Treatment Satisfaction, Patient Preferences, and the Impact of Suboptimal Disease Control in Rheumatoid Arthritis Patients in Greece: Analysis of the Greek Cohort of SENSE study

Prodromos Sidiropoulos1, Andreas Bounas2, Nikolaos Galanopoulos3, Georgios Vosvotekas4, Efthia Maria Koukli5, Panagiotis Georgiou6, Nikolaos Marketos7, Tina Antachopoulou8, Antonios Kyriakakis8, Maria Koronaiou8

1Rheumatology, Clinical Immunology and Allergy, Medical School, University of Crete, Heraklion, Greece; 2OLYMPION Hospital-General Clinic of Patras, Patras, Greece; 3Outpatient Department of Rheumatology, University General Hospital of Alexandroupolis, Thrace, Greece; 4EUROMEDICA General Clinic of Thessaloniki, Thessaloniki, Greece; 5IASIO Hospital-General Clinic of Kallithea, Athens, Greece; 6Department of Rheumatology, General Hospital of Patras “Agios Andreas”, Patras, Greece; 7Private Clinic Henry Dunant Hospital Centre, Athens, Greece; 8Medical Department, AbbVie Pharmaceuticals S.A., Neo Iraklio, Athens, Greece

ABSTRACT

Objectives: SENSE was an international, non-interventional cross-sectional study that assessed treatment satisfaction in patients with suboptimally controlled active rheumatoid arthritis (RA) who were under treatment with any approved agent exposed to ≤ 2 biological disease-modifying antirheumatic drugs (DMARDs) at the time of enrolment. The current publication concerns the subanalysis of the results from the Greek cohort. Methods: Treatment satisfaction was assessed with Treatment Satisfaction Questionnaire for Medication (TSQM), with good treatment satisfaction defined as TSQM global ≥80. Adherence to therapy was recorded on a visual analogue scale (VAS) and treatment expectations were assessed on a 7-point numerical rating scale. Results: Of 121 patients, 82.6% were women, of mean age 64.8 years and mean time from diagnosis 8.4 years. Patients had active disease (mean DAS28-ESR 4.5) and compromised functional status (mean [SD] HAQ-DI 1.1 [0.7]) while on treatment (43.8% on biologics and 5% on steroids). The mean TSQM global was 66.9. Treatment expectations were “general improvement of arthritis” and “less joint pain” (mean score [SD], 4.9 [1.8] each), “more joint flexibility” (4.8 [1.9]), and “lasting relief of RA symptoms” (4.8 [2.1]). Oral administration was preferred by 65.3% of patients. Good self-reported adherence (≥80%) was recorded in 93.4% of the patients. Treatment switch to another DMARD was planned by treating rheumatologist for only 49.6% of the participants, despite suboptimal RA control. Conclusion: Patients with suboptimally controlled RA in Greece have low treatment satisfaction and poor self-reported outcomes, albeit high self-reported treatment adherence. Similarly to the global SENSE study results, the need for patient-centric treatment approaches in order to improve disease outcomes is emphasised.

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, immune-mediated, inflammatory disease that, if not properly controlled, may result in progressive articular damage, loss of function, compromised quality of life, and increased mortality. Two types of disease-modifying antirheumatic drugs (DMARDs), biological DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs), are therapeutic options for patients with inadequate response to conventional synthetic DMARDs (csDMARDs) that are recommended by the European League Against Rheumatism (EULAR) for the management of RA. Although the number of treatment options is steadily increasing and different drug classes have managed to slow down disease progression, many RA patients remain suboptimally controlled and sustained remission is rarely achieved. It has been shown that patients who do not achieve treatment targets have worse short- and long-term outcomes and timely treatment adjustments according to treat-to-target (T2T) principles, considering patient preferences and perspectives are critical to prevent disability. Although patients' perspectives are important determinants of treatment success in RA, they have not been adequately evaluated. Most of the studies on RA have focused on outcomes reported by the treating rheumatologists. Databases worldwide and local registries have contributed information on RA patients' and disease characteristics, including standard of care. Nevertheless, the evaluation of RA patients' preferences, expectations, and self-reported outcomes, such as adherence to treatment, particularly in suboptimally controlled patients with active disease, including patients with moderate to high disease activity despite treatment with DMARDs, can contribute valuable insights on potentially unmet needs and maximize treatment benefits. Satisfaction correlates with patients' treatment expectations, which can differ from rheumatologists' treatment goals, and is in turn linked to patient treatment adherence. Increasing evidence suggests that adherence to RA treatment can be improved via patient support programs (PSPs) and patient empowerment via access to digital health-related information for informed decision-making. The effectiveness of the latter is related with the patients' digital health literacy (DHL), ie, the ability to access and use credible online health information. The international non-interventional cross-sectional SENSE study was conducted in 18 countries worldwide between September 2018 and May 2019 to determine the impact of inadequate response to DMARDs on treatment satisfaction and various disease outcomes and to analyse patients' attitudes and perspectives toward treatment and their disease. SENSE also provided an opportunity to assess DHL in a large multinational cohort of patients with RA. In Greece, local RA databases, including the Hellenic Registry of Biologic Therapies, the nation-wide e-prescription platform, and the more recent country-wide database created by the RA Working Group of the Hellenic Rheumatology Society, have contributed information on RA and afflicted patient characteristics. Here, we report a sub-analysis of the global SENSE results from the patients that have been enrolled in seven rheumatology centres (public and private hospitals) in Greece.
MATERIALS AND METHODS

Study design
The SENSE study was performed according to the Declaration of Helsinki with prior approval from each site’s Scientific Committee. Patient selection criteria included the following: Diagnosis of RA using either the 1987 revised American College of Rheumatology (ACR) or the 2010 ACR/EULAR classification criteria for RA; ongoing treatment with any approved csDMARD, tsDMARD, or bDMARD; and exposure to ≤2 bDMARDs at the time of the enrolment. All patients had to have residual disease activity as measured by Disease Activity Score, 28 joints (DAS28 >3.2) for 1 to <4 months before enrolment despite having received the full tolerable dose of current DMARD therapy for ≥3 months. Consecutive patients attending a routine rheumatologist office visit and fulfilling enrolment criteria were included in the study. Physicians collected data during a single scheduled visit.

Assessments
Clinical parameters and socio-demographic characteristics were collected for all patients. Medical history including comorbidities (coded via the Medical Dictionary for Regulatory Activities system organ class level) and concurrent treatment, both for RA and overall were collected. Past medications for RA were also collected. Physicians were asked to report if switch to a different DMARD was planned for their patient, and the mode of action of planned treatment switches was captured. The primary objective of the study was to assess patients’ treatment satisfaction related to current RA treatment using the Treatment Satisfaction Questionnaire for Medication, version 1.4 (TSQM v 1.4). This tool incorporates Effectiveness, Side Effects, Convenience, and Global Satisfaction domains, with scores ranging from 0 (poor satisfaction) to 100 (perfect satisfaction). Good treatment satisfaction is defined as TSQM global ≥80. VAS using numeric rating scales (NRS) were used to assess morning stiffness severity and duration (in minutes) as well as pain in the past 7 days (range 0 = “no stiffness/pain” to 10 = “worst possible stiffness/pain”). The following validated patient-reported outcomes (PROs) were used: Health Assessment Questionnaire – Disability Index (HAQ-DI) for physical function, Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) for fatigue, Work Productivity and Activity Impairment - Rheumatoid Arthritis (WPAI-RA) for workability, Short Form 36 Health Survey Questionnaire (SF-36) physical and mental component score for health-related quality of life (HRQoL). Self-reported adherence to medication was assessed using VAS, with good adherence defined as ≥80% on VAS. Patient medication preference information (PMPI), including preference for route of administration, combination therapy, time to effect, and acceptable side effects, was assessed by a 6-item questionnaire developed by AbbVie (Supplementary Table 2). Patient expectations for pharmacologic treatment were assessed using an 11-item questionnaire with a 7-point NRS (1 = “no improvement needed” to 7 = “the most improvement needed”). The need for PSP was assessed using a 17-item questionnaire with a 7-point NRS (1 = “not needed at all” to 7 = “very much needed”). Healthcare resource utilization (HRU) during the three months before enrolment was also recorded and used to determine HRU over the past 12 months (by multiplying 3 previous month data with 4).

DHL was assessed by eHEALS, a self-report tool of 10 questions based on individuals’ perceptions of their skills and knowledge within each measured domain, providing scores ranging from 8 to 40; a higher total eHEALS indicates greater perceived skills at using online health information to help solve health problems; a score of <26 was considered to represent poor digital health literacy (DHL).

Statistical analysis
All statistical analyses were carried out using SAS® software (version 9.4; SAS Institute, Cary, NC, USA). Quantitative data were described by the statistical parameters valid N, missing N, mean, standard deviation, median, minimum, maximum, lower quartile (25%), and upper quartile (75%). Qualitative data were described with (absolute and relative) frequency distributions. Two-sided 95% confidence intervals (CIs) were calculated when appropriate.

Descriptive statistics using the full analysis set (FAS), which included all patients who fulfilled all inclusion criteria, was employed, without data imputation. All results reported are based on the number of FAS patients, unless otherwise specified. The sample size calculation of the global study was based on standard deviation information on Global Satisfaction measured by TSQM v1.4. A sample size of n=1500 was expected to be able to provide a 95% CI with a half width of 1.01 in the overall study population. For country-specific analysis, it has been estimated that a sample of n=30 – 200 will be able to provide a 95% CI with a half width of 7.47 to 2.79. Subgroup comparisons of patients with or without any comorbidities were conducted to identify any differences in PMPI, expectations and PROs. For continuous variables, Wilcoxon-Mann-Whitney tests used; for categorical variables, chi-squared tests or exact Fisher tests were used.

RESULTS

Clinical parameters and sociodemographic characteristics
A total of 121 patients were enrolled in SENSE study in Greece and were included in the full analysis set (FAS).
Demographic characteristics, employment status, and level of education are described in Table 1. The patients had mean (SD) age 64.8 (13.9) years (range, 23–90 years) and were predominantly female (82.6%). In total, 16.5 % of the patients were employed full-time, and 57% were retired. RA was shown to have an effect on patient work-life: 4.1% had retired early due to RA-related factors and 4.2% were unemployed or part-time employed.

The patients had established moderate to severe disease (Table 2) at the time of recruitment, with a mean (SD) DAS28– erythrocyte sedimentation rate (DAS28-ESR) 4.5 (1.0) and Clinical Disease Activity Index (CDAI) 20.3 (10.1).

Most patients (86.8%) reported ≥1 comorbidity (Table 3). The mean (SD) number of comorbidities was 2.7 (2.1), with the most frequent being cardiovascular comorbidities (55.4%) followed by metabolic and nutrition disorders (43%), endocrine disorders (34.7%), musculoskeletal and connective tissue diseases (24.8%), and psychiatric disorders (24.8%).

HRU was high and a previous medical visit for RA was reported by 82.6% of the patients, all of which were on an outpatient basis. The mean (SD) number of visits was from 2.1 (1.1) to 8.5 (4.5) during the previous 3- and 12-month periods prior to enrolment, respectively.

Medication and Treatment Strategy
The most frequently used RA medications included csDMARDs, namely methotrexate (62.8%), hydroxychloroquine (17.4%), and leflunomide (11.6 %); only 5% of patients were treated with systemic corticosteroids at the time of evaluation (Table 4). Among all patients, 43.8% had been treated with bDMARDs; 45.3% of these patients were on monotherapy. Interestingly, despite long-standing disease and suboptimal symptom control

Table 1. Sociodemographic characteristics.

| Characteristic                  | Patients, n N=121 |
|--------------------------------|-------------------|
| Sex, female                    | 100 (82.6)        |
| Age, years, mean (SD)          | 64.8 (13.9)       |
| Race                           |                   |
| White                          | 121 (100)         |
| Occupation                     |                   |
| Employed full-time             | 20 (16.5)         |
| Employed part-time             |                   |
| Unrelated to RA                | 2 (1.7)           |
| Related to RA                  | 3 (2.6)           |
| Attending school or university | 1 (0.8)           |
| Unemployed                     |                   |
| Unrelated to RA                | 11 (9.1)          |
| Related to RA                  | 2 (1.7)           |
| Early retirement               |                   |
| Unrelated to RA                | 9 (7.4)           |
| Related to RA                  | 5 (4.1)           |
| Regularly retired              | 69 (57.0)         |
| Education                      |                   |
| No formal education            | 3 (2.5)           |
| Primary school                 | 28 (23.1)         |
| Secondary school (e.g. high school) | 65 (53.7)       |
| Non-university, professional education | 5 (4.1)   |
| University                     | 20 (16.5)         |
| Residence                      |                   |
| Urban centre, population >80 000 | 49 (40.5)      |
| Town, population 10 000–80 000 | 19 (15.7)         |
| Rural area, population <10 000 inhabitants | 53 (43.8) |

All data are represented as n (%) unless otherwise stated.
RA, rheumatoid arthritis.

Table 2. RA disease characteristics.

| Parameter, Score Range*     | Patients, n | Mean (SD) |
|-----------------------------|-------------|-----------|
| Time since RA diagnosis, years | 121         | 8.4 (9.4) |
| TJC28, 0–28                | 121         | 7 (6.4)   |
| SJC28, 0–28                | 121         | 3.4 (3.9) |
| PtGA, 0–10 cm              | 121         | 5.1 (1.9) |
| PGA, 0–10 cm               | 121         | 4.8 (1.7) |
| DAS28-CRP                  | 107         | 4.2 (0.9) |
| DAS28-ESR                  | 121         | 4.5 (1.0) |
| CDAI, 0–76                 | 121         | 20.3 (10.1) |
| SDAI, 0–86                 | 107         | 22.2 (10.7) |

CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS28, Disease Activity Score, 28 joints; ESR, erythrocyte sedimentation rate; RA, rheumatoid arthritis; SDAI, Simplified Disease Activity Index; SJC28, swollen joint count based on a 28-joint assessment; TJC28, tender joint count based on a 28-joint assessment.

*Score are displayed to range from best health state to worst health state.
with fully tolerable dosages of ongoing DMARD administered for ≥3 months, a switch to a different DMARD was planned by the treating rheumatologist for only half of the patients (49.6%). In 97% of the cases, a bDMARD or tsDMARD was considered as the next step in treatment (most often a tumour necrosis factor inhibitor).

An analysis of patient medical history showed that 82.6% of patients received treatment for comorbid diseases. The mean (SD) number of medications administered for concurrent diseases was 2.1 (1.9), the most frequent of which were 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (32.2%), angiotensin-converting enzyme inhibitors (23.1%), thyroid hormones (21.5%), selective beta-blocking agents (19.8%), proton pump inhibitors (16.5%), and selective serotonin reuptake inhibitors (11.6%) or other antidepressants (9.9%) (Supplementary Table 3).

### Primary Outcome: Treatment satisfaction

The mean (SD) TSQM v1.4 domain scores were as follows: Global Satisfaction, 66.9 (22.4); Effectiveness, 63.4 (21.1); Side Effects, 95.9 (15.4); and Convenience, 77.3 (18.9). The low level of satisfaction was driven by the low effectiveness subs core, in alignment with the suboptimally controlled, active RA (Figure 1).

### Secondary Outcomes

RA affected productivity, functional status and overall QoL (Table 5). Good self-perceived adherence, defined...
as ≥80% self-reported adherence, was reported by 93.4% of patients.

Patient Medication Preference Questionnaire
PMPI questionnaire revealed a preference for oral administration (65.3%) at preferred administration frequencies of once per day (37.2%) or once per week (32.2%). Those preferring parenteral administration showed a preference for biweekly (25.6%) or monthly (40.5%) administration. Notably, 33.1% of patients did not prefer to receive drug combinations. The preferred time to therapeutic effect onset was “up to one week” (ie, the shortest option of the questionnaire) for 52.9% of patients. The most acceptable adverse events were injection site reaction (21%), deterioration of laboratory values (18.5%), effect on fertility (13.4%), and weight gain (10.9%). Events reported as least acceptable were hair thinning or loss (5.0%), increased risk for cardiovascular diseases (5.9%), allergic reaction (6.7%), and increased risk for malignancies (8.4%).

Patient Expectations for Pharmacological Treatment
The highest-rated treatment expectations were general improvement of arthritis, less joint pain, lasting relief of RA symptoms, more joint flexibility, and less joint swelling (Figure 2).

PSP participation
In terms of need for patient support, patients assigned the greatest importance to having access to educational material that focused on RA disease and therapy as well as to a call centre and a starter pack with all information about the patient-support programs.

Table 5. Patient-reported outcomes.

| Parameter, Score Range       | Patients, n | Mean (SD) |
|------------------------------|-------------|-----------|
| FACIT-F, 0–52                | 121         | 30.3 (11.5)|
| Worst joint pain, 0–10, VAS  | 121         | 4.5 (2.8) |
| Severity of morning stiffness, 0–10, VAS | 121 | 3.6 (3.0) |
| Duration of morning stiffness, hours<sup>a</sup> | 88 | 1.1 (3.0) |
| HAQ-DI, 0–3                  | 121         | 1.1 (0.7) |
| SF-36 PCS, 100–0             | 121         | 39.9 (8.3) |
| SF-36 MCS, 100–0             | 121         | 43.4 (11.1)|
| WPAI-RA: Presenteeism, %    | 21          | 41.0 (25.7)|
| WPAI-RA: Absenteeism, %     | 21          | 2.6 (4.9) |
| WPAI-RA: Total work productivity impairment, % | 21 | 41.9 (53.9)|
| WPAI-RA: Total activity impairment, % | 21 | 48.1 (24.5)|

FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; HAQ-DI, Health Assessment Questionnaire–Disability Index; MCS, Mental Component Summary; PCS, Physical Component Summary; PGA, Physician Global Assessment of Disease Activity; PtGA, Patient Global Assessment of Disease Activity; RA, rheumatoid arthritis; SF-36, Short-Form, 36-item Health Survey; VAS, visual analogue scale; WPAI-RA, Work Productivity and Activity Impairment–Rheumatoid Arthritis.

Figure 2. Patients’ expectations for pharmacologic treatment of RA assessed using an 11-item questionnaire. a RA, rheumatoid arthritis. aQuestionnaire used a 7-point rating scale: 1 = no improvement needed, 7 = the most improvement needed.
**Digital health literacy**

Based on eHEALS score, the majority of patients were found to have poor familiarity with digital tools for the management of their disease. The mean (SD) patient score was 15.4 (8.8), and the highest patient score was 32. In general, more than half of the participants disagreed or strongly disagreed with the following statements: “I have knowledge of the health resources that are available on the internet”, “I know where and how to find helpful health resources”, “I know how to use the internet to answer my health questions”, and “I know how to use the health information found on the internet”. Only 12.8 % of patients of the 109 available responses agreed or strongly agreed that they can differentiate high-quality from low-quality healthcare resources on the internet, with 6.4% of patients agreed or strongly agreed that they felt confident in using information from the internet to make healthcare decisions.

**Subgroup analysis**

Subgroup analysis of PROs between patients with (n=105) versus without (n=16) comorbidities demonstrated that the presence of a comorbid disease correlated statistically significantly with worse physical function (mean [SD] HAQ-DI score 1.0 [0.7] vs 0.6 [0.5] respectively, p=0.001) and lower treatment satisfaction (TSQM Global Satisfaction score 65.5 [22.7] vs 75.9 [18.6] respectively, p=0.049). Comorbidities were also associated with higher patient expectation for “general improvement of arthritis” (5.1 [1.8] vs 3.9 [1.8], p=0.019), “less joint pain” (5.1 [1.8] vs 4.2 [1.8], p=0.044), “lasting relief of RA symptoms” (5.0 [2.0] vs 3.7 [2.2], p=0.018). The presence of comorbidities was also associated with lower DHL (total eHEALS score 14.5 [8.6] vs 21.6 [7.5], p=0.004).

**DISCUSSION**

This study aimed to assess the real-world perspective and treatment expectations of patients with suboptimally controlled RA, information that is considerably underrepresented in the literature. It has been previously shown that patients’ and physicians’ perceptions of RA-related treatment priorities and disease activity may differ. The data from the SENSE study further corroborate results from other Greek and international studies showing an inconsistency between the treatment recommendations for T2T and clinical practice. The results of a Greek study of patients in the early stages of arthritis similarly showed that only 62.4% of participants who experienced medium or high disease activity after 6 months of treatment were subject to treatment adjustments. The implementation of treatment modifications was reportedly followed by a significant decrease in disease activity after 2 years. Likewise, in a recent multinational observational study, the T2T guidelines were appropriately applied in only 59% of patient visits.

We believe that the rheumatological community needs to consider carefully these findings to identify the specific barriers of the clinical implementation of T2T concept. Comparable therapeutic inertia, defined as “the failure to initiate or intensify therapy in a timely manner, according to evidence-based clinical guidelines”, is certainly present in the treatment of other chronic diseases.
shows, the potential discordance between physicians and their patients regarding treatment target definition, disease perception and need for treatment adjustment can significantly affect therapeutic decisions in patients with suboptimal disease control, though evaluating the discordance was not the purpose of the study.53 Comorbidities in RA are common and have a negative effect on patient functioning, morbidity, and mortality.4 Similarly to the overall study results, comorbidities were encountered in the vast majority of the patients from Greece, and 82.6% reported receiving medications for other diseases, with the mean number of drugs administered being 2.1. There was an overlap in the most frequently reported comorbidity categories between the Greek cohort and the overall study population. Nevertheless, except for musculoskeletal/Connective tissue disorders, for which the incidence was comparable in the present cohort and overall study population, the incidence of cardiac, metabolic/nutrition disorders, endocrine and psychiatric disorders was higher in the Greek patients. Interestingly, the incidence of psychiatric disorders was 3-fold higher in this subanalysis. It is worth noting that the presence of a comorbid disease correlated with worse disability (HAQ-DI) and lower TSQM global satisfaction scores. These findings further support the importance of the effect of comorbidities on the outcome of RA and the necessity for their effective management. Additionally, patients had poor digital health literacy, and, therefore, poor familiarisation with tools for the management of their disease. Concerning the benefits of digital health resources, the patients reported that their highest prioritization was for receiving information on general RA disease- and medication-related topics through a PSP program and their lowest for digital lifestyle interventions, such as social media, smartphone, and website contents. The eHEALS study results revealed low DHL, highlighting the need to develop health promotional programs addressing DHL and digital tools tailored to the needs and pragmatic capabilities of the RA population. New information- and communication-technologies may substantially contribute in a more accurate monitoring of disease-related parameters while offering much-needed patient education.54 As the RA population gradually shifts towards patients with a higher degree of familiarity with digital content and applications, these educational activities could be further developed and applied to a larger group of patients. Except for the prevalence of females over males, there were differences in the sociodemographic characteristics of this subanalysis and the global SENSE results. Some of these differences, particularly in occupational status, are attributed to the age range of the participants. Thus, based on mean age, the Greek cohort patients were slightly older (mean age of overall study patients 58.4 years old), which in turn accounts for the higher percentage of retired patients in this subanalysis. The observed differences in the incidence of comorbidities between this subanalysis and the overall SENSE results are likely to be attributed to the older age of the current patients. A comparable percentage of patients in this subanalysis and the overall SENSE results had university education. Psychosocial factors, such as education and occupational status as well as demographics, amongst other factors, are likely to influence and account for the potential differences, albeit small, in patient expectations and preferences, DHL and PROs in this subanalysis and the overall SENSE results. Similarly to this subanalysis, csDMARDs were the most frequently prescribed medications. Differences between individual bDMARD prescriptions in this subanalysis and the global SENSE results can be attributed to local therapeutic protocols and potentially reimbursement policies in the participating countries. Concerning the limitations of the study, by design, non-interventional studies hold certain limitations, such as selection and recall bias and lack of a control group. The focus on a specific patient group with suboptimal disease control may limit the generalizability of our results to all RA patients. Although PROs reflect subjective patient assessments, however, this effect was counterbalanced by the use of validated PRO tools. Similarly, VAS for the determination of self-reported treatment adherence is validated and highly correlates with electronic monitoring results in patients with chronic conditions, including RA.40,41,55 No validated questionnaires were available for assessing the need for PSP, treatment preferences, and expectations. The imbalance in the sizes of groups with and without comorbidities as well as the presence of potential confounding factors warrant caution when interpreting the results of subgroup analysis. These results, therefore, need to be confirmed by using validated measures in future studies. Because of the size of the Greek sample, further subanalyses and correlations to specific outcomes were not possible. This study provides an in-depth understanding of patient needs and perspectives, also identifying unmet requirements for treatment adjustments that will align with recent therapeutic standards and the T2T principles. Attaining T2T goals under routine clinical practice conditions is increasingly investigated in RA patients. In this context, a longitudinal real-life study in Greece demonstrated that the use of glucocorticoids or ≥2 bDMARDs versus no bDMARDs negatively correlated with low disease activity.56 In the aforementioned study, younger age, lower HAQ, body mass index and co-morbidity index were negative predictors of low disease activity, whereas male sex was a positive predictor. Concluding, the herein presented data showed that RA patients with suboptimal disease control under treatment have low treatment satisfaction and compromised...
self-reported outcomes, albeit a high self-reported treatment adherence. These data further support both the value of treatment approaches targeting to abrogation of inflammation and emphasise the need of documenting patients’ perspectives to improve disease outcomes.

**AUTHOR CONTRIBUTIONS**

All participating authors contributed equally to the gathering of information and writing and reviewing of the article.

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**CONFLICTS OF INTEREST – DISCLOSURES**

Tina Antichopoulos, Antonios Kyriakakis, and Maria Koronaiou are employees of AbbVie Pharmaceuticals S.A. – Greece.

Prodromos Sidropoulos, Andreas Bounas, Nikolaos Galanopoulos, Georgios Vosvotekas, Effthia Maria Kouki, Panagiotis Georgiou, and Nikolaos Marketos participated in the study as Investigators.

Nikolaos Galanopoulos, Georgios Vosvotekas, Effthia Maria Kouki, and Nikolaos Marketos have no conflict of interest to declare.

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**ETHICS APPROVAL AND WRITTEN INFORMED CONSENT STATEMENTS**

The approval of the responsible Scientific Committee was obtained before site initiation, according to the local legislation. Written informed consent was obtained for all participants before any study procedures.

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### Supplementary Table 1. List of local ethics committees that provided ethics approval for the SENSE study.

| Site ID | Country     | Primary institution                                      | City and postal code          | Ethics committee                                                                 | Notes                                      |
|---------|-------------|----------------------------------------------------------|-------------------------------|---------------------------------------------------------------------------------|--------------------------------------------|
| AR-03   | Argentina   | DIM Clinica Privada                                       | Ramos Mejía, 1704             | Comité de Ética en Investigacion DIM Clinica Privada                             |                                            |
| AR-04   | Argentina   | Hospital Gral. de Agudos J.M. Ramos Mejía                | Buenos Aires, C1221ADC        | Comité de Ética en Investigacion Hospital de Agudos J.M. Ramos Mejía              |                                            |
| AR-05   | Argentina   | Instituto de Rehabilitación Psicofisica                  | Buenos Aires, 1428            | Comité de Ética en Investigacion Instituto de Rehabilitación Psicofisica (IREP) |                                            |
| AR-01   | Argentina   | CEIM Investigaciones Medica                               | Buenos Aires, 1425            | Comité Independiente de Ética para Ensayos en Farmacología Clínica               |                                            |
| AR-02   | Argentina   | Hospital Interzonal Gral Agudos San Martin               | La Plata, 1900                | Comité de Ética Centro Medico Framingham                                          |                                            |
| BR-01   | Brazil      | Centro Multidisciplinar de Estudos Clinicos              | Santo André, BR-CE, 09190-615 | Comité de Ética em Pesquisa da Faculdade de Medicina do ABC (CEP-FMABC)          |                                            |
| BR-02   | Brazil      | Santa Casa de Belo Horizonte                              | Belo Horizonte, BR-MG, 30150-221 | Comité de Ética em Pesquisa da Santa Casa de Belo Horizonte (CEP – SCBH)        |                                            |
| BR-03   | Brazil      | Fundacao Faculdade Regional de Medicina de São José do Rio Preto | São José Do Rio Preto, BR-CE, 15090-000 | Comité de Ética em Pesquisa em Seres Humanos da Faculdade de Medicina de São José do Rio Preto (CEP-FAMERP) |                                            |
| BR-04   | Brazil      | Centro Mineiro de Pesquisa                                | Juiz De Fora, BR-MG, 36010570 | Comité de Ética em Pesquisa do Hospital Universitário da Universidade Federal de Juiz de Fora (HU-UFJF) |                                            |
| BG-01   | Bulgaria    | UMHAT Sveti Ivan Rilski                                   | Sofia, 1612                   | Not required                                                                    |                                            |
| BG-02   | Bulgaria    | Excelsior Medical Center                                  | Sofia, 1407                   | Not required                                                                    |                                            |
| CL-02   | Chile       | Hospital Victoria                                         | Victoria, 4720 000            | Comité de Ética de la Investigacion Servicio de Salud Metropolitano Norte        |                                            |
| CL-01   | Chile       | Centro Medico Prosalud                                    | Santiago, 7510047             | Comité de Ética Científica Servicio Salud Araucania Sur                        |                                            |
**Supplementary Table 1.** List of local ethics committees that provided ethics approval for the SENSE study. (continued)

| Site ID | Country       | Primary institution | City and postal code       | Ethics committee                                                                 | Notes                                                                 |
|---------|---------------|---------------------|---------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------|
| HR-05   | Croatia       | Klinički Bolnički Centar Split | Split, 21000             | Klinički Bolnički Centar Split                                                  | 1. The SENSE study was first submitted to the central EC. Based on the submitted documentation, the central EC issued an opinion on the acceptability of the study. |
| HR-01   | Croatia       | Klinički Bolnički Centar Zagreb | Zagreb, 10000            | Klinički Bolnički Centar Zagreb                                                 | 2. After obtaining a positive opinion from the central EC, the clinical trial was submitted to the Agency for Medicinal Products and Medical Devices. Based on the submitted documentation and the central EC’s positive opinion, the Agency for Medicinal Products and Medical Devices granted approval for study conduct. |
| HR-03   | Croatia       | Klinički Bolnički Dubrava Zagreb | Zagreb, 10000            | Klinički Bolnički Dubrava Zagreb/Klinička Bolnica Dubrava Zagreb                 | 3. Some institutions (hospitals) also requested that the study be submitted to their Institutional Committees, so approvals were also obtained from the Institutional Committees in Croatia listed in column E. |
| HR-04   | Croatia       | Klinički Bolnički Centar Sestre Milosrdnice | Zagreb, 10000 | Klinički Bolnički Centar Sestre Milosrdnice                                      |                                                                      |
| HR-02   | Croatia       | Klinički Bolnički Centar Zagreb | Zagreb, 10000            | Klinički Bolnički Centar Zagreb                                                 |                                                                      |
| CZ-02   | Czech Republic| Revmatolog s.r.o.    | Jihlava, 58601           | Ethics Committee of the University Hospital Motol, V Úvalu 84, Prague 5, 150 06, Czech Republic |                                                                      |
Supplementary Table 1. List of local ethics committees that provided ethics approval for the SENSE study. (continued)

| Site ID | Country         | Primary institution          | City and postal code | Ethics committee                                                                 | Notes |
|---------|-----------------|------------------------------|----------------------|----------------------------------------------------------------------------------|-------|
| CZ-04   | Czech Republic  | Revma Praha s.r.o.           | Prague, 15800        | Ethics Committee of the University Hospital Motol, V Úvalu 84, Prague 5, 150 06, Czech Republic | —     |
| CZ-06   | Czech Republic  | Fakultni Nemocnice v Motole  | Prague, 15006        | Ethics Committee of the University Hospital Motol, V Úvalu 84, Prague 5, 150 06, Czech Republic | —     |
| CZ-01   | Czech Republic  | INREA s.r.o.                 | Ostrava,703 00       | Ethics Committee of the University Hospital Motol, V Úvalu 84, Prague 5, 150 06, Czech Republic | —     |
| CZ-05   | Czech Republic  | Revmatologicke Centrum s.r.o.| Velke Bilovice, 69102| Ethics Committee of the University Hospital Motol, V Úvalu 84, Prague 5, 150 06, Czech Republic | —     |
| CZ-03   | Czech Republic  | Revimex PRO s.r.o.           | Karvina, 733 01      | Ethics Committee of the University Hospital Motol, V Úvalu 84, Prague 5, 150 06, Czech Republic | —     |
| EE-02   | Estonia         | Tartu University Hospital    | Tartu, 50406         | Research Ethics Committee of the National Institute for Health Development        | —     |
| EE-01   | Estonia         | East Tallinn Central Hospital| Tallinn, 11312       | Research Ethics Committee of the National Institute for Health Development          | —     |
| EE-03   | Estonia         | Pärnu Hospital               | Tallinn, 11312       | Research Ethics Committee of the National Institute for Health Development          | —     |
| GR-01   | Greece          | University General Hospital  | Voutes Herakleio, 71500| IRB/IEC of the University General Hospital of Heraklion, Crete                    | —     |
| GR-02   | Greece          | Metropolitan General Hospital| Athens, 15562        | IRB/IEC of the Metropolitan General Hospital                                        | —     |
| GR-03   | Greece          | OLYMPION Hospital – General Clinic of Patras | Patras, 26221 | IRB/IEC of the OLYMPION Hospital – General Clinic of Patras | — |
| GR-04   | Greece          | IASIO-General Clinic of Kallithea | Kifissia, 14561 | IRB/IEC of the IASIO-General Clinic of Kallithea | — |
| GR-05   | Greece          | University General Hospital  | Alexandroupoli, 68100| IRB/IEC of the University General Hospital of Alexandroupoli | — |
| GR-06   | Greece          | Euromedica General Clinic of Thessaloniki | Thessaloniki, 54623 | IRB/IEC of the Euromedica General Clinic of Thessaloniki | — |
| GR-07   | Greece          | Henry Dunant Hospital Center | Athens, 11526        | IRB/IEC of the Henry Dunant Hospital Center                                         | —     |
### Supplementary Table 1. List of local ethics committees that provided ethics approval for the SENSE study. (continued)

| Site ID | Country | Primary institution | City and postal code | Ethics committee | Notes |
|---------|---------|---------------------|----------------------|-----------------|-------|
| GR-08   | Greece  | General Hospital of Patras «Agios Andreas» | Patras, 26335 | IRB/IEC of the General Hospital of Patras «Agios Andreas» | — |
| GR-09   | Greece  | Naval Hospital of Athens | Athens, 11521 | IRB/IEC of the Naval Hospital of Athens | — |
| HU-01   | Hungary | Budai Irgalmasrendi Kórház | Budapest, 1027 | Study protocol approval was obtained from the central EC: the Medical Research Council, Scientific and Research Ethics Committee, Hungary | — |
| HU-03   | Hungary | Békés Megyei Pándy Kálmán Kórháza | Gyula, 5700 | — | |
| HU-04   | Hungary | Hévizgyógyfürdő és Szent András Reumakórház | Heviz, 8380 | — | |
| HU-06   | Hungary | Szabolcs – Szatmár – Bereg Megyei Kórházak és Egyetemi Oktató Kórháza | Nőiregyhaza, 4400 | — | |
| HU-05   | Hungary | Miskolci Semmelweis Kórház és Egyetemi Oktatókórháza | Miskolc,3529 | — | |
| HU-02   | Hungary | Petz Aladár Megyei Oktató Kórháza | Gyor, 9023 | — | |
| IR-03   | Ireland | St. James’s Hospital | Dublin 8,00000 | Tallaght University Hospital/ St. James’s Hospital Joint Research Ethics Committee. Tallaght University Hospital, Dublin 24, Ireland | — |
| IR-02   | Ireland | Cork University Hospital | Cork, T12 DFK4 | Clinical Research Ethics Committee of the Cork Teaching Hospitals, Lancaster Hall, 6 Little Hanover Street, Cork, Ireland | — |
| IR-01   | Ireland | Croom Orthopaedic Hospital | Limerick, V35 F434 | HSE Mid-Western Regional Hospital Research Ethics Committee, University Hospital Limerick, Limerick, Ireland | — |
| JP-08   | Japan   | Nagasaki University | Nagasaki, 852-8501 | 小崎大学病院臨床研究倫理委員会 (Nagasaki University Hospital Clinical Research Ethics Committee) | — |
**Supplementary Table 1.** List of local ethics committees that provided ethics approval for the SENSE study. (continued)

| Site ID | Country | Primary institution | City and postal code | Ethics committee | Notes |
|---------|---------|---------------------|----------------------|------------------|-------|
| JP-06   | Japan   | Kyoto Prefectural University of Medicine | Kyoto-Shi, 602-8566 | 京都府立医科大学医学倫理審査委員会 (Kyoto Prefectural University of Medicine Medical Ethics Review Committee) | — |
| JP-05   | Japan   | Kobe University     | Kobe-Shi, 650-0017   | 神戸大学医学部附属病院臨床研究推進センター倫理審査委員会 (Kobe University Hospital Clinical & Translational Research Center) | — |
| JP-09   | Japan   | Yoshida Orthopaedic Clinic | Morioka, 020-0015 | 代々木メンタルクリニック倫理審査委員会 (Yoyogi Mental Clinic Ethical Review Committee) | — |
| JP-02   | Japan   | Setagaya Rheumatology Clinic | Tokyo, 156-0052 | 代々木メンタルクリニック倫理審査委員会 (Yoyogi Mental Clinic Ethical Review Committee) | — |
| JP-03   | Japan   | Hiroshima University | Hiroshima-Shi, 734-8551 | 広島臨床研究開発支援センター臨床研究倫理審査委員会 (Clinical Research Center in Hiroshima) | — |
| JP-07   | Japan   | Hokkaido University | Sapporo-Shi, 060-8648 | 北海道大学病院自主臨床研究審査委員会 (Hokkaido University Hospital Division of Clinical Research Administration) | — |
| JP-01   | Japan   | Yamagata University School of Medicine | Yamagata-Shi, 990-9585 | 山形大学医学部倫理審査委員会 (Ethical Review Committee of Yamagata University Faculty of Medicine) | — |
| JP-04   | Japan   | The University of Tokyo | Tokyo, 113-8655 | 東京大学大学院医学系研究科・医学部・介入等研究倫理委員会 (Graduate School of Medicine and Faculty of Medicine, the University of Tokyo) | — |
| LV-01   | Latvia  | P. Stradins Clinical University Hospital | Riga, 1002 | Ethics Committee for Clinical Research at Pauls Stradins Clinical University Hospital Development Society | — |
| LT-02   | Lithuania | Hospital of Lithuanian University of Health Sciences Kaunas Clinics | Kaunas, 50161 | Kaunas Regional Biomedical Research Ethics Committee | — |
| LT-01   | Lithuania | Klaipeda University Hospital | Klaipeda, 92288 | Kaunas Regional Biomedical Research Ethics Committee | — |
Supplementary Table 1. List of local ethics committees that provided ethics approval for the SENSE study. (continued)

| Site ID | Country | Primary institution | City and postal code | Ethics committee | Notes |
|---------|---------|---------------------|----------------------|------------------|-------|
| PL-05   | Poland  | Slaskie Centrum Reumatologii | Ustroń, 43-450 | EC not required – notification processed | — |
| PL-02   | Poland  | Specjalistyczna Praktyka Lekarska Katarzyna Smolik | Tychy, 43-100 | EC not required – notification processed | — |
| PL-04   | Poland  | Ortopedyczno-Rehabilitacyjny Szpital Kliniczny | Poznan, 61-545 | EC not required – notification processed | — |
| PL-03   | Poland  | Gabinet Internistyczno – Reumatologiczny Izabela Dornyslawska | Bialystok, 15-276 | EC not required – notification processed | — |
| PL-01   | Poland  | Prywatny Gabinet Lekarski – Grazyna Swierkowska | Lodz, 93-513 | EC not required – notification processed | — |
| RO-07   | Romania | Spitalul Clinic Dr. I. Cantacuzino | Bucharest, 020475 | National Committee of Bioethics for Medicines and Medical Devices | — |
| RO-01   | Romania | Spitalul Clinic Sfanta Maria Bucuresti | Bucharest, 011172 | National Committee of Bioethics for Medicines and Medical Devices | — |
| RO-02   | Romania | Spitalul Clinic Sfanta Maria Bucuresti | Bucharest, 011172 | National Committee of Bioethics for Medicines and Medical Devices | — |
| RO-03   | Romania | Spitalul Clinic de Recuperare Iasi | Iasi, 700661 | National Committee of Bioethics for Medicines and Medical Devices | — |
| RO-08   | Romania | Spitalul Clinic de Recuperare Iasi | Iasi, 700661 | National Committee of Bioethics for Medicines and Medical Devices | — |
| RO-04   | Romania | Spitalul Clinic Judetean de Urgenta Cluj | Cluj-Napoca, 400006 | National Committee of Bioethics for Medicines and Medical Devices | — |
| RO-05   | Romania | Spitalul Clinic de Recuperare Cluj-Napoca | Cluj-Napoca, 400437 | National Committee of Bioethics for Medicines and Medical Devices | — |
| RO-06   | Romania | Spitalul Clinic Judetean de Urgenta Targu Mures | Targu Mures, 540136 | National Committee of Bioethics for Medicines and Medical Devices | — |
| RU-03   | Russia  | Institution KhMAO-Ugra Regional Clinical Hospital | Khanty-Mansiysk, 628011 | Independent Interdisciplinary Ethics Committee for Clinical Studies | — |
| RU-02   | Russia  | Research Institute of Rheumatology | Moscow, 115522 | Independent Interdisciplinary Ethics Committee for Clinical Studies | — |
### Supplementary Table 1. List of local ethics committees that provided ethics approval for the SENSE study. (continued)

| Site ID | Country | Primary institution | City and postal code | Ethics committee | Notes |
|---------|---------|---------------------|----------------------|------------------|-------|
| RU-01   | Russia  | Moscow Regional Research Clinical Institute MF Vladimirsky | Moscow, 129110 | Independent Interdisciplinary Ethics Committee for Clinical Studies | — |
| RU-04   | Russia  | Yaroslavl State Medical University | Yaroslavl, 150000 | Independent Interdisciplinary Ethics Committee for Clinical Studies | — |
| SK-02   | Slovakia | ROMJAN s.r.o. | Bratislava, 821 08 | Ethics Committee of Bratislava Autonomous Region, Sabinovská 16, 820 05 Bratislava, Slovak Republic | — |
| SK-03   | Slovakia | Novamed s.r.o. | Banská Bystrica, 97405 | Independent Ethics Committee of Banská Bystrica Autonomous Region, Nám. SNP 23, 974 01, Banská Bystrica, Slovak Republic | — |
| SK-04   | Slovakia | Univerzitna Nemocnica Bratislava | Bratislava, 82606 | Ethics Committee, University Hospital Bratislava, Pažítková 4, 821 01 Bratislava, Slovak Republic | — |
| SK-01   | Slovakia | Ambulance Karpatská – Private Practice | Poprad, 058 01 | Ethics Committee of Prešov Autonomous Region, Námestie Mieru 2, 080 01 Prešov, Slovak Republic | — |
| TR-05   | Turkey  | Inonu University Turgut Ozal Medical Center Education and Research Hospital | Malatya, 44280 | One central EC under coordinating site per local regulation | One central EC under coordinating site per local regulation |
| TR-01   | Turkey  | Hacettepe University Faculty of Medicine | Ankara, 6100 | Hacettepe University Clinical Research Ethic Boards (one central EC under coordinating site per local regulation) | — |
| TR-02   | Turkey  | Marmara University Istanbul Pendik Education and Research Hospital | Istanbul, 34899 | One central EC under coordinating site per local regulation | — |
| TR-03   | Turkey  | Sivas Cumhuriyet University Health Services Application and Research Hospital | Sivas, 58140 | One central EC under coordinating site per local regulation | — |
### Supplementary Table 1. List of local ethics committees that provided ethics approval for the SENSE study. (continued)

| Site ID | Country | Primary institution | City and postal code | Ethics committee | Notes |
|---------|---------|---------------------|----------------------|------------------|-------|
| TR-04   | Turkey  | Istanbul University Cerrahpasa-Cerrahpasa Faculty of Medicine | Istanbul, 34098 | One central EC under coordinating site per local regulation | One central EC under coordinating site per local regulation |
| TR-07   | Turkey  | Osmangazi University Faculty of Medicine | Eskisehir, 26480 | One central EC under coordinating site per local regulation | |
| TR-08   | Turkey  | Trakya University Faculty of Medicine | Edirne, 22030 | One central EC under coordinating site per local regulation | |
| TR-10   | Turkey  | Akdeniz University Faculty of Medicine | Antalya, 07070 | One central EC under coordinating site per local regulation | |
| TR-11   | Turkey  | Adnan Menderes University Faculty of Medicine | Aydin, 09010 | One central EC under coordinating site per local regulation | |
| TR-12   | Turkey  | Gulhane Education and Research Hospital | Ankara, 06010 | One central EC under coordinating site per local regulation | |
| TR-14   | Turkey  | Necmettin Erbakan University Meram Faculty of Medicine Hospital | Konya, 42080 | One central EC under coordinating site per local regulation | |
| TR-06   | Turkey  | Bahcesehir University Hospital Medical Park Goztepe | Istanbul, 34732 | One central EC under coordinating site per local regulation | |
| TR-13   | Turkey  | Namik Kemal University Faculty of Medicine Application and Research Hospital | Tekirdağ, 59030 | One central EC under coordinating site per local regulation | |
| TR-09   | Turkey  | Mustafa Kemal University Hospital | Hatay, 31001 | One central EC under coordinating site per local regulation | |
| UY-01   | Uruguay | Medica Uruguay | Montevideo, 11300 | Comité de Etica de Medica Uruguaya | — |
| UY-02   | Uruguay | Asociacion Española Primera de Socorros Mutuos | Montevideo, 11200 | Comité de Etica AESM | — |

EC, ethics committee.
### Supplementary Table 2. Questionnaire to assess medication preferences.

We would like to ask you about your preferences regarding medication used for rheumatoid arthritis. For each question, please circle one answer which is most likely to reflect your opinion.

1. What is the preferred route of administration?
   - a. Parenteral: intravenous
   - b. Parenteral: subcutaneous
   - c. Oral

2. What is the preferred frequency of administration in the case of parenteral administration?
   - a. Biweekly
   - b. Monthly
   - c. 3-monthly
   - d. 6-monthly

3. What is the preferred frequency of administration in the case of oral administration?
   - a. Twice per day
   - b. Once per day
   - c. Once per week

4. What is the preferred time until the effect of onset?
   - a. Up to 1 week
   - b. Up to 2 weeks
   - c. Up to 1 month
   - d. Up to 3 months

5. What is your preference regarding drug combinations used for your rheumatoid arthritis?
   - a. Drug combination is not preferred
   - b. Treatment which requires daily combination is acceptable
   - c. Treatment which requires combination with another drug once a week is acceptable

6. What is the most acceptable potential side effect of the medication used for rheumatoid arthritis?
   - a. Increased risk for infections
   - b. Allergic reaction
   - c. Deterioration of my laboratory values
   - d. Increased risk for malignancies
   - e. Weight gain
   - f. Hair thinning or loss
   - g. Skin symptoms, eg, injection site reaction, rash
   - h. Effect on fertility
   - i. Increased risk for cardiovascular diseases
**Supplementary Table 3.** Medications for concomitant diseases (≥5% of patients).

| Concomitant medications* n (%)                                      | Full analysis set |
|--------------------------------------------------------------------|-------------------|
| Any concomitant medication                                         | 100 (82.6)        |
| C10AA - HMG CoA reductase inhibitors                               | 39 (32.2)         |
| C09CA - Angiotensin II receptor blockers (ARBs), plain             | 28 (23.1)         |
| H03AA - Thyroid hormones                                           | 26 (21.5)         |
| C07AB - Beta blocking agents, selective                            | 24 (19.8)         |
| A02BC - Proton pump inhibitors                                     | 20 (16.5)         |
| N06AB - Selective serotonin reuptake inhibitors                    | 14 (11.6)         |
| N06AX - Other antidepressants                                      | 12 (9.9)          |
| C03AA - Thiazides, plain                                           | 11 (9.1)          |
| N05BA - Benzodiazepine derivatives                                 | 11 (9.1)          |
| A10BA - Biguanides                                                 | 10 (8.3)          |
| C09DA - Angiotensin II receptor blockers (ARBs) and diuretics      | 10 (8.3)          |
| N03AX - Other antiepileptics                                       | 10 (8.3)          |
| A11CC - Vitamin D and analogues                                    | 9 (7.4)           |
| C08CA - Dihydropyridine derivatives                                | 8 (6.6)           |
| M05BA - Bisphosphonates                                            | 8 (6.6)           |
| B01AC - Platelet aggregation inhibitors excl. heparin              | 7 (5.8)           |
| A10BD - Combinations of oral blood glucose lowering drugs          | 6 (5.0)           |
| C05CA - Bioflavonoids                                              | 6 (5.0)           |

*Anatomical Therapeutic Chemical Classification coding level 4