IGALMI

Product Monograph

This document is intended for payers, formulary committee members (eg, pharmacy and therapeutics committees), pharmacy benefit managers, and other individuals or entities that review scientific assessments to make drug recommendations for the selection, formulary management, placement, and/or coverage of products. It is not intended for those who make prescribing decisions.

INDICATION

IGALMI is indicated for the acute treatment of agitation associated with schizophrenia or bipolar I or II disorder in adults. Limitations of Use: The safety and effectiveness of IGALMI have not been established beyond 24 hours from the first dose.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hypotension, Orthostatic Hypotension, and Bradycardia: IGALMI causes dose–dependent hypotension, orthostatic hypotension, and bradycardia. In clinical studies with IGALMI, patients were excluded if they had treatment with alpha-1 noradrenergic blockers, benzodiazepines, other hypnotics or antipsychotic drugs four hours prior to study drug administration; had a history of syncope or syncopal attacks; SBP < 110 mmHg; DBP < 70 mmHg; HR < 55 beats per minute; or had evidence of hypovolemia or orthostatic hypotension. Because IGALMI decreases sympathetic nervous system activity, hypotension and/or bradycardia may be more pronounced in patients with hypovolemia, diabetes mellitus, or chronic hypertension, and in geriatric patients. Avoid use of IGALMI in patients with hypotension, orthostatic hypotension, advanced heart block, severe ventricular dysfunction, or history of syncope. After IGALMI administration, patients should be adequately hydrated and should sit or lie down until vital signs are within normal range. If a patient is unable to remain seated or lying down, precautions should be taken to reduce the risk of falls. Ensure that a patient is alert and not experiencing orthostatic hypotension or symptomatic hypotension prior to allowing them to resume ambulation.

Igalmi™
(dexmedetomidine)
sublingual film · 120 mcg, 180 mcg

TABLE OF CONTENTS

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EXECUTIVE SUMMARY

Agitation is a common and debilitating condition for patients with schizophrenia or bipolar disorders.[1] According to the *Diagnostic and Statistical Manual for Mental Disorders, 5th Edition (DSM-5)*, agitation is an excessive motor activity associated with a feeling of inner tension and is listed as a feature of schizophrenia and a symptom of bipolar disorders.[2] It can manifest in a range of symptoms, including excitement, hostility, tension, uncooperativeness, and poor impulse control.[1,3]

How patients with schizophrenia or bipolar disorders who had experienced agitation described severity[4]

>	>	>	>
Mild	Moderate	Moderate-intense	Severe
Easier to control or ignore	Often harder to control and may get in the way of day-to-day life	Seriously disrupts and interferes with day-to-day life	Almost impossible to control

The need for clinical assistance increases with severity of agitation symptoms.

In people with agitation, mild and moderate symptoms are more prevalent, accounting for their higher prevalence of emergency department (ED) visits.[3,4]

According to expert consensus recommendations, pharmacologic treatment with a rapid onset of action, that is easily administered, that is calming without excessively sedating, with a sufficient duration of action, and with a low risk of serious adverse events (SAEs) and drug interactions should be considered for acute management of agitation.

Several unmet clinical needs remain in the management of agitation in the ED. Physical and chemical restraints require monitoring, which increases the burden on available resources.[5] Current consensus recommendations encourage verbal de-escalation and the avoidance of injectables and oversedation.[5-7] Rapid, effective, and safe intervention that does not produce excessive sedation is important in returning the agitated person to a less aroused and less potentially dangerous state, thereby facilitating further assessment of the individual and their treatment options.[8] Lastly, although noninvasive formulations require cooperation from patients, they have the potential to improve overall patient experience and facilitate future cooperation between patients and healthcare providers (HCPs).[5]

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IGALMI is an alpha-2 adrenergic receptor agonist. The mechanism of action of IGALMI in the acute treatment of agitation associated with schizophrenia or bipolar I or II disorder is thought to be due to activation of presynaptic alpha-2 adrenergic receptors.[9] IGALMI reduces norepinephrine release in the locus coeruleus, which is a key mediator of agitation.[10] IGALMI is an orally absorbed, mucoadhesive thin film (sublingual or buccal), designed so it cannot be spit out, and is self-administered under the supervision of an HCP. An HCP should monitor vital signs and alertness after IGALMI administration to prevent falls and syncope.[9]

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QT Interval Prolongation: IGALMI prolongs the QT interval. Avoid use of IGALMI in patients at risk of torsades de pointes or sudden death, including those with known QT prolongation, a history of other arrhythmias, symptomatic bradycardia, hypokalemia, or hypomagnesemia, and in patients receiving other drugs known to prolong the QT interval.

Somnolence: IGALMI can cause somnolence. Patients should not perform activities requiring mental alertness, such as operating a motor vehicle or operating hazardous machinery, for at least eight hours after taking IGALMI.

Risk of Withdrawal Reactions, Tolerance, and Tachyphylaxis: IGALMI was not studied for longer than 24 hours after the first dose. There may be a risk of physical dependence, a withdrawal syndrome, tolerance, and/or tachyphylaxis if IGALMI is used in a manner other than indicated.

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) were somnolence, oral paresthesia or oral hypoesthesia, dizziness, dry mouth, hypotension, and orthostatic hypotension.

DRUG INTERACTIONS

Drugs That Prolong the QT Interval: Avoid use. Concomitant use of drugs that prolong the QT interval may add to the QT-prolonging effects of IGALMI and increase the risk of cardiac arrhythmia.

Anesthetics, Sedatives, Hypnotics, and Opioids: Concomitant use may cause enhanced CNS-depressant effects. Reduction in dosage of IGALMI or the concomitant medication should be considered.

USE IN SPECIFIC POPULATIONS

Hepatic Impairment and Geriatric Patients (≥65 years old): A lower dose is recommended in patients with hepatic impairment and geriatric patients. See the full Prescribing Information for the recommended dosage depending on the agitation severity.

To report SUSPECTED ADVERSE REACTIONS, contact BioXcel Therapeutics, Inc. at 1-833-201-1088 or medinfo@bioxceltherapeutics.com, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.risk of falls.

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DISEASE OVERVIEW

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Acute Agitation in Schizophrenia or Bipolar Disorders

Epidemiology

Agitation, **"a state where patients cannot remain still or calm, characterized by internal features such as hyperresponsiveness, racing thoughts, and emotional tension; and external ones, mainly motor and verbal hyperactivity, and communication impairment,"*** is a common but often unaddressed problem in psychiatry.[11] It is important to note that, as of 2021, there was no commonly accepted consensus description of this common clinical phenomenon. Additionally, although aggressive and violent behavior sometimes occur together, agitation is distinct from aggression, and agitation can occur without aggression.[12]

According to the American Psychiatric Association, agitation is a recognized component of the behavioral characteristics of schizophrenia and is a diagnostic criterion for bipolar disorders.[13]

Acute episodes of psychomotor agitation accounted for approximately 900,000 visits to psychiatric emergency services in patients with schizophrenia and 560,000 ED visits yearly in the United States due to bipolar disorders.[14] Another estimate in the United States indicates that 21% of psychiatric ED visits involve a patient with agitation.[13]

Acute agitation can occur in patients with schizophrenia or bipolar disorders and range in severity from mild to severe. Results from a systematic literature review found that the rates of agitation in patients with schizophrenia or bipolar disorders are higher than the rates of agitation reported for a general ED population.[15]

*This definition for agitation was developed during the First International Expert's Meeting on Agitation and is a work-in-progress. It is not validated, as agitation is complex, with many different levels of severity and presentations.[11]

Epidemiology (cont'd)

Table 1 Results of systematic literature review characterizing epidemiology of acute agitation episodes in emergency settings, including the contribution of schizophrenia and bipolar disorder[15]

| Publication (Region or Country)	Incidence /Prevalence of Agitation in General Emergency and Psychiatric Emergency Populations		Incidence/Prevalence of Schizophrenia or Bipolar Disorder Among Emergency Setting Agitation Cases	
	Description	Value	Description	Value
Zeller et al, 2010 (USA)	Prevalence of agitation/violence in patients seen in psychiatric emergency settings	Up to 10%		
Leung et al, 2011 (USA)			Proportion of psychiatric emergency hospital visits that are acutely agitated patients with schizophrenia	21%
Strout et al, 2015 (USA)			Prevalence of schizophrenia as the primary diagnosis among psychiatric ED visits including an "acute psychiatric complaint"	12.4%
San et al, 2016 (Europe)	Prevalence of acute agitation episodes among 7295 psychiatric emergencies (27 hospitals in 6 European countries) in a 7-day period	4.6%	Prevalence of schizophrenia among acute agitation cases	47%
			Prevalence of bipolar disorder among acute agitation cases	24%
Casado-Florez et al, 2017 (Spain)	Incidence of acute agitation among all emergencies attended by Spanish EMS during a 1-year period	1.9%	Proportion of cases with a schizophrenia diagnosis among all acute psychiatric emergencies characterized by agitation attended by Spanish EMS personnel during 2013	44.9%
	Rate per 1000 (total population)	2.0%		
Miner et al, 2018 (USA)	Prevalence of agitation among patients presenting to an urban county ED	2.6%		

EMS, emergency medical services.

This systematic literature search revealed a clear evidence gap regarding the emergency healthcare system burden posed by acutely agitated patients with schizophrenia and/or bipolar disorder, despite the known prevalence of these conditions and the general volume of emergency care interactions.[15]

Epidemiology (cont'd)

Even though the studies that were identified in Table 1 varied in terms of emergency setting (general hospital ED, psychiatric emergency settings, emergency medical calls), study focus, population definition (overall agitation vs agitation in patients with schizophrenia or bipolar disorder), and reporting data by prevalence or incidence, limiting the possibility of cross-study comparisons, the data suggest that acute agitation requiring emergency medical attention is a frequent phenomenon in patients with schizophrenia and bipolar disorder.[15]

Results from a survey of community-dwelling adults with schizophrenia or bipolar disorders who experienced episodes of agitation (N=583) in Germany, Spain, and the United Kingdom found decreasing numbers of agitation episodes with increasing episoide severity (Figure 1). However, although patients in this study reported fewer moderate-intense and severe episodes than mild and moderate episodes, the percentage of episodes that required assistance from an HCP increased with increasing disease severity.[4]
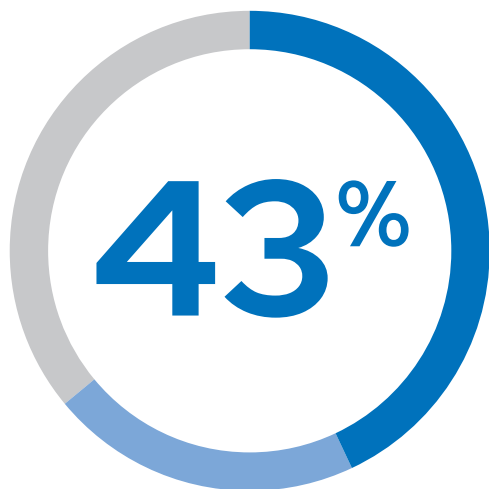
Figure 1 **Agitation Episodes in Patients With Schizophrenia or Bipolar Disorders by Episode Severity and Need for Assistance[4]***
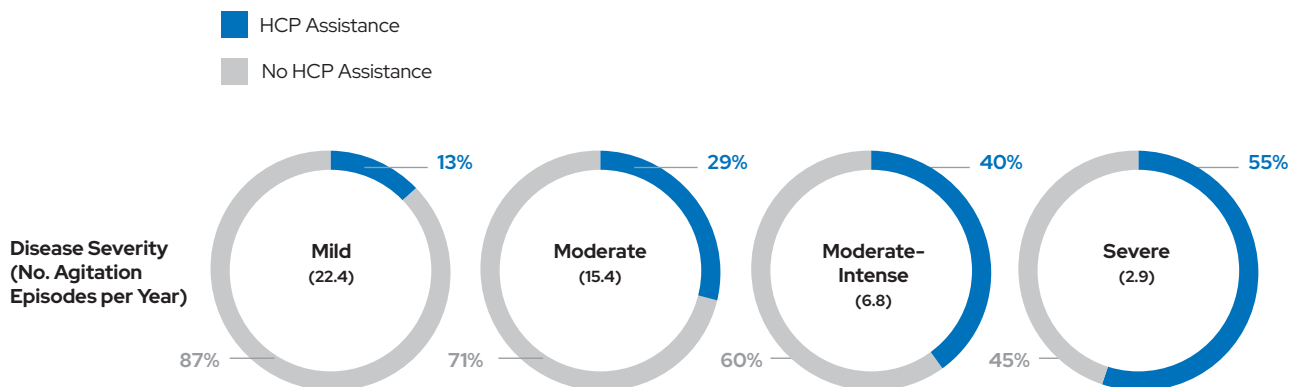
*Based on patient self-reported symptoms in the previous 12 months.

Epidemiology (cont'd)

Figure 2 Twice the Number of Drug-Treated Episodes Occurred in the ED vs Inpatient Setting

43%

When bipolar disorder or schizophrenia patients seek medical care for agitation episodes, a majority are treated in the ED or hospital setting.[16]

In a retrospective longitudinal analysis of 332,580 patients, about 2/3 of drug-treated agitation episodes are managed in an institution. Twice the number of drug-treated episodes occurred in the ED vs inpatient setting.[16]*

43% of patients were treated in the ED setting

21% were inpatients

36% were outpatients

*This data included adult (≥18 years) acute agitation patients with a history of schizophrenia or bipolar disorder with any diagnosis or prescription claims within 12 months prior and after first diagnosis, covering the period 2017-2020.

Figure 3 Most Patients Took Medication for Agitation Voluntarily

81%
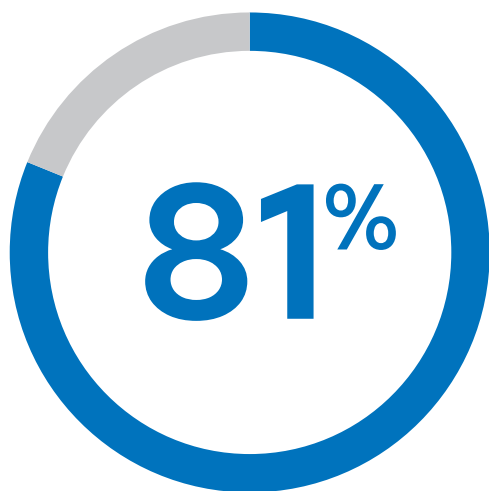
In a separate study of 400 psychiatric emergency patients, of whom 210 presented with signs of agitation, 47% (N=98) were treated with medication. Most patients took the medication voluntarily.[17]†

81% of patients treated with medication took it voluntarily

19% of patients were treated involuntarily

†A retrospective, structured chart review performed on 400 psychiatric emergency patients presenting to eight Psychiatric Emergency Research Collaboration hospitals from January 1 through June 30, 2005.

Risk Factors

Individuals with schizophrenia and bipolar disorders are vulnerable to episodes of agitation, which are prone to escalation.[5]

Risk factors for acute agitation in populations with schizophrenia or bipolar disorders have not been established. However, many patients with schizophrenia and bipolar disorders are aware of becoming agitated and can recognize triggers.[4]

Clinical Presentation

The hallmarks of agitation include cognitive and physical hyperactivity and marked emotional arousal.[11]

A broad range of features in agitation have been reported in patients with schizophrenia or bipolar disorders, including, but not limited to[4]:

Physical or mental unease	**Uncooperativeness**
Inner tension	**Anxiety**
Restlessness	**Motor tension**
Irritability	**Excessive, inappropriate, or purposeless motor activity**
Excitement	

How patients with bipolar disorder or schizophrenia who had experienced agitation described severity[4]

Mild	Moderate	Moderate-intense	Severe
Easier to control or ignore	Often harder to control and may get in the way of day-to-day life	Seriously disrupts and interferes with day-to-day life	Almost impossible to control

The need for clinical assistance increases with severity of agitation symptoms.[4] In patients with schizophrenia or bipolar disorders, agitation, if left untreated, may escalate to aggression or violence. Late recognition or inadequate initial management of agitation potentially risks escalation, which can negatively impact the patient, healthcare staff, and other patients.[1]

Caregiver Burden

In addition to increased patient burden, increased caregiver burden is reported for family members or friends caring for individuals with schizophrenia or bipolar disorders and agitation. As families are frequently participating in care for people with mental illness, the negative impact on caregiver physical and psychological health has been evaluated. A real-world survey of 297 informal caregivers of patients with schizophrenia and bipolar disorders in a community setting in the United Kingdom, Germany, and Spain conducted between October 2016 and January 2017 found that caregivers provided an average (SD) of 38.3 (40.34) hours of care each week, with 20% (N=58) providing at least 50 hours. Although patient hostility and lack of control were associated with a higher burden, all symptoms associated with agitation, including those perceived as mild manifestations that were routinely underreported, confer burden to caregivers.[18]

Challenges of Managing Agitation in the ED

The ED is an especially vulnerable environment for workplace violence, due to the high percentage of acutely agitated patients who may escalate to verbal threats or physical assaults on ED staff. A national poll in 2018 by the American College of Emergency Physicians reported that nearly half of the >3500 emergency physicians surveyed had been physically assaulted while at work. A 2016 survey of 119 emergency medicine residents showed that 66% had been physically assaulted by patients, while only 17% had previous training in violence prevention. Managing these violent behaviors by agitated patients in the ED was considered to be routine, with the use of physical restraints and chemical sedatives as the only method to control the patient's behavior.[19]

Not only can agitation escalate to physical violence and adverse outcomes for staff and patients, it can lead to substantial economic costs to the healthcare system.[1] And, while in the chaotic ED environment, a patient's qualitative experience may not always be top of mind. Physical or pharmacologic treatment that is coercive may leave them with a poor experience of care and a less trusting relationship with their provider.[5]

SD, standard deviation.

Considerations for Treatment

The treatment of agitation in emergency settings is multifaceted and includes both pharmacologic and nonpharmacologic approaches. Management of patients who are admitted to the ED for agitation may be staff- and resource-intensive and potentially costly, as mismanagement may lead to prolonged stays, behavioral disturbances, and violence.[13,20]
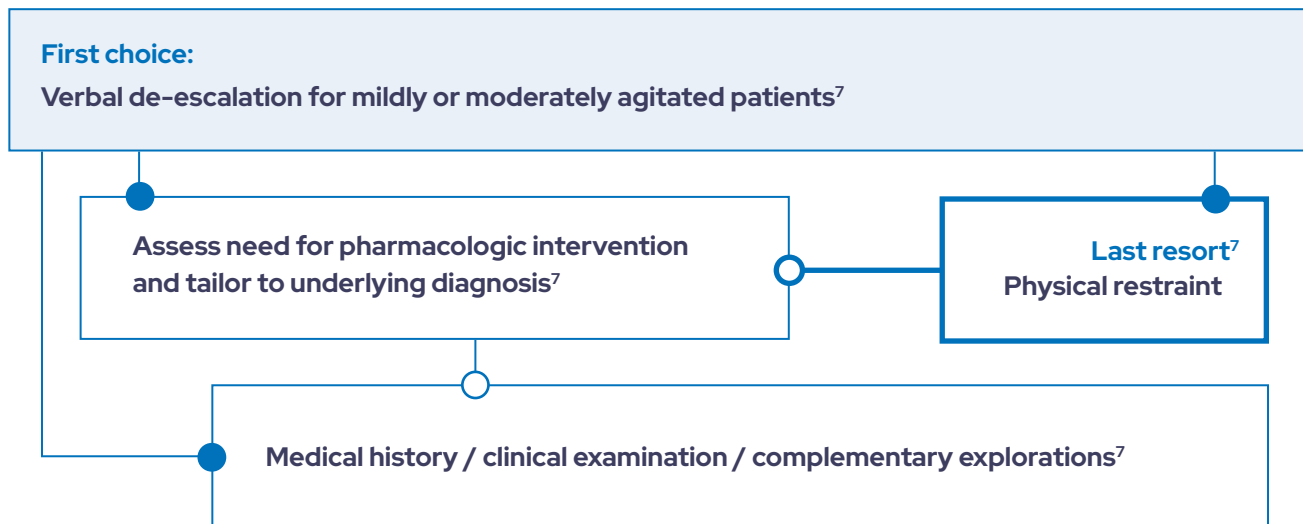
In 2010, the American Association for Emergency Psychiatry initiated Project BETA (Best practices in Evaluation and Treatment of Agitation). The goal of Project BETA was to provide guidelines that not only were effective and safe but also were in the best interest of the patient. Workgroups were formed using the basic approaches of emergency psychiatry as a foundation, with guidelines developed that addressed the patient journey (Table 2).[21]

Table 2 Overview of Project BETA Topics and Pharmacologic Recommendations[21,22]

Treatment goals of emergency psychiatry	Covered topics reflecting the patient journey	Recommendations
Exclude medical etiologies for symptoms	Medical evaluation and triage of the agitated patient	The use of medication as a restraint should be discouraged
Achieve rapid stabilization of the acute crisis	Psychiatric evaluation of the agitated patient	Nonpharmacologic approaches such as verbal de-escalation and reducing environmental stimulation should be attempted
Avoid coercion	Verbal de-escalation of the agitated patient	Medication should be used to calm patients, not to induce sleep
Treat in the least restrictive setting	Psychopharmacologic approaches to agitation	Patients should be involved in the process of selecting medication to whatever extent possible
Form a therapeutic alliance	Use and avoidance of seclusion and restraint	If the patient is able to cooperate with taking oral medications, these are preferred over intramuscular (IM) preparations
Have an appropriate disposition and after-care plan		

When treating patients with acute agitation, early intervention and de-escalation are key.[11] Current consensus recommendations emphasize establishing a collaborative environment with verbal de-escalation and an opportunity for patients to take an oral medication voluntarily. Seclusion and restraint techniques should only be used as a last resort.[23] An example algorithm for evaluating and treating patients with agitation in emergency settings is provided in the figure below.[7]

Summary of Considerations

First choice:

Verbal de-escalation for mildly or moderately agitated patients[7]

Assess need for pharmacologic intervention and tailor to underlying diagnosis[7]

Last resort[7]
Physical restraint

Medical history / clinical examination / complementary explorations[7]

De-escalation and Nonpharmacologic Management

The benefits of nonpharmacologic, noncoercive approaches such as verbal interventions and de-escalation for treating acute agitation are widespread, including potential reduced resource use, costs, and staff and patient injuries and better staff-patient relationships.[5] Conversely, the use of restraint and seclusion can create a negative response to the situation that can be physically and emotionally traumatizing to the patient and involved staff. Also, restraints can affect the trust between the patient and HCPs.[24]

The Joint Commission, formerly known as the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), noted in a 2019 publication that injuries to both patients and staff can occur when restraints are used.[24]

Current Pharmacologic Options

Although some patients may be managed using nonpharmacologic approaches alone, others may require some pharmacologic treatment.[5] According to expert consensus recommendations on the assessment and management of psychomotor agitation, rapid onset of the effect and reliability of delivery are two important factors to consider when selecting a pharmacologic treatment.[6]

The goal of pharmacologic intervention should be to calm the patient to allow assessment, avoiding sleep if possible.[5] Pharmacologic treatment should consider the provisional diagnosis and, where possible, target the underlying cause of the patient's agitation.[5,22] Both treatment timing and dosage regimen should be considered, as early, aggressive treatment can mask underlying conditions, and delay or impede accurate diagnosis, and delayed treatment can allow agitation to escalate, putting the patient and others at risk.[5] Treatment recommendations from the BETA workgroup include both antipsychotics and benzodiazepines and oral, IM, and intravenous options (Table 3).[22] Additionally, since release of the BETA workgroup recommendations, inhaled loxapine, an antipsychotic, has been approved for the treatment of acute agitation, as well as IGALMI™ (dexmedetomidine) sublingual film.[9,25]

Table 3 **Pharmacologic Therapies Recommended by the BETA Psychopharmacology Workgroup for Treatment Agitation**

Generic Name	Brand Name	Drug Class	Boxed Warnings
Oral Medications			
Risperidone[26]	Risperdal®	Atypical antipsychotic	Increased mortality in elderly patients with dementia–related psychosis
Olanzapine[27]	Zyprexa®	Atypical antipsychotic	Increased mortality in elderly patients with dementia–related psychosis
Haloperidol[28]	Haldol®	Typical antipsychotic	Increased mortality in elderly patients with dementia–related psychosis
Lorazepam[29]	Ativan®	Benzodiazepine	Risks from concomitant use with opioids; abuse, misuse, and addiction; dependence and withdrawal reactions
IM Medications			
Ziprasidone[30]	Geodon®	Atypical antipsychotic	Increased mortality in elderly patients with dementia–related psychosis
Olanzapine[27]	Zyprexa®	Atypical antipsychotic	Increased mortality in elderly patients with dementia–related psychosis
Haloperidol[28]	Haldol®	Typical antipsychotic	Increased mortality in elderly patients with dementia–related psychosis
Aripiprazole[31]	Abilify®	Atypical antipsychotic	Increased mortality in elderly patients with dementia–related psychosis; suicidal thoughts and behaviors with antidepressant drugs
Lorazepam[32]	Ativan®	Benzodiazepine	Risks from concomitant use with opioids; abuse, misuse, and addiction; dependence and withdrawal reactions
Intravenous Medications			
Haloperidol[28]	Haldol®	Typical antipsychotic	Increased mortality in elderly patients with dementia–related psychosis

All trademarks are the property of their respective owners.

Medications administered for the management of acute agitation include first- and second-generation antipsychotics and benzodiazepines.[5,22] Oral therapies can also be administered to cooperative patients.[5] Disadvantages of IM injections have led to the recommendation that noninvasive formulations should be used in situations where the patient is able to cooperate.[11]

Despite having various pharmacologic options for the treatment of agitation in schizophrenia and bipolar disorders, none of the currently available options fit all of the criteria outlined by expert consensus for an "ideal" antiagitation medication.[6] In addition, with antipsychotics and/or benzodiazepines, there is potential for oversedation, which may limit the patient's ability to interact and participate in the evaluation.[5,22]

Considerations for pharmacologic treatment[6]:

Onset of action

Route of administration

Level of sedation

Duration of action

Adverse events and drug interactions

The preceding section provides general information about agitation associated with schizophrenia or bipolar I or II disorder and is not intended to make claims about any specific treatment.

The next section discusses a product-specific treatment option. For product-specific information, please consult the full Prescribing Information.

IGALMI
PRODUCT INFORMATION

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NDC, National Drug Code; WAC, Wholesale Acquisition Cost.

Please see Important Safety Information on pages 6, 20, and 70.

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ADVERSE REACTIONS

The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) were somnolence, oral paresthesia or oral hypoesthesia, dizziness, dry mouth, hypotension, and orthostatic hypotension.

DRUG INTERACTIONS

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USE IN SPECIFIC POPULATIONS

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To report SUSPECTED ADVERSE REACTIONS, contact BioXcel Therapeutics, Inc. at 1-833-201-1088 or medinfo@bioxceltherapeutics.com, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.risk of falls.

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sublingual film · 120 mcg, 180 mcg

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Product Description

Brand name
IGALMI™ (dexemedetomidine) sublingual film[9]

Therapeutic class
Alpha-2 adrenergic receptor agonist[9]

Administration
Thin film administered sublingually or buccally (behind the lower lip) under the supervision of an HCP. HCPs should monitor vital signs and alertness after IGALMI administration to prevent falls and syncope[9]

Dexmedetomidine hydrochloride injection solution and solution concentrate (Precedex™, Pfizer, Inc.) has been approved in the US since 1999; indications include the sedation of intubated and mechanically ventilated patients in the intensive care unit and the sedation of nonintubated patients prior to or during surgical and other procedures.[33]

In May 2021, positive topline results were presented for the SERENITY I and II pivotal trials that compared a single dose of IGALMI to placebo for the acute treatment of agitation in patients with schizophrenia or bipolar I or II disorder in an acute care setting. IGALMI showed statistically significant efficacy compared with placebo as measured by the absolute change from baseline in the Positive and Negative Syndrome Scale (PANSS) Excited Component (PEC) score at 2 hours post-dose.[9,10,34] The PEC is a validated regulatory endpoint for measuring acute agitation associated with schizophrenia and bipolar disorders. This scale is used in clinical research to quantify the severity of acute agitation. The PEC rating evaluates 5 characteristics of agitation: poor impulse control, tension, hostility, uncooperativeness, and excitement; each component is scored on a scale from 1 (absent) to 7 (extremely severe). The PEC total score is the sum of these 5 elements and, thus, ranges from 5 to 35.[3]

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In both the SERENITY I and SERENITY II trials, the primary endpoint was met for both the IGALMI 120 mcg and 180 mcg doses.

In the SERENITY I trial that enrolled patients with schizophrenia and agitation, the mean improvement from baseline in PEC total scores 2 hours post IGALMI administration was –10.3 points (least squares mean [LSM] difference –5.5 [P<0.0001]) for the IGALMI 180 mcg group and –8.5 points (LSM difference –3.7 [P<0.0001]) for the IGALMI 120 mcg group, compared with –4.8 points for the placebo group. For the secondary endpoint, earliest time where an effect on agitation was statistically significant, measured by the change from baseline in PEC total score, was 20 minutes with IGALMI 180 mcg and 30 minutes with IGALMI 120 mcg. At 2 hours post-dose, PEC response rates, an exploratory endpoint defined as ≥40% decrease from baseline, were 79.1% with IGALMI 120 mcg and 88.8% with IGALMI 180 mcg doses compared with 40.5% with placebo.[9,10]

In the SERENITY II trial that enrolled patients with bipolar I or II disorder and agitation, the improvement from baseline in PEC total scores 2 hours post IGALMI administration was –10.4 points (LSM difference –5.4 [P<0.0001]) for the IGALMI 180 mcg group and –9.1 points (LSM difference –4.1 [P<0.0001]) for the IGALMI 120 mcg group, compared with –5.0 points for the placebo group. For the secondary endpoint, earliest time where an effect on agitation was statistically significant, measured by the change from baseline in PEC total score, was 20 minutes for both the IGALMI 180 mcg group and the IGALMI 120 mcg group. At 2 hours post-dose, PEC response rate, an exploratory endpoint defined as >40% decrease from baseline, was 77% with IGALMI 120 mcg and 90.5% with IGALMI 180 mcg compared with 46% with placebo.[9,34]

The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) were: somnolence, oral paresthesia or oral hypoesthesia, dizziness, dry mouth, hypotension, and orthostatic hypotension.[9]

Mechanism of Action

Dexmedetomidine is an alpha-2 adrenergic receptor agonist. The mechanism of action of IGALMI in the acute treatment of agitation associated with schizophrenia or bipolar I or II disorder is thought to be due to activation of presynaptic alpha-2 adrenergic receptors.[9]

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sublingual film · 120 mcg, 180 mcg

Use in Specific Populations

Pregnancy: There are no available data on IGALMI use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal effects. Available data from published randomized, controlled trials and case reports over several decades of use with intravenously administered dexmedetomidine during pregnancy have not identified a drug-associated risk of major birth defects or miscarriage; however, the reported exposures occurred after the first trimester. Most of the available data are based on studies with exposures that occurred at the time of cesarean-section delivery, and these studies have not identified an adverse effect on maternal outcomes or infant Apgar scores. Available data indicate that dexmedetomidine crosses the placenta.[9]

In animal reproductive studies, fetal toxicity occurred in the presence of maternal toxicity with subcutaneous administration of dexmedetomidine to pregnant rats during organogenesis at doses 5 times the maximum recommended human dose (MRHD) of 360 mcg/day based on mg/m^2 body surface area. Adverse developmental effects, including early implantation loss and decreased viability of second-generation offspring, occurred when pregnant rats were subcutaneously administered doses less than or equal to the MRHD based on mg/m^2 from late pregnancy through lactation and weaning (see Data).[10]

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data: Increased post-implantation losses and reduced live pups in the presence of maternal toxicity (decreased body weight) occurred in a rat embryo-fetal development study in which pregnant dams were administered subcutaneous doses of dexmedetomidine of 200 mcg/kg/day (equivalent to 5 times the MRHD of 360 mcg/day based on mg/m^2) during the period of organogenesis (Gestation Day [GD] 5 to 16). No embryo-fetal toxicity was observed at 20 mcg/kg/day (less than the MRHD of 360 mcg/day based on mg/m^2). No malformations were reported at any dose level.

No malformation or embryo-fetal toxicity were observed in a rabbit embryo-fetal developmental study in which pregnant dams were administered dexmedetomidine intravenously at doses up to 96 mcg/kg/day (equivalent to 5 times the MRHD of 360 mcg/day based on mg/m^2) during the period of organogenesis (GD 6 to 18).

Reduced pup and adult offspring weights and grip strength were reported in a rat developmental toxicology study in which pregnant females were administered dexmedetomidine subcutaneously at 8 mcg/kg/day (less than the MRHD of 360 mcg/day based on mg/m^2) during late pregnancy through lactation and

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weaning (GD 16 to postnatal day [PND] 25). Decreased viability of second-generation offspring and an increase in early implantation loss, along with delayed motor development, occurred at 32 mcg/kg/day (equivalent to the MRHD of 360 mcg/day based on mg/m^2) when first-generation offspring were mated. This study limited dosing to hard palate closure (GD 15-18) through weaning instead of standard dosing from implantation (GD 6-7) to weaning (PND 21).

Lactation: Available published literature report the presence of dexmedetomidine in human milk following intravenous administration. There is no information regarding the effects of dexmedetomidine on the breastfed child or the effects on milk production. Advise women to monitor the breastfed infant for irritability. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for IGALMI and any potential adverse effects on the breastfed child from IGALMI or from the underlying maternal condition.[9]

Pediatric Use: The safety and effectiveness of IGALMI have not been established in pediatric patients.[9]

Geriatric Use: Fifteen geriatric patients (≥65 years of age) were enrolled (no patients were 75 years of age and older) in the clinical studies for acute treatment of agitation associated with schizophrenia or bipolar I or II disorder. Of the total number of IGALMI-treated patients in these clinical studies, 11/507 (2.2%) were 65 years of age and older. Dosage reduction of IGALMI is recommended in geriatric patients. A higher incidence of bradycardia and hypotension was observed in geriatric patients compared with younger adult patients after intravenous administration of another dexmedetomidine product. The pharmacokinetic profile of intravenous dexmedetomidine was not altered in geriatric subjects.[9]

Clinical studies of IGALMI did not include sufficient numbers of patients 65 years of age and older to determine whether there were differences in the effectiveness of IGALMI in the acute treatment of agitation associated with schizophrenia or bipolar I or II disorder compared with younger adult patients.[9]

Hepatic Impairment: Dexmedetomidine clearance was decreased in patients with hepatic impairment (Child-Pugh Class A, B, or C). Thus, a dosage reduction of IGALMI is recommended in patients with hepatic impairment compared with patients with normal hepatic function.[9]

Pharmacokinetics

Dexmedetomidine exposure (peak plasma concentration [C_{max}] and area under the curve [AUC]) increased in a dose–proportional manner in the dose range of 20 mcg (0.17 times the lowest recommended initial dose of 120 mcg) to 180 mcg after single sublingual administration of IGALMI.[9]

The mean time for film to dissolve in the mouth was about 6 to 8 minutes and 18 minutes following sublingual and buccal administration, respectively. Dexmedetomidine was quantifiable in plasma generally after 5 to 20 minutes post–dosing.[9]

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Absorption: The absolute bioavailability of dexmedetomidine was about 72% and 82% following sublingual and buccal administration of IGALMI, respectively. When water was taken at 2 hours post-dose, comparable exposures of dexmedetomidine were observed when IGALMI was administered by both routes.[9]

Mean maximal plasma concentrations of dexmedetomidine were reached approximately 2 hours after sublingual or buccal administration of IGALMI. Following sublingual administration of 40 mcg of IGALMI (0.33 times the lowest recommended initial dose) with water drinking at 2 hours post-dose and 20 mcg dexmedetomidine intravenous infusion for 90 minutes in healthy volunteers[9]:

• The mean C_{max} of dexmedetomidine was 143 ng/L and 144 ng/L, respectively

• The mean AUC of dexmedetomidine was 851 hour*ng/L and 584 hour*ng/L, respectively.

Effect of Drinking Water on Absorption: Compared to drinking water at 2 hours post sublingual administration of IGALMI, early water intake (as early as 15 minutes post-dose) had minimal effects on the rate or extent of absorption of dexmedetomidine.[9]

Effects of early water intake (eg, before 2 hours post-dose) on the absorption of dexmedetomidine have not been evaluated following buccal administration.[9]

Distribution: The steady-state volume of distribution (Vss) of dexmedetomidine following intravenous administration was approximately 118 liters. Dexmedetomidine protein binding was assessed in the plasma of healthy male and female subjects. The average protein binding was 94% and was constant across the different plasma concentrations tested. Protein binding was similar in males and females. The fraction of dexmedetomidine that was bound to plasma proteins was significantly decreased in subjects with hepatic impairment compared with healthy subjects.[9]

The potential for protein binding displacement of dexmedetomidine by fentanyl, ketorolac, theophylline, digoxin, and lidocaine was explored in vitro, and negligible changes in the plasma protein binding of dexmedetomidine IV were observed. The potential for protein binding displacement of phenytoin, warfarin, ibuprofen, propranolol, theophylline, and digoxin by dexmedetomidine hydrochloride injection was explored in vitro and none of these compounds appeared to be significantly displaced by intravenous dexmedetomidine.[9]

Elimination

Metabolism: Dexmedetomidine undergoes almost complete biotransformation with very little unchanged dexmedetomidine excreted in urine and feces. Biotransformation involves both direct glucuronidation as well as cytochrome P450 mediated metabolism. The major metabolic pathways of dexmedetomidine are: direct N-glucuronidation to inactive metabolites; aliphatic hydroxylation (mediated primarily by CYP2A6 with a minor role of CYP1A2, CYP2E1, CYP2D6, and CYP2C19) of dexmedetomidine to generate 3-hydroxy-dexmedetomidine, the glucuronide of 3-hydroxy-dexmedetomidine, and 3-carboxy-dexmedetomidine; and N-methylation of dexmedetomidine to generate 3-hydroxy N-methyl-dexmedetomidine, 3-carboxy N-methyl-dexmedetomidine, and dexmedetomidine-N-methyl O-glucuronideglucuronide.[9]

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Excretion: The mean terminal elimination half–life ($t_{1/2}$) of dexmedetomidine is approximately 2.8 hours following sublingual or buccal administration of IGALMI. Clearance is estimated to be approximately 39 L/h following intravenous administration.[9]

Specific Populations

Male and Female Patients: There was no observed difference in dexmedetomidine pharmacokinetics due to sex.[9]

Geriatric Patients: The pharmacokinetic profile of IV dexmedetomidine was not altered by age. There were no differences in the pharmacokinetics of IV dexmedetomidine in young (18–40 years), middle age (41–65 years), and elderly (>65 years) patients.[9]

Patients with Hepatic Impairment: In subjects with varying degrees of hepatic impairment (Child–Pugh Class A, B, or C), clearance values for IV dexmedetomidine were lower than in subjects with normal hepatic function. After an intravenous infusion of 0.6 mcg/kg of this dexmedetomidine product over 10 minutes, the mean clearance values for subjects with mild, moderate, and severe hepatic impairment were 74%, 64%, and 53% of those observed in subjects with normal hepatic function, respectively. Mean clearances for free drug were 59%, 51%, and 32% of those observed in subjects with normal hepatic function, respectively.[9]

Patients with Renal Impairment: Dexmedetomidine pharmacokinetics (C_{max}, T_{max}, AUC, $t_{1/2}$, CL, and V) were not significantly different in patients with creatinine clearance <30 mL/min compared to subjects with normal renal function.[9]

Drug Interactions

Drugs That Prolong the QT Interval
Concomitant use of drugs that prolong the QT interval may add to the QT-prolonging effects of IGALMI and increase the risk of cardiac arrhythmia. Avoid the use of IGALMI in combination with other drugs known to prolong the QT interval.[9]

Anesthetics, Sedatives, Hypnotics, and Opioids
Concomitant use of IGALMI with anesthetics, sedatives, hypnotics, or opioids is likely to lead to enhanced CNS depressive effects. Specific studies with another dexmedetomidine product given intravenously have confirmed these effects with sevoflurane, isoflurane, propofol, alfentanil, and midazolam. Due to possible enhanced CNS effects when given concomitantly with IGALMI, consider a reduction in the dosage of IGALMI or the concomitant anesthetic, sedative, hypnotic, or opioid.[9]

Tmax, amount of time at peak plasma concentration; CL, drug clearance;
V, volume of distribution; CNS, central nervous system.

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Dosage and Administration

Important Recommendations Prior to Initiating IGALMI and During Therapy

IGALMI should be administered under the supervision of an HCP. An HCP should monitor vital signs and alertness after IGALMI administration to prevent falls and syncope.[9]

IGALMI is for sublingual or buccal administration. Patients should not chew or swallow IGALMI. Patients should not eat or drink for at least 15 minutes after sublingual administration, or for at least 1 hour after buccal administration.[9]

If agitation persists after the initial dose, up to 2 additional half-doses may be administered at least 2 hours apart. The dosage recommendations for additional doses vary depending on the patient population and agitation severity (Table 4). Assess vital signs, including orthostatic measurements, prior to the administration of any subsequent doses.[9]

Due to the risk of hypotension, additional half-doses are not recommended in patients with systolic blood pressure (SBP) less than 90 mmHg, diastolic blood pressure (DBP) less than 60 mmHg, heart rate (HR) less than 60 beats per minute, or postural decrease in SBP ≥20 mmHg or DBP ≥10 mmHg.[9]

Recommended Dosage for Adults <65 Years of Age

The recommended initial dose for adult patients <65 years of age is 120 mcg or 180 mcg depending on agitation severity. Lower doses are recommended for geriatric patients or those with hepatic impairment (Table 4).[9]

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Table 4 **Dosage Recommendations for IGALMI in Adults, Adult Patients with Hepatic Impairment, and Geriatric Patients with Agitation Associated with Schizophrenia or Bipolar I or II Disorder**

Patient Population	Agitation Severity	Initial Dose*	Optional 2nd/3rd Doses*	Maximum Recommended Total Daily Dosage
Adults	Mild or Moderate	120 mcg	60 mcg	240 mcg
	Severe	180 mcg	90 mcg	360 mcg
Patients with Mild or Moderate Hepatic Impairment†	Mild or Moderate	90 mcg	60 mcg	210 mcg
	Severe	120 mcg	60 mcg	240 mcg
Patients with Severe Hepatic Impairment†	Mild or Moderate	60 mcg	60 mcg	180 mcg
	Severe	90 mcg	60 mcg	210 mcg
Geriatric Patients (≥65 years old)	Mild, Moderate, or Severe	120 mcg	60 mcg	240 mcg

*IGALMI 120 mcg and 180 mcg dosage strengths may be cut in half to obtain the 60 mcg and 90 mcg doses, respectively.

†Hepatic impairment: Mild (Child-Pugh Class A); Moderate (Child-Pugh Class B); Severe (Child-Pugh Class C).

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Clinical Evidence

The clinical program for IGALMI for the acute treatment of agitation associated with schizophrenia or bipolar I or II disorder consists of two phase 3 studies that supported regulatory approval in the US for this indication (Table 5).

Table 5 Phase 3 Clinical Studies for IGALMI in Agitation with Schizophrenia or Bipolar I or II Disorder

Study Name	Study Description
SERENITY I	A Phase III, Multicenter, Randomized, Double-blind, Placebo-Controlled Study to Determine Efficacy and Safety of IGALMI in Agitation Associated with Schizophrenia
SERENITY I I	A Phase III, Multicenter, Randomized, Double-blind, Placebo-Controlled Study to Determine Efficacy and Safety of IGALMI in Agitation Associated with Bipolar I or II Disorder

Acute Agitation in Schizophrenia

BXCL501-301 (SERENITY I)

Name of study: A phase III, multicenter, randomized, double-blind, placebo-controlled study to determine efficacy and safety of BXCL501 [IGALMI] in agitation associated with schizophrenia.

Citations: Data on file. BXCL501 (dexmedetomidine) sublingual film clinical study report - protocol BXCL501-301. 2020. IGALMI. Prescribing information. BioXcel Therapeutics, Inc.; 2022.

Sponsor or funding source: BioXcel Therapeutics, Inc.

NCT identifier: NCT04268303

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Acute Agitation in Schizophrenia (cont'd)

Objective

The primary objective was to determine if a single dose of IGALMI effectively reduced symptoms of acute agitation associated with schizophrenia, schizoaffective disorder, or schizophreniform disorder assessed using the PEC change from baseline as compared with placebo.[10]

The secondary objective was to determine the earliest time where an effect on agitation was apparent as measured by the change from baseline PEC total score in contrast with placebo.[10]

Exploratory objectives aimed to further determine the efficacy, safety, tolerability, and pharmacokinetics of IGALMI in patients with acute agitation associated with schizophrenia, schizoaffective disorder, or schizophreniform disorder, included[10]:

- Determine the overall clinical improvement after drug administration as measured by the Clinical Global Impressions – Improvement (CGI-I) scale

- Describe the duration of calming as measured by PEC and Agitation and Calmness Evaluation Scale (ACES)

- Determine the safety profile of IGALMI as measured by reports of adverse events (AEs), vital signs, laboratory values, and electrocardiograms

- Describe the overall tolerability in terms of treatment-emergent adverse event (TEAE) reports and local site (buccal/sublingual) tolerability of film

- Describe the patient's opinion on taste, acceptability, and likability of study medication

Location

SERENITY I enrolled patients at 15 investigative sites within the US.[10]

Study Start and Completion Dates

The study started (first consent) on January 23, 2020, and ended (final study visit) on May 8, 2020.[10]

Trial Design, Randomization, and Blinding Procedures

BXCL501-301 was a phase 3, multicenter, randomized, double-blind, placebo-controlled study. Patients were randomized in a 1:1:1 ratio to either IGALMI 180 mcg, IGALMI 120 mcg, or placebo (Figure 4). A randomized, double-blind, parallel-groups design enabled the sponsor, all patients, and study staff involved to be shielded from treatment assignment and outcomes.[10]
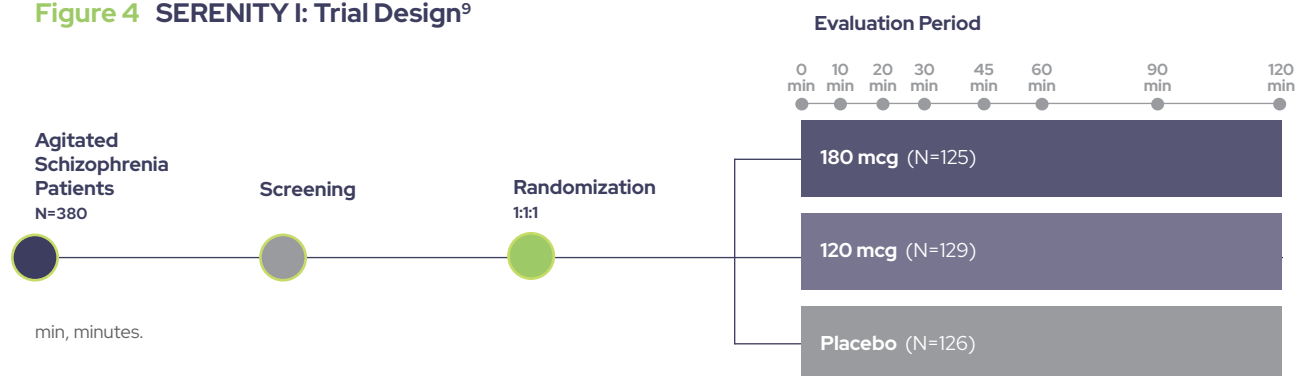
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Acute Agitation in Schizophrenia (cont'd)

Figure 4   SERENITY I: Trial Design[9]

Treatments and Interventions

Patients meeting entry criteria were randomized to IGALMI at a dose of 120 mcg, 180 mcg, or matching placebo. At the time of dosing, patients were instructed to take the product sublingually and to retain it in the sublingual cavity until dissolved. The patients self-administered the product under the supervision of a trained staff member. In the event of persistent or recurrent agitation, investigators could choose to redose the patients with 60 mcg or 90 mcg (cutting the 120 mcg or 180 mcg film in half) after the 2-hour time point. The criteria for redosing were a PEC change from baseline <40% and the absence of safety concerns. Vital signs were assessed, including orthostatic measurements, prior to the administration of any subsequent doses. Due to the risk of hypotension, additional half-doses were not recommended in patients with SBP less than 90 mmHg, DBP less than 60 mmHg, HR less than 60 beats per minute, or postural decrease in SBP ≥20 mmHg or in DBP ≥10 mmHg. The maximum number of repeat doses per patient was 2, during the 12 hours after the first dose. Doses could be administered no sooner than 2 hours after a prior dose.[10]

Following administration of the study drug, assessment of agitation was conducted at serial time points using standard agitation scales over a 24-hour period. The study included a Screening Visit, Treatment Visit (Day 1), Follow-up Visit (Day 2), Discharge (Day 3), and End of Study Visit (Day 7).[10]

Setting, Inclusion, and Exclusion Criteria

The study was conducted in patients who were either newly admitted to a hospital setting or a research unit for acute agitation, or already in-hospital for the treatment of schizophrenia.[10]

Key inclusion and exclusion criteria for the SERENITY I trial are provided in (Table 6).

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Table 6 SERENITY I: Inclusion and Exclusion Criteria

Inclusion Criteria[10]
1	Male and female patients between the ages of 18 and 75 years, inclusive.
2	Patients who met *DSM-5* criteria for schizophrenia, schizoaffective, or schizophreniform disorder.
3	Patients who were judged to be clinically agitated at Screening and Baseline with a total score of ≥14 on the 5 items (poor impulse control, tension, hostility, uncooperativeness, and excitement) comprising the PEC.
4	Patients who had a score of ≥4 on at least 1 of the 5 items on the PEC at baseline.
5	Patients who read, understood, and provided written informed consent.
6	Patients who were in good general health prior to study participation as determined by a detailed medical history, physical examination, 12-lead ECG with rhythm strip, blood chemistry profile, hematology, urinalysis, and in the opinion of the principal investigator.
7	Female participants, if of child-bearing potential and sexually active, and male participants, if sexually active with a partner of child-bearing potential, who agreed to use a medically acceptable and effective birth control method throughout the study and for 1 week following the end of the study. Medically acceptable methods of contraception that could be used by the participant and/or his/her partner included abstinence, birth control pills or patches, diaphragm with spermicide, intrauterine device, condom with foam or spermicide, vaginal spermicidal suppository, surgical sterilization, and progestin implant or injection. Prohibited methods included the rhythm method, withdrawal, condoms alone, or diaphragm alone.

Exclusion Criteria[10]
1	Patients with agitation caused by acute intoxication, including positive identification of alcohol by breathalyzer or drugs of abuse (with the exception of THC) during urine screening.
2	Use of benzodiazepines, other hypnotics, or antipsychotic drugs in the 4 hours before study treatment.
3	Treatment with alpha-1 noradrenergic blockers (terazosin, doxazosin, tamsulosin, alfuzosin, or prazosin) or other prohibited medications.
4	Patients judged to be at serious risk of suicide.
5	Female patients who had a positive pregnancy test at screening or are breastfeeding.
6	Patients who had hydrocephalus, seizure disorder, or history of significant head trauma, stroke, transient ischemic attack, subarachnoid bleeding, brain tumor, encephalopathy, meningitis, Parkinson's disease, or focal neurological findings.
7	History of syncope or other syncopal attacks, current evidence of hypovolemia, orthostatic hypotension (average of 1-, 3-, and 5-minute measurements), a screening and baseline HR of <55 beats per minutes or SBP <110 mmHg or DBP <70 mmHg.
8	Patients with laboratory or ECG abnormalities considered clinically significant by the investigator or qualified designee (advanced heart block [second-degree or above atrioventricular block without pacemaker], diagnosis of sick sinus syndrome) that would have clinical implications for the patient's participation in the study.
9	Patients with serious or unstable medical illnesses. These include current hepatic (moderate–severe hepatic impairment), renal, gastroenterologic, respiratory, cardiovascular (including ischemic heart disease, congestive heart failure), endocrinologic, or hematologic disease.
10	Patients who had received an investigational drug within 30 days prior to the current agitation episode.
11	Patients who were considered by the investigator, for any reason, to be an unsuitable candidate for receiving IGALMI; eg, patients with a history of allergic reactions to IGALMI.

ECG, electrocardiogram; THC, tetrahydrocannabinol.

Please see Important Safety Information on pages 6, 20, and 70.

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Acute Agitation in Schizophrenia (cont'd)

Baseline Patient Characteristics and Demographics

For the overall Safety Population (N=380), mean (SD) age was 45.6 (11.4) years; 63.3% were male and 78% self–identified as Black or African American (Table 7). Most patients (84.5%) were diagnosed with schizophrenia (15.5%).

Demographic and baseline disease characteristics were generally comparable among the placebo and the IGALMI treatment groups, except for a lower percentage of Black or African American patients in the IGALMI 120 mcg group compared with the IGALMI 180 mcg group and placebo groups.[10]

Mean baseline PEC total scores were comparable across all treatment groups, indicating that most patients had moderate agitation at baseline.[10]

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Table 7 SERENITY I: Demographic and Baseline Characteristics (Safety Population)[10]

	IGALMI*		Placebo	Overall
	180 mcg N=126	120 mcg N=129	N=126	N=381
Age† (Years)				
Mean (SD)	46.0 (11.9)	45.7 (11.3)	45.1 (11.1)	45.6 (11.4)
Median (min, max)	48.0 (18, 71)	48.0 (21, 68)	46.0 (21, 68)	48.0 (18, 71)
Male sex, no. (%)	82 (65.1)	77 (59.7)	82 (65.1)	241 (63.3)
Race, no. (%)				
Asian	0	1 (0.8)	2 (1.6)	3 (0.8)
Black or African American	103 (81.7)	92 (71.3)	102 (81.0)	297 (78.0)
Native Hawaiian or Other Pacific Islander	0	0	0	0
White	21 (16.7)	33 (25.6)	21 (16.7)	75 (19.7)
Multiple	1 (0.8)	3 (2.3)	0	4 (1.0)
Other	1 (0.8)	0	1 (0.8)	2 (0.5)
Ethnicity, no. (%)				
Hispanic or Latino	13 (10.3)	17 (13.2)	7 (5.6)	37 (9.7)
Not Hispanic or Latino	113 (89.7)	112 (86.8)	119 (94.4)	344 (90.3)
Body Mass Index,‡ kg/m^2				
Mean (SD)	32.52 (7.9)	31.24 (7.6)	32.56 (7.4)	32.10 (7.6)
Median (min, max)	31.40 (18.6, 60.5)	30.20 (16.8, 48.9)	31.60 (18.3, 54.2)	31.30 (16.8, 60.5)
Diagnosis, no. (%)				
Schizoaffective	25 (19.8)	16 (12.4)	18 (14.3)	59 (15.5)
Schizophrenia	101 (80.2)	113 (87.6)	108 (85.7)	322 (84.5)
Days of Current Agitation Episode				
Mean (SD)	22.9 (48.3)	25.4 (95.3)	18.3 (34.9)	22.2 (65.0)
Median (min, max)	7.0 (1, 365)	7.0 (2, 999)	7.0 (2, 297)	7.0 (1, 999)
Number of Hospitalizations				
Mean (SD)	4.5 (9.8)	4.8 (5.4)	4.1 (5.2)	4.5 (7.1)
Median (min, max)	2.0 (0, 100)	3.0 (0, 23)	2.0 (0, 30)	2.0 (0, 100)
Hours of Sleep per Night This Week				
Mean (SD)	5.5 (1.7)	5.9 (1.6)	5.7 (1.8)	5.7 (1.7)
Median (min, max)	5.0 (2, 12)	6.0 (3, 11)	6.0 (2, 12)	6.0 (2, 12)
Smoking History, no. (%)				
Current	83 (65.9)	96 (74.4)	102 (81.0)	281 (73.8)
Ex-smoker	8 (6.3)	13 (10.1)	3 (2.4)	24 (6.3)
Never	35 (27.8)	20 (15.5)	21 (16.7)	76 (19.9)
Baseline PEC, no.§	125	129	126	380
Mean (SD)	17.6 (2.7)	17.5 (2.5)	17.6 (2.3)	Range, 14–27

*Patient BXCL501-301-03-1352 was erroneously enrolled in the IGALMI 120 mcg treatment group and subsequently in the IGALMI 180 mcg treatment group; the data from both enrollments are included in the table.
† Age is calculated as the integer part of (informed consent date – birth date + 1, divided by 365.25).
‡ Body mass index (kg/m^2) was calculated by: 10000*weight/height^2, rounded to 1 decimal place.
§ Intent-to-treat population.

max, maximum; min, minimum.

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Acute Agitation in Schizophrenia (cont'd)

Baseline Patient Characteristics and Demographics (cont'd)

A total of 308 patients (80.8%) used at least 1 concomitant medication during the study. The proportion of patients who received concomitant medications was 81.7% (103/126) in the IGALMI 180 mcg group, 82.9% (107/129) in the IGALMI 120 mcg group, and 77.8% (98/126) in the placebo group. The most commonly used medications according to the World Health Organization Drug Dictionary Anatomical Therapeutic Chemical (WHO-DD-ATC) classification system were "other antipsychotics" (32.9% [125/380]) and "diazepines, oxazepines, thiazepines, and oxepines" (32.1% [122/380]). The most frequently used medications within those classes were risperidone (18.4%), quetiapine (19.7%), and olanzapine (10.5%).[10]

As previously described, patients could be re-dosed with IGALMI for persistent or recurrent agitation. Five patients (4.0%) in the IGALMI 180 mcg group received 2 doses, and 28 patients (21.7%) in the IGALMI 120 mcg group received 2 or more doses of the study drug (Table 8). In the placebo group, 53 patients (42.1%) received 2 or more doses of the study drug.[10]

Table 8 **SERENITY I: Study Drug Exposure (Safety Population)[10]**

Doses Received, No.*	Patients, No. (%)		
	IGALMI*		Placebo N=126
	180 mcg N=125	120 mcg N=129	
1 dose	121 (96.0)	101 (78.3)	73 (57.9)
2 doses	5 (4.0)	16 (12.4)	29 (23.0)
3 doses	0	12 (9.3)	24 (19.0)

*Doses 2 and 3 were at half strength as per protocol. IGALMI 120 mcg and 180 mcg dosage strengths may be cut in half to obtain the 60 mcg and 90 mcg doses, respectively. See full Prescribing Information for preparation and administration instructions.

Drop-out Rates and Procedures for Handling Drop-outs

All 380 patients enrolled in the study received 1 or more doses of the study drug and completed the inpatient study drug treatment period (Table 9). Of these, 372 (97.9%) completed the study (duration of 7 days). The percentage of patients who discontinued the study was comparable across the 3 treatment groups.[10]

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Acute Agitation in Schizophrenia (cont'd)

Table 9 SERENITY I: Patient Disposition[10]

Category	Patients, No. (%)*			
	IGALMI[†]		Placebo	Overall
	180 mcg	120 mcg		
Randomized/Enrolled	125 (100.0)	129 (100.0)	126 (100.0)	380 (100.0)
Completed Study	123 (98.4)	126 (97.7)	123 (97.6)	372 (97.9)
Discontinued Study	2 (1.6)	3 (2.3)	3 (2.4)	8 (2.1)
Reason for Discontinuation				
Voluntarily withdrew[‡]	1 (0.8)	0	1 (0.8)	2 (0.5)
Lost to follow–up	1 (0.8)	1 (0.8)	2 (1.6)	4 (1.1)
AE	0	2 (1.6)	0	2 (0.5)

*Percentages are based on randomized patients.

†The second enrollment for the subject enrolled in both the 120 mcg treatment group and subsequently the 180 mcg treatment group (at a second site) completed both courses of treatment, but is included in the 120 mcg treatment group column.

‡All patients were free to withdraw from participation in this study at any time for any reason and without prejudice.

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Igalmi™
(dexmedetomidine)
sublingual film · 120 mcg, 180 mcg

Acute Agitation in Schizophrenia (cont'd)

Clinical Endpoints

The efficacy of IGALMI in reducing acute agitation was assessed using the PEC scale. The PEC comprises 5 items associated with agitation: excitement, uncooperativeness, tension, poor impulse control, and hostility; each scored 1 (absent) to 7 (extremely severe). The PEC score, the sum of these 5 subscales, thus ranges from 5 (absence of agitation) to 35 (extreme agitation).[10]

EXCITEMENT | UNCOOPERATIVENESS | TENSION | POOR IMPULSE CONTROL | HOSTILITY[3,11]

Each item is rated on a scale of 1 (absent) to 7 (extremely severe).
The total PEC score is calculated by taking the sum of the individual items.

Mild agitation	Moderate agitation	Severe agitation

A PEC score of ≥14, with at least 1 individual item score of ≥4, was required for enrollment

Total PEC score   5   14   20   35

The overall clinical improvement in agitation in response to treatment was measured by CGI-I.[10]

CGI-I scores range from 1 to 7[10]

0   not assessed (missing)
1   very much improved
2   much improved
3   minimally improved
4   no change
5   minimally worse
6   much worse
7   very much worse

ACES: overall agitation and sedation were evaluated[10]

1   marked agitation
2   moderate agitation
3   mild agitation
4   normal behavior
5   mild calmness
6   moderate calmness
7   marked calmness
8   deep sleep
9   unarousable

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Acute Agitation in Schizophrenia (cont'd)

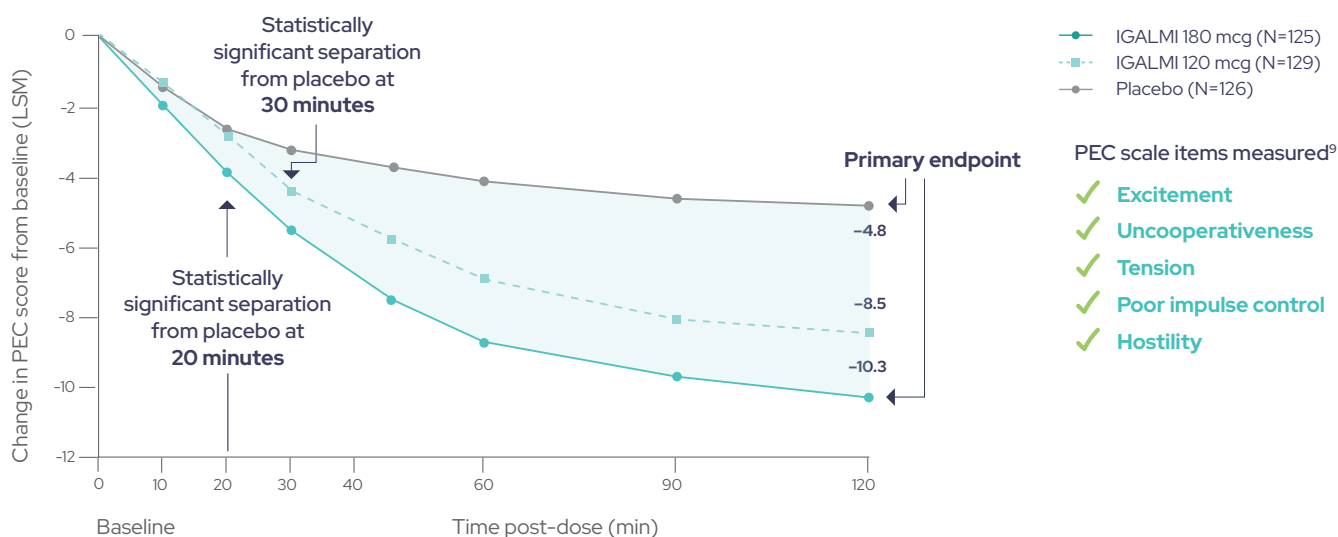### Clinical Endpoints (cont'd)

Primary Endpoint

The primary efficacy endpoint, reduction in symptoms of acute agitation assessed using the PEC change from baseline compared with placebo, was met in both IGALMI treatment groups. A statistically significant separation from placebo was observed 20 minutes post-dose for IGALMI 180 mcg and 30 minutes for IGALMI 120 mcg.[10]

Table 10 SERENITY I: Change in PEC from Baseline at 120 Minutes[10]

	Patients, No. (%)		
	IGALMI		
	180 mcg N=125	120 mcg N=129	Placebo N=126
Mean change (SD) in PEC total score from baseline	–10.3 (4.34)	–8.5 (4.83)	–4.8 (4.69)
LSM difference (SE) in PEC total score from placebo	–5.5 (0.5)	–3.7 (0.5)	NA
P-value	<0.0001	<0.0001	NA

Figure 5 SERENITY I: Change From Baseline in PEC Score Through 2 Hours Post-Dose[10]

Statistically significant separation from placebo at 30 minutes

Statistically significant separation from placebo at 20 minutes

Primary endpoint

—4.8
—8.5
—10.3

IGALMI 180 mcg (N=125)
IGALMI 120 mcg (N=129)
Placebo (N=126)

Change in PEC score from baseline (LSM)

Time post-dose (min)

Baseline

PEC scale items measured[9]
✓ Excitement
✓ Uncooperativeness
✓ Tension
✓ Poor impulse control
✓ Hostility

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Acute Agitation in Schizophrenia (cont'd)

Clinical Endpoints (cont'd)

Secondary Endpoint(s)

The earliest onset of action where an effect on agitation was apparent, measured by change from baseline PEC total score, was 20 minutes in the 180 mcg group (N=125), with statistically significant separation from placebo, LSM difference of –1.2 (*P*=0.0032), and 30 minutes in the 120 mcg group (N=129), with a statistically significant separation from placebo, LSM difference of –1.0 (*P*=0.0092).[10]

Exploratory Endpoints

Patients who had a ≥40% decrease from baseline in PEC total score after dosing were considered treatment responders. At 2 hours post–dose, response rates were higher in the IGALMI 180 mcg group (111/125 [88.8%]), LSM difference of 48.3 (*P*<0.0001), and 120 mcg (102/129 [79.1%]), LSM difference of 38.6 (*P*<0.0001), dose groups compared with placebo (51/126 [40.5%]).[10]
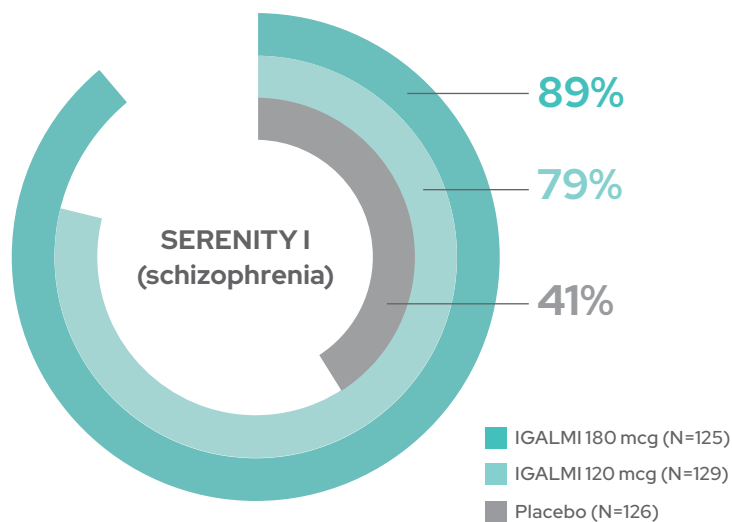
89%

79%

41%

SERENITY I
(schizophrenia)

IGALMI 180 mcg (N=125)
IGALMI 120 mcg (N=129)
Placebo (N=126)

The results on the primary efficacy parameter were consistent with results of assessments using other efficacy scales.

At 30, 60, 120, and 240 minutes post–dose, improvement in the IGALMI 180 mcg and 120 mcg groups was noted on the CGI–I scale as depicted in Figure 6.[10]

These are exploratory analysis; therefore, the results require cautious interpretation and could represent chance findings.

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Acute Agitation in Schizophrenia (cont'd)

Clinical Endpoints (cont'd)

Improvements in agitation as measured by the CGI-I (eg, lower CGI-I scores) from baseline were observed in the IGALMI 180 mcg group at 30 minutes post-dose (mean score of 2.7, "minimally improved"), 1 hour post-dose (1.9, "much improved"), and 2 hours and 4 hours (1.5, "much improved") post-dose. LSM differences from placebo post-dose were –0.5 at 30 minutes, –1.1 at 1 hour, –1.3 at 2 hours, and –1.3 at 4 hours. Improvements in agitation were also observed in the IGALMI 120 mcg group compared with placebo. LSM differences at 1, 2, and 4 hours were –0.6, –0.8, and –0.8.[10]

A responder was defined as a patient who achieved a CGI-I score of 1 ("very much improved") or 2 ("much improved") after dosing. The CGI-I responder analysis showed improvements at 2 hours post-dose (86.4% and 65.6% of patients in the IGALMI 180 mcg and 120 mcg groups, respectively), compared with 35.7% of patients in the placebo group (Figure 6).[10]

Figure 6 SERENITY I: Proportion of Responders (CGI-Scale) up to 4 hours Post-Dose[10]
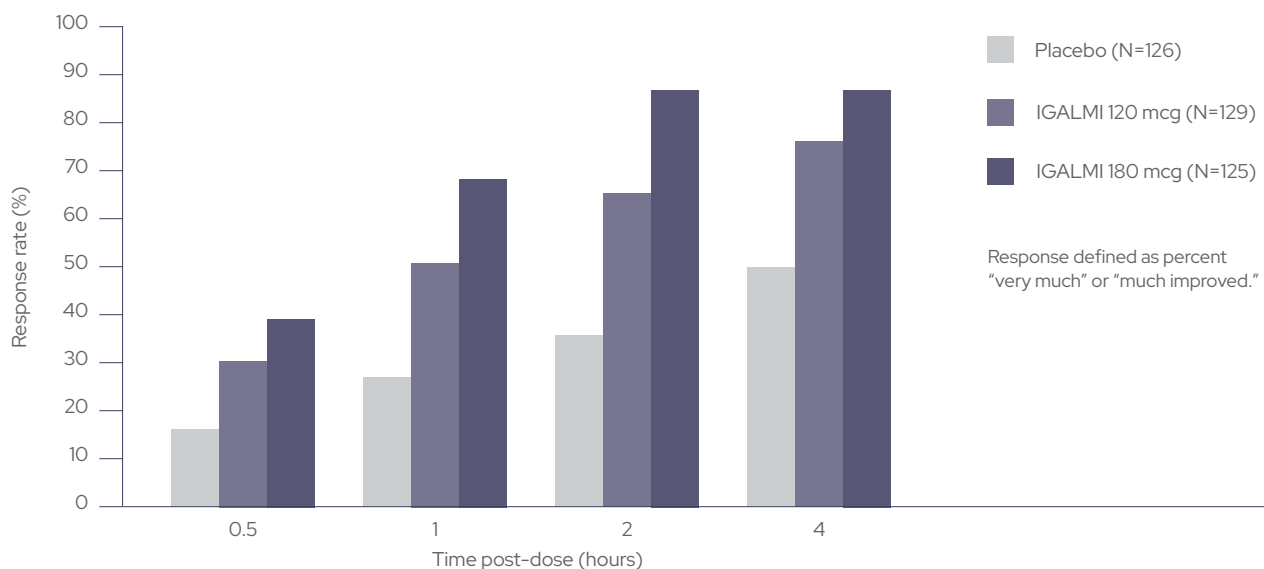
Mean scores at 2 hours post-dose were 6.0 (moderate calmness) in the IGALMI 180 mcg group, 4.9 (mild calmness) in the IGALMI 120 mcg group, and 3.3 (mild agitation) in the placebo group, from a baseline of approximately 2.3 (moderate agitation).[10]

This is an exploratory analysis; therefore, the results require cautious interpretation and could represent chance findings.

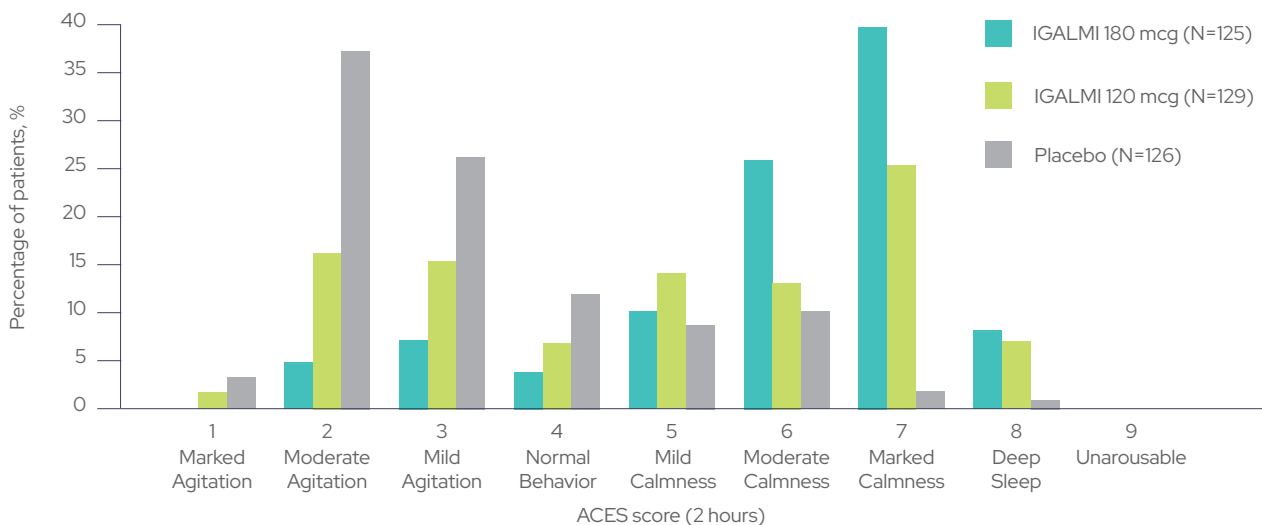**Please see Important Safety Information on pages 6, 20, and 70.**

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Acute Agitation in Schizophrenia (cont'd)

Clinical Endpoints (cont'd)

Figure 7 **Levels of calmness were assessed using the ACES[36]**

All patients were arousable at all ACES time points.

The ACES is a single–item measure rating overall agitation and sedation on a scale from 1 to 9, where 1 indicates marked agitation and 9 indicates unarousable. ACES was performed as an exploratory analysis at baseline (within 15 minutes of the first dose) and 2–, 4–, and 8–hours post-dose. Resolution of agitation was defined by an ACES score of 4 or higher.[10]

This is an exploratory analysis; therefore, the results require cautious interpretation and could represent chance findings.
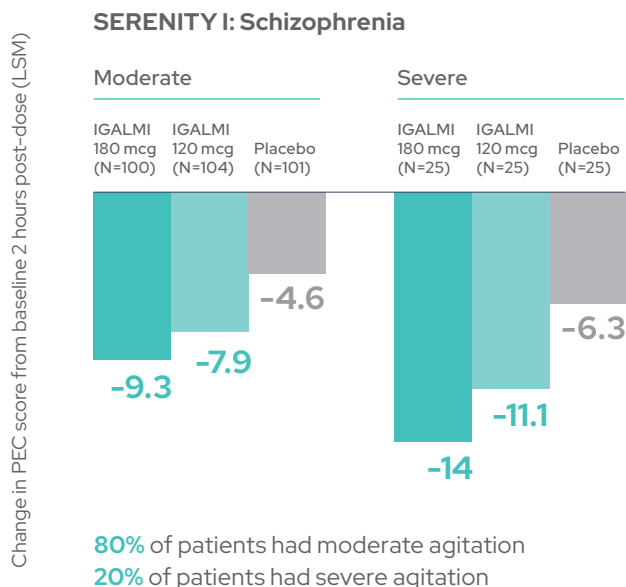
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Acute Agitation in Schizophrenia (cont'd)

Clinical Endpoints (cont'd)

Figure 8 **In an exploratory analysis, reductions in PEC score were observed across patients with moderate and severe agitation[37]**

SERENITY I: Schizophrenia

80% of patients had moderate agitation
20% of patients had severe agitation

A total PEC score of 14-19 at baseline was considered moderate agitation, and a total PEC score of 20–35 at baseline was considered severe agitation.[3,11]

Dosage recommendations for IGALMI: Adult patients <65 years old should be administered 120 mcg for mild to moderate agitation or 180 mcg for severe agitation. Lower dosages are recommended for patients with hepatic impairment and geriatric patients. Please see full Prescribing Information for complete dosing recommendations.[9]

This is an exploratory analysis; therefore, the results require cautious interpretation and could represent chance findings.

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Acute Agitation in Schizophrenia (cont'd)

Safety

Overall, a total of 117/381 patients (30.7%) experienced at least 1 TEAE (Table 11).[10] The proportion of patients who experienced TEAEs was comparable in the IGALMI 180 mcg and 120 mcg groups (47/126 [37.3%] and 51/129 [39.5%], respectively); TEAE incidence was lower in the placebo group (19/126 [15.1%]). None of the patients experienced a TEAE that was considered severe in intensity. There were no SAEs or deaths reported.[10]

Two patients in the IGALMI 120 mcg group discontinued from the study due to AEs (preferred terms of pain in extremity and oropharyngeal pain).[10]

Table 11 **SERENITY I: Summary of AEs (Safety Population)[10]***

	IGALMI		Placebo N=126	Overall N=381
	180 mcg N=126	120 mcg N=129		
Any TEAE, no. (%)	47 (37.3)	51 (39.5)	19 (15.1)	117 (30.7)
Any treatment-related TEAE, no. (%)	44 (34.9)	46 (35.7)	15 (11.9)	105 (27.6)
TEAE severity				
Mild	38 (30.2)	43 (33.3)	19 (15.1)	100 (26.2)
Moderate	9 (7.1)	8 (6.2)	0	17 (4.5)
Severe	0	0	0	0
Any SAE, no. (%)	0	0	0	0
Any AE leading to discontinuation, no. (%)	0	2 (1.6)	0	2 (0.5)

*Percentages are based on the number of Safety Population patients in each treatment arm. If a patient experienced more than 1 AE in a category, the patient is counted only once in that category.

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Acute Agitation in Schizophrenia (cont'd)

Safety (cont'd)

In the IGALMI treatment groups, TEAE incidence was highest in the nervous system disorders system organ class (SOC), with somnolence being the most frequently reported TEAE within this SOC (Table 12).[10]

Table 12 SERENITY I: TEAEs by SOC Occurring in ≥2 Patients[10]

SOC Preferred Term	Patients, No. (%)		
	IGALMI		Placebo
	180 mcg N=126	120 mcg N=129	N=126
Nervous system disorders	**38 (30.2)**	**38 (29.5)**	**16 (12.7)**
Somnolence	29 (23.0)	28 (21.7)	10 (7.9)
Headache	4 (3.2)	6 (4.7)	6 (4.8)
Hypoaesthesia oral	7 (5.6)	5 (3.9)	0
Dizziness	5 (4.0)	3 (2.3)	1 (0.8)
Paraesthesia oral	3 (2.4)	5 (3.9)	1 (0.8)
Gastrointestinal disorders	**10 (7.9)**	**13 (10.1)**	**4 (3.2)**
Dry mouth	5 (4.0)	10 (7.8)	2 (1.6)
Nausea	2 (1.6)	3 (2.3)	1 (0.8)
Vascular disorders	**13 (10.3)**	**11 (8.5)**	**2 (1.6)**
Hypotension	5 (4.0)	8 (6.2)	0
Orthostatic hypotension	7 (5.6)	2 (1.6)	0
Cardiac disorders	**0**	**3 (2.3)**	**1 (0.8)**
Sinus bradycardia	0	2 (1.6)	0
Ear and labyrinth disorders	**2 (1.6)**	**0**	**0**
Tinnitus	2 (1.6)	0	0

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Acute Agitation in Schizophrenia (cont'd)

Safety (cont'd)

Hypotension, orthostatic hypotension, bradycardia, and somnolence (cases rated moderate in severity) were considered adverse events of special interest (AESIs) (Table 12). No patient in any of the treatment groups required pharmacologic interventions to treat an AESI. All AESIs of orthostatic hypotension, hypotension, and bradycardia were reviewed by an external board-certified cardiologist.[10]

Please see pooled safety data in Table 22 of the Evidence Summary on page 69.

There were no clinically meaningful mean changes from baseline at 2 or 24 hours post-dose for PR interval, QRS duration, QTcF, and RR interval. IGALMI prolongs the QT interval. Avoid use of IGALMI in patients at risk of torsades de pointes or sudden death including those with known QT prolongation, a history of other arrhythmias, symptomatic bradycardia, hypokalemia or hypomagnesemia, and in patients receiving other drugs known to prolong the QT interval.[9]

Over 90% of the subjects in all treatment groups judged the study medication as having no unpleasant aftertaste and approximately 99% of all subjects said the medication did not have an unpleasant smell. None of the patients in any of the treatment groups had a negative reaction to the study drug at any of the prespecified timepoints, with the exception of one patient in the IGALMI 180 mcg group who had signs of local irritation based on buccal examination. Most patients responded that they found the medication to be acceptable.[10]

PR, time from the onset of the P wave to the start of the QRS complex on an electrocardiogram; QRS, electrocardiographic complex consisting of the Q, R, and S waves; QT, interval from the beginning of the QRS complex to the end of the T wave; QTcF, QT corrected for heart rate by Fridericia's cube root formula; RR, interval between successive Rs.

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Acute Agitation in Schizophrenia (cont'd)

Measures of Effect

The sample size estimate was based on results from the IGALMI phase 1b study (Study 102) using the standard deviation of PEC score change from baseline and the expected magnitude of this difference. Assuming a two-sided significance level of 0.025, a two-sample t-test, a randomization ratio of 1:1:1, an assumed power of 0.90, and standard deviations of 4.0, 4.2, 4.4, and 4.6, a sample size of approximately 375 patients (125/group) was needed to detect differences at 45 minutes or later.[10]

A blinded sample size recalculation took place when approximately 50% of the information was available. The pooled standard deviation of the change from baseline in PEC total score was computed at each time point. The sample size was then recalculated with the potential to adjust the sample size accordingly. Based on this recalculation, no readjustment of the sample size was needed.[10]

Validation of Outcomes Instruments

The proper and consistent administration of the efficacy rating scales was critical to the concise evaluations of the study objectives.

As a subscale of the PANSS, the PEC is a well-described, psychometrically validated, and clinically accepted measurement that quantifies the common core behavioral manifestations of agitation associated with psychosis, including schizophrenia. Multiple oral, IM, and inhaled antipsychotics have utilized the PEC as a primary endpoint for demonstrating clinical efficacy for the acute treatment of agitation in psychotic disorders, including schizophrenia.[10]

The CGI-S scale was performed at screening and immediately prior to the start of dosing. The CGI-S scale was focused on the severity of agitation rather than the severity of the overall illness of schizophrenia.[10]

The ACES is a single-item measure rating overall agitation and sedation.[10]

1	marked agitation		6	moderate calmness
2	moderate agitation		7	marked calmness
3	mild agitation		8	deep sleep
4	normal behavior		9	unarousable
5	mild calmness			

This scale is for rating overall agitation and sedation in research and clinical trials.[3]
There are 19 peer-reviewed published studies reporting on the use of the ACES in clinical trials.[10]

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Acute Agitation in Schizophrenia (cont'd)

Generalizability of the Population Treated

All patients enrolled in SERENITY I met *DSM-5* criteria for schizophrenia (84.5%) or schizoaffective (15.5%) disorder and ranged in age from 18 to 71 years. All patients in SERENITY I self-administered the study drug.[10]

Study Limitations (as Noted by Study Authors)

Study limitations include assessing safety and efficacy during only a single episode of agitation.[10]

END OF SERENITY I

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Acute Agitation in Bipolar I or II Disorder

BXCL501-302 (SERENITY II)

Name of study: A phase III, multicenter, randomized, double-blind, placebo-controlled study to determine efficacy and safety of BXCL501 [IGALMI] in agitation associated with bipolar disorder.

Citations: Data on file. BXCL501 (dexmedetomidine) sublingual film clinical study report - protocol BXCL501-302. 2020; IGALMI. Prescribing information. BioXcel Therapeutics, Inc.; 2022.

Sponsor or funding source: BioXcel Therapeutics, Inc.

NCT identifier: NCT04276883

Objective

The primary objective of the study was to determine if a single dose of IGALMI effectively reduced symptoms of acute agitation associated with bipolar I or II disorder assessed using the PEC change from baseline as compared with placebo.[34]

The secondary objective was to determine the earliest time when an effect on agitation was apparent as measured by change from baseline PEC total score in contrast with placebo.[34]

Exploratory objectives, aimed to further determine efficacy, safety, tolerability, and pharmacokinetics of IGALMI in patients with acute agitation associated with bipolar I or II disorder, included[34]:

- Determine the overall clinical improvement after drug administration as measured by the CGI-I

- Describe the duration of calming as measured by PEC and ACES

- Determine the safety profile of IGALMI as measured by reports of AEs and vital signs

- Describe the overall tolerability in terms of TEAE reports and local site (buccal/sublingual) tolerability of film

- Describe the patient's opinion of taste, acceptability, and likability of study medication

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sublingual film · 120 mcg, 180 mcg

Acute Agitation in Bipolar I or II Disorder (cont'd)

Location

The SERENITY II trial enrolled patients at 15 investigative sites within the US.[34]

Study Start and Completion Dates

The study started (first consent) on February 24, 2020, and ended (final study visit) on May 21, 2020.[34]

Trial Design, Randomization, and Blinding Procedures

BXCL501-302 was a multicenter, randomized, double-blind, placebo-controlled study that randomized patients in a ratio of 1:1:1 to IGALMI 180 mcg, IGALMI 120 mcg, or placebo (Figure 9).[34] The randomized, double-blind, parallel-group design ensured that the sponsor, all patients, and study staff involved were shielded from treatment assignment and outcomes and, therefore, minimized any potential bias. The randomization ratio provided an additional element to ensure blinding by decreasing the odds of guessing treatment arms.[34]

Figure 9 SERENITY II: Trial Design[9]
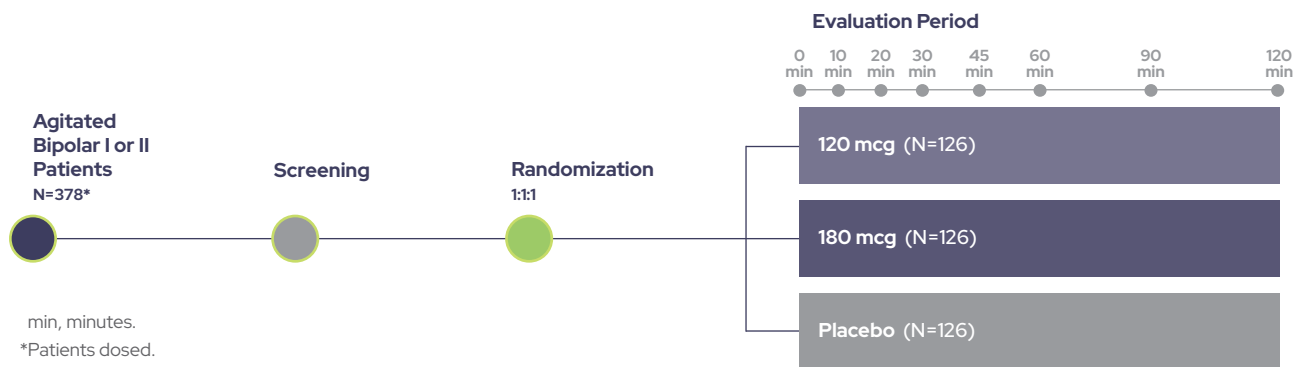
min, minutes.
*Patients dosed.

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Acute Agitation in Bipolar I or II Disorder (cont'd)

Treatments and Interventions

Treatments evaluated were IGALMI at a dose of 120 mcg or 180 mcg, or matching placebo. At the time of dosing, patients were instructed on how to take the investigational product sublingually, and that they should retain the investigational product in the sublingual cavity until dissolved. The patients self-administered the dose under the supervision of a trained staff member. In the event of persistent or recurrent agitation, investigators could choose to redose at 90 mcg or 60 mcg (by cutting the 180 mcg or 120 mcg film in half) after 2 hours as measured by a PEC change from baseline <40% but in the absence of safety concerns. Vital signs were assessed including orthostatic measurements prior to the administration of any subsequent doses. Due to the risk of hypotension, additional half-doses were not recommended in patients with SBP less than 90 mmHg, DBP less than 60 mmHg, HR less than 60 beats per minute, or postural decrease in SBP ≥20 mmHg or in DBP ≥10 mmHg.[9]

Following administration of the study drug, assessment of agitation was conducted at serial time points using standard agitation scales over a 24-hour period. The study included a Screening Visit, Treatment Visit (Day 1), Follow-up Visit (Day 2), Discharge (Day 3), and End of Study Visit (Day 7).[34]

Setting, Inclusion, and Exclusion Criteria

Eligible patients (acutely agitated patients with bipolar I or II disorder) were identified in outpatient clinics; mental health, psychiatric, or medical emergency services, including medical/psychiatric observation units; or as newly admitted to a hospital setting for acute agitation, or already hospitalized for chronic underlying conditions.[34]

Inclusion and exclusion criteria for the SERENITY II trial are provided in Table 13.

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Acute Agitation in Bipolar I or II Disorder (cont'd)

Table 13 SERENITY II: Inclusion and Exclusion Criteria

Inclusion Criteria[34]
1 Male and female patients between the ages of 18 and 75 years, inclusive.
2 Patients who met *DSM-5* criteria for bipolar I or II disorder.
3 Patients who were judged to be clinically agitated at Screening and Baseline with a total score of ≥14 on the 5 items (poor impulse control, tension, hostility, uncooperativeness, and excitement) comprising the PEC.
4 Patients who had a score of ≥4 on at least 1 of the 5 items on the PEC at Baseline.
5 Patients who read, understood, and provided written informed consent.
6 Patients who were in good general health prior to study participation as determined by a detailed medical history, physical examination, 12-lead ECG with rhythm strip, blood chemistry profile, hematology, urinalysis, and in the opinion of the Principal Investigator.
7 Female participants, if of child-bearing potential and sexually active, and male participants, if sexually active with a partner of child-bearing potential, who agreed to use a medically acceptable and effective birth control method throughout the study and for 1 week following the end of the study. Medically acceptable methods of contraception that could be used by the participant and/or his/her partner included abstinence, birth control pills or patches, diaphragm with spermicide, intrauterine device (IUD), condom with foam or spermicide, vaginal spermicidal suppository, surgical sterilization, and progestin implant or injection. Prohibited methods included the rhythm method, withdrawal, condoms alone, or diaphragm alone.

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Acute Agitation in Bipolar I or II Disorder (cont'd)

Table 13 SERENITY II: Inclusion and Exclusion Criteria (cont'd)

Exclusion Criteria[34]
1   Patients with agitation caused by acute intoxication, including positive identification of alcohol by breathalyzer or drugs of abuse (with the exception of THC) during urine screening.
2   Use of benzodiazepines, other hypnotics, or antipsychotic drugs in the 4 hours before study treatment.
3   Treatment with alpha-1 noradrenergic blockers (terazosin, doxazosin, tamsulosin, alfuzosin, or prazosin) or other prohibited medications.
4   Patients judged to be at serious risk of suicide.
5   Female patients who had a positive pregnancy test at screening or were breastfeeding.
6   Patients who had hydrocephalus, seizure disorder, or history of significant head trauma, stroke, transient ischemic attack, subarachnoid bleeding, brain tumor, encephalopathy, meningitis, Parkinson's disease, or focal neurological findings.
7   History of syncope or other syncopal attacks, current evidence of hypovolemia, orthostatic hypotension (average of 1-, 3-, and 5-minute measurements), a screening and baseline HR of <55 beats per minutes or SBP <110 mmHg or DBP <70 mmHg.
8   Patients with laboratory or ECG abnormalities considered clinically significant by the investigator or qualified designee (advanced heart block [second-degree or above atrioventricular block without pacemaker], diagnosis of sick sinus syndrome) that would have clinical implications for the patient's participation in the study.
9   Patients with serious or unstable medical illnesses. These included current hepatic (moderate–severe hepatic impairment), renal, gastroenterologic, respiratory, cardiovascular (including ischemic heart disease and congestive heart failure), endocrinologic, or hematologic disease.
10   Patients who had received an investigational drug within 30 days prior to the current agitation episode.
11   Patients who were considered by the investigator, for any reason, to be an unsuitable candidate for receiving IGALMI; eg, patients with a history of allergic reactions to IGALMI.

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Acute Agitation in Bipolar I or II Disorder (cont'd)

Baseline Patient Characteristics and Demographics

For the overall safety population (N=378), mean (SD) age was 45.6 (11.6) years (Table 14); 8 patients (3, 3, and 2 in the IGALMI 180 mcg, 120 mcg, and placebo groups, respectively) were ≥65 years of age. The majority of patients were female (54.8%) and Black or African American (56.1%). 47.6% of patients were diagnosed with mania.[34]

Demographic and baseline disease characteristics among the placebo and the IGALMI treatment groups were generally comparable, with the exception of a higher mean number of days of current agitation episode in the 180 mcg group (25.1 days [SD, 74.3%]) compared with the 120 mcg group (21.8 days [31.4%]) and the placebo group (15.7 days [21.9%]).[34]

Mean baseline PEC total scores were comparable across all treatment groups, indicating that most patients had moderate agitation at baseline.[34]

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Table 14 SERENITY II: Demographic and Baseline Characteristics (Safety Population)[34]

	IGALMI		Placebo N=126	Overall N=378
	180 mcg N=126	120 mcg N=126		
Age* (Years)				
Mean (SD)	45.9 (11.3)	46.1 (11.5)	44.8 (12.1)	45.6 (11.6)
Median (min, max)	47.0 (18, 69)	49.0 (19, 70)	48.0 (18, 67)	48.0 (18, 70)
Male sex, no. (%)	59 (46.8)	59 (46.8)	53 (42.1)	171 (45.2)
Race, no. (%)				
Asian	1 (0.8)	0	2 (1.6)	3 (0.8)
Black or African American	72 (57.1)	68 (54.0)	72 (57.1)	212 (56.1)
Native Hawaiian or Other Pacific Islander	0	0	0	0
White	49 (38.9)	56 (44.4)	50 (39.7)	155 (41.0)
Multiple	3 (2.4)	1 (0.8)	1 (0.8)	5 (1.3)
Other	1 (0.8)	1 (0.8)	1 (0.8)	3 (0.8)
Ethnicity, no. (%)				
Hispanic or Latino	15 (11.9)	12 (9.5)	11 (8.7)	38 (10.1)
Not Hispanic or Latino	111 (88.1)	114 (90.5)	115 (91.3)	340 (89.9)
Body Mass Index,[†] kg/m²				
Mean (SD)	33.27 (8.7)	31.62 (8.0)	32.50 (7.4)	32.46 (8.0)
Median (min, max)	31.70 (19.0, 66.9)	29.80 (18.0, 78.4)	31.85 (16.8, 59.6)	31.20 (16.8, 78.4)
Diagnosis, no. (%)				
Depressed	28 (22.2)	20 (15.9)	26 (20.6)	74 (19.6)
Hypomania	5 (4.0)	14 (11.1)	10 (7.9)	29 (7.7)
Mania	59 (46.8)	58 (46.0)	63 (50.0)	180 (47.6)
Mixed Episodes	30 (23.8)	27 (21.4)	22 (17.5)	79 (20.9)
Unspecified	4 (3.2)	7 (5.6)	5 (4.0)	16 (4.2)
Days of Current Agitation Episode				
Mean (SD)	25.1 (74.3)	21.8 (31.4)	15.7 (21.9)	20.9 (48.3)
Median (min, max)	9.0 (1, 730)	8.0 (1, 192)	7.0 (1, 132)	7.0 (1, 730)
Number of Hospitalizations				
Mean (SD)	2.8 (4.5)	3.5 (4.7)	2.8 (3.7)	3.0 (4.3)
Median (min, max)	1.0 (0, 20)	2.0 (0, 22)	2.0 (0, 20)	1.0 (0, 22)
Hours of Sleep per Night in Past Week				
Mean (SD)	5.1 (1.5)	5.3 (1.7)	5.1 (1.5)	5.2 (1.6)
Median (min, max)	5.0 (1, 9)	5.0 (2, 10)	5.0 (1, 10)	5.0 (1, 10)
Smoking History, no. (%)				
Current	78 (61.9)	97 (77.0)	83 (65.9)	258 (68.3)
Ex-smoker	14 (11.1)	9 (7.1)	15 (11.9)	38 (10.1)
Never	34 (27.0)	20 (15.9)	28 (22.2)	82 (21.7)
Baseline PEC				
Mean (SD)	18.0 (2.99)	18.0 (2.73)	17.9 (2.94)	Range, 14–30

*Age is calculated as the integer part of (informed consent date – birth date + 1, divided by 365.25).
†Body mass index (kg/m²) is calculated by 10000*weight/height², rounded to 1 decimal place. Weight measured in pound (lb) is converted to kilogram (kg) by a multiplication of 0.453592, rounded to 1 decimal place. Height measured in inch (in) is converted to centimeter (cm) by a multiplication of 2.54, rounded to 1 decimal place.

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Acute Agitation in Bipolar I or II Disorder (cont'd)

Baseline Patient Characteristics and Demographics (cont'd)

A total of 296 patients (78.3%) used at least 1 concomitant medication during the study. The proportion of patients who received concomitant medications was 77.0% (97/126) in the IGALMI 180 mcg group, 82.5% (104/126) in the IGALMI 120 mcg group, and 75.4% (95/126) in the placebo group. The most commonly used medications according to the WHO-DD-ATC classification system were "other antidepressants" (26.2% [99/378]), "other antipsychotics" (23.3% [88/378]), and "diazepines, oxazepines, thiazepines, and oxepines" (23.0% [87/378]). The most frequently used medications within those classes were trazodone (11.4%), divalproex sodium (7.4%), and quetiapine (18.0%).[34]

As previously described, patients could be re-dosed with IGALMI for persistent or recurrent agitation. Thirteen patients (10.3%) in the IGALMI 180 mcg group and 30 patients (23.8%) in the IGALMI 120 mcg group received 2 or more doses of the study drug (Table 15). In the placebo group, 58 patients (46.0%) received 2 or more doses of the study drug.[34]

Table 15 **SERENITY II: Study Drug Exposure (Safety Population)[34]**

Doses Received, No.*	Patients, No. (%)		
	IGALMI		Placebo N=126
	180 mcg N=126	120 mcg N=126	
1 dose	113 (89.7)	96 (76.2)	68 (54.0)
2 doses	5 (4.0)	18 (14.3)	29 (23.0)
3 doses	8 (6.3)	12 (9.5)	29 (23.0)

*Doses 2 and 3 were at half strength as per protocol. IGALMI 120 mcg and 180 mcg dosage strengths may be cut in half to obtain the 60 mcg and 90 mcg doses, respectively. See full Prescribing Information for preparation and administration instructions.

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Acute Agitation in Bipolar I or II Disorder (cont'd)

Drop-out Rates and Procedures for Handling Drop-outs

A total of 380 patients were enrolled in the study (Table 16). Two of the patients (1 patient in each of the IGALMI 180 mcg and 120 mcg treatment groups) had protocol exclusion violations and were randomized in error; these patients did not receive the study drug. Of the 380 enrolled patients, 378 received 1 or more doses of the study drug and comprised the safety population (126 patients each in the IGALMI 180 mcg, IGALMI 120 mcg, and placebo groups). Of these patients, 362 (95.3%) completed the study, and 18 patients (4.7%) discontinued from the study.[34]

Table 16 SERENITY II: Patient Disposition[34]

Category	Patients, No. (%)*			
	IGALMI		Placebo	Overall
	180 mcg	120 mcg		
Randomized/Enrolled	127 (100.0)[†]	127 (100.0)[†]	126 (100.0)	380 (100.0)[†]
Completed Study	123 (96.9)	119 (93.7)	120 (95.2)	362 (95.3)
Discontinued Study	4 (3.1)	8 (6.3)	6 (4.8)	18 (4.7)
Reason for Discontinuation				
Voluntarily withdrew[‡]	2 (1.6)	3 (2.4)	6 (4.8)	11 (2.9)
Lost to follow-up	1 (0.8)	3 (2.4)	0	4 (1.1)
AE	0	1 (0.8)	0	1 (0.3)
Other[†]	1 (0.8)	1 (0.8)	0	2 (0.5)

*Percentages are based on randomized patients.
†One patient in each of the 180 mcg and 120 mcg groups was randomized in error.
‡All patients were free to withdraw from participation in this study at any time for any reason and without prejudice.

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Acute Agitation in Bipolar I or II Disorder (cont'd)
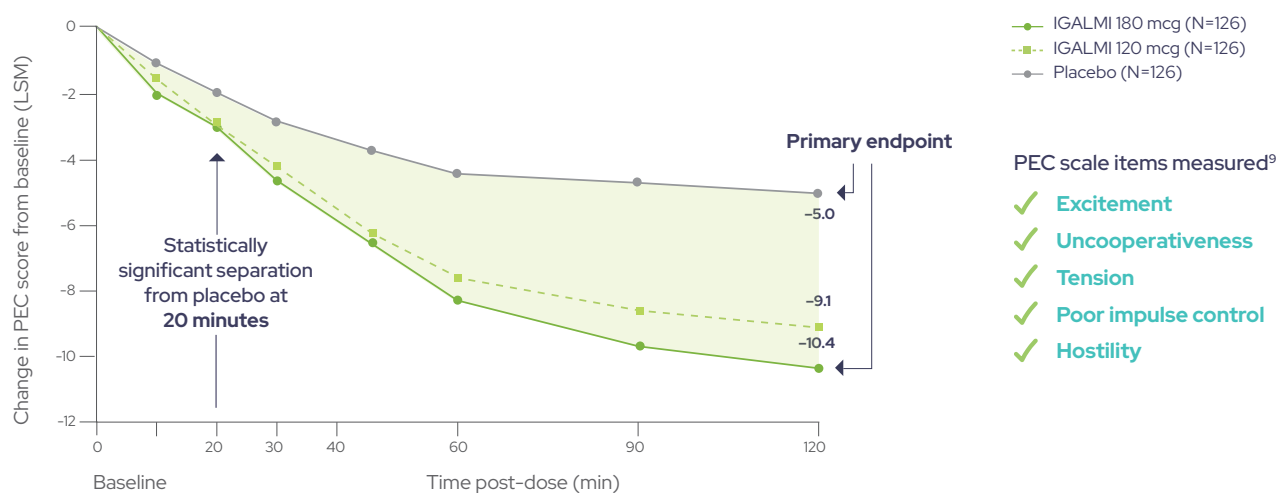
Clinical Endpoints

Please see page 37 for an explanation of PEC scale, CGI–scores, and ACES scores.

Primary endpoint: The primary efficacy endpoint, reduction in symptoms of acute agitation assessed using the PEC change from baseline compared with placebo, was met in both IGALMI treatment groups. A statistically significant separation from placebo was observed 20 minutes post–dose for both IGALMI 180 mcg and 120 mcg.[34]

Table 17 SERENITY II: Change in PEC From Baseline at 120 Minutes[34]

	Patients, No. (%)		
	IGALMI		
	180 mcg N=126	120 mcg N=126	Placebo N=126
Mean change (SD) in PEC total score from baseline	–10.4 (4.45)	–9.1 (5.26)	–5.0 (4.67)
LSM difference (SE) in PEC total score from placebo	–5.4 (0.5)	–4.1 (0.5)	NA
P-value	<.0001	<.0001	NA

Figure 10 SERENITY II: Change From Baseline in PEC Score Through 2 Hours Post-Dose[9,34]

PEC scale items measured[9]
- ✓ Excitement
- ✓ Uncooperativeness
- ✓ Tension
- ✓ Poor impulse control
- ✓ Hostility

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sublingual film · 120 mcg, 180 mcg

Acute Agitation in Bipolar I or II Disorder (cont'd)

Clinical Endpoints (cont'd)

Secondary endpoint: The earliest onset of action where an effect on agitation was apparent, measured by change from baseline PEC total score, was 20 minutes in both IGALMI treatment groups, with a statistically significant separation from placebo for the IGALMI 180 mcg group (N=126), LSM difference of –1.1 (*P*=0.0070), and the IGALMI 120 mcg group (N=126), LSM difference of –1.0 (*P*=0.0092).[34]

Exploratory endpoint: Patients who had a ≥40% decrease from baseline in PEC total score after dosing were considered treatment responders. At 2 hours post–dose, response rates were higher in the IGALMI 180 mcg group (114/126 [90.5%]), LSM difference of 44.4 (*P*>0.0001), and the IGALMI 120 mcg group (97/126 [77.0%]), LSM difference of 31.0 (*P*>0.0001), compared with placebo (58/126 [46.0%]).[34]
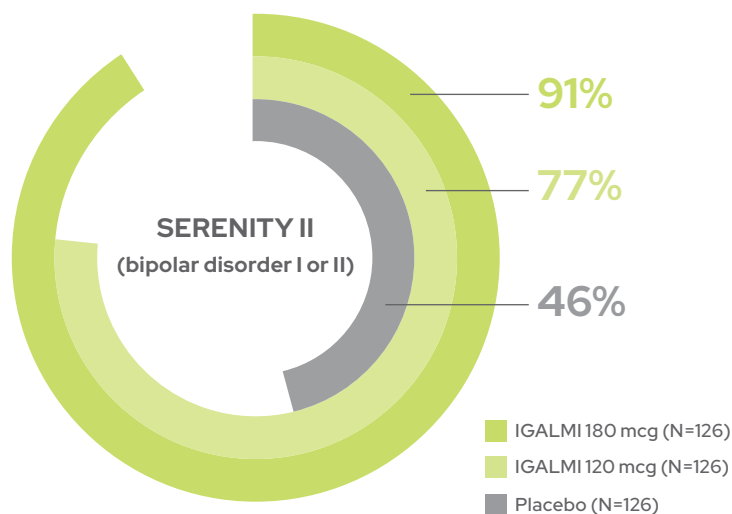
SERENITY II
(bipolar disorder I or II)

91%
77%
46%

■ IGALMI 180 mcg (N=126)
■ IGALMI 120 mcg (N=126)
■ Placebo (N=126)

The results on the primary efficacy parameter were consistent with results of assessments using other efficacy scales.

At 30, 60, 120, and 240 minutes post–dose, improvement in the IGALMI 180 mcg and 120 mcg groups was noted on the CGI-I scale as depicted in Figure 11.[34]

This is an exploratory analysis; therefore, the results require cautious interpretation and could represent chance findings.

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Acute Agitation in Bipolar I or II Disorder (cont'd)

Clinical Endpoints (cont'd)

Improvements in agitation as measured by the CGI-I (eg, lower CGI-I scores) from baseline were observed in the IGALMI 180 mcg group at 30 minutes post-dose (mean score of 3.0, "minimally improved"), 1 hour post-dose (2.0, "much improved"), 2 hours post-dose (1.6, "much improved"), and 4 hours post-dose (1.5, "much improved"). LSM differences from placebo post-dose were –0.4 at 30 minutes, –1.0 at 1 hour, –1.3 at 2 hours, and –1.1 at 4 hours. Improvements in agitation were also observed in the IGALMI 120 mcg group compared with placebo. LSM differences at 1, 2, and 4 hours were –0.8, –0.9, and –0.8.[34]

A responder was defined as a patient who achieved a CGI-I score of 1 ("very much improved") or 2 ("much improved") after dosing. The CGI-I responder analysis showed improvements at 2 hours post-dose (86.5% and 69.8% of patients in the IGALMI 180 mcg and 120 mcg groups, respectively), compared with 38.1% of patients in the placebo group (Figure 11).[34]

Figure 11 **SERENITY II: Proportion of Responders (CGI-scale) up to 4 Hours Post-Dose[34]**
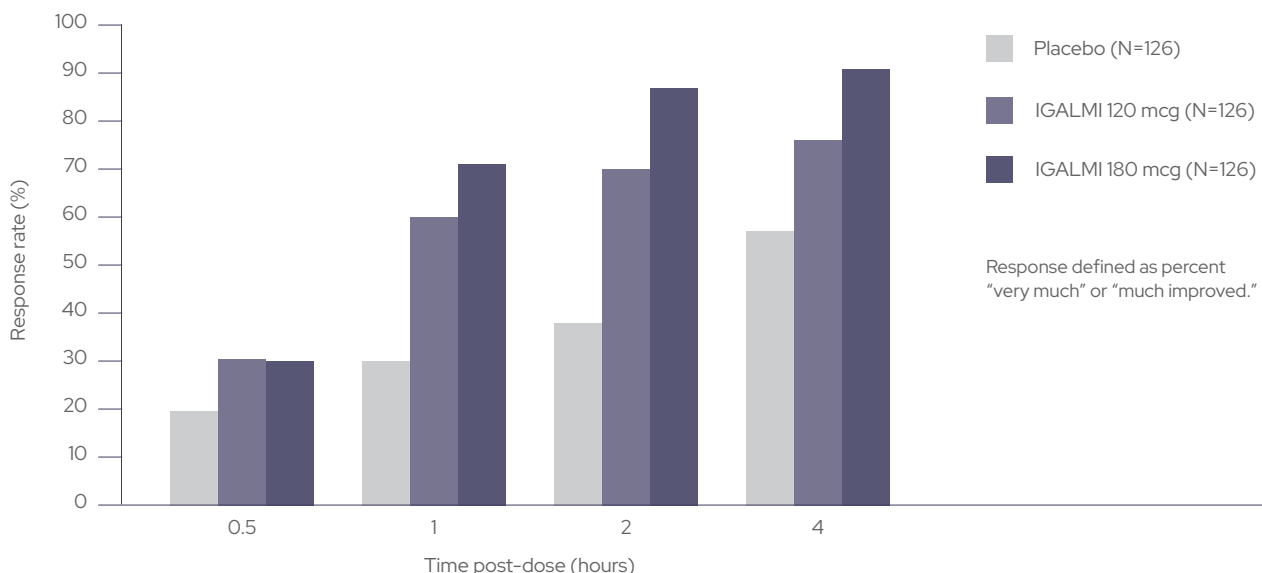
Mean scores at 2 hours post-dose were 5.6 (mild calmness) in the IGALMI 180 mcg group and 5.0 (moderate calmness) in the IGALMI 120 mcg group, compared with a mean score of 3.3 (mild agitation) in the placebo group, from a baseline of approximately 2.2 (moderate agitation).[34]

This is an exploratory analysis; therefore, the results require cautious interpretation and could represent chance findings.

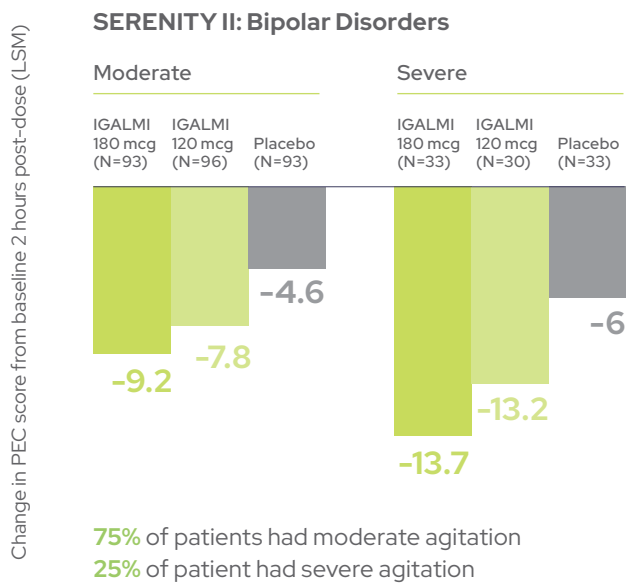**Please see Important Safety Information on pages 6, 20, and 70.**

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Acute Agitation in Bipolar I or II Disorder (cont'd)

Clinical Endpoints (cont'd)

Figure 12 In an exploratory analysis, reductions in PEC score were observed across patients with moderate and severe agitation[37]

SERENITY II: Bipolar Disorders

75% of patients had moderate agitation
25% of patient had severe agitation

A total PEC score of 14–19 at baseline was considered moderate agitation, and a total PEC score of 20–35 at baseline was considered severe agitation.[3,11]

Dosage recommendations for IGALMI: Adult patients <65 years old should be administered 120 mcg for mild to moderate agitation or 180 mcg for severe agitation. Lower dosages are recommended for patients with hepatic impairment, and geriatric patients. Please see full Prescribing Information for complete dosing recommendations.[9]

This is an exploratory analysis; therefore, the results require cautious interpretation and could represent chance findings.

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Acute Agitation in Bipolar I or II Disorder (cont'd)

Safety

Overall, a total of 111/378 patients (29.4%) experienced at least 1 TEAE (Table 18). The proportion of patients who experienced at least 1 TEAE was comparable in the IGALMI 180 mcg and 120 mcg groups (45/126 [35.7%] and 44/126 [34.9%]), compared with 22/126 (17.5%) patients in the placebo group. The proportion of patients who experienced at least 1 TEAE by SOC was generally lower in the placebo group compared with the IGALMI 180 mcg and 120 mcg groups. Almost all TEAEs were considered related to the study drug in all treatment groups.[34]

None of the patients experienced a TEAE that was considered serious. There were no deaths due to an AE reported in the study. One SAE that resulted in discontinuation from the study and was considered by the investigator to be unrelated to the study drug was reported in the IGALMI 120 mcg group. No other discontinuations related to the study drug were reported.[34]

Table 18 SERENITY II: Summary of TEAEs (Safety Population)[34]*

	IGALMI			
	180 mcg N=126	120 mcg N=126	Placebo N=126	Overall N=378
Any TEAE, no. (%)	45 (35.7)	44 (34.9)	22 (17.5)	111 (29.4)
Any treatment–related TEAE, no. (%)	39 (31.0)	41 (32.5)	15 (11.9)	95 (25.1)
TEAE severity, no. (%)				
Mild	30 (23.8)	35 (27.8)	19 (15.1)	84 (22.2)
Moderate	15 (11.9)	9 (7.1)	3 (2.4)	27 (7.1)
Severe	0	0	0	0
Any SAE, no. (%)	0	1 (0.8)	0	1 (0.3)
Any AE leading to discontinuation, no. (%)	0	1 (0.8)	0	1 (0.3)

*Percentages are based on the number of Safety Population patients in each treatment arm. If a patient experienced more than 1 AE in a category, the patient is counted only once in that category.

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Acute Agitation in Bipolar I or II Disorder (cont'd)

Safety (cont'd)

In the IGALMI treatment groups, TEAE incidence was highest in the nervous system disorders SOC, with somnolence the most frequently reported TEAE, followed by dry mouth (Table 19).[34]

Table 19 SERENITY II: TEAEs by SOC Occurring in ≥2 Patients[34]

SOC Preferred Term	IGALMI		Placebo N=126
	180 mcg N=126	120 mcg N=126	
Nervous system disorders	**31 (24.6)**	**34 (27.0)**	13 (10.3)
Somnolence	27 (21.4)	26 (20.6)	6 (4.8)
Dizziness	7 (5.6)	7 (5.6)	1 (0.8)
Headache	2 (1.6)	6 (4.8)	6 (4.8)
Gastrointestinal disorders	**20 (15.9)**	**16 (12.7)**	**5 (4.0)**
Dry mouth	6 (4.8)	9 (7.1)	1 (0.8)
Nausea	5 (4.0)	3 (2.4)	3 (2.4)
Hypoaesthesia oral	5 (4.0)	2 (1.6)	1 (0.8)
Paraesthesia oral	3 (2.4)	2 (1.6)	0
Dyspepsia	2 (1.6)	0	0
Vascular disorders	**14 (11.1)**	**10 (7.9)**	**4 (3.2)**
Hypotension	8 (6.3)	6 (4.8)	0
Orthostatic hypotension	6 (4.8)	5 (4.0)	1 (0.8)
Hypertension	0	1 (0.8)	3 (2.4)
Cardiac disorders, no. (%)	**5 (4.0)**	**3 (2.4)**	**1 (0.8)**
Bradycardia	3 (2.4)	2 (1.6)	0
Sinus bradycardia	2 (1.6)	1 (0.8)	0
Respiratory, thoracic, and mediastinal disorders	**3 (2.4)**	**0**	**0**
Dyspnea	2 (1.6)	0	0

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Acute Agitation in Bipolar I or II Disorder (cont'd)

Safety (cont'd)

Hypotension, orthostatic hypotension, bradycardia, and somnolence (cases rated moderate in severity) were considered to be AESIs (Table 19). No patient in any of the treatment groups required pharmacologic interventions to treat an AESI. All AESIs of orthostatic hypotension, hypotension, and bradycardia were reviewed by an external board-certified cardiologist.[34]

Please see pooled safety data in Table 22 of the Evidence Summary on page 69.

There were no clinically meaningful mean changes from baseline at 2 hours or 24 hours post-dose for PR interval, QRS duration, QTcF, and RR interval.[34] IGALMI prolongs the QT interval. Avoid use of IGALMI in patients at risk of torsades de pointes or sudden death including those with known QT prolongation, a history of other arrhythmias, symptomatic bradycardia, hypokalemia or hypomagnesemia, and in patients receiving other drugs known to prolong the QT interval.[9]

Over 90% of the subjects in all treatment groups judged the study medication as having no unpleasant aftertaste and approximately 99% of all subjects said the medication did not have an unpleasant smell. None of the patients in any treatment group had a negative reaction to the study drug at any of the prespecified timepoints, with the exception of 2 patients in the 120 mcg group and 1 patient in the 180 mcg group at 30 minutes post-dose. Most patients responded that they found the medication to be acceptable.[34]

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Acute Agitation in Bipolar I or II Disorder (cont'd)

Measures of Effect

The sample size was estimated using information from the phase 1b study (Study 102) using the standard deviation of PEC score change from baseline and the expected magnitude of this difference. Assuming a two-sided significance level of 0.025, a two-sample t-test, a randomization ratio of 1:1:1, an assumed power of 0.90, and standard deviations of 4.0, 4.2, 4.4, and 4.6, a sample size of approximately 375 patients (125/group) was needed to ensure that the study was well powered to detect differences at 45 minutes or later.[34]

A blinded sample-size recalculation took place when approximately 50% of the information was available. The pooled standard deviation of the change from baseline in PEC total score was computed at each time point. The sample size was then recalculated with the potential to adjust the sample size accordingly. No readjustment of the sample size was needed.[34]

Validation of Outcomes Instruments

The outcomes instruments in SERENITY II reflect those in SERENITY I and their validation is mentioned on page 46.

Generalizability of the Population Treated

Patients that enrolled in SERENITY II met *DSM-5* criteria for bipolar I or II disorder. 180 (47.6%) patients were diagnosed with mania; 79 (20.9%) patients had mixed episodes, 74 (19.6%) patients were diagnosed as depressed, 29 (7.7%) patients had hypomania, and 16 (4.2%) patients had unspecified diagnoses. Patients ranged in age from 18 to 70 years; the median duration of the agitation episodes was 7 days, ranging from 1 to 730 days. All patients in SERENITY II self-administered the study drug.[34]

Study Limitations (as Noted by Study Authors)

In February 2022, these data were published in the *Journal of the American Medical Association (JAMA)*. Limitations of this study included 1) it assessed efficacy and tolerability of sublingual IGALMI following only a single episode of agitation; 2) only those patients who were able or willing to self-administer the treatment were included; 3) participants were excluded for acute alcohol intoxication, but it was not possible to determine if drug or alcohol withdrawal contributed to agitation; 4) there is no consensus on the change in PEC score that represents the minimal clinically important difference; and 5) a large placebo effect was observed in the trial supporting the recommended use of nonpharmacologic techniques as part of the management of agitation.[35]

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Evidence Tables for Phase 3 Trials

Table 20 SERENITY I: BXCL501-301 Evidence Summary

Study name: A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Determine Efficacy and Safety of IGALMI in Agitation Associated with Schizophrenia (SERENITY I).

Citation: Data on file. BXCL501 (dexmedetomidine) sublingual film clinical study report - protocol BXCL501-301. 2020; IGALMI. Prescribing information. BioXcel Therapeutics, Inc.; 2022.

Study design: Phase III, multicenter, randomized, double-blind, placebo-controlled study.

Treatment group: IGALMI 120 mcg or 180 mcg, or to matching placebo.

Selected Inclusion Criteria
Men and women aged 18 to 75 years who met *DSM-5* criteria for schizophrenia, schizoaffective, or schizophreniform disorder.
Patients judged to be clinically agitated at screening and baseline, with a total score of ≥14 on the PEC.
Patients who had a score of ≥4 on ≥1 of the 5 items on the PEC at baseline.
Patients who read, understood, and provided written informed consent.
Patients who were in good general health prior to study participation as determined.
Selected Exclusion Criteria
Patients with agitation caused by acute intoxication.
Use of benzodiazepines, other hypnotics, or antipsychotic drugs in the 4 hours before study treatment.
Treatment with alpha-1 noradrenergic blockers (terazosin, doxazosin, tamsulosin, alfuzosin, or prazosin) or other prohibited medications.
Patients judged to be at serious risk of suicide.

Full inclusion and exclusion criteria are available on page 32.

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Evidence Tables for Phase 3 Trials (cont'd)

SERENITY I: Evidence Summary

Clinical Outcomes

- The primary efficacy endpoint, reduction in symptoms of acute agitation assessed using the PEC change from baseline compared with placebo, was met in both IGALMI treatment groups

	Patients, No. (%)		
	IGALMI		
	180 mcg **N=126**	**120 mcg** **N=129**	**Placebo** **N=126**
Mean change (SD) in PEC total score from baseline at 120 minutes	–10.3 (4.34)	–8.5 (4.83)	–4.8 (4.69)
LSM difference (SE) in PEC total score from placebo at 120 minutes	–5.5 (0.5)	–3.7 (0.5)	NA
P-value	<0.0001	<0.0001	NA

- The earliest onset of action where an effect on agitation was apparent, measured by change from baseline PEC total score, was 20 minutes in the 180 mcg group (N=125), with a statistically significant separation from placebo, LSM difference of –1.2 (*P*=0.0032), and 30 minutes in the 120 mcg group (N=129), with a statistically significant separation from placebo, LSM difference of –1.0 (*P*=0.0092)
- In an exploratory analysis, at 2 hours post–dose, response rates (≥40% decrease from baseline in PEC total score) were higher in the IGALMI 180 mcg (111/125 [88.8%]) and 120 mcg (102/129 [79.1%]) dose groups compared with placebo (51/126 [40.5%])
- In an exploratory analysis, at 30, 60, 120, and 240 minutes post–dose, improvement in the IGALMI 180 mcg and 120 mcg groups was noted on the CGI–I scale

For the exploratory analysis, the results require cautious interpretation and could represent chance findings.

Please see Important Safety Information on pages 6, 20, and 70.

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Evidence Tables for Phase 3 Trials (cont'd)

Table 21 **SERENITY II: BXCL501-302 Evidence Summary**

Study name: A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Determine Efficacy and Safety of IGALMI in Agitation Associated With Bipolar I or II Disorder (SERENITY II).

Citation: Data on file. BXCL501 (dexmedetomidine) sublingual film clinical study report - protocol BXCL501-302. 2020; IGALMI. Prescribing information. BioXcel Therapeutics, Inc.; 2022

Study design: Phase III, multicenter, randomized, double-blind, placebo-controlled study

Treatment group: IGALMI 120 mcg or 180 mcg, or to matching placebo

Selected Inclusion Criteria
Men and women aged 18 to 75 years who met *DSM-5* criteria for bipolar I or II disorder.
Patients judged to be clinically agitated at screening and baseline, with a total score of ≥14 on the PEC.
Patients who had a score of ≥4 on ≥1 of the 5 items on the PEC at baseline.
Patients who read, understood, and provided written informed consent.
Patients who were in good general health.

Selected Exclusion Criteria
Patients with agitation caused by acute intoxication.
Use of benzodiazepines, other hypnotics, or antipsychotic drugs in the 4 hours before study treatment.
Treatment with alpha-1 noradrenergic blockers (terazosin, doxazosin, tamsulosin, alfuzosin, or prazosin) or other prohibited medications.
Patients judged to be at serious risk of suicide.

Full inclusion and exclusion criteria are available on pages 51 and 52.

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sublingual film · 120 mcg, 180 mcg

SERENITY II Evidence Summary

Clinical Outcomes

- The primary endpoint, reduction in symptoms of acute agitation assessed using the PEC change from baseline compared with placebo, was met in both IGALMI treatment groups

	Patients, No. (%)		
	IGALMI		
	180 mcg **N=126**	**120 mcg** **N=126**	**Placebo** **N=126**
Mean change (SD) in PEC total score from baseline at 120 minutes	–10.4 (4.45)	–9.1 (5.26)	–5.0 (4.67)
LSM difference (SE) in PEC total score from placebo at 120 minutes	–5.4 (0.5)	–4.1 (0.5)	NA
P-value	<0.0001	<0.0001	NA

- The earliest onset of action where an effect on agitation was apparent, measured by change from baseline PEC total score, was 20 minutes in both IGALMI treatment groups, with a statistically significant separation from placebo for the IGALMI 180 mcg group (LSM difference of –1.1 [*P*=0.0070]) and the IGALMI 120 mcg group (LSM difference of –1.0 [*P*=0.0092])

- In an exploratory analysis, at 2 hours post–dose, response rates (≥40% decrease from baseline in PEC total score) in the IGALMI 180 mcg and 120 mcg dose groups were higher in the IGALMI 180 mcg group (114/126 [90.5%]), LSM difference of 44.4 (*P*>0.0001), and the IGALMI 120 mcg group (97/126 [77.0%]), LSM difference of 31.0 (*P*>0.0001), compared with placebo (58/126 [46.0%])

- In an exploratory analysis, at 30, 60, 120, and 240 minutes post–dose, improvement in the IGALMI 180 mcg and 120 mcg groups was noted on the CGI–I scale

For the exploratory analysis, the results require cautious interpretation and could represent chance findings.

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sublingual film · 120 mcg, 180 mcg

Evidence Tables for Phase 3 Trials (cont'd)

Evidence Summary—Pooled Safety Data

Table 22 **Adverse reactions that occurred at a rate of ≥2% of the IGALMI group and greater than placebo in SERENITY I (schizophrenia) and SERENITY II (bipolar disorders)[9]**

	Patients, No. (%)		
	IGALMI		
	180 mcg N=252	120 mcg N=255	Placebo N=252
Somnolence*	23%	22%	6%
Paresthesia oral or hypoesthesia oral	7%	6%	1%
Dizziness	6%	4%	1%
Hypotension	5%	5%	0%
Orthostatic hypotension	5%	3%	<1%
Dry mouth	4%	7%	1%
Nausea	3%	2%	2%
Bradycardia	2%	2%	0%
Abdominal discomfort[†]	2%	0%	1%

*Somnolence includes the terms fatigue and sluggishness.
†Abdominal discomfort includes dyspepsia and gastroesophageal reflux disease.

- No serious TEAEs were seen in clinical trials[10,35]
- No pharmacologic intervention was required for any cardiac-related adverse reaction[10,34]
- There were no cases of syncope or falls reported in these studies; however, HCPs should monitor patients for vital signs and alertness after IGALMI administration[9,10,34]
- Patients should not perform activities requiring mental alertness, such as operating a motor vehicle or operating hazardous machinery, for at least 8 hours after taking IGALMI[9]

Please see Important Safety Information on pages 6, 20, and 70.

Click here for full Prescribing Information.

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sublingual film · 120 mcg, 180 mcg

INDICATION

IGALMI is indicated for the acute treatment of agitation associated with schizophrenia or bipolar I or II disorder in adults. Limitations of Use: The safety and effectiveness of IGALMI have not been established beyond 24 hours from the first dose.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hypotension, Orthostatic Hypotension, and Bradycardia: IGALMI causes dose-dependent hypotension, orthostatic hypotension, and bradycardia. In clinical studies with IGALMI, patients were excluded if they had treatment with alpha-1 noradrenergic blockers, benzodiazepines, other hypnotics or antipsychotic drugs four hours prior to study drug administration; had a history of syncope or syncopal attacks; SBP < 110 mmHg; DBP < 70 mmHg; HR < 55 beats per minute; or had evidence of hypovolemia or orthostatic hypotension. Because IGALMI decreases sympathetic nervous system activity, hypotension and/or bradycardia may be more pronounced in patients with hypovolemia, diabetes mellitus, or chronic hypertension, and in geriatric patients. Avoid use of IGALMI in patients with hypotension, orthostatic hypotension, advanced heart block, severe ventricular dysfunction, or history of syncope. After IGALMI administration, patients should be adequately hydrated and should sit or lie down until vital signs are within normal range. If a patient is unable to remain seated or lying down, precautions should be taken to reduce the risk of falls. Ensure that a patient is alert and not experiencing orthostatic hypotension or symptomatic hypotension prior to allowing them to resume ambulation.

QT Interval Prolongation: IGALMI prolongs the QT interval. Avoid use of IGALMI in patients at risk of torsades de pointes or sudden death, including those with known QT prolongation, a history of other arrhythmias, symptomatic bradycardia, hypokalemia, or hypomagnesemia, and in patients receiving other drugs known to prolong the QT interval.

Somnolence: IGALMI can cause somnolence. Patients should not perform activities requiring mental alertness, such as operating a motor vehicle or operating hazardous machinery, for at least eight hours after taking IGALMI.

Risk of Withdrawal Reactions, Tolerance, and Tachyphylaxis: IGALMI was not studied for longer than 24 hours after the first dose. There may be a risk of physical dependence, a withdrawal syndrome, tolerance, and/or tachyphylaxis if IGALMI is used in a manner other than indicated.

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) were somnolence, oral paresthesia or oral hypoesthesia, dizziness, dry mouth, hypotension, and orthostatic hypotension.

DRUG INTERACTIONS

Drugs That Prolong the QT Interval: Avoid use. Concomitant use of drugs that prolong the QT interval may add to the QT-prolonging effects of IGALMI and increase the risk of cardiac arrhythmia.

Anesthetics, Sedatives, Hypnotics, and Opioids: Concomitant use may cause enhanced CNS-depressant effects. Reduction in dosage of IGALMI or the concomitant medication should be considered.

USE IN SPECIFIC POPULATIONS

Hepatic Impairment and Geriatric Patients (≥65 years old): A lower dose is recommended in patients with hepatic impairment and geriatric patients. See the full Prescribing Information for the recommended dosage depending on the agitation severity.

Click here for accompanying full Prescribing Information.

To report SUSPECTED ADVERSE REACTIONS, contact BioXcel Therapeutics, Inc. at 1–833–201–1088 or medinfo@bioxceltherapeutics.com, or FDA at 1–800–FDA–1088 or www.fda.gov/medwatch.

Igalmi™
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sublingual film · 120 mcg, 180 mcg

Product Information

NDC	Strength	Package Configuration	Minimum Order Qty	WAC per unit*	WAC per carton*
81092-1120-1	120 mcg	Carton of 10	1 carton	$105	$1050
81092-1180-1	180 mcg	Carton of 10	1 carton	$105	$1050

Storage Information

Controlled room temperature

(20°C–25°C / 68°F–77°F)

Ordering Information

IGALMI is available directly through wholesalers

McKesson
1-855-625-6285   https://connect.mckesson.com   120 mcg 10 CT: 2627784
180 mcg 10 CT: 2627792

Cardinal
1-800-334-5529   http://orderexpress.cardinalhealth.com   120 mcg 10 CT: 5795042
180 mcg 10 CT: 5795059

AmerisourceBergen
1-844-222-2273   https://abcorder.amerisourcebergen.com   120 mcg 10 CT: 10270111
180 mcg 10 CT: 10270110

*As of November 2022.

Please see Important Safety Information on pages 6, 20, and 70.

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