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 continous 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 fullfils 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 wihout 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 wihout 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 PhaseI/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 ≤15% and p1: recurrence-free rate at 60 weeks ≥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 ≤15% and p1: recurrence-free rate at 60 weeks ≥ 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 ≤15% and p1: recurrence-free rate at 60 weeks ≥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 occurrences (all) Cystitis noninfective subjects affected / exposed occurrences (all) Pollakiuria subjects affected / exposed occurrences (all) Urinary tract pain subjects affected / exposed occurrences (all) Micturition urgency subjects affected / exposed occurrences (all)	 3 / 42 (7.14%) 5 3 / 42 (7.14%) 3 6 / 42 (14.29%) 6 3 / 42 (7.14%) 3 3 / 42 (7.14%) 3		
Infections and infestations Cystitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	 6 / 42 (14.29%) 14 14 / 42 (33.33%) 19		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 January 2016	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). 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
08 July 2016	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.
20 July 2017	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: (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.

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