper limit of 1-sided 90% CI due to database restrictions. Upper limit of 1-sided 90% CI not applicable. A single-stage design was applied with p0: recurrence-free rate at 60 weeks $\leq 15\%$ and p1: recurrence-free rate at 60 weeks $\geq 30\%$ with a 1-sided significance level of 10% and a power of 80%. The lower boundary of the 1-sided 90% CI is higher than p0 (15%) and even higher than p1 (30%), thus the null hypothesis can be rejected and the PE is clearly reached. | |
| End point type | Primary |
| End point timeframe: 60 weeks after registration. | |

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: Statistical analyses cannot be entered for single arm studies (database restriction): A single-stage design was applied with p0: recurrence-free rate at 60 weeks $\leq 15\%$ and p1: recurrence-free rate at 60 weeks $\geq 30\%$ with a 1-sided significance level of 10% and a power of 80%. As the lower boundary of the 1-sided 90% CI is higher than p0 (15%) the null hypothesis can be rejected. The lower boundary of the 1-sided 90% CI is even higher than p1 (30%). Thus, the primary endpoint is clearly reached.

| End point values | FAS | PPS | | |
|----------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 40 | 25 | | |
| Units: Recurrence-free rate (%) | | | | |
| number (confidence interval 90%) | 49.3 (38.1 to 9999) | 44.1 (30.7 to 9999) | | |

Statistical analyses

No statistical analyses for this end point

Primary: PE | Recurrence-free rate (95% CI)

| | |
|-----------------|---|
| End point title | PE Recurrence-free rate (95% CI) ^[2] |
|-----------------|---|

End point description:

The primary endpoint (PE) was analyzed using a test statistic based on the Kaplan-Meier (KM) estimator of the cumulative hazard function. The KM estimator was evaluated at 62 weeks as we allowed 2 weeks delay in the last assessment. The recurrence-free rate at 60 weeks together with a one-sided 90% as well a two-sided 95% confidence interval (CI) estimated using the KM estimator are shown.

A single-stage design was applied as described before for the 90% CI, except the use of a 2-sided 95% CI. Even with the 2-sided 95% CI the null hypothesis can be rejected.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

60 weeks after registration.

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: Statistical analyses cannot be entered for single arm studies (database restriction): A single-stage design was applied with p0: recurrence-free rate at 60 weeks $\leq 15\%$ and p1: recurrence-free rate at 60 weeks $\geq 30\%$ with a 2-sided significance level of 5% and a power of 80%. Even with the 2-sided 95% CI the null hypothesis can be rejected and the primary endpoint is clearly reached.

| End point values | FAS | PPS | | |
|----------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 40 | 25 | | |
| Units: Recurrence-free rate (%) | | | | |
| number (confidence interval 95%) | 49.3 (32.1 to 64.4) | 44.1 (23.8 to 62.8) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Time to recurrence in the bladder

| | |
|-----------------|--|
| End point title | SE Time to recurrence in the bladder |
|-----------------|--|

End point description:

23 patients experienced a confirmed recurrence in the bladder.

The median time to recurrence in the bladder was estimated using the KM method.

Note: Dummy data ("9999") entered for 95% CI upper limit of time to recurrence due to database restrictions. Upper limit of 95% CI not reached.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From registration to tumor recurrence in the bladder.

| End point values | FAS | | | |
|-----------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 40 | | | |
| Units: Time to recurrence (years) | | | | |
| median (confidence interval 95%) | 1.3 (0.8 to 9999) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Recurrence-free rate in the bladder at 2, 3 and 4 years

| | |
|-----------------|--|
| End point title | SE Recurrence-free rate in the bladder at 2, 3 and 4 years |
|-----------------|--|

End point description:

The recurrence-free rate in the bladder at 2, 3, and 4 years were calculated using the KM estimator.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Two, three and four years after start of treatment.

| End point values | FAS | | | |
|----------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 40 | | | |
| Units: Estimator (%) | | | | |
| number (confidence interval 95%) | | | | |
| 2 years | 45.5 (28.9 to 60.7) | | | |
| 3 years | 39.5 (23.6 to 54.9) | | | |
| 4 years | 39.5 (23.6 to 54.9) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Time to recurrence

| | |
|-----------------|-------------------------|
| End point title | SE Time to recurrence |
|-----------------|-------------------------|

End point description:

Two events in addition to 23 recurrences in the bladder = 25 events.

The median time to recurrence was estimated using the KM method.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From registration to recurrence at local, regional or distant site.

| End point values | FAS | | | |
|-----------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 40 | | | |
| Units: Time to recurrence (years) | | | | |
| median (confidence interval 95%) | 1.3 (0.7 to 4.3) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Recurrence-free rate at 1, 2, 3 and 4 years

| | |
|-----------------|--|
| End point title | SE Recurrence-free rate at 1, 2, 3 and 4 years |
|-----------------|--|

End point description:

The recurrence-free rate in the bladder at 1, 2, 3, and 4 years were calculated using the KM estimator.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

One, two, three and four years after start of treatment.

| End point values | FAS | | | |
|----------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 40 | | | |
| Units: Estimator (%) | | | | |
| number (confidence interval 95%) | | | | |
| 1 year | 52.7 (35.9 to 67.0) | | | |
| 2 years | 44.5 (28.4 to 59.4) | | | |
| 3 years | 36.2 (21.2 to 51.3) | | | |
| 4 years | 36.2 (21.2 to 51.3) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Time to progression

| | |
|-----------------|--------------------------|
| End point title | SE Time to progression |
|-----------------|--------------------------|

End point description:

In the trial protocol, progression was defined as a recurrence with an increased stage (as compared to the stage at recurrence before inclusion into the trial) or increased grade or new occurrence of CIS. In case of several events, the first one was counted.

To allow comparisons with literature, another definition for progression was used in addition, counting progression to muscle-invasive disease and increase in M or N stage as progression.

According to the protocol definition, 16 patients experienced an event (12 increases in stage and 4 new occurrences of CIS). With the updated definition, 11 patients experienced an event; of those 3 and 4 were increase in M or N stage, respectively, and 4 were progressions to muscle-invasive disease.

The median time to progression was not reached at the time of this analysis. Dummy data ("9999") entered due to database restrictions.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Time to progression was defined as time from registration to progression.

| End point values | FAS | | | |
|------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 40 | | | |
| Units: Time to progression (years) | | | | |
| median (confidence interval 95%) | 9999 (9999 to 9999) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Progression-free rate in the bladder at 1, 2, 3 and 4 years

| | |
|-----------------|--|
| End point title | SE Progression-free rate in the bladder at 1, 2, 3 and 4 years |
|-----------------|--|

End point description:

The progression-free rate at 1, 2, 3 and 4 years (protocol definition or updated definition, see information provided for endpoint "Time to progression") was calculated using the KM estimator.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

One, two, three and four years after start of treatment.

| End point values | FAS | | | |
|----------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 40 | | | |
| Units: Estimator (%) | | | | |
| number (confidence interval 95%) | | | | |
| 1 year (protocol definition) | 66.3 (48.3 to 79.3) | | | |

| | | | | |
|-------------------------------|---------------------|--|--|--|
| 2 years (protocol definition) | 63.2 (45.0 to 76.8) | | | |
| 3 years (protocol definition) | 56.8 (38.7 to 71.4) | | | |
| 4 years (protocol definition) | 56.8 (38.7 to 71.4) | | | |
| 1 year (updated definition) | 78.7 (60.3 to 89.3) | | | |
| 2 years (updated definition) | 78.7 (60.3 to 89.3) | | | |
| 3 years (updated definition) | 78.7 (60.3 to 89.3) | | | |
| 4 years (updated definition) | 71.0 (51.3 to 83.9) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Overall survival

| | |
|-----------------|-----------------------|
| End point title | SE Overall survival |
|-----------------|-----------------------|

End point description:

Eleven deaths have occurred in the FAS, five of these deaths were due to progressive disease. Eighteen patients were still alive and eleven were lost to follow-up.

The median OS was not reached with a lower boundary of the 95% CI of 5 years.

The median OS was not reached at the time of this analysis. Dummy data ("9999") entered due to database restrictions.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From registration until death from any cause.

| End point values | FAS | | | |
|----------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 40 | | | |
| Units: Overall survival (years) | | | | |
| median (confidence interval 95%) | 9999 (9999 to 9999) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Survival rate at 1, 2, 3 and 4 years

| | |
|-----------------|---|
| End point title | SE Survival rate at 1, 2, 3 and 4 years |
|-----------------|---|

End point description:

The survival rates at 1, 2, 3 and 4 years were calculated by the KM estimator.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| One, two, three and four years after start of treatment. | |

| End point values | FAS | | | |
|----------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 40 | | | |
| Units: Estimator (%) | | | | |
| number (confidence interval 95%) | | | | |
| 1 year | 100 (100 to 100) | | | |
| 2 years | 80.2 (62.9 to 90.0) | | | |
| 3 years | 77.3 (59.7 to 88.0) | | | |
| 4 years | 74.5 (56.7 to 85.8) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: SE | Tolerability

| | |
|--|-------------------|
| End point title | SE Tolerability |
| End point description: | |
| Tolerability during induction phase was defined as finishing 5 instillations of VPM1002BC within 12 weeks after treatment start. | |
| End point type | Secondary |
| End point timeframe: | |
| During induction phase. | |

| End point values | FAS | | | |
|--|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 40 | | | |
| Units: Patients (%) | | | | |
| number (not applicable) | | | | |
| 1 instillation during induction phase | 2.5 | | | |
| 3 instillations during induction phase | 2.5 | | | |
| 5 instillations during induction phase | 2.5 | | | |
| 6 instillations during induction phase | 92.5 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From registration until 12 weeks after last instillation for patients not completing the overall treatment or after week 60 for patients completing the entire maintenance phase.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 25.0 |

Reporting groups

| | |
|-----------------------|------------------------|
| Reporting group title | VPM1002BC - Safety Set |
|-----------------------|------------------------|

Reporting group description: -

| Serious adverse events | VPM1002BC - Safety Set | | |
|---|--|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 10 / 42 (23.81%) | | |
| number of deaths (all causes) | 12 | | |
| number of deaths resulting from adverse events | 2 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Glioblastoma | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Small cell lung cancer | Additional description: Neuro-endocrine (small cell) lung cancer | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Neuroendocrine tumour | Additional description: Neuroendocrine tumor of the neobladder | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Non-Hodgkin's lymphoma | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|---|--|--|
| Injury, poisoning and procedural complications | | | |
| Urinary tract procedural complication | Additional description: Traumatic catheterization due to sclerotic bladder neck | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| Glaucoma surgery | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |
| Hypersensitivity | Additional description: Bcg-induced sytemic reaction | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Cystitis | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | | |
| occurrences causally related to treatment / all | 3 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| | | | |
|---|------------------------|--|--|
| Non-serious adverse events | VPM1002BC - Safety Set | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 38 / 42 (90.48%) | | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 6 / 42 (14.29%) | | |
| occurrences (all) | 10 | | |
| Pyrexia | | | |

| | | | |
|--|---------------------|--|--|
| subjects affected / exposed occurrences (all) | 3 / 42 (7.14%) 3 | | |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | | |
| occurrences (all) | 5 | | |
| Cystitis noninfective | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | | |
| occurrences (all) | 3 | | |
| Pollakiuria | | | |
| subjects affected / exposed | 6 / 42 (14.29%) | | |
| occurrences (all) | 6 | | |
| Urinary tract pain | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | | |
| occurrences (all) | 3 | | |
| Micturition urgency | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | | |
| occurrences (all) | 3 | | |
| Infections and infestations | | | |
| Cystitis | | | |
| subjects affected / exposed | 6 / 42 (14.29%) | | |
| occurrences (all) | 14 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 14 / 42 (33.33%) | | |
| occurrences (all) | 19 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|--|
| 28 January 2016 | <p>The main reason for the amendment was the change of the immunology program in the Phase II part of the trial as follows: (1) reduction of the time points for immunology assessments from 9 to 4, (2) limitation of the immunology assessments to 10 patients (immunology cohort).</p> <p>Further changes: (1) Modification of inclusion criterion: "Planned treatment starts 2-5 weeks after last TURB" to "Planned treatment starts 2-6 weeks after last TURB", (2) Modification of timeframe for computed tomography (CT) and other evaluations before registration from 8 weeks to 12 weeks, (3) Modification of timeframe for human immunodeficiency virus (HIV) testing from "within 7 days before or on registration" to "within 4 weeks before registration", (4) Update of the timelines of the trial based on the effective trial activation date, (5) Minor adaptations concerning samples handling, (6) Administrative changes: correction of typos and wording</p> |
| 08 July 2016 | <p>The main reason for the amendment was the adaptation of the trial protocol according to the requests of the Competent Authority of Germany. The following changes were made: (1) Recommended Phase II Dose was specified in the protocol, (2) The timeframe for inactivation of VPM1002BC excreted in urine was the same in Phase II as in Phase I (1 week), (3) Any shortening of the 5 years follow-up period will have to be submitted to the ECs and to the competent authorities, (4) Update of the timelines of the trial, (5) Correction of inconsistency between exclusion criterion 6.2.27 "Psychiatric or neurological disorder precluding understanding of trial information, giving informed consent, filling out QoL forms" and chapter Quality of life, section patient selection: deletion of "mental problems" as a reason for noncompletion of QoL questionnaires, (6) Update of SAKK CC address and contact details, (7) Correction of typos and wording.</p> |
| 20 July 2017 | <p>The main reason for the amendment was the adaptation of the trial protocol according to the experience collected so far during trial conduct. The following changes were made:</p> <p>(1) Change of exclusion criterion 6.2.10 in order to allow inclusion of patients with low risk prostate cancer qualifying for active surveillance according to PRIAS criteria, (2) Duration of hospital stay after the instillation was reduced from 4 hours to time until first voiding (at least 1 hour), (3) Duration of follow-up period was reduced to 3 years, (4) Update of the timelines of the trial and addition of term "Primary completion date" in order to define the timeline of primary endpoint completion and study report preparation, (5) Update of chapter "Clinical experience with VPM1002" with data from ongoing /completed clinical trials, (6) Instructions for avoidance of traumatic catheterisation and postponing of VPM1002BC instillation in case of traumatic catheterisation, (7) Update of the table "BCG-related adverse events" and of "Precautions" according to the new Summary of Product Characteristics of BCG-medac, (8) Update of the table "Management options for side effects associated with intravesical VPM1002BC", (9) Adaptation of the size of the immunology cohort in order to allow participation of more patients (at least 10 patients), (10) Update of chapter 18 with new analyses as part of the immunological assessments (translational research): multiplex analysis of serum and analysis of tumor material (including analysis of earlier tumor material from patient's history of cancer, i.e. tumor material collected at the initial occurrence of the urothelial cancer)., (11) Update of contact details, (12) Removal of schedulers of assessments from the protocol (provided separately as useful tools), (13) Correction of typos, inconsistencies and orthographic mistakes.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/32363120>

<http://www.ncbi.nlm.nih.gov/pubmed/35012889>