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ORIGINAL RESEARCH ARTICLE

Assessment of Codispensing Patterns of Mirabegron and Prespecified CYP2D6 Substrates in Patients with Overactive Bladder

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Abstract

Background Patients with overactive bladder (OAB) experience sudden, intense urges to urinate, which may include urge urinary incontinence and nocturia. Pharmacotherapy includes β_3-adrenergic receptor agonists such as mirabegron; however, mirabegron contains a label warning for cytochrome P450 (CYP) 2D6 inhibition, making coadministration with CYP2D6 substrates require monitoring and dose adjustment to avoid unintended increases in substrate concentration.

Objective To understand the codispensing patterns of mirabegron among patients using ten predefined CYP2D6 substrates with and before mirabegron dispensing.

Methods This retrospective claims database analysis used the IQVIA PharMetrics® Plus Database to assess codispensing of mirabegron with ten predefined CYP2D6 substrate groups identified on the basis of medications most frequently prescribed in the United States, those with high susceptibility to CYP2D6 inhibition, and those with evidence for exposure-related toxicity. Patients had to be ≥ 18 years old before initiation of the CYP2D6 substrate episode that overlapped with mirabegron. The cohort entry period was November 2012 to September 2019, and the overall study period was 1 January 2011 to 30 September 2019. Comparisons of patient profiles at dispensing were made between time periods with and before mirabegron use in the same patient. Descriptive statistics were used to assess the number of exposure episodes, total duration of exposure, and median duration of exposure of CYP2D6 substrate dispensing with and before mirabegron.

Results CYP2D6 substrate exposure periods totaling ≥ 9000 person-months were available before overlapping exposure to mirabegron for all ten CYP2D6 substrate cohorts. Median codispensing duration for chronically administered CYP2D6 substrates was 62 (interquartile range [IQR] 91) days for citalopram/escitalopram, 71 (105) days for duloxetine/venlafaxine, and 75 (115) days for metoprolol/carvedilol; median codispensing duration for acutely administered CYP2D6 substrates was 15 (33) days for tramadol and 9 (18) days for hydrocodone.

Conclusions In this claims database analysis, the dispensing patterns of CYP2D6 substrates with mirabegron displayed frequent overlapping of exposure. Thus, a need exists to better understand the outcomes experienced by patients with OAB who are at increased risk for drug−drug interactions when taking multiple CYP2D6 substrates concurrently with a CYP2D6 inhibitor.

1 Introduction

Overactive bladder (OAB) is a chronic disorder characterized by bothersome urinary symptoms in which patients experience sudden and intense urges to urinate, which may be associated with urge urinary incontinence or nocturia [1]. OAB prevalence in the United States is 16.5% for adults ≥ 18 years old, and this rate increases with age [2]. Patients with OAB often have comorbidities. Among patients with OAB, prevalence of any cardiovascular comorbidity has been reported as 57.6% versus 44.6% for patients without OAB [3]; prevalence of depression in patients with OAB has been shown to be 10.7% versus 4.7% in patients without OAB [4]. When combined with multiple medications across multiple indications, these comorbidities can lead to increased risk of drug−drug interactions (DDIs). Rates of polypharmacy, defined as use of ≥ 5 concurrent medications, is seen in nearly 40% of patients with OAB [5].

First-line treatment in OAB management involves behavioral therapy through bladder training, pelvic floor muscle training, and fluid management with or without pharmacotherapy. Pharmacologic treatment includes anticholinergics

Extended author information available on the last page of the article

Key Points

Concomitant use of drugs that are cytochrome P450 (CYP2D6) substrates with drugs that inhibit CYP2D6 may result in unintended increases in concentration of the substrate, potentially increasing the risk of drug–drug interactions.

Patients with overactive bladder often have comorbidities, and therefore the rate of polypharmacy and subsequent use of CYP2D6 substrates is high.

Patients receiving mirabegron, a moderate CYP2D6 inhibitor approved for the treatment of overactive bladder, showed substantial overlapping days of codispensing with CYP2D6 substrates, with ≥ 60 days of overlap frequently identified.

and/or β_3-adrenergic receptor agonists [1]. American Urological Association and American Geriatrics Society guidelines recommend reducing anticholinergic use in older adults to minimize anticholinergic burden [1, 6], which is associated with increased risk of cognitive impairment and dementia [7, 8]. β_3-adrenergic receptor agonists are recommended in patients who are using other medications with anticholinergic properties for comorbidities and have been shown to be as efficacious as anticholinergic therapies without adding to anticholinergic burden [9].

Mirabegron, a β_3-adrenergic receptor agonist, is used in the management of OAB in conjunction with or as a replacement for anticholinergic therapy. Mirabegron has a label warning for moderate inhibitory effects on cytochrome P450 (CYP) 2D6 [10]. Moderate CYP2D6 inhibitor coadministration with a CYP2D6 substrate can result in a two- to five-fold increase in area under the curve (AUC) of CYP2D6 substrate plasma concentrations [11]. In two phase 1 DDI studies, mirabegron increased the maximum plasma concentration and AUC of the CYP2D6 substrates studied, metoprolol and desipramine [12]. When exposed to increased plasma concentrations, there is an increased risk of adverse drug reactions with CYP2D6 substrate drugs when coadministered with a CYP2D6 inhibitor, such as mirabegron [12, 13]. It is equally important to consider that CYP2D6 is responsible for at least partial metabolization of approximately 25% of the drugs in clinical use in the United States [14]. A previous claims database analysis showed high rates of codispensing of CYP2D6 substrates with mirabegron [15], suggesting a lack of awareness of this potential interaction.

This study sought to understand the codispensing patterns of mirabegron among patients using CYP2D6 substrates by quantifying the duration of dispensing of ten individual or groups of CYP2D6 substrates with and before mirabegron.

2 Methods

2.1 Study Design and Database

This study is a retrospective database analysis using the IQVIA PharMetrics® Plus Database, a closed database of adjudicated medical and pharmacy longitudinal claims in the United States that includes national and subnational health plans and self-insured employer groups. The PharMetrics® Plus database has collected data from > 250 million enrollees since 2006, with data being representative of the commercially insured United States population in terms of age and gender. The database uses deidentified patient information and is compliant with the Health Insurance Portability and Accountability Act.

These analyses evaluated the amount of time with overlapping exposure to mirabegron and prespecified CYP2D6 substrates based on dispensing patterns, along with the amount of time before overlapping dispensing. The index identification period (i.e., cohort entry period) evaluated patients exposed to mirabegron and CYP2D6 substrates between November 2012 and September 2019. The overall study period was defined as 1 January 2011 to 30 September 2019.

2.2 Eligibility and Medication Exposures

Patients were included in the analysis if they had an overlapping dispensing of mirabegron, indicating the patient likely had OAB, and a CYP2D6 substrate of interest during the index period. Patients had to be ≥ 18 years of age and have 6 months of continuous enrollment in pharmacy and medical insurance before the initiation of the CYP2D6 substrate and of the identified mirabegron codispensing episode. There were no exclusion criteria. Cohorts were generated for each of ten predefined CYP2D6 substrate groups.

Mirabegron and ten predefined CYP2D6 substrate groups (amitriptyline/nortriptyline, aripiprazole, citalopram/escitalopram, donepezil, duloxetine/venlafaxine, hydrocodone, metoprolol/carvedilol, tamsulosin, tolterodine, and tramadol; Supplementary Table 1 in the electronic supplementary material [ESM]) were identified using National Drug Codes from pharmacy dispensing claims. Selection of CYP2D6 substrates was based on medications most frequently prescribed in the United States as defined previously [15, 16],

with high susceptibility to CYP2D6 inhibition, and with evidence for exposure-related toxicity that could result in an identifiable adverse effect. Medications were grouped together if they were in the same therapeutic class and were considered therapeutically interchangeable.

2.3 Codispensing and Exposure Definition

The capture window for overlapping medication use was November 2012 to September 2019. The date for cohort entry was based on the eligible initiation of the CYP2D6 substrate dispensing that overlapped with mirabegron. Overlapping time was initiated on the date of the codispensing of medications through two criteria (Fig. 1): (1) if both mirabegron and the CYP2D6 substrate were dispensed on the same date, the codispensing date was used as the start date, and (2) if mirabegron and the CYP2D6 substrate were dispensed on different dates, the latter dispensing date for either was used as the start date. A stockpiling algorithm was applied to account for early dispensing. To retain medication exposure continuation, subsequent dispensing needed to be within 1.5 times the days' supply of the most current dispensing. The medication discontinuation date was defined as the last dispensing date of the continuous drug exposure episode plus 1.5 times the days' supply of that dispensing episode. Patients were followed from the first eligible CYP2D6 substrate initiation that overlapped with mirabegron until the earliest of the following conditions: discontinuation of the CYP2D6 substrate, disenrollment, or end of data period. The overlapping dispensing time ended at the earlier of mirabegron discontinuation or end of follow-up. Only the first CYP2D6 substrate dispensation date meeting the inclusion criteria was used for analyses.

2.4 Covariates

Patient baseline characteristics were assessed at the time of initiating the CYP2D6 substrate and at the time of codispensing of the CYP2D6 substrate and mirabegron. Chronic comorbidities and comorbidity indices were assessed using all available baseline data after 1 January 2011 and before dispensing. Acute comorbidities, procedure and medication history, and healthcare resource utilization were assessed in the 183 days before dispensing.

2.5 Statistical Analyses

Descriptive statistics of patient characteristics were calculated at the time of initiating the CYP2D6 substrate and at the time of overlapping CYP2D6 substrate and mirabegron dispensation. The number of exposure episodes, total duration of exposure, and median duration of exposure were assessed for the time periods of CYP2D6 substrate dispensed alone before mirabegron and codispensed with mirabegron. Standardized mean differences (SMDs) were used to compare the differences in baseline covariates at the time of CYP2D6 substrate initiation and at the time of mirabegron codispensing initiation. This study did not test any formal hypotheses, conduct any inferential statistics, or conduct any evaluations regarding missing data.

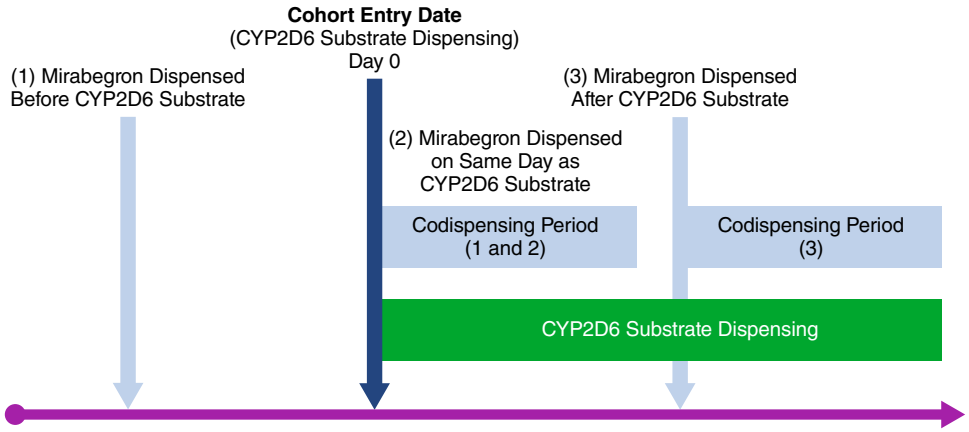

Fig. 1 Capture windows to define cohort entry and codispensing. Cohort entry was defined as the initiation of CYP2D6 substrate dispensing that overlapped with a mirabegron dispensing. (1) If mirabegron was dispensed before the CYP2D6 substrate, the date of CYP2D6 substrate dispensing was the start date. (2) If mirabegron and the CYP2D6 substrate were dispensed on the same day, the codispensing date was the start date. (3) If mirabegron was dispensed after the CYP2D6 substrate, the date of mirabegron dispensing was the start date. *CYP* cytochrome P450

3 Results

3.1 CYP2D6 Substrate Exposure Periods

CYP2D6 substrate exposure periods totaling ≥ 9000 person-months were available before overlapping exposure to mirabegron, and ≥ 9000 person-months of overlapping exposure were available for each of the ten CYP2D6 substrate cohorts. The number of patients in the ten CYP2D6 substrate cohorts ranged from 1467 patients with donepezil to 17,998 patients with hydrocodone (Table 1).

3.2 CYP2D6 Substrate Codispensing Time

Acutely administered CYP2D6 substrates, including tramadol and hydrocodone, had a median of 28 and 32 dispensing days, respectively, before mirabegron dispensing and 15 and 9 dispensing days, respectively, during mirabegron codispensing (Table 2). Chronically administered CYP2D6 substrates, such as donepezil and metoprolol/carvedilol, had a median of 186 and 251 dispensing days before mirabegron dispensing and 80 and 75 dispensing days during mirabegron codispensing. Other CYP2D6 substrates with ≥ 60 overlapping days of exposure with mirabegron were aripiprazole (61 days), citalopram/escitalopram (62 days), and duloxetine/venlafaxine (71 days). Tramadol and mirabegron dispensing overlapped 46.1% of the time, and tolterodine and mirabegron dispensing overlapped 22.6% of the time (Table 1). Among chronically administrated substrates with the greatest number of patients, the percentage of overlapping codispensing time for metoprolol/carvedilol was 29.8%; for duloxetine/venlafaxine the percentage of overlapping time was 31.4%, and for citalopram/escitalopram it was 32.2%. Other CYP2D6 substrates with ≥ 40% overlapping time were donepezil (41.3%) and tramadol (46.1%).

3.3 Baseline Covariate Assessment

Among chronically administered CYP2D6 substrates, there were few differences in patient baseline characteristics between the time of CYP2D6 substrate use with and without mirabegron codispensing (Supplementary Table 2 in the ESM). Across all cohorts, comorbidity index scores (Charlson Comorbidity Index, Elixhauser Comorbidity Index) and number of outpatient visits generally slightly increased at the time of mirabegron codispensing compared with the time of CYP2D6 substrate dispensing initiation, but |SMDs| were < 0.2, suggesting no imbalances. No differences were seen for acute CYP2D6 substrates alone versus codispensing with mirabegron.

4 Discussion

Despite mirabegron, a moderate CYP2D6 inhibitor indicated for OAB, having a drug interaction warning for prescribing with CYP2D6 substrates, substantial codispensing person-time of select substrates was observed in our administrative claims database analysis. Such codispensing without appropriate monitoring and dose adjustment may lead to DDIs, which can place patients at risk of adverse drug reactions and undue harm. The median days of overlapping mirabegron and hydrocodone or tramadol dispensing were substantially lower than other cohorts owing to the acute use of these drugs in most instances. Chronically administered drugs displayed considerable overlapping dispensing time

Table 1 Patient time contributing to CYP2D6 substrate cohorts

CYP2D6 substrate[a]	No. of patients	Time before overlapping dispensing (person-months)	Time with overlapping dispensing (person-months)	Overlapping time (%)
Tramadol	10,200	10,110	12,195	46.1
Donepezil	1467	9799	9944	41.3
Amitriptyline/nortriptyline	4068	18,638	18,101	38.6
Aripiprazole	1675	9589	8321	38.4
Hydrocodone	17,998	20,346	17,184	36.5
Tamsulosin	8029	51,734	39,259	35.2
Citalopram/escitalopram	8813	70,593	48,003	32.2
Duloxetine/venlafaxine	8991	81,973	55,202	31.4
Metoprolol/carvedilol	10,274	106,558	64,591	29.8
Tolterodine	4622	23,902	9385	22.6

CYP cytochrome P450

[a]Presented by decreasing percentage of overlapping time

Table 2 Median days of patient exposure to CYP2D6 substrates alone and with mirabegron

CYP2D6 substrate[a]	No. of patients	No. of codispensing windows	Median (IQR) days before codispensing	Median (IQR) days during codispensing
Donepezil	1467	1889	186 (354)	80 (151)
Metoprolol/carvedilol	10,274	13,678	251 (530)	75 (115)
Duloxetine/venlafaxine	8991	12,039	226 (511)	71 (105)
Citalopram/escitalopram	8813	11,498	181 (426)	62 (91)
Aripiprazole	1675	2086	123 (298)	61 (90)
Amitriptyline/nortriptyline	4068	5037	98 (280)	45 (75)
Tamsulosin	8029	9751	125 (323)	45 (100)
Tolterodine	4662	5016	87 (240)	36 (38)
Tramadol	10,200	10,680	28 (82)	15 (33)
Hydrocodone	17,998	18,911	32 (167)	9 (18)

CYP cytochrome P450, *IQR* interquartile range

[a]Presented by decreasing median days during codispensing

frames, which was expected given the nature of the drug and is an important consideration because mirabegron is also chronically administered. Limited differences in baseline characteristics between the start of the CYP2D6 substrate and the start of the overlapping period is indicative of relatively stable underlying health conditions, allowing for direct comparisons.

A previous analysis of dispensing claims has highlighted the high frequency with which CYP2D6 substrates of any kind are codispensed in patients with OAB receiving mirabegron; approximately 70% of patients who received mirabegron also received a CYP2D6 substrate [15]. Codispensing of ≥ 1 CYP2D6 substrate with mirabegron was associated with patients being older and with having increased healthcare resource utilization, baseline polypharmacy, and comorbidities compared with mirabegron users who did not receive concomitant CYP2D6 substrates [15]. In an analysis of medication dispensing in long-term care facilities, > 90% of residents who received mirabegron had also received a CYP2D6 substrate during a 5-year analysis window [17]. Especially concerning is that approximately 25% of residents had ≥ 1 claim for a CYP2D6 substrate that was contraindicated and/or had a black box warning for coadministration with CYP2D6 inhibitors [17]. In this analysis, codispensing of tramadol, which has a black box warning against administration with a CYP2D6 inhibitor, showed the highest percentage of overlapping dispensing time. Further, CYP2D6 substrates with narrow therapeutic index—including aripiprazole (38.4% person-time overlapping), donepezil (41.3%), and duloxetine/venlafaxine (31.4%)—also showed substantial codispensing.

The concerns with frequent CYP2D6 substrate codispensing with a CYP2D6 inhibitor are multifactorial. OAB is frequently treated with anticholinergics, which can be combined with a β_3-adrenergic receptor agonist [1]. Indeed, our results showed a median of 36 days of overlap of codispensed mirabegron and tolterodine. Management of anticholinergic burden (i.e., cumulative effects of taking ≥ 1 drug with anticholinergic properties) is critical for avoiding anticholinergic side effects and for helping to maintain patient quality of life. A retrospective analysis of older adults (≥ 65 years old) showed that a one-point increase in mean total daily anticholinergic burden score resulted in a 13% increased risk of cognitive impairment [18].

In addition to anticholinergic burden, medications for common comorbidities must be considered when prescribing mirabegron for OAB. Cardiovascular comorbidities are common in patients with OAB [3]. In our analysis, approximately 30% of the time that patients were dispensed the β-blockers metoprolol or carvedilol, they were also dispensed mirabegron. β-blockers often require careful dose titration to achieve appropriate therapeutic response and limit exposure-related adverse reactions, such as hypotension and bradycardia. Prior studies have shown that introducing a CYP2D6 inhibitor can increase exposure of the substrate by two to five fold [11], more than doubling the dose of the substrate received. In an analysis of over 250,000 adults with a fall injury leading to hospitalization, use of antidepressants that were CYP2D6 substrates was associated with an increased risk of fall injuries, and this risk was further magnified when the medication was administered with a CYP2D6 inhibitor [19]. Similarly, use of the CYP2D6 substrate aripiprazole concurrent with a CYP2D6 inhibitor was associated with a three-fold increase in risk of falls in patients 20–69 years of age [19]. Appropriate selection of antidepressants or antipsychotics is therefore critical, especially considering the increased rates of comorbid depression in patients with OAB [4].

Medications that require CYP2D6 metabolism to produce an active metabolite further compound the need for careful

prescribing. In a prospective observational study of patients presenting to the emergency department, coadministration of a CYP2D6 inhibitor with an opioid such as hydrocodone (a CYP2D6 substrate that requires CYP2D6 activation to achieve a therapeutic response) has been shown to lead to significantly decreased effectiveness of hydrocodone [20]. Decreased analgesic effect may result in a patient taking an increased opioid dose, which may lead to excessive opioid effect if the CYP2D6 inhibitor is discontinued without opioid dose adjustment.

Currently there is a lack of data regarding clinical outcomes of interactions between mirabegron and CYP2D6 substrates among patients with OAB. Previous studies have assessed outcomes among healthy adults. One study documented an increase in plasma concentrations of the CYP2D6 substrates metoprolol and desipramine when administered with mirabegron over 5 days (metoprolol) or on 2 separate days (desipramine); cardiovascular responses to both drugs were not affected by the addition of mirabegron [12]. A study of coadministration of mirabegron with tolterodine for 7 days in healthy females showed increased plasma concentrations of tolterodine and slight but nonsignificant increases in QT interval [21]. Notably, both studies occurred in healthy adults, and it will be important to assess safety outcomes among a real-world population of patients with OAB who may also have comorbid conditions and are taking these medications chronically. Our analysis in codispensing patterns represents a step toward understanding and addressing the potential clinical events that may occur from coprescribing mirabegron with CYP2D6 substrates.

Management of potential DDIs can be burdensome for providers in their daily practice, and increases in drug interaction alerts may lead to alert fatigue. Challenges may be due to communication challenges across multiple providers, patient complexity, and inadequate knowledge regarding specific combinations of drugs [22]. Additionally, formulary restrictions may result in prescribing drugs with increased risk of DDIs, and frequent coadministration could result in increased incidence of adverse health outcomes. It therefore remains critical for providers to consider the potential for DDIs leading to adverse effects when prescribing multiple medications.

These analyses share similar limitations to typical claims database studies. Prescription dispensing does not ensure administration of medication. Further, it is unknown if administration was aligned with indications for use because the clinical diagnosis associated with medication prescribing is not available; however, the potential for DDIs remains regardless of indication or diagnosis. Although we did not assess clinical outcomes related to codispensing and potential DDIs, our results may inform future analyses that assess the effects of codispensing on patient outcomes. Off-label use and the explicit effect of CYP2D6 inhibition may not be fully understood. Medications taken on an as-needed basis are often taken sporadically over a period of time, which can lead to a lack of associations and patterns within the data. Proactive dose reduction by a provider because of coadministration with CYP2D6 inhibitors cannot be determined. Over-the-counter medications (e.g., dextromethorphan) were not captured. Intentional medication use gaps are not clearly specified, and delimitation between doses within a drug cohort was not evaluated. Lastly, the PharMetrics® Plus database captures a primarily commercially insured population and therefore may not be generalizable to the full range of demographics in the United States; specifically, patients receiving Medicaid or those > 65 years old are poorly represented.

5 Conclusions

This retrospective database analysis evaluated prescribing patterns of specific, commonly used CYP2D6 substrates with mirabegron and showed frequent overlapping duration. Noting this frequency, a need exists to better understand the outcomes experienced by patients with OAB who may be at increased risk for DDIs. Further exploration into the effects these potential DDIs may have on both health-related quality of life and resource utilization would be highly beneficial.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40801-023-00370-6.

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Declarations

Authors' Contribution MER, JW, AC, and CJG developed the protocol. JW and MC analyzed the data. All authors contributed to the interpretation of data, revised the manuscript for intellectual content, and read and approved the final version.

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Competing Interests JW is an employee of Sumitovant Biopharma, Inc. MER was a consultant for CERobs Consulting, LLC, a consulting firm that was contracted by Urovant Sciences and consults with other pharmaceutical companies, at the time the work was conducted. KR was an employee of CERobs Consulting, LLC, at the time the work was conducted. MC was an employee of Roivant Sciences, Inc., and a consultant to Sumitovant Biopharma, Inc., at the time the work was conducted. AC is an employee of Urovant Sciences and Duke Health. NG is an employee of Urovant Sciences. JRH is a coauthor and publisher of *The Top 100 Drug Interactions: A Guide to Patient Management* and a consultant to Urovant Sciences and Seegnal US. CJG is the President of CERobs Consulting, LLC, a consulting firm

that consults with pharmaceutical companies and was contracted by Urovant Sciences.

Availability of Data and Material Datasets generated and/or analyzed during the current study are available from Sumitovant Biopharma, Inc (Jingjun Wang; monica.wang@sumitovant.com), through licensing with IQVIA, Inc, and requests will be considered from qualified researchers on a case-by-case basis with the condition of IQVIA approval.

Compliance with Ethical Standards This retrospective database analysis used deidentified claims data from the IQVIA PharMetrics® Plus database, which is compliant with the Health Insurance Portability and Accountability Act to protect patient privacy.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

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