1. ABSTRACT

- **Title**

Prospective observational study to describe routine use of XGEVA® for prevention of skeletal-related events (SREs) in subjects with bone metastases from prostate carcinoma in Bulgaria

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- **Keywords**

Prostate cancer, denosumab, skeletal-related events, bone metastases, bone targeted agent

- **Rationale and Background**

In subjects with bone metastases from cancer, persistence with the prescribed bone-targeted agent (BTA) is essential to prevent the occurrence of skeletal-related events (SREs). Ideally, this means complete conformity with the daily treatment recommendations, no missed or additional doses, and no doses taken at the wrong time (Cramer et al, 2008). Enhancing the awareness of causes and consequences of non-persistence, and developing strategies to support subjects in persisting with treatment are likely to positively impact care quality (Timmers et al, 2017). The persistence with denosumab treatment in Bulgarian subjects with bone metastases from prostate carcinoma remains unknown. This data may be used for the reimbursement maintenance negotiations by the Bulgarian heath authorities.

- **Research Question and Objectives**

In the present study, the actual persistence with denosumab treatment in subjects with prostate cancer in Bulgaria was estimated. The primary study objective was to describe real-life patterns of bone metastasis management and routine use of denosumab for SRE prevention in subjects with bone metastases from prostate carcinoma.

Secondary objectives included to estimate the incidence of SREs and symptomatic SREs (SSEs); to identify factors that influence persistence; to estimate healthcare utilization, and to describe pain severity and management.

Results were separately analysed for subjects with hormone-sensitive prostate cancer (HSPC) and castration-resistant prostate cancer (CRPC, also hormone-refractory prostate cancer).

- **Study Design**

This was a multicentre, prospective observational study conducted in Bulgaria. The study included consenting adult (≥18 years) subjects with histologically or cytologically confirmed diagnosis of prostate carcinoma with ≥1 bone metastasis confirmed by imaging (X-ray, MRI, or CT) who had received ≥1 denosumab administration in the 6 months before enrolment. Subjects with bone metastases treated with bisphosphonates or other BTAs for prevention of SREs in the 6 months before enrolment, subjects with prostate carcinoma as a second primary malignancy, subjects with brain metastases, and those enrolled in trials with an investigational drug for treatment/prevention of bone metastases and SREs at the time of study, were excluded. The study collected ≤6 months of retrospective data on demographics and disease characteristics up to the date of enrolment (baseline period) and up to 12 months of prospective data; one month of safety follow-up data was collected upon study completion or individually upon discontinuation in patients who did not complete 12 months of prospective observation.

The primary outcome measures were demographic and clinical characteristics of subjects with bone metastases from HSPC and CRPC receiving denosumab in routine clinical practice, treatment patterns, and medication persistence. Persistence with denosumab was defined as continuous use of denosumab from the first administration without exceeding a 60-day gap until the discontinuation date, withdrawal from the study, switch to another therapy, or the end of the analysis period. Secondary outcomes included the number of subjects with SREs (pathologic fractures, for surgery to bone, for spinal cord compression, for radiotherapy to bone) and SSEs, the SRE/SSE incidence rate, the time from bone metastasis diagnosis to denosumab initiation, conformity of subject's versus physician's estimate of persistence using the Beliefs about Medicines Questionnaire (BMQ) and the Perceptions of Adherence Management Questionnaire (PAMQ), the Brief Pain Inventory (BPI), the number of hospitalisations for SREs and SSEs, changes in pain severity from baseline until denosumab discontinuation, and pain medication during the study.

- **Setting**

Subjects were enrolled between January and June 2019 and data was collected between January 2019 and January 2021.

Nine study centers participated in this study. Four study centers were located in the East region of Bulgaria; the others were equally distributed across the central, West, North, Northeast, and Southwest regions of the country. There were 4 public hospitals, 2 specialised institutes, 2 university hospitals and 1 private hospital. All principal investigators were oncologists.

- **Subjects and Study Size, Including Dropouts**

The study enrolled 100 subjects (26 with CRPC and 74 with HSPC) and 28 subjects discontinued the study prior to the end of the observation period: 4 subjects withdrew their informed consent, 15 subjects died, 7 subjects were lost to follow up, 1 subject discontinued due to investigator’s decision, and 1 subject resigned because of COVID-19-related anxiety to travel and visit the study center.

- **Data Source(s) and Methods**

Retrospective data were retrieved from medical files. Prospective data were collected by the investigator during routine visits. Adverse events were coded using version 23.1. of the Medical Dictionary for Regulatory Activities (MedDRA). Data were validated using the electronic case report form (eCRF).

Additional data were collected from physicians and/or subjects by means of paper questionnaires: BMQ and BPI were entered into the eCRF by a physician or designee. PAMQ data were collected directly in the eCRF.

- **Results**

Subject Characteristics, Diagnosis and Tumor Characteristics at Baseline

At enrolment, the mean (SD) age was 72 (8.3) years (range: 54 - 92 years; Table 1). The median (Q1, Q3) time between initial diagnosis and study enrolment was 21.6 (8.1, 52.4) months and was longer among subjects with CRPC (median: 40.3 months; Q1: 19.9; Q3: 63.3) than those with HSPC (median: 18.0 months, Q1: 5.7, Q3: 46.6; Table 1). The Gleason score, defined as having a value between 1 and 10, was reported for 96 subjects. The median (Q1, Q3) Gleason score was 8.0 (7.0, 9.0) overall, 9.0 (7.0, 9.0) in CRPC, and 8.0 (7.0, 8.0) in HSPC. The median Gleason grade group, defined to be a value between 1 and 5, was 4.0 (2.0, 5.0) overall, 5.0 (2.0, 5.0) in CRPC, and 3.0 (2.0, 4.0) in HSPC (Table 1).

Table 1. Subject Characteristics, Diagnosis and TumorCcharacteristics

Variable	Statistics	Overall	Hormone	
			refractory	sensitive
		N=100	N=26	N=74
Age at enrolment				
years	N	100	-	-
	mean (SD)	72.0 (8.3)	-	-
	median	72.0	-	-
	Q1, Q3	65.8, 78.0	-	-
	min, max	54, 92	-	-
Time since the initial diagnosis				
months	N	99	26	73
	mean (SD)	38.2 (38.3)	44.8 (30.4)	35.9 (40.6)
	median	21.6	40.3	18.0
	Q1, Q3	8.1, 52.4	19.9, 63.3	5.7, 46.6
	min, max	0.6, 182.4	3.9, 110.5	0.6, 182.4
Tumour characteristics				
Histology				
Yes	N (%)	100 (100)	26 (100)	74 (100)

Variable	Statistics	Overall	Hormone	
			refractory	sensitive
		N=100	N=26	N=74
No	N (%)	0	0	0
Cytology				
Yes	N (%)	6 (6.0)	0	6 (8.1)
No	N (%)	94 (94.0)	26 (100)	68 (91.9)
Biopsy				
Gleason score	N	96	25	71
	mean (SD)	7.6 (1.6)	8.2 (1.2)	7.3 (1.7)
	median	8.0	9.0	8.0
	Q1, Q3	7.0, 9.0	7.0, 9.0	7.0, 8.0
Gleason grade group	N	89	19	70
	mean (SD)	3.3 (1.5)	3.6, (1.6)	3.2 (1.4)
	median	4.0	5.0	3.0
	Q1, Q3	2.0, 5.0	2.0, 5.0	2.0, 4.0
	min, max	1, 5	1, 5	1, 5
TNM stage – T				
T1	N (%)	26 (26.0)	6 (23.1)	20 (27.0)
T2	N (%)	32 (32.0)	8 (30.8%)	24 (32.4)
T3	N (%)	24 (24.0)	7 (26.9)	17 (23.0)
T4	N (%)	15 (15.0)	5 (19.2)	10 (13.5)
Tx	N (%)	3 (3.0)	0	3 (4.1)
TMN stage – N				
N0	N (%)	49 (49.0)	13 (50.0)	36 (48.6)
N1	N (%)	27 (27.0)	7 (26.9)	20 (27.0)
N2	N (%)	3 (3.0)	1 (3.8)	2 (2.7)
N3	N (%)	1 (1.0)	0	1 (1.4)
Nx	N (%)	20 (20.0)	5 (19.2)	15 (20.3)
TNM stage – M				
M1	N (%)	100 (100)	26 (100)	74 (100)
Risk assessment				
Very low	N (%)	3 (3.0)	0	3 (4.1)
Low	N (%)	4 (4.0)	0	4 (5.4)
Favourable intermediate	N (%)	7 (7.0)	2 (7.7)	5 (6.8)

Variable	Statistics	Overall	Hormone	
			refractory	sensitive
		N=100	N=26	N=74
Unfavourable intermediate	N (%)	3 (3.0)	2 (7.7)	1 (1.4)
High	N (%)	35 (35.0)	16 (61.5)	19 (25.7)
Very high	N (%)	22 (22.0)	6 (23.1)	16 (21.6)
Unknown	N (%)	26 (26.0)	0	26 (35.1)

Hormone refractory = CRPC; Hormone sensitive = HSPC; TNM stage = tumour stage with T = the extent of the main (primary) tumour (T category), N = cancer spread to nearby lymph nodes (N category), M = cancer spread (metastasized) to other parts of the body (M category)

Eastern Cooperative Oncology Group Performance Status at Baseline and During Study

At baseline, most subjects (63%, n=63) had Eastern Cooperative Oncology Group (ECOG) performance status 1, with 15% (n=15) having ECOG status 0 and 22% (n=22) having ECOG status 2. Over the study period, most subjects remained at ECOG performance status 1 with the frequency fluctuating between 63% and 74% (Table 2). Fifteen patients died during the study, representing ECOG status 5.

Table 2. ECOG Performance Status Over Time

ECOG	Baseline N=100	Month 3 N=85	Month 6 N=81	Month 9 N=68	Month 12 N=69	Last obs.* N=100
Grade - 0	15 (15.0)	8(9.4)	8 (9.9)	10 (14.7)	6 (8.7)	6(6.0)
Grade - 1	63 (63.0)	62 (72.9)	58 (71.6)	46 (67.6)	51 (73.9)	62 (62.0)
Grade - 2	22 (22.0)	15 (17.6)	14 (17.3)	12 (17.6)	12 (17.4)	15 (15.0)
Grade - 3	0	0	1 (1.2)	0	0	2 (2.0)
Grade - 4	0	0	0	0	0	0

ECOG, Eastern Cooperative Oncology Group; Last obs, last observation.

* The last observations represent the last observation recorded while each individual patient was still on study.

Comorbidities at Baseline

The most frequent (>10% of subjects) comorbidities at baseline were cardiovascular disorders (67 reports; 60.9% of a total of 110 comorbidity reports) and diabetes mellitus/metabolic disorders (16 reports, 14.5% of all reports).

Treatment History at Baseline

Anticancer therapy was reported for 97 subjects. Hormone therapy was administered to 89.7% of these 97 subjects (n=87), chemotherapy to 29.9% (n=29), radiation therapy to

14.4% (n=14), targeted therapy to 8.2% (n=8), and surgery was conducted in 4.1% (n=4). Calcium supplementation was reported in 82% of subjects (n=82) and 67% (n=67) received vitamin D supplementation.

The median (Q1, Q3) time between the diagnosis of bone metastases and initiation of denosumab was 1.8 (0.6, 9.6) months and was longer in CRPC with 7.9 (95% CI: 0.8–15.1) months than HSPC with 1.5 (95% CI: 1.1–2.1) months (HR=0.65 for HSPC versus CRPC). It was also longer in older than younger subjects with 1.2 (95% CI: 0.2–2.8) months in subjects aged <65 years and 2.0 (95% CI: 1.3–3.9) months in subjects aged ≥65 years (HR=0.68 for younger versus older).

The median (Q1, Q3) denosumab treatment duration before study enrolment was 4.0 (0.9, 8.9) months and was longer in subjects with CRPC (median: 6.1 months; Q1: 3.0, Q3: 11.8) than HSPC (median: 2.9 months; Q1: 0.0, Q3: 7.0). Overall, the median (Q1, Q3) duration of denosumab treatment from first dose to end of study was 15.5 months (12.7, 19.6) and comprised 5.0 (2.0, 9.0) administrations.

Bone Metastases at Baseline and Occurrence of New Bone Metastases During Study

Per definition, all subjects were in metastatic stage (bone metastasis was an eligibility criterion). In the baseline (6-months retrospective) period, 305 metastases were recorded in total. Of these 305 metastases, the most frequent locations were pelvis/ilium (19.3%, n=59), the spine with 17.0% (n=52) in the thoracic vertebrae and 15.4% (n=47) in the lumbar vertebrae, and chest/ribs (8.9%, n=27). Of these, 84.6% (n=258) were asymptomatic and detected by imaging, while 14.8% (n=45) were symptomatic; for 0.7% (n=2) the method of detection was unknown (Table 3).

In the first 6 months of prospective observation, 13 new metastases were found at the chest (sternum, n=3; ribs, n=2), pelvis (ilium, n=2; ischium, n=1) and spine (lumbar vertebrae, n=2; sacral vertebrae, n=1; and thoracic vertebrae, n=2). Of these, 92.3% (n=12) were asymptomatic and 7.7% (n=1) were symptomatic (Table 3).

During months 7 to 12, 18 new metastases were reported at arm bones (humerus, n=1; scapula, n=2), chest (sternum, n= 2; ribs, n=4), head bones (cranial, n=1), leg bones (femur, n=1), pelvis (ischium, n=2) and spine (cervical vertebrae, n=3; lumbar vertebrae, n=1; and thoracic vertebrae, n=1). All of these were asymptomatic (Table 3).

Table 3. Bone Metastases by Location at Baseline and During Study

Location	Baseline		ICF - Month 6		Month 7 - 12	
	N	%	N	%	N	%
Arm bones						
Clavicles	3	1.0 %	0	-	0	-
Humerus	7	2.3%	0	-	1	5.6%
Scapula	8	2.6%	0	-	2	11.1%
Shoulder joint	1	0.3%	0	-	0	-
Chest						
Hyoid bone	1	0.3%	0	-	0	-

Location	Baseline		ICF - Month 6		Month 7 - 12	
	N	%	N	%	N	%
Ribs	27	8.9%	2	15.4%	4	22.2%
Sternum	11	3.6%	3	23.1%	2	11.1%
Head bones						
Cranial bones	5	1.6%	0	-	1	5.6%
Facial bones	2	0.7%	0	-	0	-
Leg bones						
Femur	18	5.9%	0	-	1	5.6%
Pelvis						
Hip joint	4	1.3%	0	-	0	-
Ilium	59	19.3%	2	15.4%	0	-
Ischium	19	6.2%	1	7.7%	2	11.1%
Pubis	15	4.9%	0	-	0	-
Sacroiliac joint	1	0.3%	0	-	0	-
Sacrum	1	0.3%	0	-	0	-
Spine						
Cervical vertebrae	3	1.0%	0	-	3	16.7%
Coccygeal vertebrae	2	0.7%	0	-	0	-
Lumbar vertebrae	47	15.4%	2	15.4%	1	5.6%
Sacral vertebrae	17	5.6%	1	7.7%	0	-
Thoracic vertebrae	52	17.0%	2	15.4%	1	5.6%
Other						
Generalised bone metastases	2	0.7%	0	-	0	-
Method of detection						
Asymptomatic / imaging	258	84.6%	12	92.3%	18	100%
By symptoms	45	14.8%	1	7.7%	0	-
Unknown	2	0.7%	0	-	0	-
Total	**305**	**100%**	**13**	**100%**	**18**	**100%**

N represents the number of metastases with the sum of all metastases representing 100% in each respective period.

Note: There were occurrences of documentation for bone metastases in the same location at different timepoints. However, in most cases the diagnosis method was different (for example bone scintigraphy and a later CT). It is therefore unclear, if these

double entries reflect new metastases to the same location or the same metastasis documented twice using a different imaging/diagnosis method.

Occurrence of SREs at Baseline and During Study

In 7 subjects (7%) a total of 10 SREs and no SSEs had been recorded at baseline. The recorded SREs were radiation to bone (n=7), pathological fracture (n=2), and spinal cord compression (n=1).

Ten new SREs in 7 subjects and no SSEs were reported during the study period. There were 5 subjects with SREs recorded only at baseline, with no further events, 2 subjects with SREs at both baseline and follow-up, 5 subjects with SREs only during the follow-up period, and 2 subjects with recurrent events during the follow-up. The newly occurring SREs were radiation to bone (n=9) and pathological fractures (n=1). In the baseline period, 9 hospitalizations due to SREs occurred, the mean duration ranged from 4.5 to 13 days. In the prospective study period, 9 hospitalizations due to SREs occurred, the durations of SRE-related hospitalization ranged from 3 to 19 days.

SREs and SSEs during the study are listed in Table 4.

Table 4. Skeletal-Related Events Over Time (Subjects and Events)

Type of a SRE	Base-line	Month								End of obs.
		1	2	3	4	5	6	8	9	
Events										
Pathological fracture	2	0	0	1	0	0	0	0	0	0
Radiation to bone	7	1	1	0	1	1	1	1	1	2
Spinal cord compression	1	0	0	0	0	0	0	0	0	0
Total	**10**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**
Subjects										
Pathological fracture	2	0	0	1	0	0	0	0	0	0
Radiation to bone	5	1	1	0	1	1	1	1	1	1
Spinal cord compression	1	0	0	0	0	0	0	0	0	0
Total	**7**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**

End of obs., end of observation; SRE, skeletal-related event

Duration of Denosumab Treatment

At enrolment, the median (Q1, Q3) denosumab treatment duration since the first known administration was 15.5 (12.7, 19.6) months.

Thirty subjects temporarily or permanently discontinued denosumab during the prospective study period. The most frequent reasons for denosumab discontinuation

were death (37%, n=11), investigator's decision (27%, n=8), loss to follow up (23%, n=7), and (serious) adverse events related to denosumab (10%, n=3).

Persistence With Denosumab Treatment

The median time to loss of persistence was between day 443 and day 464 after the treatment initiation (depending on the approach to the loss to follow-up, i.e. either the loss of persistence was at the last dose before the loss to follow-up + the 60-day gap [Last Observation Carried Forward approach] or subjects were considered persistent by the date of loss to follow-up and then they were censored [Censoring approach]). Overall, 7 subjects were lost to follow-up, but 5 lost persistence due to violation of the allowed gap window before they were lost to follow-up. The Last Observation Carried Forward approach was thus applicable to two subjects. With respect to the date of enrolment, time to loss of persistence was approximately one year (not reached - 365 days), corresponding to the end of the 12-month prospective observational study period. A sensitivity analysis was conducted to estimate the change in persistence when using a 45-day or a 90-day gap, showing that the definition of the allowed window substantially changed the median time to non-persistence with the shorter window shortening it and the longer window widening the time to non-persistence (Table 5). These sensitivitly analysis results are only descriptive, with no inferential part.

Table 5. Time to Non-Persistence With Denosumab - Calculation Since the First Dose

Time	45-day gap		60-day gap		90-day gap	
No. subjects	100		100		100	
No. events	68	68%	48	48%	39	39%
Deaths	5	7.4%	8	16.7%	10	25.6%
SAEs	1	1.5%	2	4.2%	2	5.1%
Gap	59	86.8%	33	68.8%	20	51.3%
Decision	3	4.4%	5	10.4%	7	17.9
No. censored	32	32%	52	52%	61	61%
Median Survival Time, days (95% CI)	253	(156, 365)	464	N/R	N/R	-

CI, confidence interval; N/R, not reached

Physicians' and Subjects' Perceptions of Persistence

All 9 investigators completed the PAMQ at baseline and at the end of observation. The results showed that there was strong confidence among physicians regarding their awareness of persistence in general and of their subjects' persistence in particular. Most physicians had no changes in their baseline responses compared to end-of-study responses. Among those responses that worsened from baseline, only changes from

"Strongly agree" to "Agree" occurred, which means that the aggregated response was still retained. The question, where the highest number of physicians selected an improved response to baseline (n=3) was "I think that subjects discuss non-adherence with me".

The BMQ asked questions about the perception of medicines in general and was completed by physicians and subjects at baseline and at the end of observation. Physicians' responses were largely consistent, while the responses for subjects were variable and revealed concerns relating to side effects and potential discomfort caused by the medicines. In general, the level of agreement between subjects and physicians was relatively high (consistency ranging from 57.8% to 93.3%), however, the sample size was low (45 or less) for each question.

Diagnosis and Management of Pain

Subjects completed the BPI questionnaire at baseline and in 3-monthly intervals during the observation period. No trends in the mean or median scores were observed over time.

On the premise, that a pain score ≤4 represents an acceptably low level of pain, the proportions of pain scores ≤4 and >4 were analysed over time. This analysis showed the proportion of subjects reporting scores ≤4 increased over time. An additional analysis of pain worsening was performed in counting the number of subjects with any increase or with a clinically relevant (≥2 points) increase in pain each month among those subjects with baseline pain scores ≤4. Only a range of 2 to 3 subjects at each timepoint had any increase in pain. Of subjects with clinically relevant increase in pain, 2 were recorded at month 3, 4 at month 6 and 9, respectively, and 6 at month 12. The median time to clinically meaningful worsening of pain was not reached.

Pain medication was prescribed to 38 subjects, mostly metamizole sodium (34.2% of subjects with pain medication, n=13).

Adverse Events

Overall, 93 adverse events were recorded (Table 6). These adverse events occurred in 38 subjects, 20 subjects had serious adverse events and 26 had non-serious adverse events. Overall, the adverse events – irrespective of denosumab causality – which occurred in more than one subject were hypocalcemia (n=19), disease progression (n=10), anemia (n=7), death (n=7), and leukopenia (n=3). Among the 69 adverse events not related to denosumab and occurring in 25 subjects, 44 were serious and 36 were of severe intensity.

Table 6. Summary of Adverse Events in the Study (by MedDRA classification)

MedDRA classification System Organ Class →Preferred Term	**N (Event)**	**%**
Total	**93**	**100%**
Blood and lymphatic system disorders	12	12.9%
Anemia	7	58.3%
Leukopenia	3	25.0%

MedDRA classification System Organ Class →Preferred Term	**N (Event)**	**%**
Neutropenia	1	8.3%
Thrombocytopenia	1	8.3%
Cardiac disorders	1	1.1%
Cardiopulmonary failure	1	100%
Eye disorders	2	2.1%
Dry eye	1	50.0%
Visual impairment	1	50.0%
Gastrointestinal disorders	2	2.1%
Inguinal hernia, obstructive	1	50.0%
Loose tooth	1	50.0%
General disorders and administration site conditions	20	21.5%
Pain	1	5.0%
Death	7	35.0%
Fatigue	1	5.0%
Edema	1	5.0%
Disease progression	10	50.0%
Hepatobiliary disorders	1	1.1%
Hepatorenal syndrome	1	100%
Infections and infestations	1	1.1%
Osteomyelitis	1	100%
Injury, poisoning and procedural complications	2	2.1%
Lumbar vertebral fracture	1	50.0%
Thoracic vertebral fracture	1	50.0%
Investigations	6	6.5%
Blood creatinine increased	2	33.3%
Gamma-glutamyltransferase increased	1	16.7%
Platelet count decreased	1	16.7%
Weight decreased	1	16.7%
Radioisotope uptake increased	1	16.7%
Metabolism and nutrition disorders	23	24.7%
Hypocalcemia	19	82.6%
Fluid intake reduced	1	4.3%
Decreased appetite	1	4.3%
Hypophagia	2	8.7%
Musculoskeletal and connective tissue disorders	7	7.5%

MedDRA classification System Organ Class →Preferred Term	**N (Event)**	**%**
Bone pain	1	14.3%
Osteitis	1	14.3%
Osteonecrosis	1	14.3%
Pain in jaw	3	42.9%
Osteonecrosis of jaw	1	14.3%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8	8.6%
Metastases to abdominal cavity	1	12.5%
Metastases to bone	4	50.0%
Metastases to liver	2	25.0%
Metastases to lung	1	12.5%
Nervous system disorders	4	4.3%
Cerebrovascular accident	1	25.0%
Paraplegia	1	25.0%
Brain oedema	1	25.0%
Ischemic stroke	1	25.0%
Renal and urinary disorders	2	2.1%
Hematuria	1	50.0%
Acute kidney injury	1	50.0%
Respiratory, thoracic and mediastinal disorders	2	2.1%
Pleural effusion	1	50.0%
Respiratory failure	1	50.0%

Twenty-four adverse events were related to denosumab (Table 7) and occurred in 17 subjects. Of denosumab-related adverse events, 2 were serious (osteomyelitis, osteitis) and of severe intensity occurring in one subject; 22 were non-serious and mostly of mild intensity. Osteonecrosis of the jaw or related events occurred in 5 subjects (loose tooth, n=1; pain in jaw, n=2; osteonecrosis, n=1; osteonecrosis of the jaw, n=1).

Table 7. Summary of Denosumab-Related Adverse Drug Reactions (by MedDRA classification)

System Organ Class	**Preferred Term**	**Related**	**Serious**	**N (Event)**
Gastrointestinal disorders	Loose tooth	Yes	No	1
General disorders and administration site conditions	Oedema	Yes	No	1
Infections and infestations	**Osteomyelitis**	**Yes**	**Yes**	**1**

System Organ Class	Preferred Term	Related	Serious	N (Event)
Investigations	Radioisotope uptake increased	Yes	No	1
Metabolism and nutrition disorders	Hypocalcaemia	Yes	No	15
Musculoskeletal and connective tissue disorders	**Osteitis**	**Yes**	**Yes**	**1**
Musculoskeletal and connective tissue disorders	Osteonecrosis	Yes	No	1
Musculoskeletal and connective tissue disorders	Pain in jaw	Yes	No	2
Musculoskeletal and connective tissue disorders	Osteonecrosis of jaw	Yes	No	1

Bold font highlights denosumab-related serious adverse drug reactions

- **Discussion**

With HSPC and CRPC as well as older and younger subjects participating in the study, this group of Bulgarian prostate cancer receiving denosumab for prevention of SREs related to their bone metastases was very diverse. Most of the subjects had high (35%) and very high (22%) risk tumors. The fraction of subjects with very high risk tumors was similar across both clinical states (HSPC: 21.6% vs. CRPC: 23.1%).

The present study shows trends among the age and clinical status groups with regards to the denosumab treatment patterns with earlier initiation in HSPC (HR=0.65, versus CRPC) and younger subjects (HR=0.68, versus older). Overall, the median time from bone metastasis diagnosis to initiation of denosumab therapy was 1.8 months. Treatment was initiated within 0.6 month in the fastest quartile of subjects and within 8.9 months in the slowest quartile. For younger subjects (n=19), the median (Q1, Q3) was 1.2 (0.2, 2.8) months and for older subjects (n=81), the median (Q1, Q3) was 2.0 (1.3, 3.9) months. Although the study groups were small and results need to be interpreted with caution, this not statistically significant difference (95% CIs overlapping) could be related to the need for the older subjects to schedule and perform their treatment depending on management of their comorbidities and need for logistic support.

Subjects with HSPC were initiated on denosumab earlier after metastasis diagnosis than those with CRPC, but the difference was also not statistically significant (95% CIs overlapping). The median (Q1, Q3) time for the HSPC group was 1.5 (0.6, 4.2) months and for the CRPC group 7.9 (0.8, 16.4) months. It is discussed in the literature (Morote et al, 2022) that there are challenges and practical complexities with establishing the 'hormone resistant' tumor state (i.e. failure of at least one hormonal therapy, indicated by a rising prostate-specific antigen concentration).

Non-persistence with denosumab was defined as not receiving any denosumab administration on the scheduled date nor during a 60-day window thereafter. Since denosumab is administered at a once monthly schedule in the oncology setting, a 60-day gap represents two missed doses. When time to non-persistence calculations were started with the first known denosumab dose within the retrospective period, the median

time to non-persistence was 443 to 464 days, depending on the approach to handling loss to follow-up. When starting calculation from the informed-consent-date, the median time to non-persistence was 365 days, representing the full 12 months of prospective observation. Irrespective of the duration of observation (retrospective plus prospective observation or prospective observation alone), approximately half of subjects remained persistent with denosumab for the respective duration. In a previously published study of persistence with denosumab in the CEE region it was observed that persistence using a 35-day window corresponding to missing one dose varied among tumor types with prostate and breast cancer subjects generally showing higher persistence than lung cancer and cancer summarized as 'other' (Haslbauer et al, 2020). The same study also showed that persistence differed by country with Bulgaria showing the second lowest persistence rate among participating countries. In both studies, the violation of the allowed window was the most frequent reason for non-persistence (Haslbauer et al, 2020). Although there is a difference in definitions, real-world evidence from the United States and from Germany indicated that subjects using denosumab were more compliant with treatment than those using zoledronic acid (Diel et al, 2020; Qian et al, 2017; Hernandez et al, 2014). In the real-world setting, denosumab dosing schedules are often aligned with common chemotherapy regimens. Data from Canada showed administration intervals up to once every 12 weeks are common (Alzahrani et al, 2021). A retrospective study of different denosumab dosing intervals (< 5, 5–11, or ≥ 12 weeks) found no significant differences in time to first SRE and median OS with extended dosing schedules (Abousaud et al, 2020). However, there appears to be contradicting evidence with a higher SRE incidence when denosumab was administered at intervals of 31–56 days versus 27–30 days (Kettle and Patel, 2017). In the present study, very few SREs and no symptomatic SREs were recorded during observation, precluding meaningful analysis of differences in SRE rate among subjects with different administration windows.

The reported pain levels improved over the treatment period. This is in line with the previous persistence study from the region, where only very few subjects shifted from no or weak opioid analgesics (Analgesic Quantification Algorithm [AQA] score ≤ 2) at baseline, very few subjects shifted to an AQA category > 2 (i.e., strong opioids at increasing doses) at later timepoints (Haslbauer et al, 2020).

The reported adverse events were consistent with previous treatment experience with denosumab in prostate cancer or other solid tumors (Henry et al, 2014; Lipton et al, 2012; Fizazi et al, 2011; Stopeck et al, 2010).

Potential limitations of the study relate to its observational design. Data source limitations were expected to be low due to the mainly prospective design. In the case of unexpected or incorrect data, clarifications were sought based on medical records. Any inconsistencies were reviewed and resolved during frequent data extractions. Adverse drug reactions, such as osteonecrosis of the jaw, were not independently adjudicated by an expert panel. There were two major areas of potential selection bias for the study. Firstly, recruited subjects were required to have metastatic stage of the disease and to have received at least one dose of denosumab prior to enrolment. Secondly, there might have been a small group of subjects who ceased treatment after one dose, usually because of death or disease progression. The survival bias may therefore have been slightly inflated and have impacted other collected data. However, due to the prospective design of the study, subjects were alive at enrolment. The nature of an observational study involves some difficulties in obtaining data, therefore the bias of missing data was anticipated, and the number missing data was explicitly shown for each statistic.

- **Conclusions**

The primary study objective was to describe real-life patterns of bone metastasis management and routine use of denosumab for SRE prevention in subjects with bone metastases from prostate carcinoma. The present study showed that in Bulgaria denosumab was initiated sooner after bone metastasis diagnosis in HSPC subjects and in younger subjects with prostate cancer.

Secondary objectives included to estimate the incidence of SREs and symptomatic SREs (SSEs); to identify factors that influence persistence; to estimate healthcare utilization, and to describe pain severity and management. Rates of new SREs were very low and no symptomatic SREs occurred during the study. The median persistence was approximately one year and 3 months counting from the first known denosumab dose, allowing two missed doses to define persistence. The most influential factor for loss of persistence was the length of the allowed gap window. In the prospective study period, 9 hospitalizations due to SREs occurred, the durations of hospitalization ranged from 3 to 19 days. The proportion of subjects reporting acceptably low pain scores of ≤4 increased over time. The denosumab safety profile was consistent with previous evidence.

- **Marketing Authorization Holder(s)**

Amgen Europe B.V.

- **Names and Affiliations of Principal Investigators**

Not applicable.