

# Corticosteroid dosing and opioid use are high in patients with SLE and remain elevated after belimumab initiation: a retrospective claims database analysis

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## ABSTRACT

**Objectives** To investigate corticosteroid and opioid use among patients with SLE and to examine the impact of belimumab initiation on the use of other SLE therapies.

**Methods** We identified adult patients with SLE (International Classification of Diseases, 9th Revision/10th Revision 710.0 and M32) between 1 January 2012 and 31 May 2018 (earliest SLE diagnosis=index date) within MarketScan administrative claims data. Patients were followed from index date for a minimum of 12 months and until the earlier of disenrolment in their health plan or study end (31 May 2018). Corticosteroid utilisation, corticosteroid dose (in prednisone equivalents) and opioid utilisation (overall, by strength (weak, strong) and by duration (chronic use defined as >90 days of cumulative drug supply)) were measured during follow-up. Oral corticosteroid and opioid use were compared in the 6 months before and after initiation of belimumab.

**Results** There were 49 413 patients with SLE eligible for analysis (mean (SD) age: 50.1 (14.0) years, 90.2% female). Of these, 68.5% received corticosteroids, and the average number of prescriptions was 4.59 (4.11) over the first 12 months of follow-up. Among patients with oral corticosteroids, average daily dose was 19.4 (14.2) mg and 59.6% had an average daily dose of  $\geq 15$  mg. Half (52.6%) had at least one opioid prescription and of these, 34.6% had chronic use over the first 12 months of follow-up. Among patients initiating belimumab during follow-up (n=1710), oral corticosteroid use decreased by 9.1% (p=0.001), and average daily dose decreased from 14.5 (18.4) mg to 11.9 (18.0) mg (p<0.001) in the 6 months after initiation compared with the 6 months prior. Initiation of belimumab had no impact on prevalence of opioid use.

**Conclusions** A high proportion of patients with SLE are treated with corticosteroids to control SLE and opioid therapy to manage chronic pain. While there was no change in opioid use, oral corticosteroid use and dose intensity decreased following initiation of belimumab.

## INTRODUCTION

SLE is a chronic autoimmune condition involving multiple organ systems, including renal, neurological, musculoskeletal, skin and cardiovascular manifestations.<sup>1–4</sup> SLE can also

## Key messages

### What is already known?

► Current SLE treatment options include several medication classes, including immunosuppressants, corticosteroids, and pain medications, used individually or in combination to manage disease manifestations and symptoms.

### What does this study add?

► This study describes utilization patterns of the drug classes currently used in SLE patients, particularly corticosteroids and opioids. Large percentages of SLE patients had corticosteroid (68.5%) and opioid use (52.6%) over a one-year period. After initiation of belimumab treatment, oral corticosteroid use decreased, while opioid use did not change and remained high.

### How might this impact on clinical practice or future developments?

► As newer therapies become available, tapering doses of drugs with known side effects, including corticosteroids and opioids, may be possible for symptoms and chronic pain in SLE patients.

be a painful disease, with pain ranging from musculoskeletal (affecting bone, muscles, joints) to centralised (related to fibromyalgia and the central nervous system) systems.<sup>5–8</sup> There is currently no cure for SLE, standard of care has relied on a combination of anti-malarials, corticosteroids and/or immunosuppressants depending on disease severity.<sup>9</sup> Biological therapy was introduced for SLE almost a decade ago with belimumab, a B-lymphocyte stimulator cell-targeting therapy; however, treatment pattern studies have shown a relatively low uptake of this biologic in SLE.<sup>10 11</sup> Belimumab was initially introduced to the market as an intravenous formulation; more recently (2017), a subcutaneous dosage form became available. Some studies have suggested greater patient preference

with the subcutaneous compared with the intravenous form of belimumab<sup>12 13</sup> raising the potential for greater usage, although this has had limited investigation to date.

The currently available therapeutics for SLE are used individually or together with goals to reduce disease activity, prevent organ damage and improve the quality of life of patients.<sup>9</sup> An additional aim of treatment is to minimise drug side effects through reduced usage of glucocorticoids, as sustained use is associated with permanent non-SLE organ damage, including cataracts, fragility fractures and cardiovascular damage.<sup>14 15</sup> Data from the Hopkins Lupus Cohort showed the risk of developing later organ damage increased by 50% when patients were exposed to an average cumulative prednisone dose of >6–12 mg/day compared with little to no exposure (>0–6 mg/day) to prednisone.<sup>16</sup> In another analysis, it was estimated that a 1 mg/day increase in prior prednisone dose during follow-up was associated with a 2.8% increase in the risk of developing new organ damage.<sup>14</sup> Thus, reduction in the use of glucocorticoids through combination therapies of agents with immunosuppressive properties is a frequent goal in clinical trials of SLE therapies and a desired attribute in real-world settings.<sup>9 17</sup>

In patients who experience painful conditions associated with SLE, appropriate pharmaceutical treatment targeted to the type and/or severity of pain is warranted, such as non-steroidal anti-inflammatory drugs (NSAIDs) for pain associated with inflammation or antiepileptics for neuropathic pain. Stronger analgesics, such as opioids, may have a role in the management of pain related to SLE; in fact, data from a recent survey showed 31% of patients with SLE reported current use of prescription opioids.<sup>18</sup> However, there is a lack of evidence to support long-term use of opioids among patients with rheumatic diseases, so ideally treatment with such agents is limited to short-term use, as other anti-inflammatory and/or immunosuppressive therapies are able to take effect.<sup>19</sup>

The first objective of this study was to describe the utilisation of five common drug classes (antimalarials, prescription NSAIDs, corticosteroids, immunosuppressants and biologics) among patients with SLE using administrative claims data, with a focus on oral corticosteroid dosing and the extent of opioid use. The second objective examined the impact of belimumab initiation on the use of other SLE therapies, as well as corticosteroid dosing and opioid use.

## METHODS

### Data source

This observational cohort study was conducted using data from the IBM MarketScan Commercial Claims and Encounters Database and the IBM MarketScan Medicare Supplemental and Coordination of Benefits Database. The MarketScan Commercial Claims Database contains the inpatient, outpatient and prescription drug experience of employees and their dependents, covered under a variety of fee-for-service and managed care health plans,

including approximately 89 million lives from 2012 to 2018. The MarketScan Medicare Supplemental Database contains the healthcare experience of retirees with Medicare supplemental insurance paid for by employers, including 5.5 million lives between 2012 and 2018. These databases provided detailed cost, use and outcome data from claims generated by both outpatient and inpatient healthcare services rendered. Data were extracted using International Classification of Diseases, 9th Revision and 10th Revision, Clinical Modification (ICD-9-CM and ICD-10-CM) codes, Current Procedural Terminology 4th Edition codes, Healthcare Common Procedure Coding System (HCPCS) codes and National Drug Codes (NDCs).

All database records were statistically deidentified and certified to be fully compliant with US patient confidentiality requirements set forth in the Health Insurance Portability and Accountability Act of 1996. Because this study used only deidentified patient records and did not involve the collection, use or transmittal of individually identifiable data, Institutional Review Board approval to conduct this study was not necessary.

### Study population

Patients included in the study had a diagnosis of SLE between 1 January 2012 and 31 May 2018, were at least 18 years of age at the diagnosis date and had continuous enrolment in benefits both 12 months before and after their diagnosis date. SLE diagnosis was confirmed by the presence of at least one inpatient or two non-diagnostic (ie, claims that are not potentially associated with a diagnostic workup used to rule out the presence of a condition, such as a laboratory claim) outpatient claims at least 30 days apart with an ICD-9-CM or ICD-10-CM diagnosis code for SLE (710.0 and M32, respectively). The date of the earliest eligible claim with an SLE diagnosis was set as the SLE index date.

Two subpopulations were identified for secondary analyses. First, an analysis of oral corticosteroid dosing was performed among patients who had at least two outpatient pharmacy claims for oral corticosteroid prescriptions following the SLE index date and at least 12 months of study enrolment following the first prescription. Two claims were required as a more conservative approach to identify patients likely to be using steroids for treatment of SLE symptoms. The date of the earliest eligible claim for oral steroids was set as the corticosteroid index date. Second, an analysis of the impact of belimumab initiation on other SLE treatments and treatment patterns among patients with the intravenous or subcutaneous form of belimumab was performed among a cohort of belimumab patients. Patients in the belimumab cohort were newly initiating belimumab after the SLE index date, and were required to have both at least 6 months of continuous enrolment after belimumab initiation and no claims for belimumab or rituximab in the 12 months prior to the belimumab start date. The date of the earliest eligible claim for belimumab was set as the belimumab

index date. A flow diagram of patient selection is shown in online supplemental figure 1.

### Study design

Patient demographics, including age, sex, geographic region of residence and payer, were measured on the SLE index date. Baseline clinical characteristics, including the Deyo-Charlson Comorbidity Index (CCI) (which is an index measuring an individual's general health status where a patient could have a cumulative score as high as 25 points although anything over 3 is considered high), common comorbid conditions, chronic pain conditions and presence of symptomatic pain, were measured during the 12-month preindex period. The list of chronic pain conditions used in this study was adapted from Pasquale *et al.*<sup>20</sup> Chronic pain conditions were identified by codes for specific conditions which cause pain, such as osteoarthritis. Conditions identified by codes for the type of pain, such as myofascial pain, were grouped together as symptomatic pain. The code list from Pasquale *et al* was expanded on to include ICD-10-CM codes for the identified pain conditions and two additional categories of symptomatic pain: acute pain and generalised pain.

SLE treatments and opioid use were measured over 12 months following the study index date. The average daily dose of oral corticosteroid in prednisone equivalents was measured over the 12 months following corticosteroid initiation. Oral corticosteroid dose and opioid use were

also compared in the 6 months before and after the initiation of belimumab. A diagram of the study periods can be found in figure 1.

### Study outcomes

This study measured the number and per cent of patients with SLE using antimalarials, prescription NSAIDs, corticosteroids, immunosuppressants and biologics, as well as the number of prescriptions and/or administrations of each therapy. Multimodal therapy of up to all five drug classes was also measured. Drug therapy prescriptions and administrations were identified by NDC and HCPCS codes, respectively. Drugs included in this analysis are listed in online supplemental table 1. Corticosteroid use was further examined by route of administration—oral, infusion/injection and topical. For the oral corticosteroid subanalysis, dosing was analysed among outpatient pharmacy claims by using the days' supply and metric quantity fields of the claim and a prednisone conversion factor. Belimumab use was further examined by route of administration (oral and infusion).

Weak opioids were defined using the WHO analgesic ladder and are listed in online supplemental table 1.<sup>21</sup> Opioid drugs not clearly classified as weak were grouped as strong. Opioid drugs used primarily for anaesthetic purposes (alfentanil, remifentanil and sufentanil) and those in combination with cold and cough medications were not included. Opioid use was considered acute if

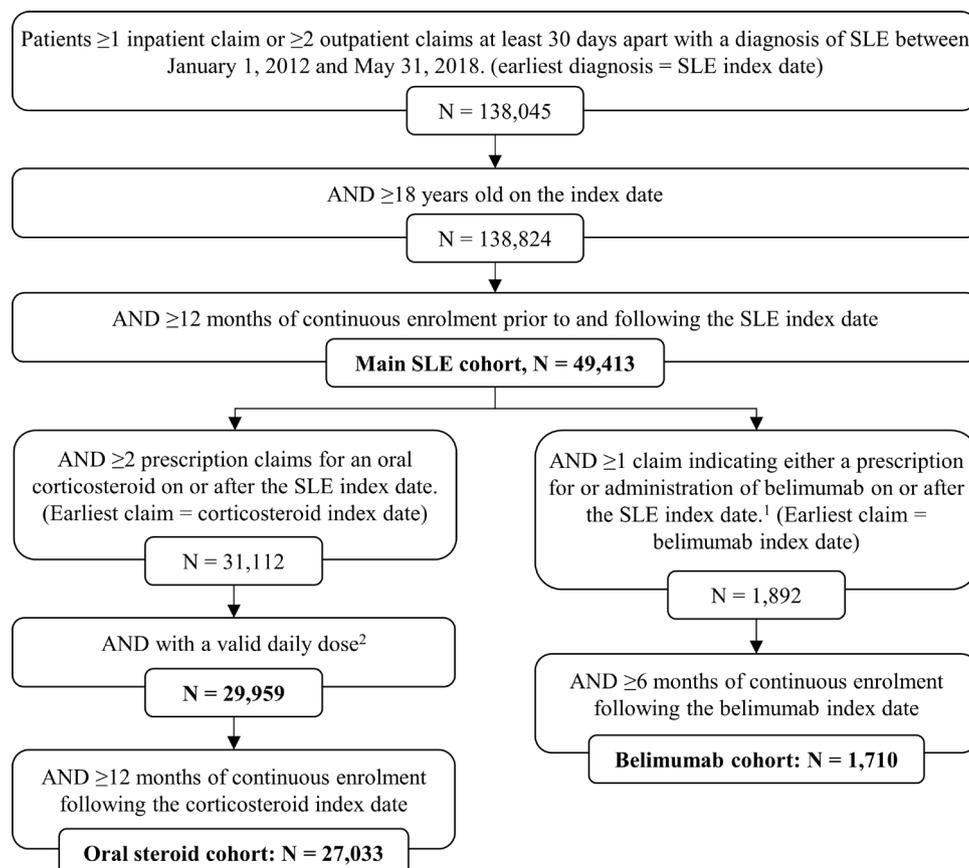


Figure 1 Patient selection.

the patient received less than 90 days of cumulative drug supply and use was considered chronic if the patient received 90 or more days' supply of opioids in total over a 12-month period.

**Table 1** Baseline demographic and clinical characteristics

|  | All patients<br>n=49 413 |        |
|--|--------------------------|--------|
| Age (mean, SD)                             | 50.1                     | 14.0   |
| Female, n (%)                              | 44 546                   | (90.2) |
| Geographic region, n (%)                   |                          |        |
| Northeast                                  | 9926                     | (20.1) |
| North Central                              | 9858                     | (20.0) |
| South                                      | 20 469                   | (41.4) |
| West                                       | 8678                     | (17.6) |
| Unknown                                    | 482                      | (1.0)  |
| Payer, n (%)                               |                          |        |
| Commercial                                 | 42 151                   | (85.3) |
| Medicare supplemental                      | 7262                     | (14.7) |
| Duration of follow-up in days (mean, SD)   | 1317                     | 691    |
| Deyo-Charlson Comorbidity Index (mean, SD) | 1.2                      | 1.4    |
| Incident SLE*, n (%)                       | 31 900                   | (64.6) |
| Clinical conditions, n (%)                 |                          |        |
| Anaemia                                    | 7366                     | (14.9) |
| Autoimmune thyroid disorders               | 933                      | (1.9)  |
| Cardiac disease                            | 14 745                   | (29.8) |
| Cerebrovascular disease                    | 2704                     | (5.5)  |
| Chronic renal disease                      | 3749                     | (7.6)  |
| Hypertension                               | 17 790                   | (36.0) |
| Myositis/myalgia (excluding fibromyalgia)  | 969                      | (2.0)  |
| Nephritis                                  | 1808                     | (3.7)  |
| Ophthalmological disorders                 | 15 751                   | (31.9) |
| Osteoporosis                               | 2502                     | (5.1)  |
| Proteinuria                                | 196                      | (0.4)  |
| Pulmonary disease                          | 10 956                   | (22.2) |
| Raynaud's syndrome                         | 2211                     | (4.5)  |
| Sjögren's syndrome                         | 3316                     | (6.7)  |
| Chronic pain conditions†, n (%)            | 26 582                   | (53.8) |
| Depression                                 | 6302                     | (12.8) |
| Fibromyalgia                               | 7401                     | (15.0) |
| Migraine                                   | 7879                     | (15.9) |
| Osteoarthritis                             | 8786                     | (17.8) |
| Rheumatoid arthritis                       | 7529                     | (15.2) |
| Symptomatic pain‡, n (%)                   | 26 989                   | (54.6) |

\*'Incident SLE' is defined as patients without any non-diagnostic medical claims for SLE during the preperiod.

†Other chronic pain conditions were found in fewer than 2.5% of the sample: ankylosing spondylitis, chronic pain syndrome, chronic pancreatitis, complex region pain syndrome, diabetic peripheral neuropathy, dysmenorrhoea, endometriosis, gout, interstitial cystitis, osteomyelitis, postherpetic neuralgia, sickle cell disease, trigeminal neuralgia and other disorders of peripheral nervous system associated with neuropathic pain.

‡Symptomatic pain conditions were those identified from codes which identified the type of pain rather than codes for conditions which cause pain. Symptomatic pain included abdominal pain, acute pain, chest pain, chronic pain, generalised pain, myofascial pain and psychogenic pain.

## Statistical methods

Mean and SD were reported for continuous variables while frequencies and percentages were reported for categorical variables. Statistical significance of medication utilisation before and after initiation of belimumab was evaluated using paired t-tests and McNemar's test. The alpha level for all statistical tests was 0.05. All data analyses were conducted using WPS V.4.1 (World Programming, UK).

## RESULTS

Among the 49 413 patients with SLE eligible for analysis, the mean (SD) age was 50.1 (14.0) years, 90.2% were female and the mean duration of follow-up was 3.6 (1.9) years (table 1). Of these patients, 64.6% had incident SLE, defined as no non-diagnostic claims for SLE during the 12-month baseline period. The mean (SD) Deyo-Charlson Index was 1.2 (1.4) and the baseline prevalence of comorbidities associated with SLE severity was 7.6% for chronic renal disease, 3.7% for nephritis and 0.4% for proteinuria. Common pain-related comorbidities included osteoarthritis (17.8%), (RA) (15.2%), migraine (15.9%), fibromyalgia (15.0%) and depression (12.8%). Over half of all patients had at least one chronic pain condition (53.8%) and 54.6% experienced symptomatic pain.

In the first 12 months following index SLE diagnosis, 89.8% of patients received pharmaceutical treatment for SLE (table 2). Corticosteroids were the most common therapy. Overall, 68.5% of patients were treated with prescription corticosteroids during the follow-up period, and the mean (SD) number of corticosteroid prescriptions per treated patient was 4.59 (4.11) over the 12-month period. Oral was the most common route of administration, followed by infusion/injection and topical. In addition, 28.8% of patients received corticosteroids through more than one route of administration.

Other prescribing patterns in the first 12 months included 59.1% of patients with claims for antimalarials, 37.4% with claims for prescription NSAIDs, 26.4% with claims for immunosuppressants and 3.2% with claims for biologics. While 10.2% of patients had no evidence of prescription pharmacotherapy for SLE, a quarter of patients had monotherapy (24.2%), and about two-thirds of patients had evidence of treatment with more than one class of SLE treatments.

Over half (52.6%) of patients with SLE had evidence of opioid use in the first 12 months after their index date, and 84.1% of opioid users had at least one claim for a strong opioid (table 2). Among all patients with SLE, 34.4% were classified as having acute opioid use while 18.2% were classified as having chronic opioid use.

## Oral corticosteroid dosing subanalysis

Among the 49 413 patients with SLE, 27 033 (54.7%) were eligible for inclusion in the oral corticosteroid subanalysis as they had at least two pharmacy claims for oral corticosteroid prescriptions following their SLE diagnosis and

**Table 2** SLE prescribing patterns and opioid use among all patients with SLE in the first 12 months after index

|   | All patients<br>n=49 413 |        |
|---|--------------------------|--------|
| Patients receiving SLE medications, n (%)               | 44 368                   | (89.8) |
| Class 1: antimalarials                                  | 29 218                   | (59.1) |
| Class 2: prescription NSAIDs                            | 18 496                   | (37.4) |
| Class 3: corticosteroids                                | 33 845                   | (68.5) |
| Oral  | 24 967                   | (50.5) |
| Infusion/injection                                      | 15 831                   | (32.0) |
| Topical   | 9 680                    | (19.6) |
| Class 4: immunosuppressants*                            | 13 042                   | (26.4) |
| Class 5: biologics                                      | 1 579                    | (3.2)  |
| Belimumab   | 1 061                    | (2.1)  |
| Belimumab intravenous                                   | 1 029                    | (2.1)  |
| Belimumab subcutaneous                                  | 43                       | (0.1)  |
| Rituximab intravenous                                   | 538                      | (1.1)  |
| Number of claims per patient (mean, SD)                 |                          |        |
| Class 1: antimalarials                                  | 5.66                     | 3.46   |
| Class 2: prescription NSAIDs                            | 3.41                     | 3.08   |
| Class 3: corticosteroids                                | 4.59                     | 4.11   |
| Oral  | 4.00                     | 3.45   |
| Infusion/injection                                      | 2.35                     | 2.50   |
| Topical   | 1.90                     | 1.72   |
| Class 4: immunosuppressants                             | 6.01                     | 4.47   |
| Class 5: biologics                                      | 5.91                     | 4.04   |
| Belimumab   | 7.28                     | 4.10   |
| Belimumab intravenous                                   | 7.33                     | 4.10   |
| Belimumab subcutaneous                                  | 4.09                     | 2.88   |
| Rituximab intravenous                                   | 2.99                     | 1.77   |
| Number of classes used, n (%)                           |                          |        |
| No therapy  | 5 045                    | (10.2) |
| One drug class (monotherapy)                            | 11 942                   | (24.2) |
| Two drug classes  | 16 937                   | (34.3) |
| Three drug classes                                      | 11 886                   | (24.1) |
| Four drug classes                                       | 3 309                    | (6.7)  |
| Five drug classes                                       | 294                      | (0.6)  |
| Opioid use, n (%)                                       | 25 982                   | (52.6) |
| Weak opioids  | 10 280                   | (20.8) |
| Strong opioids  | 21 861                   | (44.2) |
| Acute opioid use (<90 days of cumulative drug supply)   | 16 997                   | (34.4) |
| Chronic opioid use (90+ days of cumulative drug supply) | 8 985                    | (18.2) |

\*Azathioprine, cyclophosphamide, cyclosporine, intravenous immunoglobulin (IVIg), leflunomide, methotrexate, mycophenolate and tacrolimus. NSAIDs, non-steroidal anti-inflammatory drugs.

at least 12 months of study enrolment following the first corticosteroid prescription. In the 12 months following the first claim for oral corticosteroids, the average daily dose was 19.4 mg (SD: 14.2 mg) in prednisone equivalents. In the oral corticosteroid subcohort, 17.2% had an average daily dose below 7.5 mg, 23.3% had an average

daily dose of 7.5 to less than 15 mg and the majority (59.6%) had an average daily dose of 15 mg or more.

### Belimumab subanalysis

Within the main SLE cohort, 1 892 (3.8%) patients initiated belimumab therapy following the SLE index date. Of these, 1 710 patients with SLE had at least 6 months of continuous enrolment following initiation of belimumab and were eligible for inclusion in the belimumab subanalysis. Among them were 1 570 patients who initiated on the intravenous form and 140 who initiated on the subcutaneous form (table 3).

While the percentage of patients taking every class of non-biological SLE medications decreased during the 6 months following belimumab initiation (compared with the 6 months prior to initiation), these differences were significant for immunosuppressants (58.8% vs 50.8%,  $p=0.002$ ) and oral corticosteroids (73.0% vs 63.9%,  $p=0.001$ ). In the 6 months following initiation of belimumab, only 4.6% of patients were on biological therapy only while 33.0% received three SLE medication classes in addition to belimumab and 10.6% received all four classes in addition to belimumab. The initiation of belimumab resulted in no statistically significant change in opioid use, which remained above 50%.

Following belimumab initiation, the mean (SD) daily dose of oral corticosteroids decreased from 14.5 mg (18.4 mg) to 11.9 mg (18.0 mg) ( $p<0.001$ ); however, 48.6% of patients remained on a medium (7.5 to <15 mg) or high dose ( $\geq 15$  mg). Among patients with oral corticosteroid prescriptions, the average daily dose was lower after initiating belimumab (figure 2). Trends in prescribing patterns were similar regardless of the route of administration of belimumab (online supplemental table 2).

### DISCUSSION

In this analysis of patients with SLE, treatment was varied and complex, with approximately 66% of patients receiving multimodal treatment with two or more classes of SLE medications, and 7.3% using four or more different classes. Despite the introduction of belimumab for SLE almost a decade ago, prescribing practices still heavily rely on older therapies. Oral corticosteroids were the most commonly prescribed medication in this analysis (50.5% of all patients with SLE). Of patients in the oral corticosteroid cohort, 23% were prescribed oral corticosteroids at an average daily dose of >7.5–15 mg prednisone equivalents, and almost 60% at an average daily dose of 15 mg or greater. Almost 30% of patients with SLE were prescribed corticosteroids by more than one route of administration. Biological therapies included in this study (belimumab and rituximab) were used in only 3% of patients, but opioid use was observed in more than 50% of patients.

Prevalence of hypertension and cardiovascular disease measured during the 12 months prior to the index date is comparable to similar studies of SLE in claims data.<sup>4 22</sup>

**Table 3** Prescribing patterns in the 6 months before and after initiation of belimumab treatment\*

|   | 6 months before belimumab initiation<br>n=1710 |        | 6 months after belimumab initiation |         | P value, pre versus post |
|---|--|--------|-------------------------------------|---------|--------------------------|
| Patients receiving SLE medications, n (%)               | 1655   | (96.8) | 1710                                | (100.0) | 0.343                    |
| Class 1: antimalarials                                  | 1174   | (68.7) | 1088                                | (63.6)  | 0.071                    |
| Class 2: prescription NSAIDs                            | 605  | (35.4) | 582                                 | (34.0)  | 0.504                    |
| Class 3: corticosteroids                                | 1429   | (83.6) | 1357                                | (79.4)  | 0.173                    |
| Oral  | 1248   | (73.0) | 1092                                | (63.9)  | 0.001                    |
| Infusion/injection                                      | 580  | (33.9) | 692                                 | (40.5)  | 0.002                    |
| Topical   | 252  | (14.7) | 237                                 | (13.9)  | 0.498                    |
| Class 4: immunosuppressants                             | 1005   | (58.8) | 869                                 | (50.8)  | 0.002                    |
| Number of claims per patient (mean, SD)                 |  |        |                                     |         |                          |
| Class 1: antimalarials                                  | 2.15   | 2.05   | 2.00                                | 2.07    | <0.001                   |
| Class 2: prescription NSAIDs                            | 0.89   | 1.59   | 0.84                                | 1.58    | 0.059                    |
| Class 3: corticosteroids                                | 3.16   | 2.81   | 3.66                                | 3.39    | <0.001                   |
| Oral  | 2.27   | 2.18   | 2.00                                | 2.21    | <0.001                   |
| Infusion/injection                                      | 0.65   | 1.38   | 1.45                                | 2.49    | <0.001                   |
| Topical   | 0.25   | 0.80   | 0.21                                | 0.66    | 0.044                    |
| Class 4: immunosuppressants                             | 2.10   | 2.50   | 1.73                                | 2.35    | <0.001                   |
| Number of classes, other than biologics, n (%)          |  |        |                                     |         |                          |
| No therapy  | 55   | (3.2)  | 78                                  | (4.6)   | 0.046                    |
| One drug class  | 220  | (12.9) | 297                                 | (17.4)  | 0.001                    |
| Two drug classes  | 554  | (32.4) | 588                                 | (34.4)  | 0.314                    |
| Three drug classes                                      | 639  | (37.4) | 565                                 | (33.0)  | 0.033                    |
| Four drug classes                                       | 242  | (14.2) | 182                                 | (10.6)  | 0.004                    |
| Opioid use, n (%)                                       | 901  | (52.7) | 861                                 | (50.4)  | 0.341                    |
| Weak opioids  | 356  | (20.8) | 312                                 | (18.2)  | 0.089                    |
| Strong opioids  | 699  | (40.9) | 695                                 | (40.6)  | 0.915                    |
| Acute opioid use (<90 days of cumulative drug supply)   | 538  | (31.5) | 486                                 | (28.4)  | 0.165                    |
| Chronic opioid use (90+ days of cumulative drug supply) | 363  | (21.2) | 375                                 | (21.9)  | 0.165                    |
| Oral corticosteroid dosing†                             |  |        |                                     |         |                          |
| Average daily dose (mean, SD)‡§                         | 14.5   | 18.4   | 11.9                                | 18.0    | <0.001                   |
| Low average daily dose (>0 to <7.5 mg), n (%)           | 210  | (12.3) | 255                                 | (14.9)  | 0.037                    |
| Medium average daily dose (7.5 to <15 mg), n (%)        | 389  | (22.7) | 334                                 | (19.5)  | 0.041                    |
| High average daily dose (15+ mg), n (%)                 | 643  | (37.6) | 497                                 | (29.1)  | <0.001                   |

\*Average follow-up time after biological index was shorter than average follow-up time after SLE diagnosis, especially among the belimumab cohort, so inclusion criteria required a 6-month preindex/postindex period of continuous enrolment to maintain the sample size.

†Claims with ≤0 value for fields used to calculate dose were dropped (<1% of patients without a valid claim).

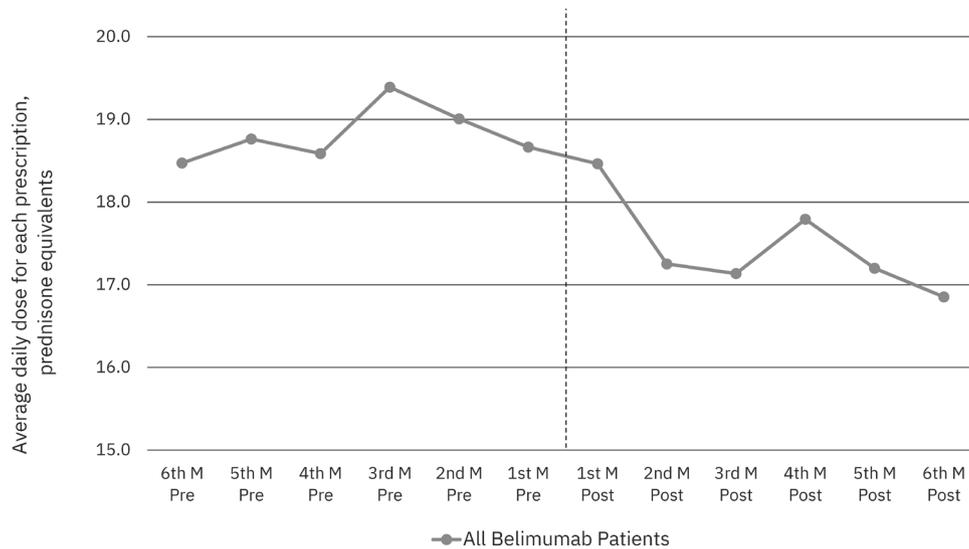
‡Daily dose in prednisone equivalents=(strength × quantity)/days of supply. Claims with ≤0 value for fields used to calculate dose were dropped (resulted in dropping <1% of patients without a valid claim), therefore n went from 1248 to 1242 patients when reporting these results.

§For those with an invalid daily dose (>100 mg/day), doses were capped at 100 mg. This occurred for <2% of belimumab patients in both time periods reported.

¶NSAIDs, non-steroidal anti-inflammatory drugs.

Ophthalmological disorders, affecting about a third in our sample, match recent literature reviews on ocular manifestations in SLE.<sup>23</sup> However, our sample has notably

lower prevalence of nephritis (3.7%) and proteinuria (0.4%), as well as a lower average of Deyo-CCI score, than has been seen in other SLE literature.<sup>22 24</sup> This is likely



**Figure 2** Oral steroid dosing before and after initiation of belimumab, by month.

due to undercoding of specific SLE manifestations and lack of specificity for the diagnosis of SLE, especially with similar diseases such as Sjogren's syndrome or undifferentiated connective tissue disease. Because patient selection criteria did not require patients to be on treatment or in the care of a specialist, patients with milder lupus-like conditions might have been included in the study population. Future research restricted to patients receiving care from specialists, such as rheumatologists, nephrologists and dermatologists, would likely provide a population with more severe and active SLE, more lupus nephritis, proteinuria and comorbidities, and should be pursued.

Our findings match both clinical trials and observational studies that have shown high frequency of steroid use<sup>25</sup> and a steroid-sparing effect after treatment with belimumab.<sup>26–28</sup> Our analysis also showed a decrease in usage of oral corticosteroids during the 6 months after initiation of belimumab (compared with the 6 months prior to initiation), confirming similar studies that found a significant decrease in oral steroids before and after belimumab use.<sup>25</sup> Unlike oral steroids, intravenous steroid use increased pre-to-post belimumab use for the intravenous belimumab patients, consistent with data published by Bell *et al.*<sup>25</sup> The opposite trend was observed in subcutaneous belimumab patients: use of intravenous steroids decreased. We hypothesise that intravenous steroids may have been administered to reduce infusion reactions, which can be common in intravenous treatment of SLE and other rheumatic diseases.<sup>29 30</sup>

Dosing for intravenous steroids is not well captured in claims data, so our results on steroid dosing focus on oral steroid use. In this study, the average daily oral corticosteroid dose among patients with at least one claim for oral corticosteroids decreases from the 6 months before belimumab use (range: 18.5–19.4 mg) to the 6 months after index (range: 16.9–18.5 mg). Similar results were seen in a prior retrospective claims study, in which 66.5% (103 of 155) of patients with SLE had at least one claim

for an oral corticosteroid in the 6 months prior to initiating belimumab with an average daily dose ranging from 14.2 to 20.8 mg, which decreased to a range of 14.3–19.4 over the 6 months after index.<sup>10</sup> However, in our analysis, despite seeing a decrease in steroid usage during the 6 months after belimumab initiation, 30% of all patients with SLE treated with belimumab were still receiving an average daily steroid dose of 15 mg or higher. Due to the small sample size of patients using subcutaneous belimumab (10% of belimumab initiators) and the smaller number of these patients with steroid use in each month, no robust comparison of intravenous versus subcutaneous belimumab on month-to-month steroid dose can be conducted. Future studies with a large number of subcutaneous belimumab users would shed light on the impact of different routes of belimumab administration on monthly steroid usage.

A high frequency of chronic and acute pain conditions has been associated with SLE.<sup>7</sup> These could be diverse in origin such as musculoskeletal, neurological, gastrointestinal, neuropathic or multifactorial.<sup>8</sup> We identified through medical claims a wide variety of painful conditions reported in patients with SLE. We also identified a relatively large usage of opioids. Over half (53%) of all patients with SLE used opioids during a 12-month observation period and 18.2% had evidence of chronic opioid usage. Similar data were found from another retrospective observational study using the Truven MarketScan Database from 2003 to 2014. This study compared the number of opioid prescriptions among treated patients with SLE, RA, psoriatic arthritis or ankylosing spondylitis. They found 46% of treated patients with SLE received an opioid prescription over a year of observation period with 16% having long-term use ( $\geq 90$  days cumulative over the 1-year follow-up). In this study, opioid use was similar to patients with RA (48%), but a bit less than patients with ankylosing spondylitis (52%).<sup>27</sup> It is of note in our analysis that initiation of belimumab was associated with no

significant change in opioid utilisation. Future research is needed to understand the underlying reasons of such a high opioid use rate and the opioid usage in other SLE populations, especially among those covered with non-commercial insurance or having no insurance.

Opioid usage in patients with SLE is of interest as literature has been drawing attention to it, related to the overall opioid epidemic highlighted in the media. In a survey of 462 patients with SLE from the Michigan Lupus Epidemiology and Surveillance Cohort, 31% of patients reported using prescription opioids, with 22% of opioid users reporting taking more than one opioid concurrently.<sup>15</sup> The discrepancy in opioid use between administrative claims-based analyses and survey studies is likely driven by two factors. First, opioid use may be under-reported in a survey study because there is a negative social stigma associated with opioid use that may bias patient self-reporting. Second, opioid use may be overestimated by claims analysis as it is only possible to determine that a prescription was filled not that it was taken as prescribed.

The impact of chronic pain in SLE can at least partially be quantified through the need and use of healthcare resources. In a study using electronic health records, chronic pain was found to be a main cause of emergency room (ER) use among patients with SLE who had frequent ER visits.<sup>31</sup> In addition, long-term opioid use was seen in one out of three patients with SLE who frequented the ER.

This study highlights the continued reliance on steroids and utilisation of chronic and higher doses, in addition to the broad use of opioids in patients with SLE. This speaks to the existing unmet needs with current therapies and draws attention to the burden and impact of chronic pain in these patients. As the drug development pipeline continues to evolve, hopefully new therapies to meet these unmet needs will be realised.

### Strengths and limitations

There are several strengths to the analyses presented here. First, this study used retrospective claims data, which provide a longitudinal tracking of a large, heterogeneous patient population. Unlike clinical trials that are subject to strict inclusion criteria and surveys which are subject to small samples and memory biases, this real-world claims study captured medication utilisation data from a broad sample of patients with SLE. However, claims studies are subject to several limitations. First, these data are subject to data entry errors or miscoding which can be more common in difficult to diagnose and heterogeneous diseases like SLE. Inclusion criteria were designed to require multiple points of contact in order to affirm that a single SLE diagnosis was not made in error. SLE is overdiagnosed in the USA, especially by non-specialist providers. Additionally, by requiring patients to have multiple points of contact with the healthcare system over a period of months, the study population is likely skewed towards those patients with greater access to care. While other studies have decreased the risk of miscoded or

misdiagnosed patients by requiring at least one diagnosis claim from a specialist associated with SLE treatment (eg, rheumatologist, nephrologist or neurologist), this approach can result in a bias towards patients with access to specialist care. Furthermore, the key outcomes in this study were measured among belimumab users, which is only indicated for the treatment of SLE. Previous claims-based studies in patients with SLE have similarly relied on specificity of the belimumab indication to reduce the likelihood of misdiagnosed patients entering the study population.<sup>25</sup> Second, claims data identify that a medication was dispensed, not that the medication was administered or taken as the prescribed and over-the-counter medications are not captured, thus we were only able to capture prescription NSAID use, but not over-the-counter use. Third, corticosteroid dosing could be determined most reliably only for patients taking oral corticosteroids received in the outpatient pharmacy setting. Thus, our daily dosage calculations likely underestimate the total corticosteroid exposure. Fourth, steroids used as premedication for rituximab infusions were not systematically accounted for in this study. Finally, this analysis was performed among patients with commercial or Medicare supplemental insurance, who tend to be older and healthier, and therefore may not be generalisable to those with other insurance types or without insurance coverage.

### Future work

As new therapies become more available, prescribers will need to continue to re-examine how they address the reliance on corticosteroids to manage the symptoms of SLE as well as the burden of chronic pain on patients with SLE. Analysis of longer term biological therapy is needed to further examine the impact on subsequent corticosteroid and opioid use.

### CONCLUSION

In this large, recent commercially insured population, a high proportion of patients with SLE were treated with corticosteroids to control the disease and opioid therapy to manage chronic pain. While there was no change in opioid use, oral corticosteroid use and dose intensity decreased following initiation of belimumab, although almost 50% of patients remained on medium to high doses.

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**Ethics approval** This manuscript does not contain personal and/or medical information about any identifiable living individual. It does not involve animal subjects.

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**Data availability statement** Data may be obtained from a third party and are not publicly available. The data that support the findings of this study are available from IBM Watson Health. Restrictions apply to the availability of these data, which were used under licence for this study.

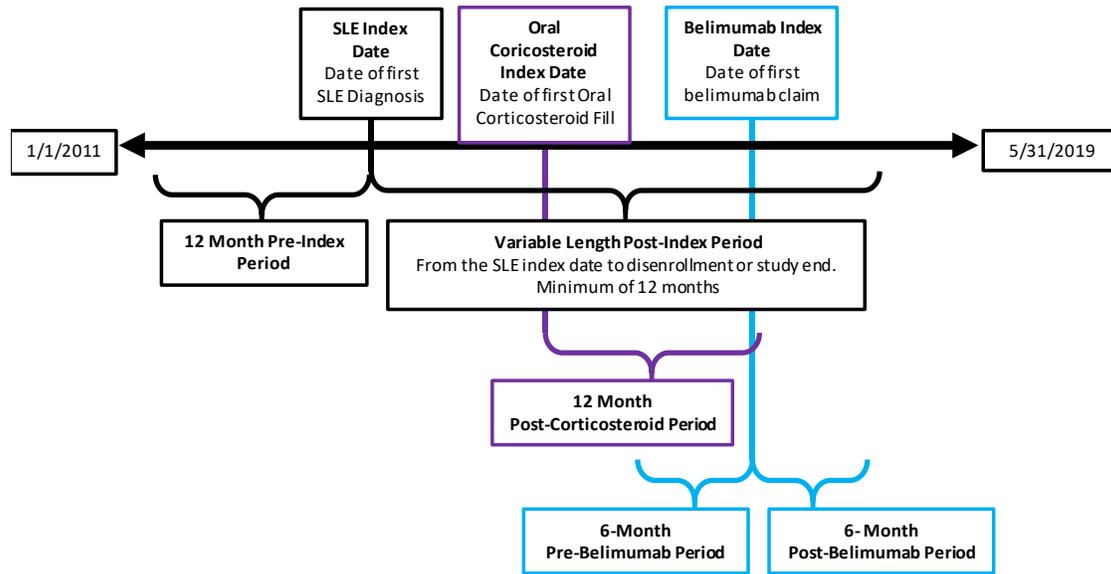
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Supplemental Figure 1: Study Time Periods



Supplementary Table 1: List of drugs used in assessing treatment landscape of SLE

| Category                         | Drugs   |
|----------------------------------|---|
| Antimalarials                    | chloroquine and hydroxychloroquine  |
| Biologics                        | belimumab (intravenous or subcutaneous), and rituximab  |
| Corticosteroids                  | alclometasone, amcinonide, betamethasone, clobetasol, clocortolone, cortisone, deflazacort, desonide, desoximetasone, dexamethasone, diflorasone, fludrocortisone, fluocinolone, fluocinonide, flurandrenolide, fluticasone, halcinonide, halobetasol, hydrocortisone, methylprednisolone, mometasone, prednicarbate, prednisolone, prednisone, triamcinolone |
| Immunosuppressants               | azathioprine, cyclophosphamide, cyclosporine, intravenous immunoglobulin, leflunomide, methotrexate, mycophenolate, and tacrolimus  |
| Nonsteroidal anti-inflammatories | bromfenac, celecoxib, diclofenac, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, rofecoxib, sulindac, tolmetin, and valdecoxib  |
| Opioids, strong                  | buprenorphine, fentanyl, hydromorphone (or oxymorphone), methadone, morphine, oxycodone, tapentadol, butorphanol, dezocine, hydrocodone, levomethadyl, levorphanol, meperidine, nalbuphine, pentazocine   |
| Opioids, weak                    | codeine, dihydrocodeine, tramadol, propoxyphene (included but no longer used in US)   |

Supplementary Table 2: Prescribing patterns in the 6 months before and after initiation of belimumab treatment segmented by belimumab route of administration

|  | 6 Months Before Belimumab IV Initiation |       | 6 Months After Belimumab IV Initiation |        | p-value, pre vs. post | 6 Months Before Belimumab SC Initiation |       | 6 Months After Belimumab SC Initiation |        | p-value, pre vs. post |
|--|---|-------|--|--------|-----------------------|---|-------|--|--------|-----------------------|
|  | N =                                     |       | N =                                    |        |                       | N =                                     |       | N =                                    |        |                       |
| <b>Patients with SLE Drugs (N, %)</b>                              | 1,518                                   | 96.7% | 1,570                                  | 100.0% | 0.349                 | 137                                     | 97.9% | 140                                    | 100.0% | 0.857                 |
| Class 1: Antimalarials   | 1,079                                   | 68.7% | 996                                    | 63.4%  | 0.068                 | 95                                      | 67.9% | 92                                     | 65.7%  | 0.826                 |
| Class 2: Prescription NSAIDs                                       | 563                                     | 35.9% | 541                                    | 34.5%  | 0.508                 | 42                                      | 30.0% | 41                                     | 29.3%  | 0.913                 |
| Class 3: Corticosteroids   | 1,313                                   | 83.6% | 1,256                                  | 80.0%  | 0.261                 | 116                                     | 82.9% | 101                                    | 72.1%  | 0.309                 |
| Oral   | 1,145                                   | 72.9% | 1,001                                  | 63.8%  | 0.002                 | 103                                     | 73.6% | 91                                     | 65.0%  | 0.389                 |
| Infusion/Injection   | 532                                     | 33.9% | 662                                    | 42.2%  | 0.000                 | 48                                      | 34.3% | 30                                     | 21.4%  | 0.042                 |
| Topical  | 237                                     | 15.1% | 224                                    | 14.3%  | 0.545                 | 15                                      | 10.7% | 13                                     | 9.3%   | 0.705                 |
| Class 4: Immunosuppressants  | 927                                     | 59.0% | 803                                    | 51.1%  | 0.003                 | 78                                      | 55.7% | 66                                     | 47.1%  | 0.317                 |
| Class 5: Biologics   |   |       | 1,570                                  | 100.0% |                       |   |       | 140                                    | 100.0% |                       |
| Belimumab  |   |       | 1,570                                  | 100.0% |                       |   |       | 140                                    | 100.0% |                       |
| Belimumab IV   |   |       | 1,570                                  | 100.0% |                       |   |       | 5                                      | 3.6%   |                       |
| Belimumab SC   |   |       | 8                                      | 0.5%   |                       |   |       | 140                                    | 100.0% |                       |
| Rituximab IV   |   |       | 13                                     | 0.8%   |                       |   |       | 1                                      | 0.7%   |                       |
| <b>Number of claims per patient, among all patients (Mean, SD)</b> |   |       |  |        |                       |   |       |  |        |                       |
| Class 1: Antimalarials   | 2.15                                    | 2.05  | 2.00                                   | 2.06   | <0.001                | 2.14                                    | 2.08  | 2.05                                   | 2.17   | 0.370                 |
| Class 2: Prescription NSAIDs                                       | 0.91                                    | 1.60  | 0.85                                   | 1.60   | 0.101                 | 0.74                                    | 1.51  | 0.63                                   | 1.33   | 0.252                 |
| Class 3: Corticosteroids   | 3.18                                    | 2.83  | 3.77                                   | 3.45   | <0.001                | 2.94                                    | 2.54  | 2.45                                   | 2.38   | 0.012                 |
| Oral   | 2.28                                    | 2.19  | 2.01                                   | 2.22   | <0.001                | 2.15                                    | 2.01  | 1.93                                   | 2.07   | 0.168                 |
| Infusion/Injection   | 0.64                                    | 1.39  | 1.54                                   | 2.57   | <0.001                | 0.66                                    | 1.38  | 0.40                                   | 0.90   | 0.009                 |
| Topical  | 0.26                                    | 0.83  | 0.22                                   | 0.67   | 0.047                 | 0.14                                    | 0.42  | 0.12                                   | 0.42   | 0.733                 |
| Class 4: Immunosuppressants  | 2.08                                    | 2.48  | 1.73                                   | 2.35   | <0.001                | 2.26                                    | 2.63  | 1.66                                   | 2.38   | 0.001                 |
| Class 5: Biologics   |   |       | 6.06                                   | 2.08   |                       |   |       | 5.27                                   | 1.90   |                       |
| Belimumab  |   |       | 6.04                                   | 2.10   |                       |   |       | 5.26                                   | 1.92   |                       |
| Belimumab IV   |   |       | 6.03                                   | 2.10   |                       |   |       | 0.12                                   | 0.65   |                       |

|  |      |       |      |       |        |      |       |      |       |       |
|--|------|-------|------|-------|--------|------|-------|------|-------|-------|
| Belimumab SC   |      |       | 0.01 | 0.20  |        |      |       | 5.14 | 1.99  |       |
| Rituximab IV   |      |       | 0.02 | 0.24  |        |      |       | 0.01 | 0.17  |       |
| <b>Number of Classes Utilized, other than biologics (N, %)</b> |      |       |      |       |        |      |       |      |       |       |
| No therapy   | 52   | 3.3%  | 71   | 4.5%  | 0.087  | 3    | 2.1%  | 7    | 5.0%  | 0.206 |
| One drug class (monotherapy)                                   | 195  | 12.4% | 264  | 16.8% | 0.001  | 25   | 17.9% | 33   | 23.6% | 0.294 |
| Two drug classes   | 508  | 32.4% | 545  | 34.7% | 0.254  | 46   | 32.9% | 43   | 30.7% | 0.750 |
| Three drug classes   | 589  | 37.5% | 518  | 33.0% | 0.033  | 50   | 35.7% | 47   | 33.6% | 0.761 |
| Four drug classes  | 226  | 14.4% | 172  | 11.0% | 0.007  | 16   | 11.4% | 10   | 7.1%  | 0.239 |
| <b>Opioid Use (N, %)</b>                                       | 843  | 53.7% | 801  | 51.0% | 0.300  | 58   | 41.4% | 60   | 42.9% | 0.854 |
| Weak opioids   | 332  | 21.1% | 294  | 18.7% | 0.129  | 24   | 17.1% | 18   | 12.9% | 0.355 |
| Strong opioids   | 658  | 41.9% | 642  | 40.9% | 0.657  | 41   | 29.3% | 53   | 37.9% | 0.216 |
| Acute Opioid Use   | 505  | 59.9% | 452  | 56.4% | 0.153  | 33   | 56.9% | 34   | 56.7% | 0.980 |
| Chronic opioid use   | 338  | 40.1% | 349  | 43.6% | 0.153  | 25   | 43.1% | 26   | 43.3% | 0.980 |
| <b>Oral Corticosteroid Dosing<sup>1</sup></b>                  |      |       |      |       |        |      |       |      |       |       |
| Average daily dose (Mean, SD) <sup>2,3</sup>                   | 14.6 | 18.6  | 11.8 | 18.1  | <0.001 | 13.4 | 16.1  | 12.6 | 17.3  | 0.512 |
| Low (N, %)   | 197  | 12.5% | 237  | 15.1% | 0.055  | 13   | 9.3%  | 18   | 12.9% | 0.369 |
| Medium (N, %)  | 352  | 22.4% | 307  | 19.6% | 0.080  | 37   | 26.4% | 27   | 19.3% | 0.211 |
| High (N, %)  | 591  | 37.6% | 453  | 28.9% | <0.001 | 52   | 37.1% | 44   | 31.4% | 0.414 |

<sup>1</sup>Oral steroid dosing can only be reliability calculated among outpatient pharmacy claims, therefore oral steroids identified on outpatient office visit claims were not included in this analysis. This occurred for <0.6% of belimumab patients in both time periods reported.

<sup>2</sup>Daily dose in prednisone equivalents = (strength \* quantity)/ days of supply. Claims with <=0 value for fields used to calculate dose were dropped (resulted in dropping <1% of patients without a valid claim).

<sup>3</sup>For those with an invalid daily dose (>100 mg/day), doses were capped at 100 mg. This occurred for <2% of belimumab patients in both time periods reported.