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Methods: In a study across 14 sites in India, 406 patients with preterm labor symptoms received up to 48 hours of atosiban infusion. Tocolysis efficacy was gauged by the 72-hour undelivered rate, while safety was assessed via maternal-fetal and neonatal adverse events.

Results: In 400 evaluated patients, the gestation period in 89% of patients was prolonged for more than 48 hours and 83.75% of patients continued their pregnancy up to 72 hours. Amongst the tocolyzed patients, 77% of preterm births were prevented for more than 7 days. The mean duration of gestational period prolongation after the tocolysis was 31.28 days with a mean gestational age at delivery of 35.0 ± 3.15 weeks. Singleton and twin pregnancy prolongation rates for 72 hours were 84.95% and 67.86% respectively. Birth weight of more than 2500 grams was in 54.44% of neonates and an APGAR score of more than 7 after 5 minutes was in 91.82% of neonates. Patients receiving atosiban were more likely to have nausea (2.71%), tachycardia (2.46%), and headache (1.97%). No new or unexpected adverse events were reported in this study.

Keywords: preterm labor; oxytocin receptor antagonist; atosiban; tocolysis.

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Conclusion: Atosiban is effective in prolonging the gestational period by a mean of 31 days in patients with pre-term labor, with a low incidence of maternal-fetal adverse effects. The requirement of 'Neonatal Intensive Care Unit' admission for the newborn is reduced, thus saving a huge cost associated with hospitalization.

Keywords: preterm labor; oxytocin receptor antagonist; atosiban; tocolysis.

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I. INTRODUCTION

Preterm labor is defined as regular uterine contractions leading to cervical changes before 37 weeks of completed gestation that may result in preterm birth and is 'extremely preterm' (less than 28 weeks), 'very preterm' (28 to <32 weeks) and 'late preterm' (32 to <37 weeks). [1,2]The estimated global preterm birth rate is 10.6% and India contributes 23.4% of global preterm births. [3]Moreover, India alone accounts for 61.2% of preterm labor cases in Southern Asia.[4]

Preterm birth resulting from preterm labor poses a considerable risk to infants' health and survival, especially if it happens during the early stages of pregnancy. Premature infants, having underdeveloped organ systems, become highly susceptible to various complications, both in the short term and in the long term. These complications can significantly impact their health and well-being. The majority of newborn morbidities include cerebral palsy, cognitive impairment, blindness, deafness, respiratory illness, and complications of neonatal intensive care.[5] Globally, preterm birth complications accounted for 17.8% of all deaths and became a leading cause of death in children under 5 years of age. [6]Currently, the main focus of treatment for preterm labor is directed toward pharmacologically inhibiting uterine contractions using tocolytic agents.[7]The primary objective of tocolytic therapy is to achieve a delay in preterm delivery, providing a long enough time for antenatal corticosteroids which promote fetal lung maturation and improve neonatal outcomes. Additionally, the delay in delivery allows for the

safe transfer of the mother to an equipped facility to provide optimal neonatal care. By extending the duration of pregnancy, tocolytic therapy aims to maximize the chances of a healthier outcome for both the mother and the newborn.[8]

Oxytocin causes uterine contractions through a direct effect on membrane-bound receptors that exist on the myometrium and decidua parietalis.[9] In the myometrium, the oxytocin and oxytocin-receptor complex activates phospholipase C, leading to the production of inositol 1, 4, 5-triphosphate, which increases intracellular free calcium. Calcium ions bind to calmodulin, forming a complex known as Ca^{2+}-calmodulin. This complex plays an important role in activating myosin light-chain kinase, a key enzyme responsible for inducing contractions in the myometrial muscle.[10] In decidua, oxytocin interacts with its receptor and releases prostaglandins. These locally produced prostaglandins increase the uterine sensitivity to oxytocin and increase the number of gap junctions in the adjacent myometrium.[11]The onset of labor involves a combination of factors that contribute to its progression. Cervical changes, persistent uterine contractions, and activation of the decidua and myometrial membranes contribute to labor.[12]

The oxytocin system, which acts via uterine oxytocin receptors, plays a central role in the mechanisms of human parturition. Increased concentrations of oxytocin receptors appear to be important in the onset of preterm labor.[1] [3]Atosiban is an oxytocin analog with modification of amino acids located at positions 1, 2, 4, and 8.[10] It competes with oxytocin binding at oxytocin receptors resulting in reduced myometrial contraction.[14]

Atosiban is the only oxytocin antagonist in use for the treatment of preterm labor in Europe and other countries.[15]The European Medicines Agency (EMA, EU) in 2000 and the Central Drugs Standard Control Organization (CDSCO, India) in 2015 authorized the use of atosiban in preterm labor. In clinical practice, atosiban is the most common tocolytic agent administered to pregnant women presenting with preterm labor. This study was conducted to generate clinical evidence for the efficacy and safety of atosiban in preterm labor.

II. MATERIALS AND METHODS

2.1 Ethics

The study was performed in compliance with the requirements of the Central Drugs Standard Control Organization (CDSCO),India. The study protocol was approved by the Subject Expert Committee (SEC) nominated by the CDSCO andthe Institutional Ethics Committee of each study center. The study was performed in accordance with the International Council for Harmonization for Good Clinical Practice, Declaration of Helsinki and New Drugs and Clinical Trials, Rules, 2019 India. Informed consent was obtained from all participants before enrolment.

2.2 Participants

The study was conducted from March 2017 to January 2022 at obstetric units of 14 geographically distributed sites across India. A total of 406 pregnant patients with>24 gestational weeks who presented with preterm labor were included in the study. A diagnosis of preterm labor was based on the presence of regular uterine contractions—defined as >4 contractions of ≥30 seconds' duration every 30 minutes - confirmed by cardiotocography, alongside evidence of cervical dilatation of 0–3 cm in nulliparous women or 1–3 cm in primi- or multiparous women with ≥50 % effacement. Patients with chorioamnionitis, ruptured membranes, vaginal bleeding, preeclampsia, intrauterine growth restriction, intrauterine fetal death, congenital or acquired uterine malformation, severe placental insufficiency, placenta previa, abruptio placentae, fetal distressor women who were otherwise judged inappropriate for inclusion in the study by the investigator were excluded.

2.3 Atosiban Regimen

Atosiban (Tosiban™, Zuventus Healthcare Limited, India)was administered as a single intravenous bolus dose of 6.75 mg over 1 minute followed by an intravenous infusion (using an

infusion pump or diluted in normal saline) at a speed of300 mcg/minfor3 hours and continued it at a speed of 100 mcg/min fora period of 45 hours. The woman who didn't respond and hadsigns oflabor progress was considered for re-treatment with atosibanor another alternative tocolytic agent at the investigator's discretion.

2.4 Outcome Measures

The outcomes of the study measured were:(a) the proportion of patients remaining undelivered at 48 hours, 72 hours and 7 days after the start of atosiban treatment; (b) time gained in-utero, defined as the number of days gained in-utero after the start of atosiban tocolysis;(c) the proportion of patients re-treated with atosiban and/or alternative tocolytic agents;(d) incidences of adverse events.

2.5 Statistical Analysis

Descriptive statistics were used to summarize baseline characteristics and represented as mean ± standard deviation (SD). Non-continuous data was presented in number and percentage. Paired student's t-test was used to assess change in maternal characteristics from baseline to 48 and 72 hours.A p-value of less than 0.05 was considered statistically significant.Adverse Events were assessed as the number and percentage. The data were analyzed using STATA/IC15.0 software (StataCorp LLC).The study sample size of 400 patients was sufficient to show at least 65% atosiban tocolytic efficacy as compared to the published data[16,17] with a 95% level of significance and 80% power.

III. RESULTS

3.1 Disposition of Patients

A total of 406 patients with preterm labor were enrolled in the study based on the eligibility criteria. During the study, 5 patients discontinued the study due to adverse events and 1 patient dropped out from the study on her own (left against medical advice). At the end of the study, 400 patients completed the study and were considered for the statistical analysis. The flow diagram of the study is displayed in Figure 1.

3.2 Study Population

The age range of patients was 18 to 48 years, with a mean of 25.37 ± 4.84 years. The average gestational age during enrolment in the study was 30.5 weeks. The median gravidity, parity and abortions were 2 (IQR: 2; range: 0-10), 1 (IQR: 1; range: 0-9) and 0 (IQR: 0; range: 0–6), respectively. The demographic characteristics of the study population are shown in Table 1.

3.3 Efficacy Assessment

3.3.1 Overall Efficacy of Atosiban

The overall success rate in prolongation of pregnancy by 48 hours was 89% (356/400). The prolongation of pregnancy by72 hours or more was achieved in 83.75% (335/400) patients, of which, 77% (308/400) got their pregnancy extended by more than 7 days.

3.3.2 Time Gained In-Utero after Initiation of Treatment

The overall mean number of days gained after the start of atosiban was 31.28 days, whereas, in the subgroup of patients with a singleton pregnancy, the interval until delivery was 32.40 days, and in patients with twin pregnancies 16.46 days. The duration of pregnancy prolongation in subgroups is given in Table 2. Prolongation in pregnancies beyond 34 weeks was observed in 62% (231/372) of patientsand48% (110/231) of them gave birth after 37 weeks of gestation.

3.3.3 Tocolytic Effect Based on Gestational Age

Among the enrolled patients, 14.50%, 51.75% and 33.75% population belonged to the extremely preterm (<28 weeks), very preterm (28 to <32 weeks)and late preterm (32 to<37 weeks) groups, respectively. The success rate at 72 hours of atosiban was 84.48%in the 'extremely preterm' group, 87.44% in the 'very preterm group and 77.78%in the 'late preterm group.The details of the tocolytic efficacy of atosiban at 48 hours, 72 hours and day 7 are given in Table 3.

3.3.4 Tocolytic Effect Based on the Type of Gestation

Among the enrolled patients, 372 patients carried singleton pregnancy of which 84.95% of patients

remained undelivered at 72 hours. Among the 28 patients with twin pregnancies, 67.86% of the patients remained undeliveredat72 hours. The success rates of atosiban in singleton and twin pregnancies are given in Table 3.

3.3.5 Tocolytic Effect Based on Parity of Pregnancy

There were 46.75% of nulliparous patients who underwent atosiban tocolytic whereas 33% of primiparous and 20.25%of multiparous patients received atosiban in preterm labor (Table 3).

3.3.6 Tocolytic Effect with Different Cervical Dilatation

A total of 54% of patients had a cervical dilatation of 2 cm or more, while 46% of patients had a cervical dilatation of less than 2 cm. The success rate of atosiban treatment between these two cases is given in Table3.

The mean cervical dilatation was 1.66 ± 0.85 cm on admission, with a gradual reduction to 1.23 ± 0.99 cm and 1.1 ± 1.04 cm at 48 hours and 72 hours respectively. The mean frequency of uterine contractions per 30 min showed a gradual reduction from 3.97 ± 1.41 to 1.38 ± 1.60 (mean difference: 2.59, 95% CI: 2.38 to 2.83) from the time of admission to the completion of treatment (i.e. 48 hours) and 1.13 ± 1.67 (mean difference: 2.84, 95%CI: 2.50 to 2.96) at 72 hours. Similarly, the mean cervical effacement (%) gradually reduced from 44.94 ± 16.91 to 30.1 ± 21.11 (mean difference: 14.84, 95%CI: 13.27 to 17.05) and 28.48 ± 23.13 (mean difference: 16.46, 95%CI: 12.12 to 18.20) at 48 hours and 72 hours respectively. All these parameters showed a significant change ($p<0.001$) from baseline.

3.4 Need of Retreatment with Atosiban or Alternative Tocolytics

There was no requirement for alternative tocolytics during the first 48 hours of atosiban treatment. Retreatment with atosiban or alternative tocolysis was required in 14 patients after the completion of the study treatment. Alternate tocolytics (Isoxsuprine, and Nifedipine) were used in 6 (1.5%)patients whereas 8 (2%) patients were retreated with atosiban after 48 hours (mean 13.3 days, 95% CI: 3.8-22.8 days). The mean number of days gained *in-utero* was 31.27 ± 24.48 days excluding these patients.

3.5 Safety Assessment

3.5.1 Neonatal Outcomes

APGAR (Appearance, Pulse, Grimace, Activity and Respiration) test was performed to assess the health of newborns. The mean APGAR score at 1 min was 7.92 ± 1.53 and at 5 min of birth was 8.77 ± 1.31. Out of 428 neonates, 393 (91.82%) hadan APGAR score of more than 7 after 5 minutes.The average neonatal birth weight was 2318 ± 242.64 gm. A total of 233 (54.44%) babies were born weighing more than 2500 gm. Data on neonatal outcomes are shown in Table 4.

3.5.2 Safety Analysis based on Maternal, Fetal and Neonatal Adverse Events

The treatment with atosiban injection was well tolerated by the patients. Amongst 45 (11.08%) patients, 49 instances of adverse events were observed.The most frequent adverse events were nausea (11 incidences, 2.71%), tachycardia (10 incidences, 2.46%), headache (8 incidences, 1.97%), epigastric pain, and constipation (3 incidences each, 0.70%), dizziness, dyspnea and fever (2 incidences each, 0.47%). Five patients (1.23%) discontinued due to adverse events. Fetal and neonatal adverse events observed were bradycardia (2 fetuses, 0.47%) and hypoxia(1 fetus, 0.23%), congenital anomaly of heart and respiratory distress (1 neonate, 0.23%). No new or unexpected adverse events were reported in the study.

3.5.3 Clinical Laboratory Tests, Vital Sign Examination

After completion of treatment, no clinically significant changes were noted in the laboratory data of the patients as compared to the baseline.Vital signs examination during the study showed no clinically significant changes as compared to the baseline. Fetal heart rate was monitored using cardiotocography at the time of admission and after every 12 hours till 72 hours.

IV. DISCUSSION

Premature delivery is a common problem during pregnancy, and the rates of preterm birth vary from country to country. According to a systematic review and modeling analysis, 81% of preterm births occur in countries in sub-Saharan Africa and South Asia. [3]Comparatively, India has a higher rate of preterm birth complications, ranking second as the common cause of 'under-5 mortality' as observed in 2019, with preterm birth complications accounting for 6.3% to 25.7% of all under-5 deaths. [18]It is important to diagnose the causes of premature delivery and low birth weight babies to improve the birth outcomes, and to find ways to make existing interventions more effective and clinically evident.

In this study, patients who were experiencing labor contractions with gestational age>24 weeks of pregnancy were hospitalized and treated with atosiban to prolong pregnancy. Out of these patients, 89% of them, were able to continue pregnancy for at least 48 hours after receiving atosiban as a tocolytic agent. The results are consistent with published studies with atosiban where it was found to be effective in delaying delivery for at least 48 hours in a significant proportion of patients.[19-22]

The use of atosiban in patients with preterm labor was effective in delaying delivery, with a low rate of maternal or fetal adverse effects. [23-25]Our findings in the current study indicate that the usage of atosiban did not lead to any significant or severe adverse effects in the mother or fetus.Mild adverse events were observed in 12% of patients consisting of nausea, tachycardia, and headache. The published studies show consistently, a lower incidence of adverse effects associated with the usage of atosiban in pregnancy, suggesting better tolerability as compared to the other tocolytics. [17,26,27]These findings highlight the advantages of atosiban in terms of maternal tolerability and safety.

In the current study, the mean duration gained *in-utero*after atosiban treatment was 31 days, and for those who were enrolled at gestational age <28 weeks was prolonged to 47.4 days. Similar results were reported in earlier published clinical studies with the mean number of days gained *in-utero*ranging from 31 to 35 days with atosiban treatment.[16,28,29]In the case of twin pregnancies, among 28 patients, 75% of them remained undelivered after 48 hours of atosiban tocolysis and 54%of the patients were able to continue their pregnancy for more than 7 days without experiencing any complications. Published data on atosiban demonstrates similar efficacy in postponing delivery in twin pregnancies.[16,30]

It was observed that there was a comparable success rate in prolonging pregnancy among cases of extremely preterm labor, very preterm labor, and late preterm labor p=0.311; Pearson chi^2 test).Similar findings were reported by Salim *et al.* in a randomized clinical trial where it was observed that 70% of patients with early preterm labor (before 28 weeks) and 68.3% of patients with late preterm labor (after 28 weeks) did not deliver within 48 hours after receiving atosiban treatment. [16]Another prospective clinical study demonstrated atosiban as a viable and successful tocolytic option in 18 and 24 weeks of pregnancy.[31]

Khalil *et al.* showed that initial cervical changes have a significant impact on the success of atosiban and the prolongation of pregnancy. [32]Kashanian *et al.* reported that atosiban is effective in uterine hyperactivity in the active phase of labor. [33]The present study achieved uterine quiescence within48 hours following the administration of atosiban (p<0.001). Similar results were observed in one of our earlier published clinical study, where atosiban reduced the frequency of uterine contractions significantly (p<0.001).[34]

Preterm labor is a multifactorial condition associated with a high risk of morbidity and mortality, particularly at early gestational ages. The major concern of extreme preterm birth is the significant risk of neonatal mortality as the survival rates are very low in such pregnancies (0.4% at 22 weeks, 7% at 24 weeks, 77% at 28 weeks and 97% at 36 weeks).[35] Tocolytics can improve neonatal survival rates by approximately 3% per day with a concomitant reduction in neonatal morbidity.[7]In this study, 97.5% of

neonates survived without major complications. Neonatal Intensive Care Unit (NICU) admission was not required in 79% of the neonates. The mean neonatal birth weight was 2318 ± 242 gm. Despite 195 (46%) of the newborns having low birth weight, only 90 required (21.02%) NICU admission. Takagi *et al* reported that newborns with birth weights of at least 2000 grams had a 95% survival rate. [36] There is a positive correlation between birth weight and neonatal survival. The findings revealed that newborns with higher birth weights have a better chance of survival.

An optimal tocolytic agent would effectively postpone delivery with minimal maternal and fetal adverse effects.Our findings show that atosiban had fewer failures within 48 hours,which is in line with the published clinical data[37] and highlights the importance of atosiban- based tocolysis in preterm labor and favors its use as a first-line treatment in preterm labor due to its efficacy and good safety profile. This study did not have a comparative arm but on comparing with the published data, it shows benefits in safety over other tocolytic agents.

V. CONCLUSION

Atosiban is an effective tocolytic agent acting through oxytocin receptor antagonism, and the clinical data suggests that it helps in delaying delivery by a mean of 31 days in patients with preterm labor, with a low rate of maternal-fetal adverse effects.The requirement of NICU admission is reduced, thus saving a huge cost associated with hospitalization. This was an open-label study without a comparator arm, future randomized comparative studies on a larger population are recommended.

Conflict of Interest: The authors declare that they have no conflict of interest.

Source of Funding: None

Ethical Approval:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional ethics committee, the Indian Council of Medical Research (ICMR), and the Declaration of Helsinki. Approval was obtained from the Institutional Ethics Committee of each study center. Informed consent was obtained from all individual participants included in the study.

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Author Contributions

Bhupesh Dewan contributed to the study design, interpretation of the data, and manuscript editing and revising. Siddheshwar Shinde contributed to the data acquisition and drafting of the manuscript. Both authors are responsible for the integrity of the data and the accuracy of the analysis and approve the final version of the manuscript for submission.

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Table 1: Maternal Baseline Data

Characteristics	Enrolled patients (n=406)	Patients considered for final statistical analysis (n=400)
Maternal age (years)	25.37 ± 4.84	25.36 ± 4.84
Body mass index (kg/m²)	23.40 ± 3.44	23.38 ± 3.45
Average gestational age at admission (weeks)	30.5 ± 2.5	30.5 ± 2.5
Type of Gestation		
Nulliparous	189 (46.55)	187 (46.75)
Primiparous	134 (33.01)	132 (33.00)
Multiparous	83 (20.44)	81 (20.25)
Type of pregnancy		
Singleton	378 (93.10)	372 (93.00)
Twins	28 (6.90)	28 (7.00)
Gestational age groups		
<28 weeks	59 (14.53)	58 (14.50)
≥28 to < 32 weeks	210 (51.72)	207 (51.75)
≥32 to <37 weeks	137 (33.74)	135 (33.75)
Cervical dilatation		
<2 cm	187 (46.06)	184 (46.00)
≥2 cm	219 (53.94)	216 (54.00)
Previous preterm delivery	149 (36.70)	146 (36.50)

Datain Mean ± SD and n (%)

Table 2: Prolongation of Pregnancy

Overall time gained *in-utero*	31.28 ± 24.44 days
Gestational age at admission	
<28 weeks	47.44 ± 31.37 days
≥28 to <32 weeks	34.49 ± 23.45 days
≥32 to <37 weeks	19.42 ± 16.50 days
Cervical dilatation at the start of treatment	
<2 cm	36.28 ± 25.07 days
≥2 cm	27.03 ± 23.12 days
Type of gestation	
Singletons	32.40 ± 24.45 days
Twin	16.46 ± 19.36 days
Parity of pregnancy	

Nulliparous	32.39 ± 26.32 days
Primiparous	29.91 ± 23.81 days
Multiparous	30.98 ± 20.87 days

Data in Mean ± SD

Table 3: Tocolytic Efficacy of Atosiban

	48 hr, n (%)	72 hr, n (%)	Day 7 n (%)
Gestational age			
<28 weeks		49 (84.48)	46 (79.31)
≥28 to < 32 weeks	189 (91.30)	181 (87.44)	173 (83.58)
≥32 to <37 weeks	117 (86.67)	105 (77.78)	89 (65.93)
Type of gestation			
Singletons	335 (90.05)	316 (84.95)	293 (78.76)
Twin	21 (75.00)	19 (67.86)	15 (53.57)
Parity of pregnancy			
Nulliparous	162 (86.63)	151 (80.75)	139 (74.33)
Primiparous	118 (89.40)	109 (82.58)	98 (74.24)
Multiparous	76 (93.83)	75 (92.59)	71 (87.65)
Cervical dilatation at the start of treatment			
Overall			
<2 cm	169 (91.85)	161 (87.5)	156 (84.78)
≥2 cm	187 (86.57)	174 (80.56)	152 (70.37)
Twin pregnancies			
<2 cm	9 (90)	8 (80)	8 (80)
≥2 cm	12 (66.67)	11 (61.11)	7 (38.89)

Table 4: Neonatal Outcomes

Neonatal Birth Record (n)	428
Gestational age at birth, weeks (Mean ± SD)	35.00 ± 3.15
Birth weight, gm (Mean ± SD)	2318 ± 242.64
Neonates with birth weights less than 2500 gm, n (%)	195 (45.56%)
APGAR Score	
APGAR score 1 minute after birth (Mean ± SD)	7.92 ± 1.538 (7-9)[a]
APGAR score 5 minutes after birth (Mean ± SD)	8.77 ± 1.31 9 (8-10)[a]
APGAR score ≥7 after 1 minute, n (%)	346 (80.84)
APGAR score ≥7 after 5 minutes, n (%)	393 (91.82)
NICU admission, n (%)	90 (21.02)

[a]*Data in Median(IQR)*

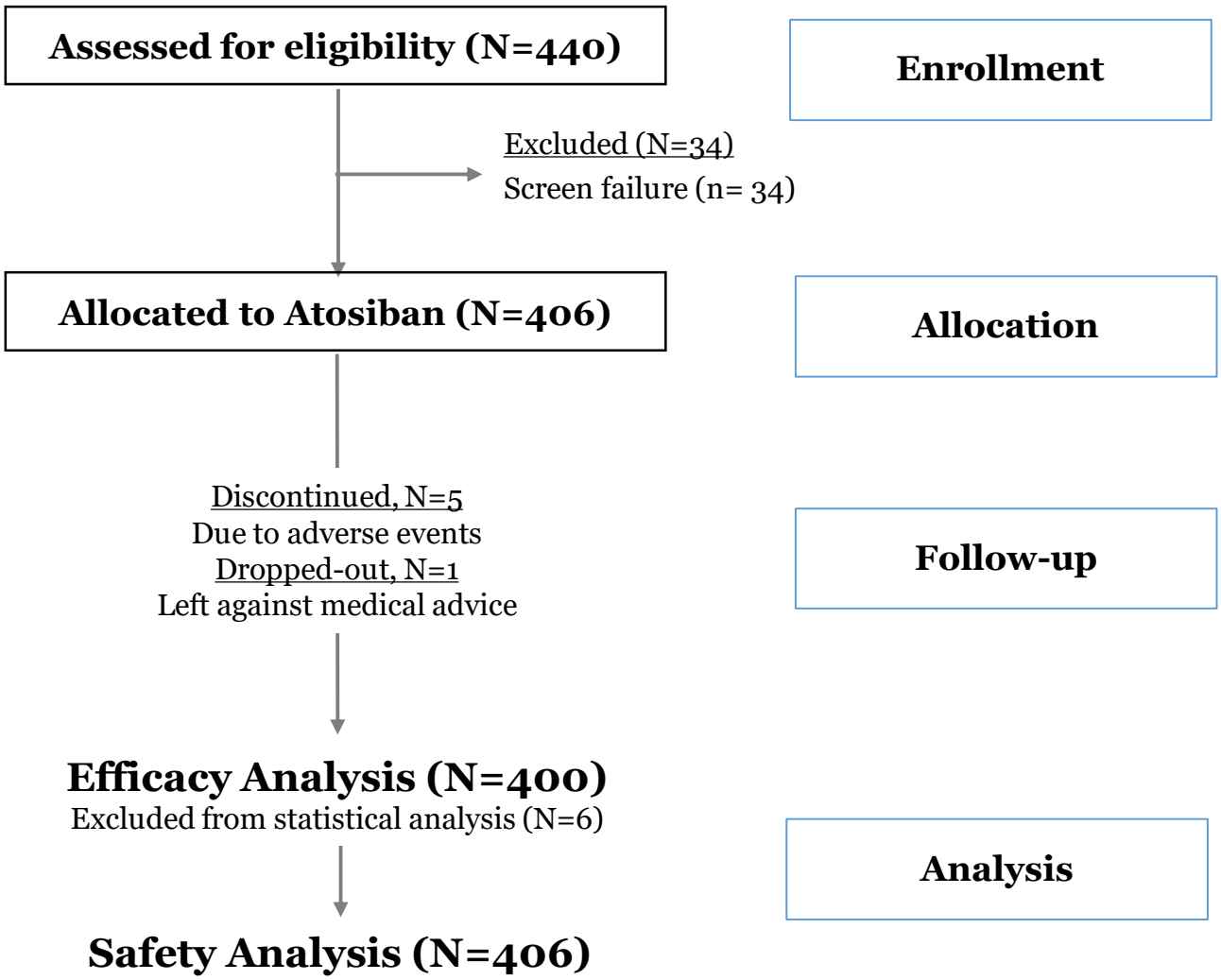

Figure 1: Consort Flowchart of the Study