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## Treatment Patterns, Adherence, Persistence, and Healthcare Resource Utilization in Acromegaly: A Real-World Analysis

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1 **Treatment Patterns, Adherence, Persistence, and Healthcare Resource Utilization in**  
2 **Acromegaly: A Real-World Analysis**

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12  
13 **ABSTRACT**

14 Treatment of acromegaly is multimodal for many patients, and medical treatments include  
15 somatostatin receptor ligands (SRLs), dopamine agonists (DAs), and growth hormone receptor  
16 antagonists (GHRAs). However, recent real-world evidence on treatment patterns for patients  
17 with acromegaly is limited. This study evaluated medication usage, treatment changes,  
18 adherence, persistence, comorbidities, and healthcare resource utilization, using de-identified  
19 data from MarketScan<sup>®</sup>, a US claims database. Eligible patients (n=882) were those receiving  
20 monotherapy or combination therapy for  $\geq 90$  days without treatment gaps. Mean age at  
21 diagnosis was 48.6 years; 50.1% of patients were female. Over half (59.4%) had one line of  
22 treatment (LOT); 23.1% had two LOTs; 17.5% had at least three LOTs. Most patients (94.6%)  
23 initiated treatment with monotherapies. The most common first-line monotherapy  
24 treatments were cabergoline (DA, 36.8%), octreotide long-acting release (first-generation SRL,  
25 29.5%), and lanreotide depot (first-generation SRL, 22.5%). Adherence for first-line treatments  
26 (proportion of days covered), was higher for first-generation SRLs (lanreotide depot: 0.8),  
27 compared with DAs (0.7). Treatment persistence (time between the first treatment record and a  
28 change in LOT/censoring) in LOT 1 was higher for GHRAs (24.8 months) and first-generation  
29 SRLs (20.0 months), compared with DAs (14.4 months). Female patients and those diagnosed

1 at a younger age were more likely to have shorter treatment persistence. The most prevalent  
2 comorbidities were hyperlipidemia, essential hypertension, and sleep apnea. Patients with more  
3 comorbidities had more healthcare visits during the first year after diagnosis, suggesting  
4 increased disease burden. Real-world evidence on treatment patterns provides insights into  
5 recommendations for individualized therapy.

6 **Keywords** (6 maximum): acromegaly, real-world evidence, treatment adherence, treatment  
7 persistence, comorbidities, healthcare resource utilization

## 9 **INTRODUCTION**

10 Acromegaly is usually caused by a growth hormone (GH)-secreting pituitary adenoma. Excess  
11 GH production in turn results in elevated levels of insulin-like growth factor 1 (IGF-1) [1-3].

12 Elevated levels of circulating GH and IGF-1 stimulate excessive growth of bone and soft tissues,  
13 with associated comorbidities including hypertension and hyperlipidemia [4,5]. Mortality among  
14 patients with biochemically uncontrolled acromegaly is higher than that of the general  
15 population, although the difference has become less pronounced over time [3,4,6,7].

16 Acromegaly can be treated with surgery, medical therapy, and/or radiotherapy; medical therapy  
17 is recommended as an adjuvant for patients experiencing residual disease after surgery, or as  
18 primary treatment if surgical treatment is contraindicated [8]. Medical therapies include four  
19 classes of pharmaceutical treatment: first-generation somatostatin receptor ligands (SRLs;  
20 lanreotide depot, octreotide long-acting release [LAR], and oral octreotide); second-generation  
21 multiligand SRLs (pasireotide LAR); dopamine agonists (DAs; cabergoline); and GH receptor  
22 antagonists (GHRAs; pegvisomant) [9-11].

1 Elucidating real-world evidence (RWE) on aspects of acromegaly treatments, such as  
2 medication adherence, medication persistence, and overall healthcare resource utilization,  
3 increases understanding and awareness of the disease and its associated manifestations. Key  
4 insights from RWE may be incorporated into recommendations for individualized treatments,  
5 contributing to optimal outcomes for patients.

6 However, recent real-world studies on treatments for patients with acromegaly are scarce.  
7 Updated evaluations of treatment patterns for acromegaly are needed to assess whether  
8 recommendations for treating acromegaly are followed, and to consider any recent changes or  
9 updates in available therapies [2,4,12]. This study explored United States (US) administrative  
10 claims from January 2010 to July 2022, to describe comorbidities (prevalence and relationship  
11 with healthcare resource utilization), analyze treatment patterns (including treatment changes,  
12 adherence, and persistence), and assess the impact of treatment and demographic factors on  
13 treatment persistence among patients with acromegaly.

## 14 **METHODS**

### 15 **Study design**

16 This study was a retrospective, observational cohort study using real-world administrative  
17 claims data from a large US commercial claims database, MarketScan<sup>®</sup>. This database is  
18 compliant with the US Health Insurance Portability and Accountability Act of 1996 (HIPAA), with  
19 all patient-level data de-identified. This quarterly updated database includes quality-checked  
20 medical and prescription drug claims for inpatient and outpatient healthcare services for  
21 individuals insured commercially or as part of the national Medicare program for retired people  
22 and people with disabilities [13].

1 Two MarketScan<sup>®</sup> databases were used: *MarketScan<sup>®</sup> Commercial Claims and Encounters*  
2 *Database* (containing prescription drug details of employees and their dependents) and  
3 *MarketScan<sup>®</sup> Medicare Supplemental and Coordination of Benefits (COB) Database* (containing  
4 medical and pharmacy healthcare information of retired individuals). The data were extracted  
5 from the period of January 1st, 2010, to July 31st, 2022.

## 6 **Patients**

7 Patients were eligible for inclusion in the cohort if they had  $\geq 2$  condition claims associated with  
8 diagnosis of acromegaly (identified using International Classification of Diseases (ICD)-10  
9 codes), with  $\geq 30$  days between the first and second claim, and the first claim dated prior to  
10 January 1st, 2022; were  $\geq 18$  years old on the index date (defined as the date of the first  
11 diagnosis of acromegaly); received a medical treatment for acromegaly (lanreotide depot,  
12 octreotide LAR, oral octreotide, pasireotide LAR, cabergoline, or pegvisomant), with a minimum  
13 period of treatment of three months; had claims data  $\geq 3$  months before and  $\geq 6$  months after  
14 either the claim for first treatment or the claim for first diagnosis of acromegaly (the earlier  
15 date); and were continuously enrolled during the study period (defined based on enrollment  
16 start and end date). All patients from the MarketScan<sup>®</sup> dataset who met the study eligibility  
17 requirements were included in the study.

## 18 **Exposure**

19 The line(s) of therapy (LOT) were defined for each patient, using claims information for medical  
20 treatments for acromegaly: prescription dates, days of supply, ingredients, and dose. The start  
21 date of a LOT was defined as the first prescription date of a given treatment, and the end date  
22 was defined as the last prescription date of a given treatment plus the number of days' supply  
23 associated with the last prescription. A treatment was considered a LOT if it lasted for  $\geq 3$

1 months. Change in dosage for the same medical treatment was not considered a change in  
2 LOT. A treatment interruption was defined as a gap in prescriptions of a specified therapy of  $\geq 3$   
3 months.

4 Treatments were categorized as monotherapies or combination therapies. A combination  
5 therapy was defined as two or more treatments overlapping for  $>3$  months. If the overlap was  
6  $\leq 3$  months, it was considered a treatment change. Treatment patterns for medication classes  
7 were evaluated overall and for first, second, and third lines of treatment (LOT 1, LOT 2, and  
8 LOT 3), among patients without treatment gaps who had one, two, and at least three LOTs,  
9 respectively.

## 10 **Study outcomes**

11 Outcomes evaluated for the entire cohort included demographic characteristics on the index  
12 date, comorbidities, healthcare resource utilization, and type of insurance plan. Index  
13 characteristics included age, sex, and geographical distribution. Acromegaly-related  
14 comorbidities included type 2 diabetes mellitus and hyperglycemia, cardiovascular disorders,  
15 sleep apnea, arthritis and musculoskeletal disorders, bone disorders, hypopituitarism and  
16 disorders of hypothalamus, and malignant neoplastic disease, identified using International  
17 Classification of Disease (ICD)-10 codes. These comorbidities were chosen based on published  
18 consensus guidelines to reflect those seen in clinical practice [2,3]. Additionally, obesity was  
19 included in the descriptive analysis of the prevalence of comorbidities in the cohort. Healthcare  
20 resource utilization, including visits unrelated to the acromegaly diagnosis (inpatient admissions,  
21 emergency room visits, non-hospital institution visits, and outpatient services), was calculated  
22 only for the first year after the index date, for patients with  $>6$  months of follow-up after the  
23 index date.

1 Outcomes evaluated by medication class (DAs [cabergoline], first-generation SRLs [lanreotide  
2 depot, octreotide LAR], and GHRAs [pegvisomant] included medication use (number and  
3 percentage of patients who received each medication class as a LOT), treatment adherence,  
4 treatment persistence, and treatment changes. Treatment adherence was measured as  
5 medication possession ratio (MPR) and the proportion of days covered (PDC) for  
6 monotherapies. MPR was defined as the ratio of the total number of days of a medication  
7 supply within a LOT to the total number of days in the LOT. PDC was defined as the ratio of the  
8 number of days covered for a treatment within a LOT to the total number of days in LOT  
9 (**Figure 1**). Treatment persistence (defined as the duration of time between the first treatment  
10 record and a change in LOT or censoring [loss to follow-up or data cut-off on July 31<sup>st</sup>, 2022,  
11 whichever occurred first]) was evaluated for patients receiving monotherapies, using the  
12 Kaplan–Meier estimator. Frequency of medication classes and changes of treatments for  
13 patients receiving monotherapies or combination therapies were represented in a Sankey plot.

14 The following outcomes were evaluated for lanreotide depot and octreotide LAR only: treatment  
15 uptitration and downtitration ( $\geq 30\%$  change in dosage, compared to the previous three-month-  
16 long reference window; once a sliding window exceeded the initial 30% threshold, it became  
17 the new reference window), and use of extended dosing intervals (EDIs), defined as a  
18 prescription of lanreotide depot ( $\leq 120$  mg) or octreotide LAR ( $\leq 40$  mg) within a period of 6–8  
19 weeks. This time range captured dosing intervals that are greater than monthly prescriptions  
20 but shorter than treatment gaps of three months.

21 As the MarketScan<sup>®</sup> database is a claims database, clinical outcome data (including adverse  
22 reactions) and biochemical control data are not available.



## 1 **Statistical analysis**

2 Demographic characteristics were analyzed using descriptive statistics, with continuous  
3 variables presented as the mean/median and standard deviation (SD) and 95% confidence  
4 interval [CI] of the mean and/or median, and categorical or discrete variables presented as  
5 percentages. Statistical significance was based on non-overlapping 95% CIs. There was no  
6 predefined sample size due to the claims database source of data (all patients meeting the  
7 eligibility criteria were included in the study). Univariate Cox regression models were used to  
8 investigate the relationship between potential prognostic factors (age, sex, medical treatments,  
9 and comorbidities) and treatment persistence for LOT 1 monotherapies. Factors that met the  
10 threshold p-value of  $<0.20$  were retained and included in a multivariate Cox model. Medication  
11 class was included in the multivariate model independently of its univariate statistical test result,  
12 as the effect of medication class was the main point of interest in this study.

## 13 **RESULTS**

### 14 **Patient disposition and characteristics**

15 In the MarketScan® database, 5,150 patients were identified with two or more acromegaly-  
16 associated claims at different dates within a period of  $>30$  days. Among them, 3,093 patients  
17 were continuously enrolled for  $\geq 3$  months prior to the index date and  $\geq 6$  months following the  
18 index date. Of those, 882 patients had  $\geq 1$  claim for the prescription or administration of the  
19 medications listed in the eligibility criteria and were  $\geq 18$  years old on their index date. Those  
20 882 patients were included in the study cohort (**Figure 2**).

21 The mean age at index date was 48.6 years, and approximately half (50.1%) of patients were  
22 female. The US South Region was most common geographical origin (39.9%), and most  
23 patients (65.8%) had the preferred provider organization (PPO)/point-of-service (POS)

1 insurance plan (**Table 1**). The median follow-up time in the database after the index date was  
2 approximately 2.7 (95% CI: 2.53–2.83) years.

### 3 **Medication use and changes in LOTs**

4 Over half of patients (59.4%) had only one LOT; 23.1% had two LOTs, and 17.5% had at least  
5 three LOTs (**Figure 3**). Most patients (94.6%) initiated treatment with monotherapies.  
6 Combination therapy, while only initiated in LOT 1 by 5.4% of the cohort, was received at some  
7 point during treatment by 16.0% of the entire cohort. The most common monotherapies in LOT  
8 1 were DAs (cabergoline, 36.8%) and first-generation SRLs (lanreotide depot [22.5%] and  
9 octreotide LAR [29.5%]; **Table 2**). Only 18 patients received pasireotide LAR (second-  
10 generation SRL) and 5 patients received oral octreotide (first-generation SRL) in total; due to  
11 the small sample size, those two treatments were excluded from the adherence (**Table 3**) and  
12 persistence (**Figure 4**) analyses and the multivariate Cox regression model (**Table 4**).

### 13 **Treatment adherence and persistence**

14 Adherence as measured by mean MPR was similar for all medication classes in each LOT,  
15 ranging from 0.84 for DAs (cabergoline) to 0.90 (lanreotide depot) in LOT 1 (**Table 3**).  
16 However, mean PDC in LOT 1 was highest for first-generation SRLs (lanreotide depot: 0.77  
17 [95% CI: 0.75–0.79]; octreotide LAR: 0.74 [95% CI: 0.72–0.76) and lowest for DAs  
18 (cabergoline): 0.67 [95% CI: 0.60–0.70]. This trend for SRLs was similar for other LOTs (**Table**  
19 **3**).

20 Persistence for DAs was lowest across all three LOTs when compared to first-generation SRLs  
21 (based on non-overlapping 95% CI intervals). In LOT 1, median persistence (time between the  
22 first treatment record and change in LOT or censoring) was 14.4 (95% CI: 12.2–16.8) months  
23 for DAs, 20.0 (95% CI: 17.0–23.9) months for first-generation SRLs, and 24.8 (95% CI: 16.6–

1 32.5) months for GHRAs (**Figure 4**). The multivariate Cox regression model showed that  
2 patients who were female (hazard ratio [HR]=1.25; 95% CI: 1.06–1.48; p=0.0071) were more  
3 likely to have shorter persistence. Patients who were older on the index date (HR=0.98; 95%  
4 CI: 0.98–0.99; p<0.0001), or who received lanreotide depot (HR=0.70; 95% CI: 0.56–0.88;  
5 p=0.0019), octreotide LAR (HR=0.077, 95% CI: 0.63–0.95; p=0.013), or pegvisomant  
6 (HR=0.69; 95% CI: 0.52–0.92; p=0.011) as a medical treatment (versus cabergoline) were  
7 more likely to have longer persistence. The number of comorbidities was not associated with  
8 persistence (**Table 4**).

### 9 **Use of first-generation SRLs**

10 Of the patients treated with lanreotide depot, the most common dosage in LOT 1 and LOT 2  
11 was 90 mg (64.0%, and 48.3%, respectively), while the most common dosage in LOT 3 was  
12 120 mg (56.7%). Of those receiving octreotide LAR, 20 mg was the most common dosage in  
13 LOTs 1, 2, and 3 (54.5%, 43.1%, and 53.3%, respectively); the 30 mg dosage was received by  
14 28.7%, 15.5%, and 6.7%, respectively (**Table 5**).

15 Among patients on lanreotide depot monotherapies, 48.6% had a dose up titration and 35.1%  
16 had a dose down titration. Among patients on octreotide LAR monotherapies, 35.8% had a dose  
17 up titration and 22.3% had a dose down titration. Among patients who received lanreotide  
18 depot, few (n=5; 1.7%) were administered a dosage higher than the maximum approved  
19 dosage in the US label (>120 mg) [14]; however, among patients who received octreotide LAR,  
20 a greater proportion (n=77; 22.1%) received a dosage higher than the maximum approved  
21 dosage in the US label (>40 mg) [15].

22 EDIs were seldom used. Among all patients receiving monotherapies, EDIs were observed  
23 among 9.7% (n=22) of those administered lanreotide depot and among only 3.3% (n=9) of

1 those administered octreotide LAR. The median length between two injections in an EDI was  
2 6.0 weeks.

### 3 **Incidence of comorbidities**

4 Half (50.0%) of all male patients and 40.3% of all female patients in the cohort presented with  
5 acromegaly-associated comorbidities, or obesity. Hyperlipidemia (61.3%), essential  
6 hypertension (56.2%), and sleep apnea (32.9%) were the most prevalently identified  
7 comorbidities (**Table 6**).

### 8 **Healthcare resource utilization**

9 Almost all patients in the cohort (99.8%) had a record of an outpatient service; the mean  
10 number of outpatient services among patients with  $\geq 1$  service was 21.1 (SD: 13.8) during the  
11 year after the index date. Over one-third of the cohort (34.6%) had a record of an inpatient  
12 admission; 28.3% had a record of an emergency room visit during the year after the index date  
13 (**Table 7**). The mean number of healthcare visits during the year after the index date increased  
14 significantly with the number of comorbidities, ranging from 16.1 (95% CI: 15.07–17.28)  
15 outpatient services and 2.0 (95% CI: 1.75–2.36) inpatient admissions/emergency room visits  
16 for patients with no comorbidities to 29.1 (95% CI: 27.10–31.22) outpatient services and 3.1  
17 (95% CI: 2.55–3.68) inpatient admissions/emergency room visits for patients with two or more  
18 comorbidities (**Table 8**).

## 19 **DISCUSSION**

20 Low medication adherence is a significant concern for patients being treated for chronic  
21 diseases, and it may lead to increased morbidity and mortality [16]. Furthermore, poor  
22 medication adherence has been linked to increased healthcare resource utilization [16].  
23 Treatment persistence may also increase if treatment schedule is acceptable to patients [17].

1 These are important considerations for patients with acromegaly, as the disorder and its  
2 comorbidities may require lifelong monitoring and medical therapy across multiple specialties  
3 [18]. RWE sheds light on diverse aspects of disease management, including treatment patterns,  
4 medication adherence and persistence, and healthcare resource utilization [19,20]. Updated  
5 evaluations of treatment patterns for acromegaly are needed to assess whether treatment  
6 recommendations and guidelines are followed, and to consider recent changes or updates in  
7 available therapies [2,4,12]; such information increases understanding of the impact of  
8 medication on patients' disease outcomes and quality of life.

9 In this real-world analysis of US administrative claims data, in a cohort of 882 patients with  
10 acromegaly, most patients initiated with a monotherapy treatment; less than 30% of patients  
11 switched to a second-line treatment, and fewer than 20% of patients initiated a third-line  
12 treatment. Interestingly, among potentially eligible patients who had at least two condition  
13 claims associated with diagnosis of acromegaly (>30 days apart) and were continuously  
14 enrolled from January 1st, 2010, to July 31st, 2022, with claims data  $\geq 3$  months before and  $\geq 6$   
15 months after the index date (n=3,093), only 28.5% (n=882) received a prescription for a  
16 medical treatment and were eligible for inclusion in the present analysis. In clinical practice, a  
17 considerable proportion of patients with acromegaly may be contraindicated for surgical  
18 treatment or experience residual disease [21]; the relatively low proportion of patients eligible  
19 for our analysis could be due to the stringent study eligibility criteria, as some patients may  
20 have received a medical treatment but did not have claims data  $\geq 3$  months before and  $\geq 6$   
21 months after their index date, or were not continuously enrolled during the study period. Some  
22 patients may have been excluded due to intermittent health insurance coverage that may have  
23 prevented continuous enrollment during the study period, possibly limiting the inclusion of  
24 patients with acromegaly across all socioeconomic groups. Nevertheless, we consider that the

1 study results may be extrapolated to other populations of patients with acromegaly. In addition,  
2 stringent eligibility criteria in our study allowed reliable identification of a large cohort of  
3 patients with acromegaly who received specific medical treatments, increasing the quality of the  
4 data analysis.

5 Adherence and persistence varied across medication classes, observed to be highest with  
6 first-generation SRLs and GHRAs and lowest with DA monotherapies. Median persistence for  
7 LOT 1 treatments was 14.4 months (1.2 years; DAs), 20.0 months (1.7 years; first-generation  
8 SRLs), and 24.8 months (2.1 years; GHRAs), which was relatively high, given the median  
9 follow-up time of 2.7 years. This evidence of high treatment adherence and persistence  
10 suggests that most patients in this study received an appropriate first-line medical treatment.  
11 However, as biochemical control data were not available, it is possible that some patients may  
12 have had uncontrolled acromegaly despite following their prescribed first-line treatment  
13 regimen. We postulate that an appropriate first-line medical treatment could be effective for  
14 most patients. Less than half of patients receiving first-generation SRLs had a dose uptitration  
15 or downtitration, and few patients received higher-than-approved dosages or EDIs. These  
16 findings highlight the importance of the choice of first-line treatment, and suggest that patient  
17 outcomes could be further optimized through appropriate uptitration to higher SRL doses, as  
18 recommended [1,4,22]. The majority of the cohort had acromegaly-related comorbidities, with  
19 greater prevalence of comorbidities corresponding with greater healthcare resource utilization.  
20 EDIs could be explored more frequently for those patients as a means to relieve the burden of  
21 treatment and healthcare utilization [23,24].

22 Selection of first-line acromegaly therapies with the greatest adherence and persistence records  
23 may potentially reduce patient burden directly or indirectly associated with the disease.

1 Evaluating adherence is a key factor of treatment success, including long-term outcomes, as  
2 well as patient quality of life and treatment satisfaction [25-27]. This study employed two  
3 methods of assessing treatment adherence: MPR and PDC. MPR is the most commonly used  
4 measurement for claims-based adherence [28]. However, the definition of MPR varies among  
5 studies, and this measure may overestimate adherence rates [28]. PDC is a newer approach  
6 that estimates adherence more conservatively in scenarios involving switches of medications  
7 and concomitant therapies within a medication class [28]. Mean adherence as measured by PDC  
8 was relatively low for all medication classes across all LOTs. DA monotherapies had the lowest  
9 adherence in LOT 1, compared to first-generation SRL and GHRA monotherapies, and this  
10 difference may be clinically meaningful, as adherence is an important factor of treatment  
11 success [25,29]. This finding is consistent with a previous retrospective observational study that  
12 evaluated adherence as the proportion of patients with PDC  $\geq 80\%$ , showing that the adherence  
13 rate for cabergoline (18.2%) was lower than that of lanreotide (22.6%) and octreotide (32.8%)  
14 [30]. A report on treatment adherence and persistence among patients with acromegaly  
15 receiving lanreotide depot and octreotide LAR from 2007 to 2012, also using the MarketScan<sup>®</sup>  
16 database, demonstrated comparably good adherence for both medications but greater  
17 persistence for lanreotide depot [29]. Another study reported relatively high and comparable  
18 treatment adherence (using MPR) for lanreotide and octreotide (87% and 89%, respectively)  
19 [29]. Consistent with those results, the present study shows that first-generation SRLs have  
20 relatively high adherence records as treatments for acromegaly.

21 Persistence is another important aspect of treatment success [29]. In the present study, highest  
22 persistence was seen for GHRAs and SRLs; DAs had the lowest persistence in LOT 1. Of note,  
23 the median follow-up time in the cohort (2.7 years) may have affected the observed persistence  
24 among all medication classes, as not all treatment records may have been captured and as a

1 result, actual persistence may have been longer. Over half (59.4%) of the cohort did not switch  
2 treatments, which suggests either successful medical treatment or a degree of inertia regarding  
3 escalation of treatments for acromegaly. While we did not investigate the relationship between  
4 treatment patterns and disease control due to unavailability of biochemical control data, clinical  
5 inertia is a major barrier to favorable outcomes for patients with chronic diseases; further  
6 treatment changes should be implemented for patients with abnormal IGF-1 levels [31,32].

7 Surprisingly, cabergoline was the most common first-line medical treatment (initiated by 34.5%  
8 of patients), possibly owing to its low cost, as well as oral route of administration, even though  
9 this medication class had the lowest treatment adherence and persistence. Furthermore,  
10 consensus guidelines recommend cabergoline only for few select patients with mild acromegaly  
11 or IGF-1 <2.5 times the upper limit of normal [4]. We observed that despite relatively high  
12 adherence and persistence records, neither lanreotide depot nor octreotide LAR was the most  
13 commonly prescribed treatment for acromegaly, although SRLs were the most commonly  
14 prescribed medication class. As medication adherence and persistence are key factors behind  
15 optimal patient outcomes, considering those characteristics of a medication class may be  
16 important when initiating a personalized treatment for acromegaly.

17 Our results expand on understanding of the factors affecting treatment persistence for  
18 acromegaly. We found that patients' sex, age, and medical treatment were associated with  
19 persistence for LOT 1 monotherapies. Patients who were female, younger when diagnosed, or  
20 receiving cabergoline were more likely to have a shorter time to treatment change. The effect  
21 of sex on treatment persistence could be due to the trend of women more frequently utilizing  
22 healthcare resources than men, increasing their likelihood to be regularly evaluated and their



1 treatment kept up-to-date [33]. Younger patients with acromegaly present with more  
2 aggressive acromegaly features [1,11], and are more likely to be re-evaluated.

3 Few patients in this study (5.4%) initiated treatment with combination therapies; the proportion  
4 increased in subsequent LOTs, in line with consensus guidelines recommending this approach  
5 for patients with either impaired glucose tolerance or tumor mass concern, as well as with  
6 evidence that combination therapy may improve outcomes for patients who respond poorly to  
7 SRLs [4,34]. However, the number of combination therapy LOTs as first and second lines of  
8 treatment was lower than expected [35], even though combination therapies may be efficient  
9 and cost-effective for patients with uncontrolled acromegaly [36,37].

10 Most patients receiving monotherapy treatment with first-generation SRLs received low or  
11 medium doses [14,15]. However, many of these patients had dosage adjustments over the  
12 treatment course; over one-fourth of patients received a downtitration. Indeed, dosage  
13 adjustment to 120 mg for lanreotide depot and to 40 mg for octreotide LAR may optimize  
14 disease control [14,15,22]. Use of high doses of SRLs was not frequently observed in the  
15 cohort, despite guidelines recommending higher doses and/or more frequent dosing of SRLs for  
16 patients who are inadequately controlled on standard doses but respond to SRL therapy [4,38].  
17 High doses were utilized more frequently for patients receiving octreotide LAR versus lanreotide  
18 depot, although the range of approved doses for octreotide LAR (10 mg, 20 mg, 30 mg, and 40  
19 mg) is greater than for lanreotide depot (60 mg, 90 mg, and 120 mg) [14,15]. Use of high  
20 doses of SRLs, per guideline recommendations [4,38], could be explored more regularly prior to  
21 changing LOTs. Notably, few patients had an EDI, even though EDIs are included as an option  
22 in the label for lanreotide depot [14]. EDIs can achieve clinical outcomes similar to standard  
23 treatment regimens, as well as high patient satisfaction, while presenting a lower expense

1 [17,24], EDI regimens using high doses of lanreotide depot ( $\geq 120$  mg) or octreotide LAR ( $\geq 40$   
2 mg) may optimize treatment persistence, provided a well-established tolerability profile [4,23].  
3 Physicians may consider more frequent EDI use for some patients, particularly if low normal  
4 IGF-1 levels are encountered. This approach may ameliorate both the clinical and economic  
5 burden on those patients, improve patients' quality of life, and reduce healthcare resource  
6 utilization by lowering the number and frequency of injections [23].

7 As a chronic and systemic disease, acromegaly is often complicated by comorbidities, such as  
8 cardiovascular and respiratory disorders, which are in turn linked to an increased number of  
9 concomitant medications that are prescribed to patients [3,39,40]. Common  
10 acromegaly-associated comorbidities were cardiovascular disorders (68.6%), hypopituitarism  
11 (17.6%), and malignant neoplastic disease (16.7%). Previous studies utilizing administrative  
12 claims data have demonstrated that patients with acromegaly experience significantly more  
13 comorbidities and are prescribed significantly more concomitant medications than patients  
14 without the disease [3], and that acromegaly is linked with multiple comorbidities associated  
15 with inpatient hospital admissions [30]. In addition, a Markov cohort decision analytics model  
16 showed that compared with the general population, controlled and uncontrolled acromegaly  
17 were associated with a 1.1- and 1.6-fold increase, respectively, in comorbidities across patients'  
18 remaining lifespan [41]. Multimorbidity, or having at least two long-term health conditions, is  
19 associated with treatment burden for patients, including clinical impact and medication side  
20 effects [42,43]. Managing acromegaly together with associated comorbidities may present  
21 additional challenges for treatment adherence and persistence, possibly compromising patients'  
22 outcomes and increasing use of healthcare resources due to the need for additional care and  
23 treatments associated with each comorbidity and increased mortality risk. Indeed, we observed  
24 substantial healthcare resource utilization, as approximately one-third of the cohort had an

1 inpatient admission, and almost one-third visited an emergency room. The proportion of  
2 inpatient admissions we observed for patients with acromegaly (34.6%) is considerably higher  
3 compared with the rate observed in the general population (5.2% in 2018) [44]. This finding is  
4 consistent with a previous study showing increased use of healthcare resources among patients  
5 with versus without acromegaly [20]. Not surprisingly, in this study, patients with more  
6 comorbidities had more outpatient services during the first year after diagnosis, which may  
7 reflect consultations with different specialists regarding management of comorbidities. In  
8 addition, patients with two or more comorbidities had more inpatient admissions and  
9 emergency room visits, compared with patients with zero or one comorbidity. A previous study  
10 has shown that patients with cardiovascular comorbidities had increased odds of being  
11 hospitalized [45]. However, to our best knowledge, this study is the first to more broadly  
12 demonstrate that having more acromegaly-related comorbidities is positively associated with  
13 healthcare resource utilization, including outpatient visits, inpatient admissions, and emergency  
14 room visits. This novel finding corroborates disease burden and highlights the importance of  
15 managing comorbidities to reduce adverse outcomes [38].

16 Strengths of this study include use of a large database that contains up-to-date person-level  
17 data of over 273 million patients [46]; prolonged duration (11.5 years); and exhaustive  
18 investigation of treatment patterns, as well as comorbidities, treatment adherence and  
19 persistence, and healthcare resource utilization, to capture a more comprehensive picture of the  
20 patient treatment journey. Limitations of this study include lack of biochemical data in the  
21 database; analysis of US-specific data, which limits the generalizability of findings to other  
22 geographic regions and populations; the possibility of coding errors or missing data in the  
23 database, possibly underestimating the number of patients who had EDIs; and the possibility of  
24 the study cohort not fully representing all patients with acromegaly due to stringent eligibility

1 criteria. Future RWE studies may obtain real-world experience data from registries, which can  
2 provide valuable insights on key biomarkers and clinical outcomes.

3 In conclusion, we provide insights into current medical practices within a heterogeneous  
4 population of patients over an extended period. We found that adherence and persistence vary  
5 among different medical therapies, and that age, sex, and treatment regimen may impact  
6 treatment persistence. As patients with acromegaly have a higher risk of cardiovascular and  
7 other complications, treatment burden and associated healthcare resource utilization is high,  
8 presenting an additional challenge to adherence and persistence. EDIs could be explored and  
9 offered to reduce the burden of treatment administration, especially in patients for whom  
10 dosage decrease is considered. Physicians should consider real-world data on treatment  
11 patterns to optimize long-term outcomes for patients and individualized treatment for  
12 acromegaly [1,22,47].

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### 17 **DATA AVAILABILITY STATEMENT**

18 Restrictions apply to the availability of some or all data generated or analyzed during this study  
19 to preserve patient confidentiality or because they were used under license. The corresponding  
20 author will on request detail the restrictions and any conditions under which access to some  
21 data may be provided.

### 22 **AUTHORS' CONTRIBUTIONS**

1 Substantial contributions to study conception and design: **MF, AB, TB, ED, MdPS, AH, AROJr,**  
2 **SM**; substantial contributions to analysis and interpretation of the data: **MF, AB, TB, ED,**  
3 **MdPS, AH, AROJr, SM**; drafting the article or revising it critically for important intellectual  
4 content: **MF, AB, TB, ED, MdPS, AH, AROJr, SM**; final approval of the version of the article  
5 to be published: **MF, AB, TB, ED, MdPS, AH, AROJr, SM.**

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20

## 21 **Figure and Tables**

## 22 **Figure Legends**

### 23 **Figure 1. Methodology of evaluating treatment adherence using MPR and PDC**

24 MPR and PDC are two methods of evaluating treatment adherence. MPR considers the total  
25 number of days of a medication supply (pink) within a LOT duration (blue), while PDC considers  
26 the number of days covered for a treatment (gray) within a LOT duration (blue).

1 **Abbreviations:** LOT, line of treatment; MPR, medication possession ratio; PDC, proportion of  
2 days covered.

3

#### 4 **Figure 2. Study design**

5 This study was a retrospective, observational cohort study using real-world administrative  
6 claims data from the MarketScan® database. In the database, 5,150 patients were identified  
7 with two or more acromegaly-associated claims, and 3,093 patients were continuously enrolled.  
8 The study cohort included 882 patients who had at least one claim for the prescription or  
9 administration of DAs (cabergoline), first-generation SRLs (lanreotide depot, octreotide LAR,  
10 oral octreotide), second-generation SRLs (pasireotide), and GHRAs (pegvisomant), and were  
11 also at least 18 years old on their index date (date of diagnosis). Among them, 827 patients had  
12 received DAs (cabergoline), first-generation SRLs (lanreotide depot, octreotide LAR, oral  
13 octreotide), and GHRAs (pegvisomant) as monotherapies in LOT 1 and were included in the  
14 adherence, persistence, and Cox analyses; as few patients had received pasireotide and oral  
15 octreotide, they were excluded from those analyses.

16 **Abbreviations:** DA, dopamine agonist; GHRA, growth hormone receptor antagonist; LAR,  
17 long-acting release; LOT, line of treatment; SRL, somatostatin receptor ligand.

18

#### 19 **Figure 3. Changes in LOT for monotherapies and combination therapies**

20 This analysis included DAs (cabergoline [green]), first-generation SRLs (lanreotide depot [teal],  
21 octreotide LAR [pink]), and GHRAs (pegvisomant [light blue]). As few patients had received  
22 pasireotide and oral octreotide, they were excluded from this analysis. Over half of patients  
23 (59.4%) had LOT 1; 23.1% had LOT 2, and 17.5% had LOT 3. The most common  
24 monotherapies in LOT 1 were DAs (cabergoline [36.8%]) and first-generation SRLs (lanreotide

1 depot [22.5%] and octreotide LAR [29.5%]). Most patients (94.6%) initiated treatment with  
2 monotherapies.

3 **Abbreviations:** DA, dopamine agonist; GHRA, growth hormone receptor antagonist; LAR,  
4 long-acting release; LOT, line of treatment; SRL, somatostatin receptor ligand.

5  
6 **Figure 4. Kaplan–Meier estimate of treatment persistence for monotherapies in LOT**  
7 **1**

8 This analysis included DAs (cabergoline [blue]), first-generation SRLs (lanreotide depot,  
9 octreotide LAR [green]), and GHRAs (pegvisomant [pink]); LOT 1 results are presented here. As  
10 few patients had received pasireotide and oral octreotide, they were excluded from this  
11 analysis. LOT 1 persistence for DAs (14.4 [95% CI: 12.2–16.8] months) was lowest when  
12 compared to first-generation SRLs (20.0 [95% CI: 17.0–23.9] months), based on non-  
13 overlapping 95% CI intervals. LOT 1 persistence for GHRAs was 24.8 (95% CI: 16.6–32.5)  
14 months.

15 **Abbreviations:** CI, confidence interval; GH, growth hormone; LAR, long-acting release; SRL,  
16 somatostatin receptor ligand.

17  
18 **Table 1. Demographic Characteristics**

	n of patients (% of cohort, n=882)
<b>Sex</b> (female)	442 (50.1%)
<b>Age at index date</b>	
<40 years	236 (26.8%)
40–60 years	481 (54.5%)
>60 years	165 (18.7%)

<b>Geographic origin</b>	
Northeast	181 (20.8%)
North Central	185 (21.3%)
South	347 (39.9%)
West	156 (17.5%)
<b>Insurance plan</b>	
HMO/EPO	102 (11.6%)
PPO/POS	580 (65.8%)
CDHP/HDHP	123 (14.0%)
Comprehensive	52 (5.9%)
Other/unknown	25 (2.8%)

- 1 **Abbreviations:** CDHP, consumer-directed health plan; EPO, exclusive provider organization;  
 2 HDHP, high-deductible health plan; HMO, health maintenance organization; POS, point-of-  
 3 service; PPO, preferred provider organization.

4 **Table 2. Proportion (%) of patients receiving monotherapies in each LOT**

	DAs (cabergoline)	First-generation SRLs		GHRAs (pegvisomant)
		Lanreotide depot	Octreotide LAR	
LOT 1 (n=827)	36.8%	22.5%	29.5%	11.2%
LOT 2 (n=262)	39.3%	22.9%	22.1%	15.6%
LOT 3 (n=120)	32.5%	25.0%	25.0%	17.5%

- 5 **Abbreviations:** DAs, dopamine agonists; GHRAs, growth hormone receptor antagonists; LAR,  
 6 long-acting release; LOT, line of treatment; SRLs, somatostatin receptor ligands.

7

1 **Table 3. Treatment adherence among patients with acromegaly**

Treatment adherence measure		DAs (cabergoline)	First-generation SRLs		GHRAs (pegvisomant)
			Lanreotide depot	Octreotide LAR	
MPR (mean, 95% CI of mean)	LOT 1	0.84 (0.82–0.86)	0.90 (0.88–0.91)	0.87 (0.85–0.89)	0.87 (0.85–0.90)
	LOT 2	0.82 (0.73–0.86)	0.85 (0.81–0.89)	0.83 (0.78–0.87)	0.85 (0.80–0.90)
	LOT 3	0.80 (0.73–0.86)	0.87 (0.83–0.91)	0.84 (0.77–0.90)	0.82 (0.73–0.90)
PDC (mean, 95% CI of mean)	LOT 1	0.67 (0.60–0.70)	0.77 (0.75–0.79)	0.74 (0.72–0.76)	0.75 (0.71–0.78)
	LOT 2	0.63 (0.60–0.67)	0.69 (0.64–0.73)	0.66 (0.61–0.71)	0.66 (0.58–0.72)
	LOT 3	0.60 (0.52–0.66)	0.76 (0.70–0.81)	0.65 (0.57–0.72)	0.53 (0.38–0.66)

2 **Abbreviations:** CI, confidence interval; DAs, dopamine agonists; GHRAs, growth hormone  
3 receptor antagonists; LAR, long-acting release; LOT, line of treatment; MPR, medication  
4 possession ratio; PDC, proportion of days covered; SRLs, somatostatin receptor ligands.

5 \*pasireotide LAR and oral octreotide were excluded from this analysis as few patients received  
6 them.

1 **Table 4. Multivariate Cox analysis: factors associated with treatment persistence**

<b>Variable</b>	<b>n</b>	<b>HR**</b>	<b>HR 95% CI</b>	<b>Chi-2</b>	<b>p-value</b>
<b>N = 827*</b>					
<b>Age at index date***</b>	827	0.98	0.98–0.99	29.19	<b>&lt;0.0001</b>
<b>Sex</b>					<b>0.007</b>
Male	405	Ref	N/A	N/A	N/A
Female	422	1.25	1.06–1.48	7.24	0.0071
<b>Medical treatment</b>					<b>0.003</b>
Cabergoline	305	Ref	N/A	N/A	N/A
Lanreotide depot	189	0.70	0.56–0.88	9.65	0.0019
Octreotide LAR	250	0.77	0.63–0.95	6.16	0.013
Pegvisomant	102	0.6	0.52–0.92	6.50	0.011
<b>Number of comorbidities</b>					<b>0.206</b>

2 \*Patients who received monotherapies. Pasireotide LAR and oral octreotide were excluded from  
3 this analysis as only few patients received those treatments.

4 \*\*HR>1 indicated likelihood of shorter persistence; HR<1 indicated likelihood of longer  
5 persistence.

6 \*\*\*Higher age was associated with longer persistence.

7 **Abbreviations:** CI, confidence interval; DAs, dopamine agonists; GHRAs, growth hormone  
8 receptor antagonists; HR, hazard ratio; LAR, long-acting release; N/A, not applicable; Ref,  
9 reference; SRLs, somatostatin receptor ligands.

1 **Table 5. Treatment dosage among patients receiving lanreotide depot and**  
 2 **octreotide LAR monotherapies**

Medical treatment (number of patients)	LOT	Dosage*	n of patients (% of patients receiving medical treatment in the LOT)**
Lanreotide depot (n=276)	LOT 1 (n=186)	60 mg	55 (29.6%)
		90 mg	119 (64.0%)
		120 mg	88 (43.3%)
	LOT 2 (n=60)	60 mg	15 (25.0%)
		90 mg	29 (48.3%)
		120 mg	26 (43.3%)
	LOT 3 (n=30)	60 mg	5 (16.7%)
		90 mg	12 (40.0%)
		120 mg	17 (56.7%)
Octreotide LAR (n=332)	LOT 1 (n=244)	10 mg	43 (17.6%)
		20 mg	133 (54.5%)
		30 mg	70 (28.7%)
	LOT 2 (n=58)	10 mg	10 (17.2%)
		20 mg	25 (43.1%)
		30 mg	9 (15.5%)
	LOT 3 (n=30)	10 mg	3 (10.0%)
		20 mg	16 (53.3%)
		30 mg	2 (6.7%)

1 \*Recommended starting dosage for lanreotide depot is 90 mg every four weeks for three  
 2 months; recommended starting dosage for octreotide LAR is 20 mg every four weeks for three  
 3 months.[14,15]

4 \*\*Some patients were counted more than once within the same LOT due to receiving different  
 5 doses.

6 **Abbreviations:** LAR, long-acting release; LOT, line of treatment; SRLs, somatostatin receptor  
 7 ligands.

8 **Table 6. Comorbidities among patients with acromegaly**

Comorbidities	Patients with $\geq 1$ occurrence of claims record of comorbidities, n (%)
Cardiovascular disorders	605 (68.6%)
Hyperlipidemia	541 (61.3%)
Essential hypertension	496 (56.2%)
Hypercholesterolemia	252 (28.6%)
Cardiac arrhythmia	210 (23.8%)
Heart valve disorder	177 (20.1%)
Cerebrovascular disease	124 (14.1%)
Disorder of coronary artery	98 (11.1%)
Heart failure	72 (8.2%)
Sleep apnea	290 (32.9%)
Malignant neoplastic disease	272 (30.8%)
Hypopituitarism	260 (29.5%)
Diabetes insipidus	76 (8.6%)
Syndrome of inappropriate vasopressin secretion	11 (1.3%)



Diabetes type 2 and hyperglycemia	124 (14.1%)
Arthritis and muscular skeletal disorders	94 (10.7%)
Arthritis	174 (19.7%)
Intervertebral disc prolapse	41 (4.7%)
Carpal tunnel syndrome	77 (8.7%)
Bone disorders	86 (9.8%)
Fracture of vertebral column	14 (1.6%)
Osteoporosis	97 (11.0%)

1

2 **Table 7. Healthcare resource utilization in the cohort (n=882) during the year**

3 **following the index date**

Inpatient admissions	Resource utilization
Patients with any admission, n (%)	305 (34.6%)
Number of admissions (among patients with ≥1 admission) mean (SD) (95% CI)	1.8 (1.48) (1.68–2.01)
Emergency room visits	
Patients with any visit, n (%)	250 (28.3%)
Number of visits (among patients with ≥1 visit) mean (SD) (95% CI)	1.66 (1.36) (1.50–1.82)
Outpatient services	
Patients with any service, n (%)	880 (99.8%)

Number of visits (among patients with $\geq 1$ visit) mean (SD) (95% CI)	21.13 (13.84) (20.17–22.03)
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1 **Abbreviations:** CI, confidence interval; SD, standard deviation.

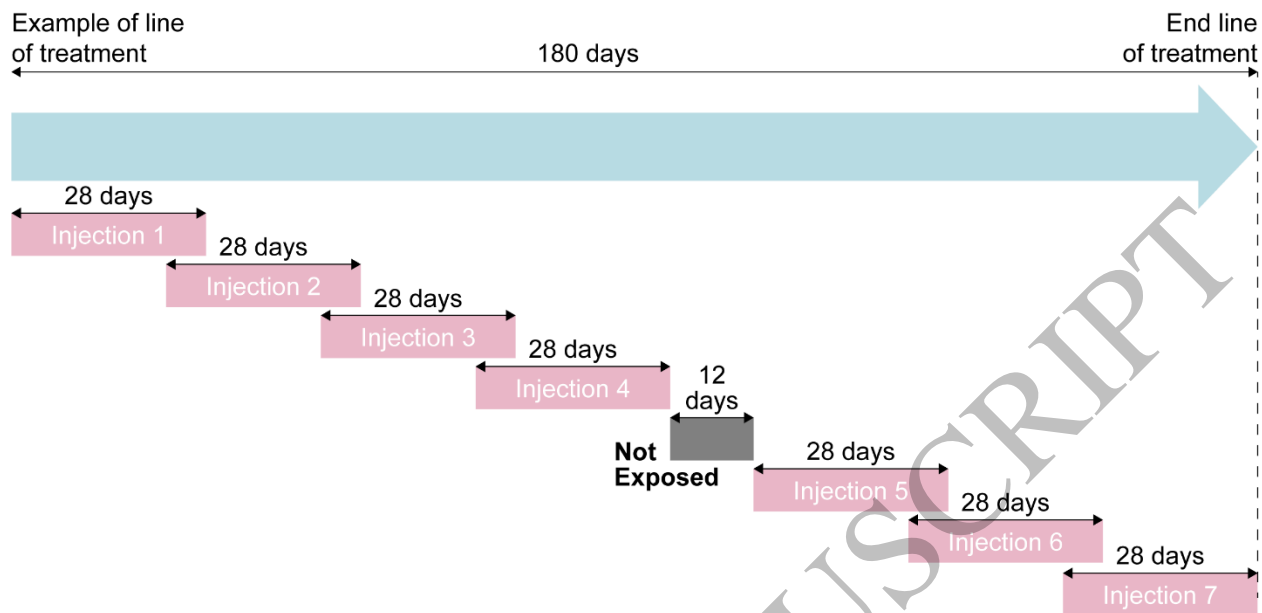
2 \*Five patients (0.6%) had non-hospital institutions visits.

3 **Table 8. Healthcare resource utilization among patients with comorbidities**

Number of comorbidities	Proportion of patients in the cohort (n=882)	Number of visits		95% CI
0	35.7%	Inpatient admissions/ emergency room visits	2.0	(1.75–2.36)
		Outpatient visits	16.1	(15.07–17.28)
1	41.2%	Inpatient admissions/ emergency room visits	2.1	(1.91–2.32)
		Outpatient visits	21.0	(19.68–22.53)
$\geq 2$	23.1%	Inpatient admissions/ emergency room visits	3.1	(2.55–3.68)
		Outpatient visits	29.1	(27.10–31.22)

4 **Abbreviations:** CI, confidence interval.

5



**MPR (Medication Possession Ratio):**

Sum of the **days' supply** for all fills of a treatment in a particular time period, divided by the number of days in the time period (e.g., 180 days)

MPR

Area

Area

$$= (7 \times 28 / 180) > 1 \rightarrow = 1$$

**PDC (Proportion of Days Covered):**

Sum of the **days' covered** for a treatment in a particular time period, divided by the number of days in the time period (e.g., 180 days)

PDC

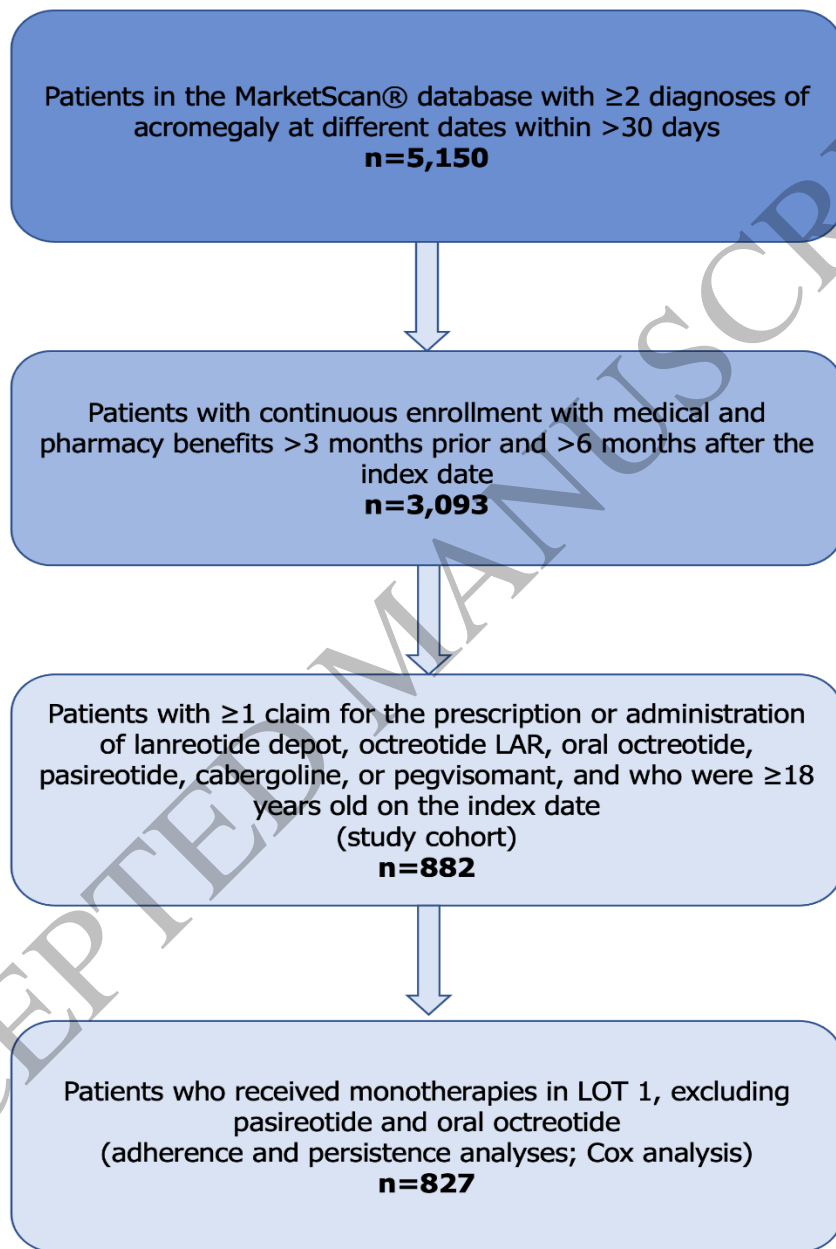
Area

Area

$$1 - \frac{12}{180} = 1 - 0.0667 = 0.9333 \approx 0.93$$

Figure 1  
209x174 mm ( x DPI)

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2  
3  
4



1  
2  
3  
4

Figure 2  
163x289 mm (x DPI)

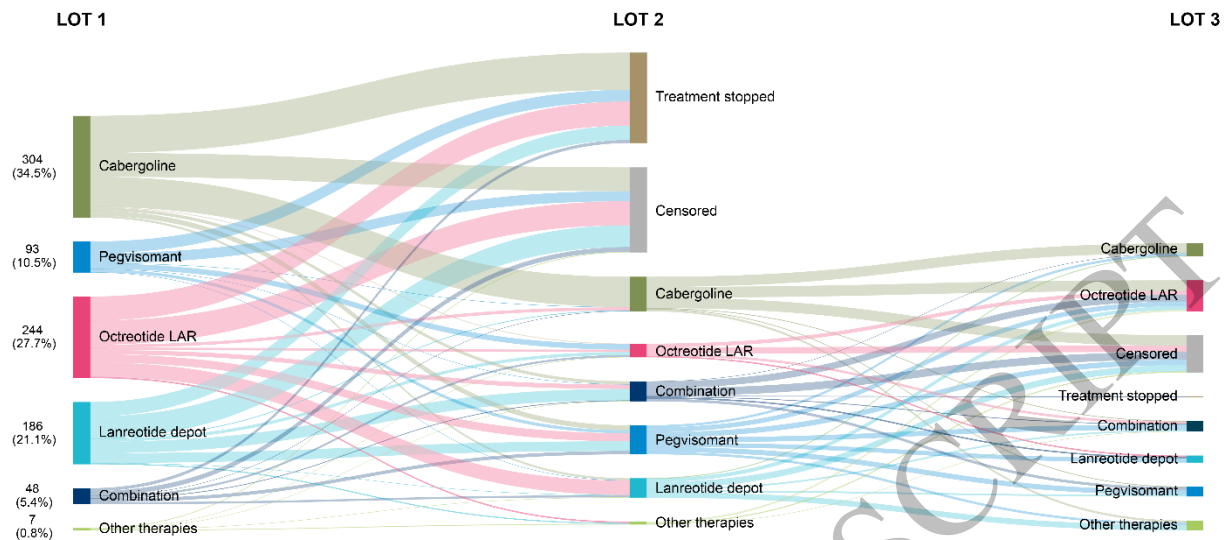


Figure 3  
492x208 mm (x DPI)

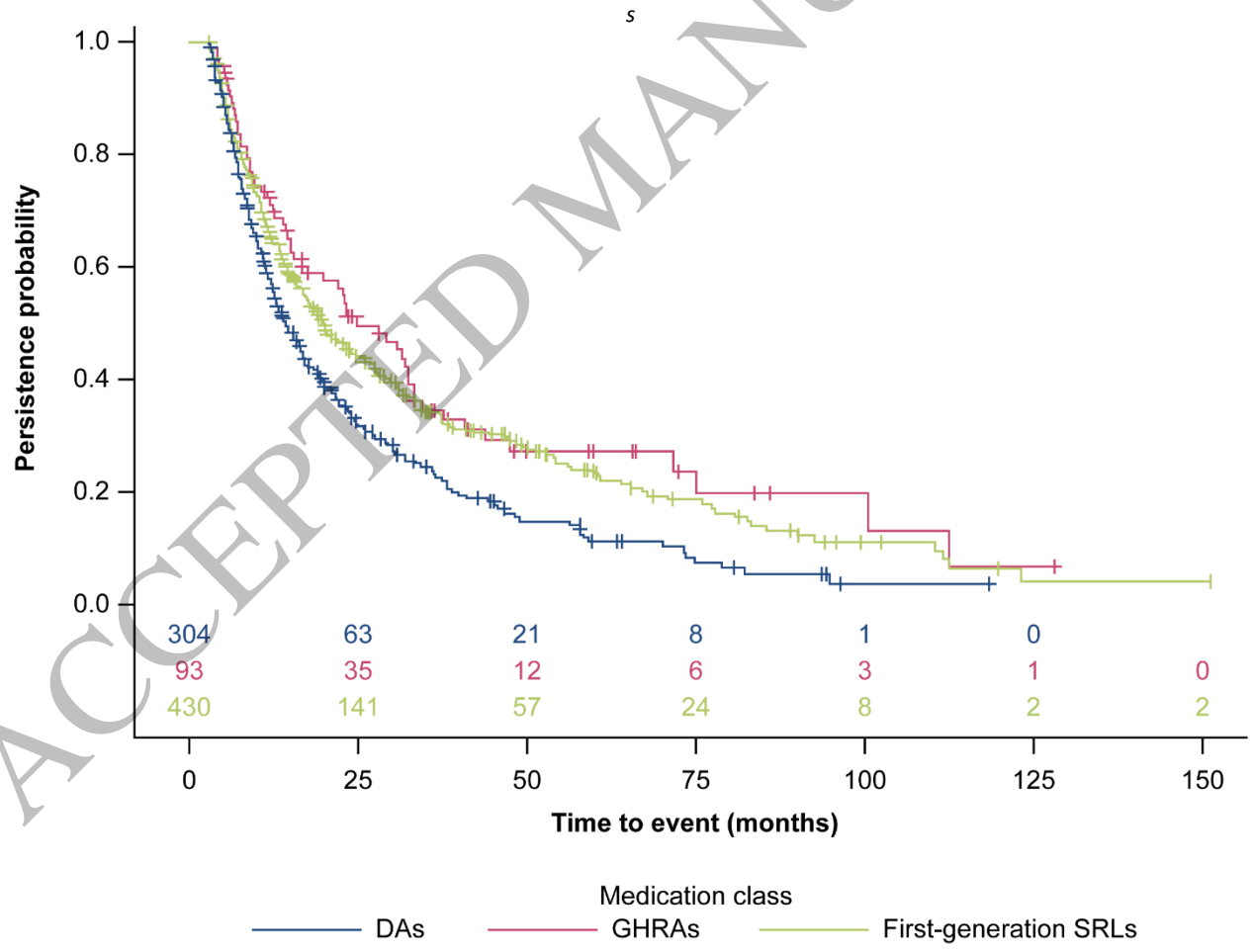


Figure 4  
200x149 mm (x DPI)

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