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ORIGINAL ARTICLE

# An observational time and motion study of denosumab subcutaneous injection and zoledronic acid intravenous infusion in patients with metastatic bone disease: results from three European countries

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**Abstract**
*Purpose* Denosumab (administered via subcutaneous injection) demonstrated superior efficacy versus the intravenously administered zoledronic acid in the prevention of skeletal-related events in an integrated analysis of three head-to-head phase III trials in patients with bone metastases secondary to solid tumors. To date, no studies have evaluated treatment administration duration endpoints of these two agents.
*Methods* A multinational, multi-site, observational time and motion study conducted in 10 day oncology units (DOUs) across Belgium, Germany, and Italy. Observations of process time included task time and active healthcare professional (HCP) time for pre-defined tasks. Patient time measurements included entering/exiting the DOU, treatment room, and treatment chair or examination table.
*Results* A total of 189 patients were enrolled (82 received zoledronic acid and 107 received denosumab) and 238 observations were recorded (104 for zoledronic acid and 134 for denosumab). Mean total task time was reduced by 81% when denosumab was used versus zoledronic acid (8.4 versus 44.2 min; $p < 0.0001$; pooled analysis across all countries). Pooled estimates for active HCP time were 12.2 min for zoledronic acid and 6.9 min for denosumab (44% reduction; $p < 0.0001$).
*Conclusions* In the countries studied, using denosumab compared with zoledronic acid reduced total task time and active HCP time. Thus, HCPs have more time to dedicate to other patients or care activities. An ability to increase the volume of appointments within DOUs could reduce waiting lists in sites operating at full capacity and increase overall productivity and efficiency in hospital processes.

**Keywords** Denosumab · Zoledronic acid · Metastatic bone disease · Time and motion study

**Electronic supplementary material** The online version of this article (doi:10.1007/s00520-017-3697-5) contains supplementary material, which is available to authorized users.

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## Introduction

In patients with advanced solid tumours, the most common site for metastasis is the bone. More than 70% of patients with advanced breast cancer [1], up to 90% of patients with advanced prostate cancer [2, 3] and 60% of patients with advanced lung cancer have radiologic evidence of bone

metastases [2, 4]. Bone metastases are commonly associated with bone complications, known as skeletal-related events (SREs), including pathologic fracture, spinal cord compression and radiation or surgery to bone. SREs cause severe pain, reduced mobility, functional dependency, increased demand for analgesics and result in a reduced overall health-related quality of life [5–8].

Treatment and management of SREs impose a substantial burden on healthcare resources [9, 10]. Hoefeler et al. reported that approximately one third of SREs require an inpatient stay, with an average duration of 18.3 to 22.5 days across all SRE and tumour types [10]. In the study, all SREs were associated with substantial increases from baseline in the frequency of procedures and approximately two thirds of SREs required at least one outpatient visit (mean number of visits per SRE ranged between 2.6 and 6.7) [10]. Similarly, an observational study conducted by Body et al. reported an increase from baseline in the mean number of inpatient stays per SRE by approximately 0.5–1.5 stays and an increase in the total duration of inpatient stays of 6–37 days per event [9]. Thus, SREs are associated with substantial healthcare resource utilization consumption, placing an additional burden on healthcare systems [9, 10].

Treatment options indicated to prevent and delay SREs in patients with bone metastases secondary to solid tumours are primarily bone-targeted agents. Until recently, the mainstay of treatment in Europe has been the bisphosphonate zoledronic acid, given via intravenous (IV) infusion. Zoledronic acid should be administered every 3 to 4 weeks over a minimum of 15 min [11]. In 2011, denosumab (a receptor activator of nuclear factor kappa-B ligand inhibitor) administered as a subcutaneous (SC) injection every 4 weeks was approved by the European Medicines Agency for SRE prevention in patients with bone metastases from solid tumours [12]. An integrated analysis of three head-to-head phase III trials demonstrated that denosumab was superior to zoledronic acid in delaying time to first on-study SRE by a median of 8.2 months and in reducing the risk of a first SRE by 17% (hazard ratio 0.83; 95% confidence interval [CI] 0.76, 0.90) [13]. Other bisphosphonates are also used to prevent SREs in patients with breast cancer [14–16]. Pamidronate is approved at a country level in Europe to treat bone pain and osteolytic bone metastases of breast cancer (it is given as a 2-h infusion of 90 mg every 3–4 weeks) [15, 17], and ibandronate is indicated for the prevention of SREs in patients with breast cancer and bone metastases (it is given as an infusion of 6 mg over at least 15 min every 3–4 weeks) [16].

The time associated with treatment administration may place an additional burden on patients and healthcare providers; a study of patient wait time by Kallen et al. in the USA showed that reducing waiting time improves patient satisfaction. The same study showed that shorter treatment time allows nursing staff to be deployed more effectively, increasing patient flow and thus reducing overtime expenses. It may also eliminate the need to acquire additional patient treatment space [18].

In a previous time and motion study conducted in US patients with breast or prostate cancer, the mean (standard deviation, SD) administration time for zoledronic acid monotherapy was 69.4 (41.8) min, of which 78% was infusion time (mean 53.9 min). By definition, monotherapy meant chemotherapy was not administered on the same day and the process included pre-infusion tasks (vital signs, blood draw, and physical examination), zoledronic acid preparation (hydration and infusion), and follow-up [19, 20].

Here, we describe the first time and motion study to assess the administration time of denosumab and zoledronic acid in real-world practice in three European countries. The primary objectives were to estimate total task time and total active healthcare professional (HCP) time for pre-defined tasks associated with denosumab and zoledronic acid monotherapy administration. Secondary objectives included estimating patient time in the day oncology unit (DOU), time in the treatment unit, and time in the treatment chair or on the examination table.

## Methods

### Study design

A multinational, multi-site, observational time and motion study was conducted in 10 DOUs in Belgium, Germany, and Italy. Time and motion methodology was applied to identify all relevant steps (i.e. pre-defined tasks) in the denosumab and zoledronic acid processes and to define the patient journey (Table 1).

Observations of process time involved measuring the task time and active HCP time for each pre-defined task that occurred within the treatment room. Observations of patient time were restricted to measuring the time of entering/exiting the DOU, time in the treatment room and time in the treatment chair (for IV or SC) or on the examination table (for SC). Information was collected on activities occurring outside the DOU (e.g. patient travel time, time from hospital entry to arrival at the DOU, physician consultation, blood sampling and other activities prior to entering the DOU), but no time and motion measurements were performed. Key study definitions are presented in Table 2.

### Eligibility criteria

Eligible patients had a diagnosis of bone metastases secondary to a solid tumour, were scheduled to receive denosumab or zoledronic acid in a DOU setting where both treatments were readily available and were aged ≥18 years. Patients

**Table 1** Process flow

| Term | Definition |
|---|---|
| Zol IV | 1. Patient arrival/registration |
| | 2. Installation of peripheral catheter or flushing of permanent line/take Zol ready-to-use bag/connection of Zol[a] |
| | OR |
| | Zol reconstitution/installation of peripheral catheter or flushing of permanent line/blood sampling/connection of pre-medication/connection of Zol[b] |
| | OR |
| | Installation of peripheral catheter or flushing of permanent line/Zol reconstitution/connection of Zol[c] |
| | 3. Zol infusion duration (task time)/patient monitoring during Zol infusion (active HCP time) |
| | 4. Disconnection of Zol infusion |
| | 5. Patient monitoring post-infusion |
| Dmab SC | 1. Patient arrival/registration |
| | 2. Installation of peripheral catheter or flushing of permanent line/blood sampling[d] |
| | 3. Filling of Dmab syringe |
| | 4. Dmab injection and disposal |
| | 5. Patient monitoring post-injection |

Task sequence varied across countries and sites[a] Process observed in Germany [b] Process observed in Belgium, blood sampling and pre-medication only at one site [c] Process observed in Italy [d] Process observed at one site in Belgium

*Dmab* denosumab, *HCP* healthcare professional, *IV* intravenous, *SC* subcutaneous, *Zol* zoledronic acid

participating in an interventional trial or requiring any inpatient admission were excluded.

For each country, 39 recorded observations per treatment were planned (equivalent to a total of 234 observations; 78 per country, 117 per treatment). Although more than one observation was permitted per patient, most patients contributed only one observation to the analysis.

## Data collection

Baseline patient demographic and clinical characteristics were collected using a Subject Information Data Form. Data relating to time variables were collected using two Observation Data Forms (ODFs) to observe denosumab and zoledronic acid administration processes, respectively. A generic ODF was constructed following semi-structured interviews with relevant site staff (a physician, nurse and pharmacist) at one site in Belgium. Clear and unambiguous start and stop points for each step in the treatment administration process were defined to ensure accurate time measurements (e.g. for the patient arrival/registration pre-defined task, the start point was 'hand social security card to nurse' and the stop point was 'send patient to waiting area'). At each site, a semi-structured interview was conducted with one HCP in order to understand site-specific patient management practices. Site-specific tailoring of ODFs was kept to a minimum to enable pooled analyses to be carried out. Pre-defined tasks for both treatment options are shown in Table 1.

Active HCP time was measured using a stopwatch and recorded in minutes and seconds. Task time and patient time

**Table 2** Key study definitions

| Term | Definition |
|---|---|
| Task time | Time from initiation until completion of a pre-defined task, including potential disruptions (during which the HCP was not actively dedicated to the performance of the task) |
| Active HCP time | Time an HCP was actively dedicated to the performance of the task |
| Observed time | Time collected through stopwatch measurement for pre-defined tasks related to Dmab SC and Zol IV treatment preparation, administration and post-treatment monitoring |
| Chair time | Time between entry and exit of the chair (or entry and exit of the examination table for Dmab SC) |
| Treatment room | The place where Dmab SC or Zol IV was administered |
| Treatment room time | Time between entry and exit of the treatment room (for receiving Dmab SC or Zol IV) |
| Day oncology unit time | Time between entry and exit of the day oncology unit |

*Dmab* denosumab, *HCP* healthcare professional, *IV* intravenous, *SC* subcutaneous, *Zol* zoledronic acid

variables were recorded in hours and minutes. Two observers per site were trained and assigned to recording time data. All tasks were sequential; thus, no simultaneous occurrences of multiple tasks were anticipated. Data collection was monitored remotely and queries clarified using data clarification forms.

### Statistical analyses

Out study was not designed to test any formal hypotheses. Each completed ODF represented one observation of a single process. Analyses were performed per site and pooled by country and across countries.

Primary time outcomes were mean total task time and mean total active HCP time. Secondary time outcomes included mean drug administration duration, mean patient chair time, mean treatment room time and mean day oncology unit time.

Descriptive statistics for continuous variables included the number of observations, mean and SD and for categorical variables including frequency and percentage of patients in each observation group.

Imputation for missing time data was performed using the mean of available observations at a given site only if ≥50% of observations at that site had non-missing values. Time was considered as zero in cases where the following tasks were not performed: patient monitoring during and post-zoledronic acid infusion and patient monitoring post-denosumab injection. Outlier values were queried consistently as part of a formal data clarification process, and a value could be excluded if the site could not certify its correctness. This imputation scheme was considered acceptable due to a significant correlation of the observations within a site, compared with the variation seen between sites.

Mean total task time and mean total active HCP time were derived variables: For each observation, task time and active HCP time for each pre-defined task were summed to yield total process time. For each time variable, 'goodness-of-fit' tests were performed using all data from a country to determine the best fitted distribution: gamma, normal, lognormal, or Weibull distribution. Across all countries, gamma distribution was the preferred distribution and was used to calculate mean total time and corresponding 95% CIs for each site. Given the small sample sizes for each site, median values are presented within Supplementary Figs. S1–S6.

A random intercept model with site as a random effect was used to analyse all time outcomes for each observation group within and across countries. The model assumed a normal distribution for the random effect as well as the random error. Mean total time and corresponding 95% CIs are reported by country and pooled across countries. Because of possible site-clustering effects, median values were not calculated. As part of the exploratory analyses, the difference in time by route of administration was tested. Observation group was included as a fixed effect within the random intercept model, and descriptive $p$ values were calculated.

All statistical analyses were performed using SAS©, version 9.1 or higher for Windows (SAS Institute, Cary, NC, USA) or Microsoft® Office Excel® 2007.

## Results

### Study participants

In total, 189 patients were enrolled (82 received zoledronic acid and 107 received denosumab), contributing 238 observations (104 for zoledronic acid [29, 40 and 35 for Belgium, Germany and Italy, respectively] and 134 for denosumab [44, 40 and 50, respectively]). A total of 33 patients (denosumab 16; zoledronic acid 17) were observed twice, and one patient was observed three times. Patient demographics and clinical characteristics for both treatment groups are summarized in Table 3 and appeared to be well aligned across treatments in all countries. Prior to study enrolment, patients had received zoledronic acid treatment for a mean (SD) of 1.7 (1.8) years and for a median (range) of 1.0 (0–10.3) years. Patient had received denosumab for a mean (SD) of 1.0 (0.7) years and a median (range) of 0.9 (0–2.6) years. The majority received zoledronic acid every 3–4 weeks and denosumab every 4 weeks.

### Activities prior to drug administration

At most sites (7 out of 10), a physician consultation was performed prior to the patient entering the treatment room. Other pre-treatment activities included blood sampling and documentation of vital signs. At four sites, blood sampling occurred on the treatment day for both zoledronic acid and denosumab. At two sites, this time was measured and recorded as the blood was drawn at patient arrival (Belgium, site 2) or immediately before drug administration (Germany, site 1).

### Task time (per treatment administration)

Across all countries (pooled data set), mean (95% CI) total task time was 44.2 (37.3, 51.1) min for zoledronic acid and 8.4 (1.5, 15.2) min for denosumab, equating to a statistically significant relative reduction of 81% ($p < 0.0001$). By country, relative reduction in task time ranged from 69 to 85% (Fig. 1a).

The principal task in both processes was drug administration (i.e. infusion for zoledronic acid and syringe filling and injection for denosumab). Mean (95% CI) drug administration time across countries was 25.1 (20.9, 29.3) min for zoledronic acid and 1.5 (0.0001, 5.6) min for denosumab (−94%; $p < 0.0001$) (Fig. 2a). At a site level, mean zoledronic acid

**Table 3** Patient and clinical characteristics

| | Pooled | | Belgium | | Germany | | Italy | |
|---|---|---|---|---|---|---|---|---|
| | Zol (*n* = 82) | Dmab (*n* = 107) | Zol (*n* = 28) | Dmab (*n* = 37) | Zol (*n* = 26) | Dmab (*n* = 29) | Zol (*n* = 28) | Dmab (*n* = 41) |
| Age at cancer diagnosis | | | | | | | | |
| Mean (SD) | 54.6 (12.0) | 57.1 (12.9) | 53.4 (13.5) | 57.5 (13.6) | 52.5 (10.1) | 56.7 (11.6) | 57.9 (11.8) | 57.4 (13.4) |
| Median (range) | 52.0 (26–77) | 57.0 (26–89) | 49.0 (26–76) | 58.0 (29–89) | 49.0 (31–72) | 53.0 (37–75) | 59.5 (36–77) | 57.0 (26–79) |
| Years since cancer diagnosis | | | | | | | | |
| Mean (SD) | 7.4 (6.8) | 6.7 (5.9) | 7.4 (6.2) | 4.9 (4.6) | 6.4 (7.4) | 6.6 (5.5) | 8.3 (6.9) | 8.3 (6.9) |
| Median (range) | 5.5 (0–27) | 5.0 (0–31) | 6.0 (0–18) | 3.0 (1–19) | 3.0 (0–27) | 6.0 (0–21) | 7.0 (0–20) | 7.0 (0–31) |
| Age at diagnosis of bone metastases, years | | | | | | | | |
| Mean (SD) | 60.0 (11.2) | 61.4 (12.5) | 58.1 (12.6) | 60.3 (12.3) | 57.5 (9.4) | 60.5 (12.2) | 64.4 (10.2) | 63.4 (13.1) |
| Median (range) | 61.0 (34–80) | 63.0 (34–89) | 56.0 (34–80) | 61.0 (34–89) | 60.5 (44–73) | 63.0 (42–81) | 66.0 (47–80) | 67.0 (35–84) |
| Years since onset of bone metastasis | | | | | | | | |
| Mean (SD) | 2.0 (1.9) | 2.4 (3.0) | 2.8 (2.4) | 2.1 (2.2) | 1.4 (1.5) | 2.8 (3.7) | 1.8 (1.6) | 2.2 (3.2) |
| Median (range) | 1.0 (0–10) | 2.0 (0–19) | 2.0 (0–10) | 1.0 (0–13) | 1.0 (0–6) | 2.0 (0–19) | 1.0 (0–6) | 2.0 (0–18) |
| Female, n (%) | 68 (82.9) | 86 (80.4) | 26 (92.9) | 26 (70.3) | 25 (96.2) | 29 (100) | 17 (60.7) | 31 (75.6) |
| Primary tumour type, *n* (%) | | | | | | | | |
| Breast | 61 (74.4) | 83 (77.6) | 21 (75.0) | 24 (64.9) | 24 (92.4) | 29 (100) | 16 (57.1) | 30 (73.2) |
| Prostate | 12 (14.6) | 14 (13.1) | 2 (7.1) | 5 (13.5) | - | - | 10 (35.7) | 9 (22.0) |
| Lung | 4 (4.9) | 2 (1.9) | 2 (7.1) | 1 (2.7) | 1 (3.8) | - | 1 (3.6) | 1 (2.4) |
| Other | 5 (6.1) | 8 (7.5) | 3 (10.7) | 7 (18.9) | 1 (3.8) | - | 1 (3.6) | 1 (2.4) |
| Visceral metastasis, *n* (%) | | | | | | | | |
| All[a] | 42 (51.2) | 51 (47.7) | 15 (53.6) | 25 (67.6) | 17 (65.4) | 14 (48.3) | 10 (35.7) | 12 (29.3) |
| Liver | 20 (24.4) | 26 (24.3) | 5 (17.9) | 11 (29.7) | 13 (50) | 9 (31) | 1 (3.6) | 4 (9.8) |
| Lung | 17 (20.7) | 19 (17.8) | 5 (17.9) | 9 (24.3) | 6 (23.1) | 5 (17.2) | 1 (3.6) | 2 (4.9) |
| Other | 23 (28.0) | 20 (18.7) | 11 (39.3) | 14 (37.8) | 7 (26.9) | 3 (10.3) | 6 (21.4) | 6 (14.6) |
| Current hormone therapy, *n* (%) | 56 (68.3) | 75 (70.1) | 19 (67.9) | 18 (48.6) | 12 (46.2) | 21 (72.4) | 25 (89.3) | 36 (87.8) |
| GFR, *n* (%) | | | | | | | | |
| < 60 mL/min | 7 (8.5) | 15 (14) | 4 (14.3) | 9 (24.3) | 2 (7.7) | 5 (17.2) | 1 (3.6) | 1 (2.4) |
| ≥ 60 mL/min | 53 (64.6) | 64 (59.8) | 24 (85.7) | 28 (75.6) | 24 (92.3) | 24 (82.8) | 5 (17.9) | 12 (29.3) |
| Missing | 22 (26.8) | 28 (26.2) | – | – | – | – | 22 (78.6) | 28 (68.3) |
| ECOG score, *n* (%) | | | | | | | | |
| 0 | 47 (57.3) | 57 (53.3) | 21 (75) | 24 (64.9) | 14 (53.8) | 13 (44.8) | 12 (42.9) | 20 (48.8) |
| 1 | 28 (34.1) | 45 (42.1) | 7 (25) | 11 (29.7) | 11 (42.3) | 15 (51.7) | 10 (35.7) | 19 (46.3) |
| 2 | 1 (1.2) | 3 (2.8) | – | 2 (5.4) | 1 (3.8) | 1 (3.4) | – | – |
| 3 | - | 1 (0.9) | – | – | – | – | – | 1 (2.4) |
| Missing | 6 (7.3) | 1 (0.9) | – | – | – | – | 6 (21.5) | 1 (2.4) |
| Pain (BPI), *n* (%) | | | | | | | | |
| 1–4 mild | 53 (64.6) | 72 (67.3) | 21 (75.0) | 26 (70.3) | 11 (42.3) | 14 (48.3) | 21 (75.0) | 32 (78.0) |
| 5–6 moderate | 7 (8.5) | 11 (10.3) | 2 (7.1) | 5 (13.5) | 2 (7.7) | 1 (3.4) | 3 (10.7) | 5 (12.2) |
| 7–10 severe | 5 (6.1) | 6 (5.6) | 5 (17.9) | 6 (16.2) | - | - | - | - |
| Not available | 17 (20.7) | 18 (16.8) | - | - | 13 (50.0) | 14 (48.3) | 4 (14.3) | 4 (9.8) |

Mean ± SD

*BPI* Brief Pain Inventory, *Dmab* denosumab, *ECOG* Eastern Cooperative Oncology Group, *GFR* glomerular filtration rate, *SD* standard deviation, *Zol* zoledronic acid

[a] Patients may have had more than one type of visceral metastasis

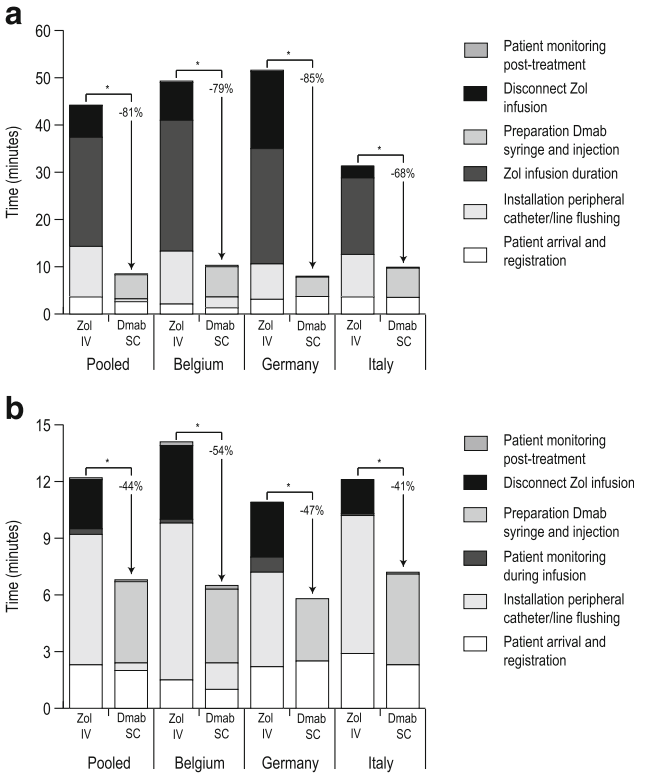


**Fig. 1** Process time variables per treatment administration. **a** mean task time and **b** mean active HCP time *$p < 0.0001$. Note for panel **b**: The 'Patient arrival and registration' task was typically the same for Zol and Dmab and pooled estimates were comparable. For one site in Belgium, the 'Installation of peripheral catheter' task was also performed in patients receiving Dmab because of the need for blood sampling; pre-medication was also sometimes given. Active patient monitoring during infusion, post-infusion and post-injection was rare in most centres. The 'Preparation of Dmab SC syringe and injection' task differed across centres in terms of time required and the sub-tasks involved. *Dmab* denosumab, *HCP* healthcare professional, *IV* intravenous, *SC* subcutaneous, *Zol* zoledronic acid

infusion duration ranged between 10.5 and 47.8 min whereas denosumab syringe filling/injection time ranged from 2.2 to 9.9 min (Supplementary Fig. S1). Among sites, the absolute reduction in total drug administration time (zoledronic acid minus denosumab) ranged from 11.0 to 57.5 min. Two sites (Belgium, site 2 and Germany, site 1) reported longer mean infusion durations (47.8 and 39.3 min, respectively) for zoledronic acid. For two other sites (Germany, site 2, and Italy, site 5), the reported mean duration was less than the recommended time of 15 min (12.9 and 10.5 min, respectively).

### Active HCP time (per treatment administration)

Pooled estimates for mean (95% CI) active HCP time were 12.2 (9.5, 14.9) min for zoledronic acid and 6.9 (4.2, 9.5) min for denosumab, showing a significant reduction in mean total active HCP time of 5.3 min when denosumab was administered versus zoledronic acid (−44%; $p < 0.0001$). On a country level, estimated

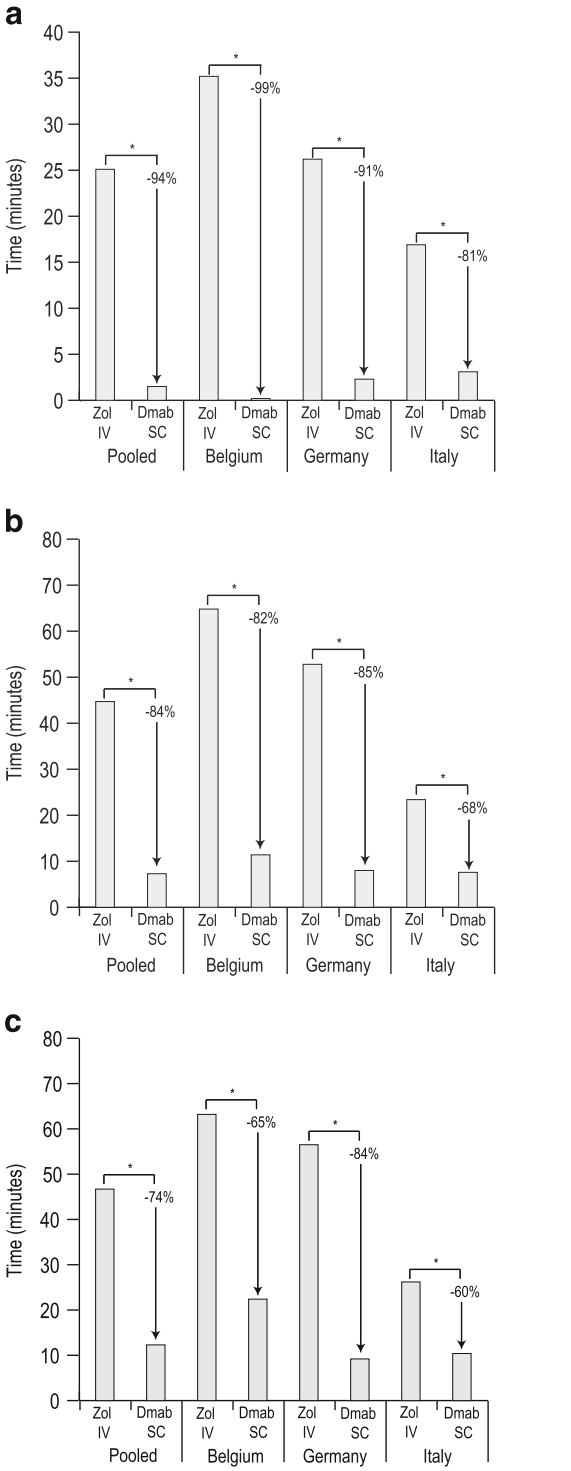


**Fig. 2** Patient time variables per treatment administration. **a** Mean drug administration duration, **b** mean patient chair time and **c** mean patient treatment room time. *$p < 0.0001$. *Dmab* denosumab, *IV* intravenous, *SC* subcutaneous, *Zol* zoledronic acid

time savings in favour of denosumab were 6.5 (−49%), 5.1 (−47%) and 5.2 min (−43%) for Belgium, Germany and Italy, respectively (all $p < 0.0001$) (Fig. 1b). For site-specific data, see Supplementary Figs. S2 and S3.

### Patient time (per treatment administration)

Mean (95% CI) chair time across countries was 44.7 (34.9, 54.5) min for zoledronic acid and 7.3 (0.0001, 17.0) min for denosumab (−84%; $p < 0.0001$), with mean chair time reductions of 53.8 (−82%), 44.8 (−85%) and 15.8 (−68%) min for Belgium, Germany and Italy, respectively (all $p < 0.0001$) (Fig. 2b). At four sites, patients received denosumab while seated or lying on an examination table. At all sites, zoledronic acid was administered while patients were sitting in an infusion chair. Site-specific data are presented in Supplementary Fig. S4.

Patients receiving denosumab spent less time in the treatment room than did those receiving zoledronic acid, with a mean (95% CI) time of 46.7 (34.8, 58.7) min for zoledronic acid versus 12.3 (0.5, 24.1) min for denosumab (Fig. 2c). Mean patient time in the DOU (from arrival for registration until discharge) was 103.0 (67.3, 138.7) min for zoledronic acid and 68.8 (33.2, 104.4 min) for denosumab (Fig. 3). Variation in local practices resulted in important differences in mean DOU time across sites (see Supplementary Figs. S5 and S6 for site-specific treatment room and DOU times).

## Discussion

This is the first time and motion study to assess, in real-world routine clinical practice, the administration time of denosumab and zoledronic acid at 10 sites across Belgium, Germany and Italy. Both zoledronic acid and denosumab are approved for preventing SREs in patients with solid tumours and bone metastases. As per the approved summary of product characteristics, zoledronic acid should be administered over a minimum of 15 min to reduce the risk of renal toxicity [11]. This short infusion time has been considered an advantage for zoledronic acid, compared with the other available IV bisphosphonates that require longer infusion times (e.g. pamidronate). However, data from this study demonstrate that in clinical practice, zoledronic acid may be administered over a long period of time (up to 48 min), depending not only on physician preference but also on the patient preference and renal status.

Although there were clear differences in the real-world practices among sites, the results show consistent reductions for all time outcomes across the 10 sites and for each country. For mean total task time, reductions ranged between 11.0 and 57.5 min across all sites (45–91% reduction) when denosumab was administered versus zoledronic acid. Mean total active HCP time was reduced between 2.7 and 9.4 min across all sites (24–76% reduction) when denosumab was used instead of zoledronic acid. Typically, these time savings were the result of avoiding 'installation of peripheral catheter/infusion connection' and 'infusion disconnection,' which were partially offset by the time for 'preparation of the denosumab syringe and injection'. For mean total duration of drug administration, reductions ranged between 6.7 and 46.1 min (56–96% reduction) for denosumab versus zoledronic acid across all sites. This was the main driver for reported reductions in mean total chair time (4.9–61.4 min; 28–90% reduction).

Across all sites, zoledronic acid infusion duration ranged between 10.5 and 47.8 min. Two sites recorded longer infusion durations (47.8 and 39.3 min), citing 'reducing potential side effects that might occur' or 'elderly patients with an increased risk of renal insufficiency'. Other published time and

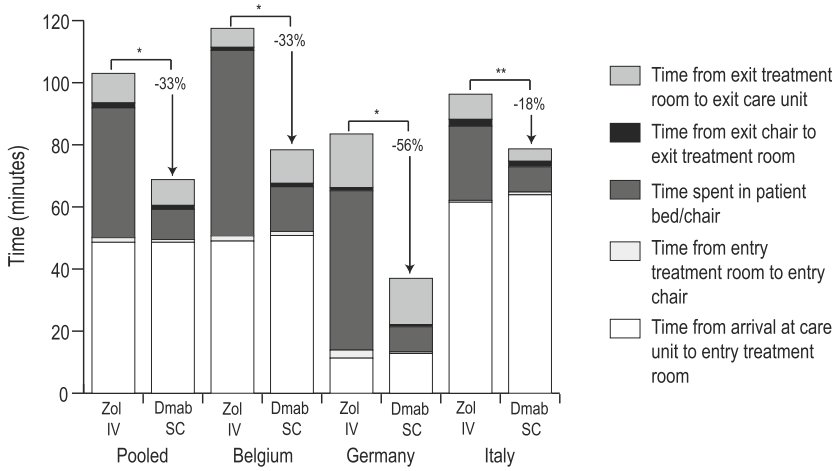


**Fig. 3** Mean patient DOU time per treatment administration. *$p < 0.0001$; **$p = 0.0228$. Notes: One site in Germany reported a mean of 15 min (across both Zol and Dmab) between arrival at DOU and entry in treatment room, due to blood sampling and control of vital parameters, and a mean of 30 min between exit of treatment room and exit of DOU because of a physician consultation. In Belgium, one site reported a mean of 35 min between arrival at DOU and entry in treatment room, due to a physician consultation, while in another site this task took on average 100 min because of blood sampling and physician consultation. In Italy, the majority of sites performed a physician consultation before drug administration; in one site, blood sampling was performed on treatment day and patients waited for the laboratory results before entering the treatment room. *Dmab* denosumab, *DOU* day oncology unit, *IV* intravenous, *SC* subcutaneous, *Zol* zoledronic acid

motion studies have reported a median zoledronic acid infusion time of 47.7 min in the USA [14, 15] and an average 18 min (range 13–35 min) in the UK [21]. Of note, an infusion time of less than the recommended 15 min should be avoided owing to the risk of renal toxicity [11].

Pooled analyses showed that reductions in patient chair time were driven by a reduction in zoledronic acid administration time. Assuming each patient receives approximately 13–15 cycles of zoledronic acid (every 3–4 weeks) and 13 cycles of denosumab (every 4 weeks) annually, applying those numbers to mean chair time per session (pooled dataset) resulted in an estimated 1–1.2 days (assuming an 8-h day) of chair time that could be freed up annually for a single patient treated with denosumab. Of course, it should be recognized that time spent by patients travelling to the centre and waiting time are not expected to change because these times depend on factors other than drug choice.

Findings from this study suggest that using denosumab instead of zoledronic acid reduces both patient and HCP burden as well as the use of infusion chair resources. Freed-up infusion chair time could be reallocated for the administration of other anticancer treatments or other infusions. In turn, this could increase the volume of day oncology unit appointments and the number of patients that could be treated, thereby potentially cutting waiting lists for sites operating at full capacity. Performing other infusions could result in alternative revenue options for sites that operate according to a fee-for-service structure. However, quantifying the complete financial implications of such efficiency gains was outside the scope of this study. Cost differences between the two agents and across countries within Europe have been reported in cost analysis studies [22–24].

Although not formally tested in this study, using an SC injection adds flexibility in the way that treatment is delivered, offering physicians an opportunity to develop a new patient care pathway. Indeed, where available, patients may prefer to receive an SC injection either at the hospital DOU or more locally with their primary care physician, or to even have a nurse visit them at home. In a patient preference study conducted in individuals with breast cancer, strong patient preference was reported for SC versus IV administration of trastuzumab [25, 26]. Furthermore, denosumab may provide an additional benefit of an improved patient experience because cannulation can be avoided. Indeed, findings from a UK time tradeoff study indicated that treatment modality had an impact on preference and utility, with patients receiving IV infusion of bisphosphonates experiencing a higher disutility and greater inconvenience compared with SC injection of denosumab [27]. Although it would have been interesting to study the effect of administration route on patient health-related quality of life (HRQoL), it was outside the remit of this study. The main reasons for this were the potential impact of survey administration on patient time during the observation day and avoidance of additional study burden. However, an integrated analysis of data from three pivotal studies in patients with solid tumours has shown that worsening of patient HRQoL and strong opioid use were less common with denosumab than with zoledronic acid treatment [28]. Further comparator studies may be required to examine the effect of antiresorptive therapy administration route on the HRQoL of patients in more detail.

Our study was not designed to test any formal hypotheses. It was not possible to conduct a sample size calculation because there was a lack of a priori information on the expected mean process time and variance for primary outcomes measured for denosumab. A previous time and motion study quantified the process time for zoledronic acid; however, the process included tasks that were not considered in our study and was also limited to a US population, making it difficult to use these data as benchmarking information for sample size calculations [20]. Hence, the study protocol specified target sample sizes by country and by treatment that were based on study feasibility considerations. The achieved sample sizes differed slightly from those targets because the real-world use of both treatments at the participating sites was different from that assumed in the study protocol. During the data collection period, a smaller proportion of patients received zoledronic acid compared with denosumab at some sites. Logically, imbalances in total sample size and the composition (i.e. sample size by site) between IV and SC treatment groups would impact on the pooled estimates by country when applying simple statistics and would make any comparison between IV and SC difficult. As such, based on a similar published multi-site study [29], a site effect (i.e. clustering of data by site) was assumed as part of a random intercept model with site as a random effect. Such a model was used to correct for any imbalances in sample size. As part of exploratory analyses, and in order to generate a meaningful comparison between both observation groups, the model assumed route of administration as a fixed effect and results were statistically significant at country level and for all countries combined for all time variables. It should be noted that wide 95% CIs were observed for both observation groups in Germany and Belgium, reflecting important differences in mean time across the sites. However, for the results of all-country pooled-data, the associated CIs were relatively narrow, and should this study be repeated in a different selection of sites across these three countries, the mean values for these would be expected to fall within the 95% CIs reported here.

Differences in site practices were probably the most important drivers of observed differences in mean total time between sites. As part of the study interviews, inter-site differences in activities occurring outside the DOU (e.g. physician consultation, installation of a peripheral line, installation and opening of a permanent line and blood sampling) were recorded. These activities typically took place across different locations, such as the physician consultation area or the blood

sampling area, so time and motion observations across the various locations were difficult to implement. A second reason that time and motion measurements were not collected for those activities is that they were typically performed using a similar process and with a similar frequency for both treatments and were not deemed to be critical in light of the study's objectives. Indeed, blood sampling is recommended before administration of both treatments [11, 12]. Patients should have their serum creatinine levels assessed before each dose of zoledronic acid, owing to the risk of renal toxicity [11]. Denosumab is associated with a risk of hypocalcemia, so serum calcium levels should be measured before the initial dose of denosumab, within 2 weeks of the initial dose and if symptoms suggestive of hypocalcaemia occur [12]. In general, blood sampling during this study took place at least 1 day before drug administration or on the same day, but before the patient entered the treatment room for drug administration. However, in two sites, blood sampling was measured as part of the observations because it either happened immediately before zoledronic acid or denosumab administration or upon patient arrival. In both sites, time associated with blood sampling could not be excluded from time and motion measurements because it was intertwined with the time taken for other relevant tasks. However, blood sampling time was found to be similar for zoledronic acid and denosumab, and therefore, the addition of these activities did not impact on the absolute reduction in time. Given that this was the case for only two of the 10 study sites, the impact on total process time for the pooled dataset (across all countries) was limited. Irrespective of the differences in each bisphosphonate treatment workflow observed between sites, the estimated reduction in time (IV zoledronic acid versus SC denosumab) was consistent across all participating sites and countries. However, the fact that differences in site practises were observed in this study makes it of interest to examine further the differences in bisphosphonate treatment workflows that occur across different oncology units; findings from such studies could enable the optimization of such workflows at an individual site level.

Caution should be exercised when comparing the results obtained in our study with those previously reported. One study focused on the time required for all tasks associated with zoledronic acid, including pre-infusion activities (vital signs, blood sampling and physical examination) and reported a median administration time of 60 min for patients receiving monotherapy [20]. Our study excluded any activities a priori that were expected to be similar between zoledronic acid and denosumab (i.e. not impacting on the potential reduction in time), including blood draw and physician consultation visit performed on treatment day prior to entering in the drug administration room. When excluding pre-infusion tasks, the total time of 50.4 min [20] was similar to the mean total time reported in our study (49 min for Belgium, 52 min for Germany and 31 min for Italy).

In conclusion, although differences in clinical practice were observed among sites and countries, important reductions in time were seen when denosumab was compared with zoledronic acid for all time outcomes in each country. Trends were confirmed statistically in pooled analyses by country and across all countries. Reductions in chair time and DOU time were driven by a clear reduction in drug administration duration. Findings suggest that the use of denosumab instead of zoledronic acid may reduce the amount of time that patients spend in hospitals, may free up HCP time to dedicate to other patient care activities and may free up limited infusion chair resources at the DOU level in the countries studied. The ability to increase the volume of appointments within DOUs could reduce waiting lists in sites operating at full capacity and increase the overall productivity and efficiency of busy oncology units.

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## Compliance with ethical standards

**Conflict of interest** This study was funded by Amgen (Europe) GmbH. Jean-Jacques Body has received speaker and consulting fees from Amgen; Francesca Gatta is an employee of Amgen; Erwin De Cock and Persefoni Kritikou were employees of UBC: An Express Scripts Company at the time when the study was conducted; Sunning Tao is an employee of UBC: An Express Scripts Company, who carried out this research on behalf of Amgen; Pauline Wimberger has received honoraria for research projects and oral presentations from Roche, Novartis, Amgen, MSD and Pfizer; Jeroen Mebis has participated in advisory boards for Bristol Myers Squibb and MSD and has received speakers fees from Novartis and Pfizer; Marc Peeters has participated in advisory boards for Amgen and has been involved in corporate-sponsored Amgen research; Paolo Pedrazzoli has been involved in corporate-sponsored Amgen research; Augusto Caraceni has received remuneration from Gruenenthal, Molteni, Pfizer, Helsin, Menarini and Italfarmco and has received institutional funding from Gruenenthal, Prostrakan, Amgen, Italfarmaco, GW Pharmaceuticals, Ipsen and Molteni; Vincenzo Adamo has nothing to disclose; Guy Hechmati is an employee of Amgen and holds Amgen stock.

The authors have full control of all primary data and agree to allow the journal to review their data if requested.

**Human and animal rights and informed consent** This study was approved and performed in accordance with each country's official governmental and institutional ethical regulations. Patients provided written informed consent prior to enrolment. The study protocol, consent form, and other study-related materials were approved by appropriate national and local ethics committees, as applicable.

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