Title Page

Protocol Title: Evaluation of atomoxetine and oxybutynin for obstructive sleep apnea in children with Down syndrome

Protocol Number: 1908864846

Amendment Number: 2

Short Title: Ato-Oxy for OSA in children with Down Syndrome

Sponsor Name and Legal Registered Address:

National Institutes of Health (NIH)
9000 Rockville Pike
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1 Protocol Summary

1.1 Synopsis

Protocol Title: Evaluation of atomoxetine and oxybutynin for obstructive sleep apnea in children with Down syndrome

Phase 2

Sponsor: National Institutes of Health

Rationale:

Atomoxetine 80 mg/oxybutynin 5 mg (ato-oxy) has been shown support for efficacy and safety in adults without Down syndrome (DS) with obstructive sleep apnea (OSA). Children with DS have a high prevalence of OSA, and there most children with DS and OSA are not effectively treated for their OSA. Given that airway hypotonia is a cardinal feature of OSA in children with DS, and that ato-oxy specifically targets airway hypotonia, ato-oxy may be particularly effective for OSA treatment in children with DS. This Phase 2 clinical study will examine the efficacy of ato-oxy in children with DS and OSA. Overall, the study is expected to provide evidence of ato-oxy efficacy in OSA treatment as well as potential improvement in health-related quality of life.

Objectives	Endpoints
Primary To evaluate the short-term efficacy of high dose ato-oxy vs. low dose ato-oxy for treatment of OSA in children with DS	Primary Efficacy Endpoint • Change in obstructive AHI from baseline (high dose ato-oxy vs. low dose ato-oxy).
Secondary To assess the effects of high dose ato-oxy vs. low dose ato-oxy on OSA-related health-related quality of life and sleep quality in children with DS	Secondary Efficacy Endpoints High dose ato-oxy vs low dose ato-oxy, in order: • Change in OSA-18 score from baseline • Change in arousal index from baseline
Tertiary/Exploratory	Unranked Efficacy Endpoints High dose ato-oxy vs low dose ato-oxy: • Change in PedsQL total score from baseline • Change in Caregiver Global Impression of Change from baseline • Change in N1 sleep (%) from baseline • Change in REM sleep (%) from baseline • Change in N3 sleep (%) from baseline • Vineland 3 adaptive behavior composite scale • Conners-3 ADHD Index

Abbreviations: AHI = apnea-hypopnea index; Ato-oxy = atomoxetine and oxybutynin; DS= Down syndrome; OSA = obstructive sleep apnea

Overall Design:

This is a randomized, double blind, cross-over study of the combination of atomoxetine and oxybutynin (ato-oxy) in children with DS and OSA documented by polysomnography (PSG). Participants will receive high dose ato-oxy for four weeks as well as low dose ato-oxy for four weeks in random order. During the high dose ato-oxy period, participants will take 5 mg oxybutynin and 0.5mg/kg/day (max 40 mg) atomoxetine nightly for one week. Atomoxetine dose will then be increased to 1.2 mg/kg/day (max 80 mg). During the low dose ato-oxy period, participants will take 5 mg oxybutynin and 0.5mg/kg/day (max 40 mg) atomoxetine. Dosing of the study treatment will occur approximately 30 minutes prior to bedtime. Participants who withdraw from the study will not be replaced.

Study participants will undergo eligibility screening that will include an initial screening to determine whether non- PSG enrollment criteria are met, followed by a 1-night in-lab PSG and health-related quality of life assessment for participants who qualify based on non-PSG criteria. For participants who are eligible and enroll in the study, the screening PSG night will serve as the baseline measure for apnea-hypopnea index (AHI) and other PSG endpoints. On the final night of dosing for both high dose ato-oxy and low-dose ato-oxy, participants will return for inpatient PSG and health-related quality of life assessment. The primary efficacy endpoint is the change in obstructive AHI from baseline (high dose ato-oxy vs. low dose ato-oxy).

Number of Participants:

Approximately 27 participants will be randomized to study treatment.

Treatment Groups and Duration:

All participants will receive both high dose ato-oxy and low dose ato-oxy in random order.

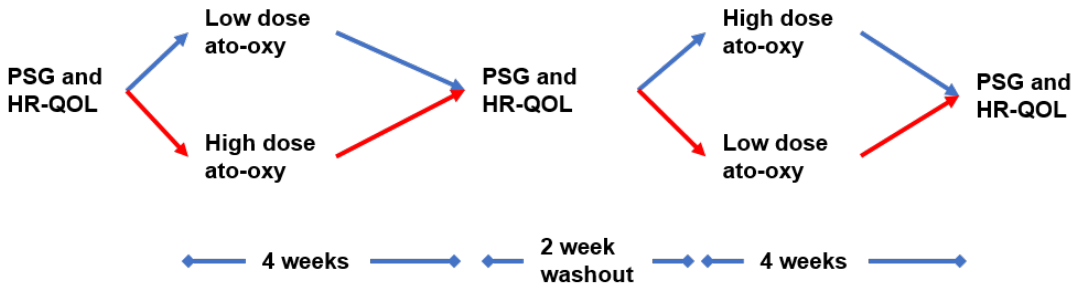
The overall study duration will be up to 15 weeks, as follows:

- Up to 28 days for screening and baseline PSG;
- 28 nights of high dose ato-oxy (with PSG and health-related quality of life assessment on the last night of high dose ato-oxy)

- 14-21 days of wash-out period between high dose ato-oxy and low dose ato-oxy periods
- 28 nights of low dose ato-oxy (with PSG and health-related quality of life assessment on the last night of low dose ato-oxy)

1.2 Schema

Figure 1 Study Design Schema



Participants will be randomized to either high dose ato-oxy or low dose ato-oxy at baseline. Polysomnography (PSG) and health-related quality of life (HR-QOL) assessment will be performed after four weeks of treatment. Participants will then take no drug for two weeks, then take the alternate treatment for four weeks with repeat PSG and HR-QOL assessment at the end of therapy.

1.3 Schedule of Activities (SoA)

Table 1 Schedule of Activities

	Visit 1[1,2]	**Post-visit 1**	**Phone call 1**	**Phone Call 2**	**Phone Call 3**	**Visit 2[3]**	**Post-visit 2[4]**	**Phone call 4**	**Phone Call 5**	**Phone Call 6**	**Visit 3[3]**
Trial Day (Visit Window)	**-28 to -1**	**1**	**7±4**	**14±4**	**21±4**	**28±4**	**42**	**49±4**	**56±4**	**63±4**	**70±4**
Inclusion/Exclusion Criteria	X										
Demography	X										
Informed Consent[5]	X										
Vital Signs[6]	X					X					X
Polysomnography	X					X					X
Quality of Life and behavioral assessments[7]	X					X					X
Randomization		X									
Drug dispensed[8]		X					X				
Adverse event screening			X	X	X	X		X	X	X	X

Prior/concomitant medication monitoring	X		X	X	X	X		X	X	X	X
Counting of returned study drug						X					X
LENA language evaluation[9]	X					X					X

1 Pre-screening including verification of inclusion/exclusion criteria, demography as well as informed consent may be performed prior to visit 1 at investigator/participant preference, including at the study recruitment site. Baseline polysomnography may occur up to one month prior to initiation of study drug, but preferably within one week. This will be done to assist with scheduling of on-therapy PSG, which should occur on the last night of therapy. This will additionally allow participants to spread PSGs over a longer time period if desired.

2 Final study eligibility is determined after the baseline PSG exam, based on PSG and non-PSG findings, and enrolled participants are randomized and dispensed the study drug.

3 Polysomnography and health-related quality of life assessment should occur on the last day of therapy, but may vary by 4 days if needed due to extenuating circumstances. Participants must bring and consume study medication in the sleep lab on polysomnography nights.

4 Drug washout period will be 14 days (preferable and minimum), but may be extended to no more than 21 days to assist with scheduling of the second on-therapy PSG, which should occur on the last night of therapy.

5 No trial-related assessment is to be carried out before the participant has signed the ICF. Any participant who provides informed consent will have a screening number assigned.

6 Vital signs include the following: seated blood pressure, pulse, Participants who experience systolic blood pressure ≥ 140, or diastolic blood pressure ≥ 90, or heart rate ≥ 130 beats per minute will be further evaluated.

7 Quality of life assessment will include completion of the OSA-18, Peds-QL and caregiver global impression of change. Behavioral assessments will include the Conners-3 and Vineland 3rd edition.

8 Daily bedtime dosing continues through the next PSG visit (for 28 days of therapy). The final night of study treatment dosing is PSG night.

9 Language assessment using the LENA device may take place at any point in the baseline period prior to drug administration (preferably within the week preceding baseline polysomnography, and will be repeated at any point within the last week of each drug regimen (prior to polysomnography)

2 Introduction

2.1 Study Rationale

Atomoxetine 80 mg/oxybutynin 5 mg (ato-oxy) has been shown support for efficacy and safety in adults without Down syndrome (DS) with obstructive sleep apnea (OSA). Children with DS have a high prevalence of OSA, and there most children with DS and OSA are not effectively treated for their OSA. Given that airway hypotonia is a cardinal feature of OSA in children with DS, and that ato-oxy specifically targets airway hypotonia, ato-oxy may be particularly effective for OSA treatment in children with DS. This Phase 2 clinical study will examine the efficacy of ato-oxy in children with DS and OSA. Overall, the study is expected to provide evidence of ato-oxy efficacy in OSA treatment as well as potential improvement in health-related quality of life.

2.2 Background

2.2.1 Obstructive Sleep Apnea in Children with Down Syndrome

DS is the most common genetic cause of intellectual disability, with a prevalence of one in 700 births (Parker, Mai et al. 2010). DS is associated with multiple comorbidities such as hypothyroidism, congenital heart disease and other conditions. OSA is one of the most common comorbidities present in children with DS. In children without DS, OSA has a prevalence of 2-5% (Marcus, Brooks et al. 2012). For comparison, the prevalence of OSA in children with DS has been estimated to be between 50–79% in prior studies (Dyken, Lin-Dyken et al. 2003, Shott, Amin et al. 2006, Hill, Evans et al. 2016, Maris, Verhulst et al. 2016), with this prevalence increasing to 82-100% in adulthood (Trois, Capone et al. 2009, Cornacchia, Sethness et al. 2019). OSA in children with DS appears to be more severe than in children without DS, as OSA may be severe in 50% of cases in children with DS (Maris, Verhulst et al. 2016). Additionally, OSA is common even in children with DS without reported symptoms of OSA. Even among children with DS with no history of snoring or witnessed apneas, 53% of participants in a prior study were found to have OSA (Maris, Verhulst et al. 2016). Additionally, typical risk factors for OSA such as tonsil size or body mass index (BMI) may not be associated with the risk of OSA in children with DS (Hill, Evans et al. 2016, Maris, Verhulst et al. 2016). Given this high prevalence of OSA with limited reported symptoms, screening polysomnography is recommended for all children with DS (Bull and Committee on 2011).

Children with DS have multiple risk factors that increase their risk for OSA. Adenotonsillar hypertrophy is common, as are structural features such as mid-face hypoplasia and relative macroglossia that result in a narrow airway (Shott 2006). Additionally, hypotonia is essentially universal in infants with DS, and this persists into childhood. This hypotonia includes airway

hypotonia, which typically worsens during sleep and contributes to OSA risk for children with DS (Donnelly, Shott et al. 2004).

OSA is a well-known cause of neurocognitive impairment (Bass, Corwin et al. 2004, Beebe 2006, Gozal, Kheirandish-Gozal et al. 2010), impaired school performance (Gozal 1998) and impaired health-related quality of life (Jackman, Biggs et al. 2013) in children without DS. Research in children with DS has similarly shown that OSA is associated with neurocognitive and health-related quality of life impairment (Andreou, Galanopoulou et al. 2002, Churchill, Kieckhefer et al. 2015). Treatment of OSA in children without DS has been shown to improve neurocognitive function (Chervin, Ruzicka et al. 2006, Yuan, Sohn et al. 2012) and health-related quality of life (Garetz, Mitchell et al. 2015). There are no DS-specific studies on the neurocognitive and HR-QOL effects of OSA treatment. One study performed a subgroup analysis of children with developmental delays (6/10 included participants had DS) which did show improvement in parent-reported neurobehavioral and HR-QOL outcomes after OSA treatment with PAP therapy (Marcus, Radcliffe et al. 2012). One other study also showed improvement in HR-QOL after OSA treatment with adenotonsillectomy in a mixed group of children with either mucopolysaccharidoses or DS (Sudarsan, Paramasivan et al. 2014).

2.2.2 Unmet Medical Need

Current treatments for OSA in children primarily include adenotonsillectomy or PAP therapy (Marcus, Brooks et al. 2012). Medication therapy with nasal steroids and/or leukotriene inhibitors has also been shown to have some efficacy in children with mild-moderate OSA (Kheirandish-Gozal, Bhattacharjee et al. 2014). These medications can reduce adenotonsillar hypertrophy and can be used as an alternative to adenotonsillectomy but may not be efficacious in children who have already underwent adenotonsillectomy. Unfortunately, current treatments for OSA have limited effectiveness in children with DS. Treatments targeted towards adenotonsillar hypertrophy such as adenotonsillectomy have been shown to have limited efficacy, as 65-73% of children with DS have residual OSA after adenotonsillectomy (Shete, Stocks et al. 2010, Thottam, Trivedi et al. 2015). Similarly, while PAP therapy is highly efficacious when used, effectiveness is limited by poor adherence, as only 46% of children with DS prescribed PAP therapy for OSA are adherent to therapy (Trucco, Chatwin et al. 2018). Airway hypotonia has been linked to OSA treatment failure in children with DS (Donnelly, Shott et al. 2004). Given this hypotonia, OSA treatment aimed at improving airway tone is likely particularly well-suited to children with DS. Consistent with this, hypoglossal nerve stimulation has been shown to be effective in adolescents with DS, reducing apnea-hypopnea index (AHI) up to 85% (Diercks, Wentland et al. 2017). However, use of hypoglossal nerve stimulation may be limited in children given that multiple revision surgeries would likely be necessary in younger

children to adjust for growth over time. Additionally, an invasive surgical procedure is necessary to implant the hypoglossal nerve stimulator. Given that children with DS appear to be at higher risk for surgical complications due to DS-associated comorbidities (Bartz-Kurycki, Anderson et al. 2018), a non-surgical treatment modality for OSA would be preferable.

2.2.3 Biological Rationale

Atomoxetine is a pre-synaptic norepinephrine reuptake inhibitor indicated for the treatment of attention deficit hyperactivity disorder in children and adults. Oxybutynin is an antispasmodic drug that inhibits the muscarinic action of acetylcholine on smooth muscle and is indicated for the treatment of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder such as urgency, frequency, urinary leakage, urge incontinence and dysuria.

Efficacy of the combination of these 2 small molecules for the signs and symptoms of OSA has been previously evaluated in a small number of patients in National Institutes of Health-supported studies in the academic setting. The pharmacokinetics (PK) of the atomoxetine and oxybutynin combination have recently been studied in a Phase 1 clinical program sponsored by Apnimed. New research in animals improved understanding of the state-dependent neurotransmitters involved in pharyngeal muscle activation during sleep, namely that both noradrenergic and antimuscarinic processes are involved. Specifically, the loss of noradrenergic activity is now thought to play a key role in the sleep-related hypotonia of pharyngeal muscles during non-rapid eye movement (NREM) sleep and muscarinic activity is involved in rapid eye movement (REM) atonia.

Chan and colleagues (Chan, Steenland et al. 2006) showed in rats that the noradrenergic antagonist terazosin substantially reduced genioglossus (a major muscle of the upper airway) activity (i.e., genioglossal electromyographic [EMG_{gg}] activity) during wakefulness and produced REM-like atonia during NREM sleep, illustrating the importance of noradrenergic mechanisms. Other studies (Lai, Kodama et al. 2001, Fenik, Davies et al. 2005) also support the notion that progressive withdrawal of noradrenergic tone, from wakefulness to NREM and REM sleep, is the major mechanism causing sleep-related pharyngeal hypotonia. While noradrenergic withdrawal is thought to be the main cause of pharyngeal hypotonia in NREM sleep, there are additional mechanisms that cause further reduction during REM sleep. Chan and colleagues (Chan, Steenland et al. 2006) failed to reverse REM atonia with alpha-1 receptor agonists applied to the hypoglossal nucleus, suggesting that another, possibly inhibitory, mechanism is at work. Horner and colleagues identified this inhibitory process as muscarinic by demonstrating restoration of EMG_{gg} activity during REM sleep with the muscarinic antagonist scopolamine

applied directly to the hypoglossal nucleus in rats (Grace, Hughes et al. 2013, Grace, Hughes et al. 2013).

However, due to the only recent identification of these processes, until now there has not yet been an attempt to stimulate the pharyngeal muscles with both noradrenergic and antimuscarinic drugs in sleeping humans. Atomoxetine (a noradrenergic) and oxybutynin (an antimuscarinic) are 2 drugs within these pharmacologic classes that have been Food and Drug Administration-approved for over 16 years and 40 years, respectively, thereby having a long history of clinical use. Atomoxetine and oxybutynin as individual drugs have well-established PK, tolerability and safety profiles, but have not previously been studied in combination.

3 Objectives and Endpoints

Objectives	Endpoints
Primary To evaluate the short-term efficacy of high dose ato-oxy vs. low dose ato-oxy for treatment of OSA in children with DS	Primary Efficacy Endpoint • Change in obstructive AHI from baseline (high dose ato-oxy vs. low dose ato-oxy).
Secondary To assess the effects of high dose ato-oxy vs. low dose ato-oxy on OSA-related health-related quality of life and sleep quality in children with DS	Secondary Efficacy Endpoints High dose ato-oxy vs low dose ato-oxy, in order: • Change in OSA-18 score from baseline • Change in arousal index from baseline
Tertiary/Exploratory	Unranked Efficacy Endpoints High dose ato-oxy vs low dose ato-oxy: • Change in PedsQL total score from baseline • Change in Caregiver Global Impression of Change from baseline • Change in N1 sleep (%) from baseline • Change in REM sleep (%) from baseline • Change in N3 sleep (%) from baseline • Vineland 3 adaptive behavior composite scale • Conners-3 ADHD Index
Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder, AHI = apnea-hypopnea index; Ato-oxy = atomoxetine and oxybutynin; DS= Down syndrome; OSA = obstructive sleep apnea	

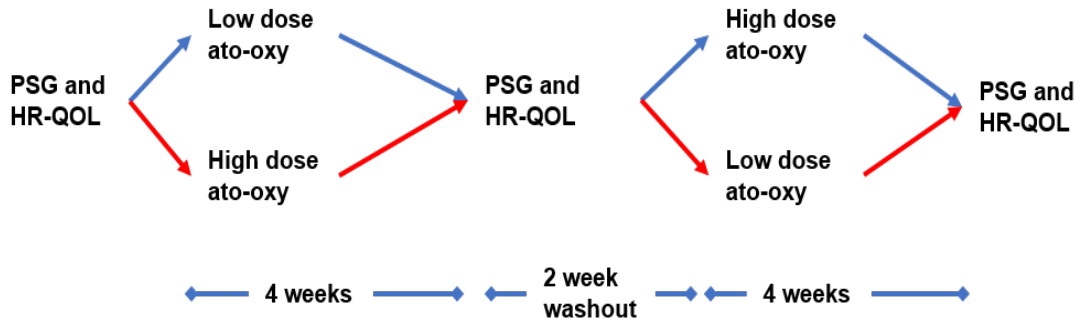
4 Study Design

4.1 Overall Design

This is a randomized, double blind, cross-over study of the combination of atomoxetine and oxybutynin in children with DS and OSA documented by polysomnography (PSG). Approximately 27 participants will be randomized in the study. Participants will receive high dose ato-oxy for four weeks as well as low dose ato-oxy for four weeks in random order. During the high dose ato-oxy period, participants will take 5 mg oxybutynin and 0.5 mg/kg/day (max 40 mg) atomoxetine nightly for one week. Atomoxetine dose will then be increased to 1.2 mg/kg/day (max 80 mg) and oxybutynin will remain at 5 mg. During the low dose ato-oxy period, participants will take 5 mg oxybutynin and 0.5 mg/kg/day (max 40 mg) atomoxetine nightly. Overall study duration will be 10-15 weeks. Dosing of the study treatment will occur approximately 30 minutes prior to bedtime. Participants who withdraw from the study will not be replaced.

Study participants will undergo eligibility screening that will include an initial screening to determine whether non- PSG enrollment criteria are met, followed by a 1 night in-lab PSG and health-related quality of life assessment for participants who qualify based on non-PSG criteria. For participants who are eligible and enroll in the study, the screening PSG night will serve as the baseline measure for apnea hypopnea index (AHI) and other PSG endpoints. On the final night of dosing for both high dose ato-oxy and low dose ato-oxy, participants will return for inpatient PSG and health-related quality of life assessment. The primary efficacy endpoint is the change in obstructive AHI from baseline (high dose ato-oxy vs. low dose ato-oxy).

Figure 2: Overview of Study Design



Participants will be randomized to either high dose ato-oxy or low dose ato-oxy at baseline. Polysomnography (PSG) and health-related quality of life (HR-QOL) assessment will be performed after four weeks of treatment. Participants will then take no drug for two weeks, then take the alternate treatment for four weeks with repeat PSG and HR-QOL assessment at the end of therapy.

4.2 Scientific Rationale for Study Design

Atomoxetine 80 mg/oxybutynin 5 mg (ato-oxy) has been shown support for efficacy and safety in adults without Down syndrome (DS) with obstructive sleep apnea (OSA). Children with DS have a high prevalence of OSA, and most children with DS and OSA are not effectively treated for their OSA. Given that airway hypotonia is a cardinal feature of OSA in children with DS, and that ato-oxy specifically targets airway hypotonia, ato-oxy may be particularly effective for OSA treatment in children with DS. This Phase 2 clinical study will examine the efficacy of ato-oxy in children with DS and OSA. Overall, the study is expected to provide evidence of ato-oxy efficacy in OSA treatment as well as potential improvement in health-related quality of life.

4.3 Justification for Dose

The prior study of ato-oxy in adults used a dosing regimen of 80 mg atomoxetine and 5 mg oxybutynin given at night (Taranto-Montemurro, Messineo et al. 2018). Based on the atomoxetine package insert, the pediatric weight-based equivalent for 80 mg atomoxetine is 1.2 mg/kg. Additionally, package insert dosing suggests starting at 0.5 mg/kg (max 40 mg) and increasing to 1.2 mg/kg (max 80 mg) after a minimum of three days. Given this, for high dose ato-oxy, participants will be titrated from 0.5 mg/kg to 1.2 mg/kg atomoxetine after one week on 0.5 mg/kg therapy to reduce the risk of adverse effects. For low dose at-oxy, we will use the package insert suggested starting dosing of 0.5 mg/kg (max 40 mg). This will allow the evaluation of a lower atomoxetine dose, which may be associated with fewer adverse events. Recommended dosing of oxybutynin in children >5 years old starts at 5 mg twice daily for

overactive bladder and the planned oxybutynin dose for this proposal is 5 mg once at night. Therefore, we did not consider it necessary to include a lower dose of oxybutynin, as the dose used in this proposal is already lower than the current FDA-approved dose recommendation.

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the Schedule of Activities (SoA).

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the study.

5 Study Population

The study population will consist of male and female participants between 6 and 17 years of age, inclusive, with a documented history of DS and OSA on initial study PSG. Participant's parent or guardian must be able to provide written consent and meet all the inclusion criteria and none of the exclusion criteria.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex

1. Male or female participants between 6 to 17 years of age, inclusive, at the Screening Visit. Enrollment will be stratified to ensure equal representation of children age 6-12 and age 13-17. No more than 14 subjects will be randomized for each age group.

Type of Participant and Disease Characteristics

2. Participants are eligible for screening PSG if any of the following:

- Down syndrome diagnosis (trisomy 21, but not translocation or mosaicism).

Informed Consent/Assent

3. Participant's parent or guardian voluntarily agrees to have their child participate in this study and signs an Institutional Review Board (IRB)-approved informed consent prior to performing any of the Screening Visit procedures.
4. Participant's parent or guardian must be able to understand the nature of the study and must have the opportunity to have any questions answered.
5. Participants age ≥8 years provide assent as described in section 10.1.4.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Exclusion Criteria at study entry (prior to baseline polysomnography)
1. Presence of central sleep apnea on polysomnography (central AHI ≥ 5)

2. Currently using and adherent to PAP therapy (>4 hours per night for 70% of nights in the past 30 days based on device download or parent report)
3. MAO inhibitor use
4. Urinary retention
5. Prematurity < 37 weeks estimated gestational age
6. Seizure disorder
7. Untreated or inadequately treated hypothyroidism
8. Significant traumatic brain injury
9. Congenital heart disease and not cleared to participate by the patient's cardiologist
10. History of current, untreated depression
11. History of liver disease
12. 3+ or greater tonsillar hypertrophy
13. Positive urine pregnancy test
Exclusion Criteria based on baseline polysomnography (prior to randomization)
1. Hypoxemia independent of respiratory events on polysomnography (≥5 minutes with oxygen saturation <90%)
2. Presence of central sleep apnea on polysomnography (central AHI ≥ 5)
3. Absence of OSA defined as total AHI <5

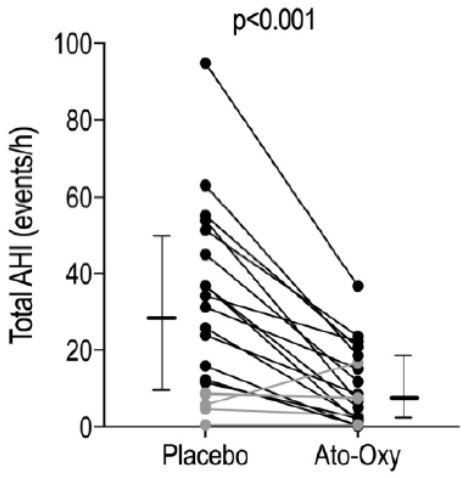
Children with or without history of prior adenotonsillectomy will be enrolled as long as they have current OSA (defined as AHI >5) on baseline polysomnography. Children who are initially excluded due to tonsillar hypertrophy will be eligible to participate in the study if they have persistent OSA after adenotonsillectomy. Additionally, children will be eligible regardless of body mass index (BMI), as the prior study of ato-oxy in adults included participants with

significant obesity, and ato-oxy was demonstrated to be effective in adults with a BMI as high as 40 (Taranto-Montemurro, Messineo et al. 2018).

Pediatric OSA is defined in the International Classification of Sleep Disorders (3rd edition) by an obstructive AHI ≥1. While we considered using this as our inclusion criteria to maximize generalizability to all children with OSA, we decided against this approach for several reasons.

First, half of our study population will be adolescents, and based on American Academy of Sleep Medicine guidance in the current polysomnography scoring manual, use of the adult definition of OSA (total AHI ≥5) may be more appropriate in adolescents.

Second, the prior adult study of ato-oxy as well as the ongoing study of hypoglossal nerve stimulation in children with Down Syndrome both required a total AHI>10 to enroll in the study. The preliminary data published to date from the ongoing study of hypoglossal nerve stimulation does not show any evidence of a floor effect in the outcome of AHI % reduction (Caloway, Diercks et al. 2020), which may be due to their selected AHI threshold that includes only children with moderate-severe OSA. However, in the study, despite an 85% reduction in AHI as well as significant improvement in OSA-related quality of life, only a single participant (5%) had an AHI <1 after intervention. An apparent floor effect did appear to be present in the prior study of ato-oxy in adults, which did include participants with mild OSA (defined by a total AHI >5 and <15 in adults) (Taranto-Montemurro, Messineo et al. 2018)as visually apparent from their Figure 2b (below).



Given these prior findings, we were concerned that the use of an obstructive AHI ≥1 as an inclusion criterium would potentially create a floor effect, where we would see no overall significant improvement due to a lack of improvement in participants with mild OSA, even though participants with moderate to severe OSA may show improvement.

Based on this rationale, we selected total AHI ≥5 as the threshold for progressing to drug randomization in the study. This threshold is likely more appropriate for many adolescent participants and will reduce the likelihood of a floor effect in the current study. If the current study does show a significant improvement in AHI, a future study would be needed to evaluate the efficacy of ato-oxy in children with mild OSA.

5.3 Meals and Dietary Restrictions

1. Participants should refrain from consumption of any nutrients known to modulate CYP enzyme activity (e.g., grapefruit or grapefruit juice, pomelo juice, star fruit, pomegranate, and Seville or Moro [blood] orange products) within 72 hours before the first administration of study drug, during the study, and until final discharge.
2. Diet should be generally stable during the study, e.g., new diet programs should not be initiated.

5.4 Caffeine

1. Moderate consumption of caffeinated beverages, containing up to a total of 400 mg caffeine per day, is permitted, consumed no less than 3 hours prior to bedtime.

5.5 Activity

There are no restrictions on physical activity during the study other than that physical activity should be generally stable during the study (e.g., new exercise programs should not be initiated).

5.6 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized to study treatment/entered into the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants that meets the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) will not be rescreened, except if the opportunity for rescreening has been enabled by protocol amendment.

6 Study Treatment

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Study Treatment(s) Administered

Two different blinded capsules are taken each night of drug treatment, as arranged in blister packaging. On nights of randomized study treatment, 1 capsule of atomoxetine (either high or low dose as appropriate to randomization) and 1 capsule of oxybutynin , are taken approximately

30 minutes before the participant's planned bedtime. If needed, for participants who cannot take capsules, liquid formulations of both medications are available, and have been shown to have identical pharmacokinetics to the solid formulation.

Study Treatment Name:	**Atomoxetine hydrochloride**	**Oxybutynin chloride**
Dosage Formulation:	Capsule	Capsule
Dosage Level:	0.5 mg/kg (max 40 mg) to 1.2 mg/kg (max 80 mg)	5 mg
Route of Administration:	Oral	Oral
Dosing Instructions:	1 capsule will be administered daily with at least 20 mL water	1 capsule will be administered daily with at least 20 mL water
Storage/Packaging/Labeling:	Store per package insert. Study treatment will be provided in blister packaging. Each blister package will be labeled as required per country requirement.	Store per package insert. Study treatment will be provided in blister packaging. Each blister package will be labeled as required per country requirement.

6.2 Preparation/Handling/Storage/Accountability

1. The Investigator or designee must maintain a log to confirm appropriate temperature conditions have been maintained during transit for all study treatments received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatments and only authorized site staff may supply or administer study treatments. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized study staff.
3. The Investigator is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Unused or partially used study treatment will be returned to the Banner University Medical Center Investigational Pharmacy for destruction.

6.3 Measures to Minimize Bias: Randomization and Blinding

All participants (if AHI >5 on screening PSG) will be randomized to receive both high dose ato-oxy and low dose ato-oxy in random order. Each participant will be assigned a unique number

(randomization number) that encodes the participant's assignment to 1 of the 2 treatment orders of the study, according to the randomization schedule generated using a validated computer program.

Study treatment will be dispensed after PSG screening, as summarized in Section 1.3.

Returned study treatment should not be redispensed to the participants.

In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's study treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's study treatment assignment is unblinded, the DSMB must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable.

Participants will be randomly assigned in a 1:1 equal allocation ratio (stratified by age 6-12 and 13-17) to receive 1 of 2 different study treatment orders, using permuted blocked randomization. Investigators will remain blinded to each participant's assigned study treatment throughout the study.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study treatment records at the site(s) to verify that randomization/dispensing has been done accurately.

6.4 Study Treatment Compliance

Participants will be required to return any unused study treatment capsules at Visit 2 and 3. Unused capsules will be counted and recorded by study personnel to assess study treatment compliance.

6.5 Concomitant Therapy

Concomitant therapy with the following medications is disallowed:

- MAOIs or other drugs that affect monoamine concentrations (e.g., rasagiline) [MAOIs are contraindicated for use with atomoxetine]
- CYP2D6 inhibitors
- Strong CYP3A4 inhibitors (e.g., ketoconazole)
- Benzodiazepines and other anxiolytics

- Opioids
- Sedatives including nonbenzodiazepine “Z-drugs” (zolpidem, zaleplon, eszopiclone)
- Muscle relaxants
- Pressor agents
- Drugs with clinically significant cardiac QT-interval prolonging effects
- Drugs known to lower seizure threshold (e.g., chloroquine)
- Antiepileptics
- Antiemetics
- Modafinil or armodafinil
- Anticholinergics and anticholinesterase inhibitors, including drugs with substantial anticholinergic side effects, (e.g., first generation antihistamines)
- Sedating antihistamines
- Pseudoephedrine, phenylephrine, oxymetazoline

Medications that do not have substantial effects on the central nervous system (CNS), respiration, or muscle activity are generally allowed if dose and frequency is stable for 3 months prior to enrollment and during the course of the study, including, but not necessarily limited to, the following drugs and drug classes:

- Antihypertensives (angiotensin-converting-enzyme/angiotensin II receptor blocker inhibitors, calcium channel blockers, spironolactone, hydrochlorothiazide, etc.)
- Statins
- Proton pump inhibitors and histamine h_2 receptor blockers
- Over-the-counter (OTC) antacids
- Non-sedating antihistamines (e.g., cetirizine, loratadine)
- Melatonin
- Non-steroidal anti-inflammatory drugs and acetaminophen
- Laxatives
- Inhaled corticosteroids (e.g., fluticasone)

- Antidiabetics
- Ocular hypotensives and other ophthalmics (e.g., timolol)
- Hormonal therapy (e.g., estrogen replacement or anti-estrogens) and hormonal contraceptives
- Thyroid medications
- Anticoagulants
- OTC topicals (e.g., topical pain relievers)
- Patients currently on medications for Attention Deficit Hyperactivity Disorder will be included, but should not change their medication regimen/dosage during the study.

6.6 Dose Modification

Through protocol amendment, planned doses may be decreased on an individual or group basis according to emerging safety and tolerability data.

6.7 Treatment After the End of the Study

Not applicable. No subsequent open-label extension is planned following the study.
Study treatment will not be available after the end of study participation.

7 Discontinuation of Study Treatment and Participant Discontinuation

Refer to the SoA for data that are to be collected at the time of study discontinuation, during follow-up, and for any further evaluations that need to be completed.

7.1 Discontinuation of Study Treatment

If a clinically significant finding is identified, the Investigator will determine if the participant can continue in the study and if any change in participant management is needed. Any new clinically relevant finding should be reported as an adverse event (AE).

7.2 Stopping Criteria

7.2.1 Individual Participant Stopping Criteria

- Incidents of abuse, diversion, or misuse of the study treatment.

- Incidents of clinical significance: hallucinations, amnesia, delusional thinking, delirium, manic symptoms, aggressive behavior, suicidality, homicidality, agitation, confusion, or convulsions/seizures.
- Participants reporting any SAE.
- Acute urinary obstruction.
- Any other AE that in the judgment of the Investigator necessitates the participant stopping to protect participant safety.

Participants discontinued from dosing will undergo end of study procedures with follow-up monitoring of the AE(s) as clinically indicated.

7.3 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- All participants who withdraw from the study with an ongoing AE must be followed until the event is resolved or deemed stable.
- Participation may be terminated before completing the study and the reason recorded as follows:
    - Withdrawal due to AE
    - Withdrawal due to incident abuse, diversion, or misuse of the study treatment
    - Loss to follow-up
    - Participant withdrew consent at own request
    - Other

7.4 Loss of Participants to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- Study staff must attempt to contact the participant and reschedule the missed visit as soon as possible (and within the visit window, where one is defined) and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- In cases in which the participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record/eCRF.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8 Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1 Efficacy Assessments

8.1.1 Efficacy Endpoint Scales

- The OSA-18 is an 18-question pediatric OSA-specific health-related quality of life questionnaire. The ESS is a self-administered questionnaire with 8 questions. Respondents are asked to rate, on a 7-point scale (1-7) how frequently they experience OSA-related symptoms or problems. The OSA-18 score is a sum of 18 item scores (range 18-126), with higher scores indicating lower quality of life. The questionnaire takes approximately 5 minutes to answer. The OSA-18 is a secondary outcome and is measured at all PSG visits.

- The Peds-QL is a 23-question general pediatric health-related quality of life questionnaire with subscales for physical, emotional, social and school function. Respondents rate common problems on a scale from 0-4. Answers are reverse-scored and linearly transformed to a 0-100 scale, with lower scores indicating worse quality of life. The questionnaire takes approximately 5 minutes to answer. The Peds-QL is an exploratory outcome and is measured at all PSG visits. A change of 4.36 in Peds-QL total scale score has been shown to represent the minimal clinically important significant difference.
- The Caregiver Global Impression of Change scale consists of a 1-item questionnaire designed to assess the caregiver's satisfaction with the experimental treatment, considering both safety and efficacy. The scale is administered at the end of both high dose ato-oxy and low dose ato-oxy treatment periods.
- The Vineland 3 is a validated measure of adaptive behavior commonly used in studies of children with developmental disabilities such as Down syndrome. This is an exploratory outcome and is measured at all PSG visits. The adaptive behavior composite scale will be the outcome of interest.
- The Conners 3rd edition is a validated measure of behavior, primarily related to attention. This is an exploratory outcome and is measured at all PSG visits. The Conners ADHD Index will be the outcome of interest.

8.1.2 Polysomnography

- Methods: Standard overnight PSG recording and data interpretation will be performed in accordance with the American Academy of Sleep Medicine (AASM) scoring manual. Participants will be instrumented with standard PSG electrodes. Time of lights out will be established according to the participants' habitual schedule and kept constant across the PSG study nights. The participants will be given approximately 8 hours of time in bed.
- Technically Adequate Test: The screening/baseline PSG study must meet the following criteria for participants to enroll:
    - At least 4 hours of sleep.
    - At least 2 electroencephalograms (EEGs) and 2 electrooculography traces for the full night.
    - P nasal for at least 60% of the night and thermistor or both respiratory belts signals for the full night for scoring respiratory events.

Participants who do not have a technically adequate test at baseline can be retested at the discretion of the investigator.

- Scoring: Scoring will be conducted according to the American Academy of Sleep Medicine manual scoring criteria. All studies will be reviewed and overscored by a board-certified pediatric sleep medicine specialist blinded to study randomization.

8.2 LENA Language Evaluation

Language evaluation will be done using the Language ENvironment Analysis (LENA) digital language processor (LENA Foundation, Boulder, CO). The LENA device has been used in studies in children with developmental disabilities for more than 10 years, with 16 publications including children with developmental disabilities listed on the LENA device website bibliography (https://www.lena.org/wp-content/uploads/pdf/ResearchPublications.pdf). Additionally, it is included in ongoing NIH-funded studies in children with developmental disabilities, including the current PANDABox study (grant # MH111955).

The LENA device has been previously used in children with Down syndrome and has shown that sleep problems were associated with worse language abilities in children with Down syndrome(Edgin, Tooley et al. 2015). Similarly, in a prior study of OSA in children with Down syndrome, verbal IQ was specifically impaired(Breslin, Spano et al. 2014). Given these prior findings, it follows that OSA treatment may lead to improvement of language abilities in children with DS. There are no published studies to our knowledge evaluating the effects of OSA treatment on language in children with DS. This may be potentially in part due to the associated difficulties of performing laboratory-based assessments of language in children with Down syndrome, which may be a lengthy and stressful experience for the child. The LENA device provides a low-stress language evaluation that takes place in the child's own home. This provides a snap-shot of the child's language abilities in their natural environment.

LENA is a wearable digital recorder that stores 16 continuous hours of the sound environment for later analysis by LENA software speech-identification algorithms or manual coding. Children will wear the device on a necklace for a full day of recording at baseline as well as in the last week of each ato-oxy dose regimen. LENA software will be used to extract language-related variables (including total vocalizations of the child, total number of conversational turns of the child as well as measures of language complexity such as longest utterance of the child). Following download and extraction of these variables, the raw audio recording from the LENA device will be destroyed. This means that no human review of the audio recording will be performed, eliminating the risk of any inadvertent disclosure of private information from either consented individuals or background individuals. Additionally, consent for the LENA portion of the study will be "opt-in," and parents will initial a separate box to indicated interest in participating in this optional portion of the study. Participants will also be reminded prior to each

LENA recording that this is an optional procedure. They will also be provided with instructions on how to pause the device, as well as told that they can request to have the recording deleted without analysis if desired after completion of the procedure.

The primary goal of inclusion of the LENA device will be to determine feasibility of including this outcome in future studies. Specifically, our outcome will be the percentage of participants with usable data at all three study timepoints.

8.3 Safety Assessments

- Planned time points for all safety assessments are provided in the SoA.
- Safety monitoring will be guided by the established safety profiles of atomoxetine and oxybutynin, and by Phase 1 safety data for the combination. Safety assessments will include measurement of vital signs, monitoring and recording of AEs, SAEs, suicidality assessment, recording of study or treatment discontinuations. Effects on OSA and sleep parameters (e.g., sleep time and sleep stages) will also be monitored by PSG.
- Adverse events of special interest include effects on urine outflow, as both atomoxetine and oxybutynin are associated with urinary retention. Effects of atomoxetine on heart rate and blood pressure are expected to be modest, as indicated by the initial data described above, and will also be monitored. Participants with congenital heart disease will require clearance from their cardiologist in order to participate in the study. Suicidal ideation in children and adolescents is a boxed warning for atomoxetine. Therefore, safety monitoring in the dose-finding study will use an appropriate questionnaire to monitor for the potential emergence of suicidal ideation or depression. We will also specifically monitor for symptoms of reactive airway disease during safety monitoring. This will include questions related to wheezing as well as use of bronchodilator medications.

8.3.1 Vital Signs

- Assessment of vital signs (seated blood pressure, pulse rate,) will be performed at the time points indicated in the SoA (Section 1.3).
- Vital signs will be measured at all visits in a seated position after 5 minutes rest and will include systolic/diastolic blood pressure and pulse. Measurements should be made in the same arm of the participant at each visit.
- Systolic and diastolic blood pressure will be repeated for a total of 3 measurements, each at least 2 minutes apart.

8.3.2 Clinical Safety Laboratory Assessments

- To minimize discomfort to the child participants of the study, no routine blood draws will be included as part of the study. Both study agents are FDA-approved and do not require any laboratory monitoring.
- A urine pregnancy test will be performed on all female participants age 10 and older prior to study randomization.
- There are case reports of liver toxicity associated with atomoxetine, however large scale studies have not shown any increased risk of liver toxicity. There were no cases of liver-related SAEs during all clinical trials of atomoxetine in children and adults, which included 7,691 participants. Additionally, there are only three reports of liver toxicity related to atomoxetine in post-marketing surveillance of atomoxetine (with >10 years of monitoring), which all resolved with drug discontinuation. Therefore, to minimize risk of harm to participants, we will specifically inquire about evidence of jaundice or skin color changes during weekly phone calls while on study drugs but will not require blood draws for all participants. Participants that are found to have jaundice will have study drug discontinued and be referred for further medical management. These participants will be monitored until their condition stabilizes or resolves.

8.3.3 Suicide Risk Monitoring

Suicidal ideation in children and adolescents is a boxed warning for atomoxetine. However, post-marketing safety data has not shown an increased risk of suicidality associated with atomoxetine use (Bangs, Wietecha et al. 2014, Reed, Buitelaar et al. 2016). Additionally, suicidality appears uncommon in individuals with DS, regardless of atomoxetine use. There are no reports of suicide or suicidal ideation occurring in any children or adolescents with Down syndrome (DS), and a total of three reported suicide attempts in older individuals with DS (none associated with atomoxetine). Given this, the likelihood of suicidal ideation appears very low for this study. To further reduce the risk of suicide, we have excluded participants with current depression. Given the paucity of literature on suicidal ideation in DS, there are no available screening tools available for suicidality in DS. Therefore, we will instead monitor mood using the depression subscale of the Anxiety, Depression and Mood Scale (ADAMS), a screening tool for individuals with cognitive impairment which has been validated in a sample that included children with DS. In addition, we will use a single screening question from the Child Behavior Checklist (a validated behavior questionnaire for age 6-18) for suicidality: “Does your child talk about killing themselves?” For subjects that answer positively (somewhat true or often true), they will be flagged for immediate detailed assessment by the study PI, and appropriate actions will be taken,

including discontinuation of study medication as well as referral to behavioral health emergency services if indicated. This screening will occur weekly while subjects are on study medications. If this occurs, participants would be monitored until their suicidal ideation resolves.

8.4 Adverse Events, Serious Adverse Events and Unanticipated Problems

The definitions of AEs,SAEs and UPs can be found in Appendix 1.

Adverse events will be reported by the participant's parent/caregiver.

The Investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE, SAE or UP and remain responsible for following up on AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study and/or study treatment (see Section 7).

8.4.1 Time Period and Frequency for Collecting AE,SAE and UP Information

All AEs, SAEs and UPs will be collected from the signing of informed consent form (ICF) until Visit 3/EOS at the timepoints specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to the DSMB within 24 hours, as indicated in Appendix 1. The Investigator will submit any updated SAE data to the DSMB within 24 hours of it being available.

Investigators are not obligated to actively seek AEs, SAEs or UPs after the conclusion of study participation. However, if the Investigator learns of any UP or SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the DSMB.

The method of recording, evaluating, and assessing causality of AEs, SAEs and UPs and the procedures for completing and transmitting SAE and UP reports are provided in Appendix 1.

8.4.2 Method of Detecting AEs, SAEs and UPs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE or UP occurrence. The only exception to this is the specific monitoring for risk of suicidal ideation

(as described in section 8.2.3),potential liver toxicity (as described in section 8.2.2) and specific monitoring for reactive airway disease.

8.4.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is given in Appendix 1.

8.4.4 Regulatory Reporting Requirements for SAEs and UPs

- Prompt notification (within 24 hours, see Appendix 3) by the Investigator to the DSMB of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB, and Investigator.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy.

8.5 Treatment of Overdose

For this study, any dose of atomoxetine greater than 80 mg and of oxybutynin greater than 5 mg more frequently than QHS will be considered an overdose.

In the event of an overdose, the Investigator should refer to the approved product label for advice on overdose and:

1. Closely monitor the participant for AE/SAE.
2. Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator based on the clinical evaluation of the participant.

8.6 Pharmacokinetics

PK parameters are not evaluated in this study.

9 Statistical Considerations

9.1 Statistical Hypotheses

The null hypothesis is no difference in change from baseline in obstructive AHI in the high dose ato-oxy study period compared to the low dose ato-oxy study period.

9.2 Sample Size Determination

Under the mixed effects model setting the primary analysis for comparing high dose ato-oxy with low dose ato-oxy is reduced to a two-sample t test with a common variance of $\sigma^2/2$, where σ^2 is the residual variance (Hills and Armitage 2004). Based on prior research with a sample size of 20 subjects, a median change of -15.9 in AHI with interquartile range (-35.9, -7.3) was observed with a p-value of <0.001 (effect size [Cohen's d] of 1.4) (Taranto-Montemurro, Messineo et al. 2018). Given this, we plan to use 24 subjects (12 per dose sequence) which will have a power of 80% to detect an effect size of 1.20 standard deviations for changes in AHI, OSA-18 total score and arousal index, respectively, based on a two-sided test with α=0.05. We estimate a 10% attrition rate for the study and, therefore, will recruit a total of 27 participants.

9.3 Populations for Analyses

For the purposes of analysis, the following analysis sets are defined:

Population	Description
Enrolled	All participants who signed the ICF (including screening failures).
Modified Intent to Treat (mITT) Population	The mITT Population comprises all participants who are randomized, take at least 1 dose of any of the study treatments, and have at least 1 measurement on the primary endpoint. Participants will be analyzed for efficacy according to the treatment group into which they are randomized.
Safety Population	The Safety Population consists of all participants who are randomized and receive at least 1 dose of any of the study treatments. Participants will be analyzed for safety based on the treatment received.
Per Protocol (PP) Population	The PP Population consists of all participants without any major protocol violations that could influence efficacy assessment, and who are at least 80% compliant with the study medication. Participants in this population will be analyzed according to the treatment they actually received.

The primary endpoint comparison between the high dose ato-oxy and low dose ato-oxy will consider all mITT participants randomized to those 2 groups.

9.4 Primary and Secondary Analyses

Below is a summary of planned statistical analyses of the primary, secondary and exploratory endpoints.

For the primary outcome, each participant's changes in obstructive AHI from baseline will be derived for both periods (high dose ato-oxy and low dose ato-oxy). To account for the features of a 2 by 2 crossover design, a linear mixed effects model with a subject random effect and a dose sequence indicator (e.g. high dose ato-oxy➔ low dose ato-oxy sequence indicator), a period indicator (e.g. 2nd period indicator) and a high dose ato-oxy dose indicator as the covariates will be fitted to the changes in obstructive AHI. This model will allow us to evaluate the effect of high dose ato-oxy on changes in obstructive AHI compared with the effect of low dose ato-oxy (primary analysis) while accounting for the potential carry-over, period and subject effects. In addition, it will also allow us to evaluate whether the overall mean change from baseline is different from zero by testing the intercept of the model and whether the carry-over or period effect exists by testing the regression coefficient estimate for the treatment sequence indicator and the period indicator, respectively (secondary analysis). Prior research has shown that obstructive AHI is likely to be not normally distributed. Therefore, a suitable transformation will be sought and applied to changes in AHI before the mixed effects model is fitted if necessary.

For health-related quality of life aims**,** a similar statistical analysis plan will be implemented. Specifically, a linear mixed effects model with a subject random effect and a treatment sequence indicator (e.g. high dose ato-oxy➔ low dose ato-oxy sequence indicator), a period indicator (e.g. 2nd period indicator) and a high dose ato-oxy dose indicator as the covariates will be fitted to the changes in OSA-18 (secondary outcome), PedsQL and Caregiver global impression of change (exploratory outcomes), respectively. If necessary, a suitable transformation will be sought and applied to changes in these measures, although prior research has shown that OSA-18 is normally distributed (Jung, Kim et al. 2011).

For sleep architecture outcomes, we will again use a similar statistical analysis plan. Specifically, a linear mixed effects model with a subject random effect and a treatment sequence indicator (e.g. high dose ato-oxy➔ low dose ato-oxy sequence indicator), a period indicator (e.g. 2nd period indicator) and a high dose ato-oxy dose indicator as the covariates will be fitted to the changes in arousal index (secondary outcome) and percentage of N1, N3 and REM sleep (exploratory outcomes), respectively. For all aims, due to the cross-over design of the study, baseline covariates such as age, gender, baseline oAHI, etc. will not be included in the model as this would potentially create cross-over bias. (Kenward and Roger 2010, Mehrotra 2014).

9.5 Interim Analyses

No formal interim analysis is planned.

10 Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
    - Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
    - Applicable laws and regulations.

- The protocol, protocol amendments, ICF and other relevant documents (e.g., advertisements) must be submitted to an IRB by the Investigator and reviewed and approved by the IRB before the study is initiated.
- Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB.
    - Notifying the IRB of SAE or other significant safety findings as required by IRB procedures.
    - Overall conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH GCP guidelines, the IRB guidelines, and all other applicable local regulations.

10.1.2 Financial Disclosure

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant and his/her legally authorized representative and answer all questions regarding the study.
- Participants (and their parent/guardian) must be informed that their participation is voluntary. Parents/guardians will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB.
- A copy of the signed ICF(s) must be provided to the participant’s legally authorized representative.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the appropriate IRB, and signed by all participants subsequently enrolled in the study.

10.1.4 Assent

- Assent will be waived for all children age 7 and below (age ≤7 years old). For all other children, assent will be obtained (in addition to parental consent). To maximize participant understanding of the study, a social story style presentation/picture book will be used to explain study procedures to children. During this presentation, study staff will monitor for any signs of distress (crying, restlessness, etc.) that may indicate that the participant does not want to participate in the study.
- Assent will be documented via an assent form read to the child. When able, children will sign the assent form. For children unable to write, assent based on child's individual communication style will be obtained (verbal yes, head nod, etc.). Confirmation of assent will be documented by parent as well as obtaining study staff.
- All consenting staff will receive training on working with children and families with developmental disabilities. This training will include information specifically related to assent for children with developmental disabilities, as well as training on monitoring for distress in children with developmental disabilities.
- In addition to the initial assent process above, participants will be monitored throughout the study to ensure continued assent. Children with evidence of distress may be withdrawn from the study by study staff or by parents at any time in the study. For instance, if children show significant signs of distress at any point in the study (such as crying inconsolably or asking to stop), that procedure will be terminated.

10.1.5 Monitoring for Continued Consent/Assent

- An independent monitor will be used to confirm that participants wish to continue in the study. This monitor will have no vested interest in the study or study outcome. The monitor will check in via telephone with all participating families at several planned time points:
  1. After study enrollment and prior to the initial sleep study.
  2. After the first sleep study
  3. After the second sleep study

- The monitor will also be available at any point via phone. During the first telephone call, the monitor will review potential study risks and benefits with the family (as outlined in the consent form). During all phone calls, the monitor will assess any family desire to withdraw from the study. Any families identified as desiring withdrawal from the study will be contacted by study staff for potential study withdrawal.
- Families will be assured at all points that study participation or withdrawal will have no negative effects, as noted in the consent form: "Your child's participation is voluntary. If you decide to take part in the study, your child may leave the study at any time. No matter what decision you make, there will be no penalty to you or your child, and you will not lose any of your usual benefits. Your decision will not affect your future relationship with The University of Arizona. If you are a student or employee at the University of Arizona, your decision will not affect your grades or employment status."
- Additionally, to monitor for continued child assent, a systematic evaluation of stress related to polysomnography will be obtained during each sleep study. Specific measures that will be collected and reported to the DSMB include:

    1. Significantly delayed sleep onset (>60 minutes from lights out)
    2. Greater than 20-minute period of crying or child cannot be consoled by parents
    3. Unable to complete set up within 90 minutes of beginning.
    4. Number of episodes of crying overnight (excluding confusional arousals or other parasomnias)
    5. Number of times parent intervention was needed during the sleep study after lights out.

- Item #1 (sleep latency) is a standard sleep study measure and sleep onset is automatically included in all sleep study reports at our institution. The time from lights out to the first epoch of sleep can also be easily determined by the sleep technician in real time during the study as well. Item #2 (periods of crying) will be estimated by the technician during the study and duration can be easily determined from the sleep study record which includes time as a marker and is charted in 30 second epochs. Item #3 (sleep study set up) will be estimated by the technician from the start of set up to lights out. Technicians will record the time set up begins and lights out is recorded on the sleep study record.
- Sleep studies may be terminated by parents at any time if desired, as well as by polysomnography technicians if the child is noted to have significant distress. Markers of distress indicating the need for potential study termination include items 1-3 above. If items 1-3 occur, the technician will offer study termination to the family. Additionally, if the technician has any other concerns that the sleep study is excessively stressful to the child, the study can be terminated at the technician's discretion.

10.1.6 Data Protection

- Participants will be assigned a unique identifier by the investigator or their designee. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

10.1.7 Dissemination of Clinical Study Data

A summary of the study results will also be posted in a publicly accessible database (e.g., www.ClinicalTrials.gov). The results may also be submitted for publication.

10.1.8 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data).
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors may perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for 5 years after study completion (or after subject turns 18 if longer) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.
- All data generated by the site personnel will be captured electronically at each study center using eCRFs. Once the eCRF clinical data have been submitted, corrections to the data fields will be captured in an audit trail. The reason for change, the name of the person who performed the change, together with the time and date will be logged to provide an audit trail.
- If additional corrections are needed, the responsible coordinator will raise a query in the electronic data capture (EDC) application. The appropriate staff at the study site will answer queries sent to the Investigator. The name of the staff member responding to the query, and time and date stamp will be captured to provide an audit trail. Once all source data verification is complete and all queries are closed, the monitor will lock the database.
- The EDC application will be REDCap for this protocol.

10.1.9 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Section 10.1.11.1.

10.1.10 Study and Site Closure

The Sponsor designee reserves the right to terminate the study at any time for any reason at the sole discretion of the Sponsor.

The Investigator may initiate study termination at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

10.1.11 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.12 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IRB, in accordance with local legal requirements. The Investigator must ensure that all ethical and legal requirements have been met before the first participant is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB approval prior to implementation (if appropriate).

Administrative changes (not affecting the participant benefit/risk ratio) may be made without the need for a formal amendment.

The Sponsor will arrange for participants participating in this study to be insured against financial loss due to personal injury caused by the pharmaceutical products being tested or by medical steps taken in the course of the study.

10.1.12.1 Access to Source Data

During the study, a monitor may make site visits to review protocol compliance, compare EDC/eCRF entries and individual participant's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. The EDC/eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that participant confidentiality is maintained.

Checking of the EDC/eCRF entries for completeness and clarity, and cross-checking with source documents, will be required to monitor the progress of the study. Moreover, regulatory authorities of IRBs, and/or the Sponsor's Clinical Quality Assurance Group may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be

required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality.

10.2 Appendix 1: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect

Other situations

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical treatment to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Definition of UP

UP Definition
• An UP is Any incident, experience, or outcome that meets all of the following criteria: • unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied; • related or possibly related to participation in the research (there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and • suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Events Meeting the UP Definition
• Examples of unanticipated problems may include: • Unusual medical events: medical events that are not considered “serious” but may be important for the study, such as a reaction to a study procedure, pregnancy, a suspected safety issue concerning any aspect of the trial that is unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied; • Atypical problems: examples of these include breach of confidentiality and inadvertent loss of study records. related or possibly related to participation in the research (there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).

Recording and Follow-up of AE and SAE

AE and SAE Recording
• When an AE/SAE/UP occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event. • The Investigator will then record all relevant AE/SAE/UP information in the eCRF. • It is **not** acceptable for the Investigator to send photocopies of the participant's medical records in lieu of completion of the AE/SAE/UP eCRF page. • The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories: • Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe. An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality
• The Investigator is obligated to assess the relationship between study treatment (or procedures for UPs) and each occurrence of each AE/SAE/UP.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The Investigator will also consult the Product Information, for marketed products, in his/her assessment.
- For each AE/SAE/UP, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/UP and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the DSMB. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial report to the DSMB.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE,SAE and UP

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the AE, SAE or UP as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to DSMB within 24 hours of receipt of the information.

Unanticipated Problems (UPs)
• Participants will be screened for unanticipated problems at the same time as they are screened for AEs or SAEs. Additionally, any breach of confidentiality will be reported per institutional guidelines as soon as it is identified and would be considered an unanticipated problem necessitating report as a UP • All identified problems will be reviewed by the study PI upon identification of the potential problem to determine if it meets the definition of an unexpected problem as defined previously in the protocol. • UPs will be reported to the DSMB within 7 days and to the local IRB within 10 days. The Investigator will also provide annual safety updates to the regulatory authorities and DSMB responsible for the study. These updates will include information on UPs and other relevant safety findings.

Reporting Serious Adverse Events

The Investigator must report any SAEs to the DSMB within 24 hours of becoming aware of the event.

The Investigator will review each SAE report and evaluate the seriousness and the causal relationship of the event to study treatment. In addition, the Investigator will evaluate the expectedness according to the reference documents (US product labeling for atomoxetine or oxybutynin). Based on the Investigator and DSMB's assessment of the event, a decision will be made concerning the need for further action.

All SAEs will be recorded from signing of informed consent until the end of the study. Serious adverse events occurring after the end of the study and coming to the attention of the Investigator must be reported only if they are considered (in the opinion of the Investigator) causally-related to study treatment.

10.3 Appendix 2: List of Abbreviations

ADHD	Attention deficit hyperactivity disorder
AHI	apnea-hypopnea index
AE	adverse event
BMI	body mass index
CFR	Code of Federal Regulations
CNS	central nervous system
CPAP	continuous positive air pressure
CYP2D6	cytochrome P450 2D6
CYP3A4	cytochrome P450 3A4
DS	Down syndrome
eCRF	electronic case report form(s)
EDC	electronic data capture
EMG_{gg}	genioglossal electromyographic
EOS	end of study
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
OSA	obstructive sleep apnea
OSA-18	Obstructive Sleep Apnea-18
OTC	over-the-counter
MAOI	monoamine oxidase inhibitor
NREM	non-rapid eye movement
PEDS-QL	Pediatric Quality of Life Inventory
PK	pharmacokinetic(s)
PSG	polysomnography
QHS	1 dose every night at bedtime
REM	rapid eye movement
SAE	serious adverse event
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction
UP	Unanticipated problem
US	United States

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