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Long-term efficacy and safety of intravesical Bacillus Calmette-Guerin Moreau Polish substrain in the treatment of non-muscle invasive bladder cancer

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Introduction Bacillus Calmette-Guerin (BCG) Moreau is under-represented in literature and comparisons with other BCG strains are rare.

Material and methods We conducted a retrospective data analysis in patients with intermediate or high-risk non-muscle invasive bladder cancer (NMIBC) to assess effectiveness and safety of BCG Moreau Polish substrain to BCG RIVM. The primary objective was to describe the real-world effectiveness of BCG Moreau in the treatment of patients with NMIBC in terms of recurrence free survival (RFS) 2 years post-treatment initiation compared to BCG RIVM.

Results The database to be analysed comprised of 967 patients with NMIBC. The primary endpoint was met since BCG Moreau was non-inferior to BCG RIVM in terms of RFS [HR: 0.920 (95%CI: 0.725; 1.168)]. There was no statistically significant difference in all secondary endpoints including time to recurrence, progression-free survival, time to progression, and overall survival. The safety profile of BCG Moreau Polish substrain was consistent with side effects and frequency of complications observed with BCG RIVM and study reports in the literature.

Conclusions BCG Moreau was effective and safe in the treatment of patients with intermediate- or high-risk non-muscle invasive bladder cancer. There was no statistically significant difference in treatment outcome between BCG Moreau and BCG RIVM strains based on real-world data.

Key Words: non-muscle invasive bladder cancer ‹› real-world data ‹› Bacillus Calmette Guerin ‹› recurrence

INTRODUCTION

Bladder cancer is the most common malignancy of the urinary tract in Europe, with higher incidence rates observed in men than in women. The age-standardised incidence rate per 100,000 persons is 19.1 for men and 4.0 for women [1]. The age-standardised mortality rate is 5.5 and 1.2, respectively [2]. At initial diagnosis, approximately 75 % of the patients present with non-muscle invasive bladder cancer (NMIBC). Due to the risk to recur and progress, NMIBC in general is treated by a sequential therapeutic approach comprising transurethral resection of the bladder (TUR-B) followed by intravesical instillation therapy [3, 4].

Intravesical Bacillus Calmette-Guérin (BCG) has become the standard of care in the treatment of patients with intermediate and high-risk tumours [5], as it reduces the risk of recurrence, and it is more

effective than TUR-B alone or TUR-B followed by intravesical chemotherapy [4].
BCG Moreau [Polish] live attenuated Brazilian BCG Moreau substrain was brought to Poland in 1954 and first approved in 1999 [6]. Even though Moreau has been available for 20 years, clinical data gained from prospective clinical trials are limited. Furthermore, BCG Moreau is under-represented in literature and prospective comparisons with other BCG strains are rare [5]. However, there is sufficient data from daily practice (real-world data, RWD) that may enable the generation of real-world evidence (RWE). A prospective non-interventional register of BCG treatment was established at the Urology Department, University Hospital in Wroclaw in 1998, that we could use for our analysis.
The purpose of this data analysis was to evaluate effectiveness and tolerability and to show a non-inferiority of BCG Moreau in the treatment of intermediate- or high-risk NMIBC compared to RIVM based on the data mentioned above.

MATERIAL AND METHODS

This was a retrospective database analysis that used the register on BCG treatment of the Urology Department, University Hospital in Wroclaw. Approval by the local ethics committee was obtained. Data analysis was conducted in accordance with all applicable laws and regulations including Regulation (EU) 2016/679 (General Data Protection Regulation).
It was the primary objective of this study to evaluate the real-world effectiveness of BCG Moreau in the treatment of patients with NMIBC in terms of recurrence-free survival (RFS) and to show non-inferiority of BCG Moreau (Onko BCG 100; Synthaverse) compared to BCG RIVM (BCG-medac, Medac).
Secondary objectives include but were not limited to:
- Time to Recurrence
- Progression-free survival (PFS),
- Time to progression,
- Event-free survival (EFS)
- Overall survival (OS)
- Safety.

Progression was defined as rise to muscle-invasive bladder cancer (T2 or higher). Event was defined as occurrence of recurrence, progression or death from any cause. Safety was assessed based on explorative comparison of the two BCG strains.

Patient selection

Eligibility criteria for inclusion:
1) Adult male or female patients with histologically confirmed NMIBC (Ta, T1, Tis) treated with at least one instillation of Moreau or RIVM after TUR-B. Tumours could be primary or recurrent and single or multiple.
2) Patients with intermediate or high-risk NMIBC according to European Organisation for Research and Treatment of Cancer (EORTC) scoring system.

Exclusion criteria:
1) History of muscle invasive bladder cancer.
2) Previous systemic or radiation therapy for bladder cancer.
3) Change of BCG strain.

There was no randomization to BCG strains. Choice of BCG strain was mainly dependent on supply and the physician's decision.
The following variables were considered potential influencing variables and were included as covariates in the analyses of endpoints and for Propensity Score Matching (PSM):
- Gender (male / female)
- Age (years)
- Tumour grade (WHO 2004/2016) (low grade / high grade / PUNLMP / tis)
- EORTC Risk groups (intermediate risk / high risk)

The following analysis populations were considered:
Full-Analysis-Set (FAS): All patients enrolled according to the ITT principle.
Per-Protocol-Set (PP): All patients of the FAS who received at least 6 instillations of BCG and who have valid entries for status of death, status of recurrence as well as observation time. In case of T1 tumour and no muscle in primary TUR-B specimen, a RE-TURB must have been performed.
Propensity-Score-Matching-Set (PSM): All patients of the PP who were successfully matched to another.

Statistical Methods

Sample size estimation was based on a non-inferiority approach to compare BCG Moreau with BCG RIVM.
The following assumptions were made: The non-inferiority log-rank test with a power of 80.0% at a significance level of 0.025 was designed to detect an equivalence hazard ratio (HR) of 1.44, assuming that the true HR is an equivalence HR of 1.00 and the reference group HR of 0.0011987. The latter corresponds to a recurrence-free survival rate of 75% at 24 months. Patient data were collected in the registry since 1998, resulting in a prolonged follow-up period for the majority of patients. Therefore, a period of 48 months was assumed for the accumulation time in the power assessment. This resulted in a minimum total sample size of 642 subjects (321 in the BCG Moreau group and 321 in the BCG RIVM group).

Demographics and baseline parameters: Categorically scaled variables were presented by absolute and relative frequencies, and continuously scaled variables were reported by number of observations, mean, standard deviation, minimum, Quartiles (Q1; Q3), median, and maximum.
Primary effectiveness analysis: Descriptive statistics of effectiveness data were provided as described in demographics. Time-to-event data were given as Kaplan-Meier estimates by BCG strain. The primary effectiveness analysis was conducted using Cox regression analysis to take the potential covariates into account. Cox regression was realized via the SAS procedure PROC PHREG.
Safety variables were mainly described as absolute and relative frequencies.
Sensitivity analysis for homogeneous follow-up times
Primary effectiveness analysis was repeated for the per protocol (PP) subgroup PP60, including all patients with the theoretical chance of 60 months of follow-up. Thus, possible differences between BCG strains in the therapy assignment to the patients and the affected event probability due to unbalanced event-free follow-up times were avoided.

Sensitivity analysis using propensity-score-matched samples (PSM)

In addition, a propensity score matching of BCG strains was performed to assess the outcome in comparable subsamples:
First, the propensity score was generated using a logistic regression model in which the BCG strain was regressed on observed baseline characteristics. Then, a matching procedure (1:1, Greedy Nearest Neighbor Matching using a Caliper of 0.2 of the pooled standard deviation of the logit of the propensity score) was applied to form pairs based on the propensity score.
Finally, matched pairs were used for analyses of differences between BCG strains, accounting for sample dependence.
For RFS, Kaplan-Meier estimates for specific time points (12, 24, and 60 months), means and quartiles, and number of patients at risk were reported. Further, a univariate Cox proportional hazards model accounting for the matched nature of the sample via a robust variance estimator that accounts for the clustering within matched sets was estimated.
Secondary effectiveness analyses:
All secondary endpoints in the form of time-to-event data were analysed using Cox regression, with HR calculated using the appropriate 95% confidence intervals (CIs) for BCG strains.
Rates and continuous endpoints were modelled using a generalised linear or linear regression model accounting for the covariates listed previously. Estimates for the BCG strain effect were reported with the corresponding 95% CIs.

RESULTS

The data set contained data of 967 patients who have been registered between April 1994 and December 2018. Thereof, 176 patients had to be excluded from analysis since they had not received at least one instillation of BCG Moreau or RIVM but were treated with another BCG strain. Thus, the primary and secondary effectiveness analyses were performed for 749 PP patients (Moreau: N=493, RIVM: N=256) and 512 PSM (256 matched pairs of Moreau and RIVM patients).
The mean age of patients was 66.3 (±9.5) years and significantly more males than females (79.4% vs 20.6%) were part of this analysis. The vast majority was in the high EORTC risk group (80.7%) and had a high tumour grade (67.6%). The demographic data and baseline characteristics of the FAS by BCG strain are described in Table 1.

Table 1. *Patient characteristics by Bacillus Calmette Guerin strain (Full-Analysis-Set)*

	BCG Moreau N = 525	BCG RIVM N = 266	Total N = 791
Age [years]			66.3 (9.5)
mean (SD)	66.0 (9.5)	66.7 (9.5)	
Min; Max	27; 89	39; 86	27; 89
Age groups [N (%)]			
≥18 to <65 years	206 (39.2)	113 (42.5)	319 (40.3)
≥65 to <75 years	224 (42.7)	91 (34.2)	315 (39.8)
≥75 years	95 (18.1)	62 (23.3)	157 (19.8)
Gender [N (%)]			
Female	119 (22.7)	44 (16.5)	163 (20.6)
Male	406 (77.3)	222 (83.5)	628 (79.4)
Number of instillations			
Mean (SD)	15.2 (7.1)	19.3 (7.5)	16.6 (7.5)
Median	15	21	15
Min; Max	1; 40	2; 42	1; 42
EORTC Risk Group [N (%)]			
Intermediate	117 (22.3)	36 (13.5)	153 (19.3)
High	408 (77.7)	230 (86.5)	638 (80.7)
T-Stage [N (%)]			
pTa	186 (35.4)	79 (29.7)	265 (33.5)
pT1	259 (49.3)	147 (55.3)	406 (51.3)
pTis	80 (15.2)	40 (15.0)	120 (15.2)
Tumour Grade WHO 2004/2016 [N (%)]			
High Grade	347 (66.1)	188 (70.7)	535 (67.6)
Low Grade	178 (33.9)	78 (29.3)	256 (32.4)
PUNLMP	0 (0.0)	0 (0.0)	0 (0.0)

BCG – Bacillus Calmette Guerin; EORTC – European Organization for Research and Treatment of Cancer; FAS – Full Analysis Set; N – Number; PUNLMP – papillary urothelial neoplasm of low malignant potential; SD – standard deviation; WHO – World Health Organization

Propensity Score Matching

Propensity Score matching was successfully applied for 100 % of the smaller group of RIVM patients (N = 256). The standardised differences for the matched sample were below 0.1 for all matching variables, demonstrating that the variables were well balanced between groups.

Effectiveness results

Primary endpoint: Non-inferiority of BCG Moreau

Non-inferiority of BCG Moreau vs BCG RIVM in terms of RFS was shown with an upper confidence limit of the estimated HR of 1.168, which is significantly below the margin (< 1.440; p < 0.001). The estimated HR = 0.920 favours BCG Moreau but is not statistically superior.

Recurrence-free survival

The mean recurrence-free survival (RFS) was 41.7 months with BCG Moreau and 40.1 months with BCG RIVM. The Kaplan-Meier estimates for RFS for the Moreau and RIVM BCG Strain did not differ statistically significantly in the PP population as shown in Figure 1.

Non-inferiority of BCG Moreau compared to BCG RIVM was supported by both sensitivity analyses based on the PP subgroup PP60 and PSM population (Table 2).

Age had a significant influence on RFS, whereby older patients had a higher risk of recurrence or death. The estimated 10-years-HRs are 1.184 [1.044; 1.344] for the Cox regression in the PP population and 1.210 [1.054; 1.389] in the PP60 subgroup (Table 3). The estimates of further covariates (gender, tumour grade (WHO 2004/2016) and EORTC Risk group) did not indicate any impact on the RFS.

Secondary endpoints

Progression-free survival

The mean progression-free survival (PFS) was 51.0 months under BCG Moreau and 49.4 months under BCG RIVM. There was no statistically sig-

Table 2. *Cox proportional hazards model for recurrence-free survival (sensitivity analyses)*

Description	Estimate	Hazard Ratio	LCL	UCL	NI margin	p-value
PP60						
Moreau vs RIVM	-0.0265	0.974	0.750	1.264	1.440	0.002
PSM						
Moreau vs RIVM	-0.0999	0.905	0.687	1.191	1.440	<0.001

LCL – lower confidence limit; NI – non-inferiority; PP – per protocol; PSM – propensity score matched; RFS – recurrence-free survival; UCL – upper confidence limit

Table 3. *Hazard ratio and related confidence limits for further independent variables for RFS*

Variable	p-value	Categories	Hazard Ratio	LCL	UCL
PP					
Gender	0.729	Female vs male	1.051	0.794	1.391
Age [10-year-steps]	0.009		1.184	1.044	1.344
Tumour Grade WHO 2004/2016	0.517	HG vs LG	1.218	0.870	1.706
		HG vs tiss	1.039	0.755	1.432
		LG vs tiss	0.853	0.564	1.290
EORTC Risk Group	0.301	High vs intermediate	0.820	0.563	1.194
PP60					
Gender	0.548	Female vs male	1.099	0.808	1.496
Age [10-year-steps]	0.007		1.210	1.054	1.389
Tumour Grade WHO 2004/2016	0.459	HG vs LG	1.250	0.878	1.779
		HG vs tiss	1.084	0.765	1.536
		LG vs tiss	0.867	0.562	1.339
EORTC Risk Group	0.421	High vs intermediate	0.852	0.576	1.260

EORTC – European Organisation for Research and Treatment of Cancer; HG – high grade; LCL – lower confidence limit; LG – low grade; PP – per protocol; PSM – propensity score matched; RFS – recurrence-free survival; UCL – upper confidence limit

nificant difference in the Kaplan-Meier estimates for PFS between the Moreau and the BCG Strain (PP population, see Figure 2), however, the estimated probability favors BCG RIVM. Results were supported by sensitivity analysis (PSM).

Time to recurrence, Time to progression, and Cystectomy

In total, 167 (33.9%) patients in the BCG Moreau group and 101 (39.5%) patients in the BCG RIVM group had at least one recurrence during the observation time. Of those, the mean time to recurrence was 19.3 (28.0) months in the BCG Moreau group and 16.5 (16.7) months in the BCG RIVM group.
Time to Progression was reported in 64 (13%) patients in the BCG Moreau group and 33 (12.9%) patients in the BCG RIVM group during the observation period. Of those, the mean time to progression was 27.8 (29.2) months in the BCG Moreau group and 30.6 (23.8) months in the BCG RIVM group.
Cystectomy was reported for 120 patients in the PP population (Moreau: n = 76 [15.4%], RIVM: n = 44 [17.2%]). Of those, the mean time to cystectomy was 22.1 ±20.5 months and 25.2 ±19.2 months in the Moreau and RIVM group, respectively.
Results for all three endpoints are summarized in Table 4.

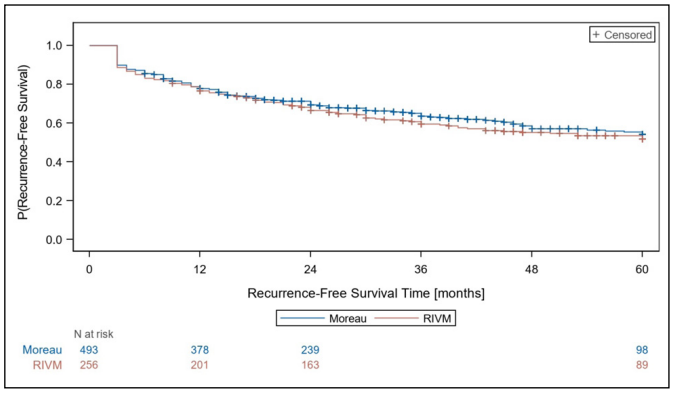

Figure 1. *Kaplan-Meyer survival curve of recurrence-free survival by Bacillus Calmette Guerin strain (Per Protocol population). The estimated probability for RFS is slightly higher for the Moreau patients at each time point (12 months: 0.78 vs 0.77; 24 months: 0.69 vs 0.66; 60 months: 0.54 vs 0.52). These estimates for the PP population were not adjusted for the covariates.*

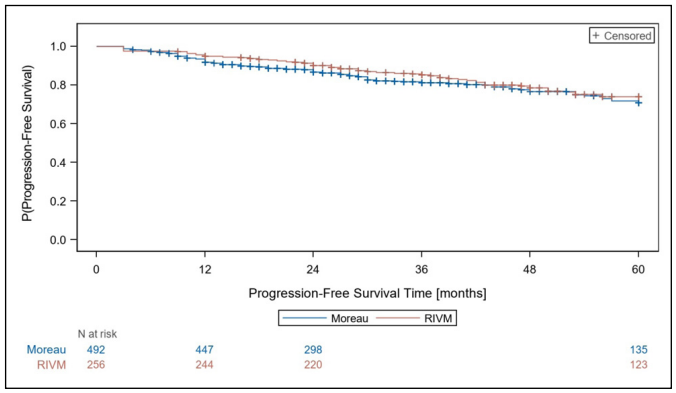

Figure 2. *Kaplan-Meyer survival curve of progression-free survival by Bacillus Calmette Guerin strain (Per Protocol population).*

Table 4. *Time to Recurrence, Time to Progression, and Cystectomy Results (Per Protocol population)*

Secondary and additional endpoints	BCG Moreau	BCG RIVM
Recurrence [N (%)]		
Yes	167 (33.9)	101 (39.5)
No	326 (66.1)	155 (60.5)
Time to recurrence [months]		
Mean (SD)	19.3 (28.0)	16.5 (16.7)
Progression [N (%)]		
Yes	64 (13.0)	33 (12.9)
No	428 (87.0)	222 (87.1)
Time to progression [months]		
Mean (SD)	27.8 (29.2)	30.6 (23.8)
Cystectomy [N(%)]		
Yes	76 (15.4)	44 (17.2)
No	417 (84.6)	212 (82.8)
Time to cystectomy [months]		
Mean (SD)	22.1 (20.5)	25.2 (19.2)
Cystectomy-free survival [% (LCL, UCL)] 60 months	67.6 (61.8, 72.7)	67.9 (61.2, 73.6)

BCG – Bacillus Calmette Guerin; LCL – lower confidence limit; SD – standard deviation; UCL – upper confidence limit

Table 5. *Frequency of adverse reactions (Full-Analysis-Set)*

Adverse reaction	BCG Moreau (N = 525) [N (%)]	BCG RIVM (N = 266) [N (%)]	Total (N = 791) [N (%)]
Complications			
Yes	426 (81.1)	215 (80.8)	641 (81.0)
No	99 (18.9)	51 (19.2)	150 (19.0)
Cystitis	382 (72.8)	198 (74.4)	580 (73.3)
Haematuria	175 (33.3)	93 (35.0)	268 (33.9)
Body temperature			
>37.5	209 (39.8)	85 (32.0)	294 (37.2)
>38.5	109 (20.8)	55 (20.7)	164 (20.7)
Influenza-like symptoms	81 (15.4)	37 (13.9)	118 (14.9)
Epididymitis	13 (2.5)	8 (3.0)	21 (2.7)
Sepsis	1 (0.2)	2 (0.8)	3 (0.4)
Contracted bladder	24 (4.6)	9 (3.4)	33 (4.2)
Other complications			
Yes	32 (6.1)	10 (3.8)	42 (5.3)
No	493 (93.9)	256 (96.2)	749 (94.7)

BCG – Bacillus Calmette Guerin; FAS – Full analysis set; N – Number

Overall survival

The mean overall survival (OS) was 52.0 months in the BCG Moreau group and 55.2 months in the BCG RIVM group.
Similar to PFS, there was no statistically significant difference in the Kaplan-Meier estimates in OS between the Moreau and BCG Strain in the PP population. Results were supported by sensitivity analysis (PSM).
A summary of the HRs related to recurrence-free-survival (RFS), progression-free survival (PFS), event-free survival (EFS), and overall survival (OS) is presented in Figure 3.

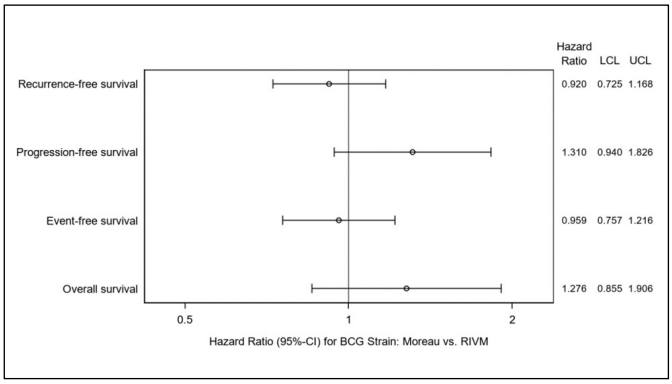

Figure 3. *Forest Plot Hazard Ratios for Bacillus Calmette Guerin strain (Per Protocol Population)*

CI – confidence interval; LCL – lower confidence limit; UCL – upper confidence limit

Safety

Complication occurred in 426 out of 525 patients (81.1%) in the BCG Moreau group and in 215 out of 266 patients (80.8%) in the BCG RIVM group. The dose was reduced due to complications in 23.9% and 32.0% of patients in the BCG Moreau and RIVM group, respectively. Cystitis, haematuria, and body temperature >37.5°C were the most frequently documented adverse reactions. Details of adverse reactions occurring in the FAS are presented in Table 5.
Adverse reactions occurred after a mean of 2.4 and 3.3 instillations in the BCG Moreau and RIVM group and worsened after a mean of 7.5 and 7.6 instillations, respectively.

DISCUSSION

BCG immunotherapy is the choice of care for intermediate- and high-risk NMIBC after TUR-B [7–9]. Due to the BCG shortage worldwide and the lack of effective alternatives there is an urgent medical need to generate clinical data for the use of other BCG strains aiming at prevention of cystectomy known to be associated with a significant decrease in quality of life [10, 11]. Therefore, we performed a retrospective analysis of registry data of the Urology Department Hospital in Wroclaw, which was also done in 2018. The new analysis includes more patients and more comprehensive statistical methods. Overall, 791 patients with a mean age of 66 years were included and most patients were male (79.4%), which is typical for bladder cancer. All patients were classified as having at least an intermediate risk based on EORTC.
The primary objective of this analysis was met since non-inferiority of BCG Moreau compared to RIVM in terms of RFS was shown in Cox regression including an adjustment for the covariates gender, age, tumour grade (WHO 2004/2016) and EORTC Risk group. The upper CI of the estimated HR was 1.168 and therefore significantly below the margin (<1.440; p <0.001). Results were verified in two sensitivity analyses: Propensity score matched samples were used to further account for the potential confounders and a subset of patients with a theoretical chance of 60 months of follow-up was used to exclude bias due to different patient distribution in BCG strains over time.
There was no statistically significant difference between the two BCG strains in any of the secondary endpoints, e.g., time to recurrence, PFS, time to progression, and OS. Of note, the mean survival time is underestimated due to the restriction of 60 months follow-up period. Results of our analysis are in line with other retrospective analyses [5, 12] and a systematic review and meta-analysis by Boehm et al. [13] who did not detect any significant differences when comparing efficacy of various BCG strains. However, only rare data are available on BCG Moreau and it seems that this strain is underrepresented in the literature [14, 10] making our analysis particularly important. Overall, our data support the broad clinical experience with BCG Moreau showing no significant difference regarding efficacy and safety.
Out of the covariates age had a significant influence on survival, whereby older patients had a higher risk of undergoing events for RFS, PFS and OS. These findings were confirmed by another retrospective analysis focusing on BCG therapy in older patients [1].
Complications due to the treatment with any BCG strain occurred with approximately the same frequency (Moreau = 81.1% vs RIVM = 80.8%). Disseminated BCG infection presenting as granulomatous hepatitis or pneumonitis occurred in one patient of the Moreau group and in 2 patients of the RIVM group – in the literature a frequency of this infections is also very rare [15].

Registry data provide a high external validity since they are real-life data but a lower internal validity due to missing randomization and controls. It was a limitation of this analysis that registry data entry had been performed without automatic checks for plausibility and was not standardized. However, data integrity was improved by an extensive query process including comprehensive plausibility checks. In addition, analyses were done using multivariable methods considering potential confounders as well as propensity score matching for sensitivity analyses.

When performing retrospective studies, it is important to remember that these data were not collected for research purposes, meaning they were not collected in a pre-specified format - such as a clinical trial – which may result in missing variables that have the potential to influence the outcome.

Analysis was further impacted by the fact that resections were done in various centres leading to heterogeneous quality of TUR-B and histopathological assessment, but efforts were made that the majority of specimens were evaluated by the specialists of the Urology Department of the University of Wroclaw. Conclusions on pre-treated patients were limited by the fact that in some cases there was no information available regarding previous treatment of NMIBC.

CONCLUSIONS

Our data support the effective and safe clinical use of BCG Moreau for the treatment of patients with intermediate- or high-risk NMIBC. BCG Moreau was non-inferior to BCG RIVM in terms of RFS and there was no statistically significant difference in treatment outcome as well as in terms of safety between both strains based on real-world data. The evidence level of this retrospective analysis should be considered.

CONFLICTS OF INTEREST

Stefanie Witecy is an employee of APOGEPHA Arzneimittel GmbH. Tobias Mudra was an employee of APOGEPHA Arzneimittel GmbH until December 2021. Rolf Jünemann received remuneration for statistical work and data management. The rest of the authors declare no conflict of interest.

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