Safety of Binodenoson, a Selective Adenosine A2A Receptor Agonist Vasodilator Pharmacologic Stress Agent, in Healthy Subjects with Mild, Intermittent Asthma

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Abbreviations List:
AE Adverse Event
DBP Diastolic blood pressure
FEF25%-75% Forced expiratory flow during the middle 50% of the FVC
FEV1 Forced expiratory volume in 1 second
FVC Forced vital capacity
HR Heart rate
MPI Myocardial perfusion imaging
PEF Peak expiratory flow
PFT Pulmonary function test
PS Pharmacologic stress
SBP Systolic blood pressure
SD Standard deviation
SPECT Single photon emission computed tomography
ABSTRACT

Background: The pharmacologic stress (PS) agents adenosine and dipyridamole are contraindicated in asthma patients because of the risk of adenosine receptor-mediated bronchospasm. Binodenoson, a selective adenosine A$_{2A}$ receptor agonist, produces maximal coronary hyperemia during PS testing, yet has a low affinity for the adenosine A$_1$, A$_{2B}$, and A$_3$ receptors likely responsible for bronchospasm. This study was conducted to assess the safety of binodenoson in 87 healthy young adult volunteers with documented mild, intermittent asthma.

Methods and Results: This study consisted of a dose-escalating, single-blind phase and a placebo-controlled, double-blind phase conducted in healthy, young adults with documented mild, intermittent, asthma. In the single-blind phase, 3 sequential cohorts of 8 subjects received intravenous binodenoson (0.5, 1.0, and 1.5 $\mu$g/kg). In the double-blind phase, commenced after medical review of results from the single-blind phase, subjects were randomized 2:1 to either binodenoson 1.5 $\mu$g/kg (n=41) or placebo (n=22). The primary endpoint was clinically significant bronchoconstriction, defined as a decrease in forced expiratory volume in 1 second (FEV$_1$) of $\geq$ 20% from the pre-injection measure. Secondary safety endpoints were changes from pre-injection measure in FEV$_1$, forced vital capacity (FVC), and forced expiratory flow during the middle 50% of the FVC (FEF$_{25\%-75\%}$); vital signs; pulse oximetry; and adverse events. Binodenoson caused no clinically significant bronchoconstriction or alterations in pulmonary function parameters, and transiently increased heart rate and systolic blood pressure. The most common treatment-emergent adverse events were tachycardia, dizziness, and flushing.

Conclusions: Binodenoson was safe, well tolerated, and caused no clinically significant bronchoconstriction or pulmonary responses in a small population of healthy subjects with mild, intermittent asthma.

Keywords: binodenoson; pharmacologic stress; bronchoconstriction; asthma.
INTRODUCTION

Approximately half the myocardial perfusion imaging (MPI) procedures performed in the United States are conducted using pharmacologic stress (PS) testing in patients who are unable to adequately exercise to produce a diagnostic exercise stress test. (1,2) The 2 most commonly used pharmacologic stressors during MPI, adenosine and dipyridamole, are contraindicated in patients with asthma and should also be used with caution in patients with obstructive lung disease not associated with bronchoconstriction (e.g., emphysema, bronchitis). (2-4) Patients with asthma may develop exercise-induced bronchospasm. (5) Adenosine is a naturally occurring ligand of 4 subtypes of G-protein–coupled cell membrane receptors (A₁, A₂A, A₂B, and A₃) involved in cellular signaling. (6) Adenosine-induced coronary hyperemia that enables PS imaging results from direct activation of the adenosine A₂A receptors in coronary vascular smooth muscle. (7) Dipyridamole produces coronary hyperemia by indirectly activating adenosine A₂A receptors by inhibiting uptake of adenosine, and thereby increasing levels of endogenous adenosine. (2) However, both vasodilators also nonselectively activate adenosine A₁, A₂B, and A₃ receptors, actions that may be associated with undesirable side effects such as atrioventricular block, chest pain, flushing, shortness of breath, and bronchospasm. (8-10) Of the 3 available PS agents, only dobutamine, a positive inotrope/chronotrope, does not produce bronchospasm in patients with asthma, but it is associated with significant subjective side effects, ventricular and supraventricular arrhythmias, is more complicated to administer, and is diagnostically less accurate than adenosine or dipyridamole. (2, 11) There is a clear unmet need for a safer PS agent for the population of patients with asthma and other obstructive lung diseases who require MPI.
The bronchoconstrictor responses to adenosine observed in patients with obstructive airway diseases are believed to result from adenosine $A_{2B}$ receptor-mediated mast cell degranulation and bronchial smooth muscle contraction.\(^{(6,12)}\) If activation of the $A_{2B}$ receptor is the primary trigger for bronchospasm in asthmatics, we considered it likely that binodenoson, an adenosine receptor agonist that was 24,000-fold more selective for the $A_{2A}$ than for the $A_{2B}$ receptor in \textit{in vitro} assays \(^{(13)}\), would not produce bronchoconstriction in subjects with reactive airways. Binodenoson produced maximal coronary vasodilatation equivalent to that produced by intracoronary adenosine, was as efficacious as adenosine in detecting the extent and severity of perfusion defects with single photon emission computed tomography (SPECT) imaging, and was associated with fewer and less intense side effects than adenosine \(^{(14,15)}\).

The objectives of the current study were to assess the safety and tolerability of binodenoson, particularly with respect to bronchoconstriction, in healthy adult volunteers with mild, intermittent asthma.

\section*{METHODS}

\textbf{Study Endpoints}

The primary endpoint was clinically significant bronchoconstriction, defined as a decrease in forced expiratory volume in 1 second (FEV\textsubscript{1}) of $\geq 20\%$ from the pre-injection measure. Secondary safety endpoints were the changes from the pre-injection measure in FEV\textsubscript{1}, forced vital capacity (FVC), and forced expiratory flow during the middle 50\% of the FVC (FEF\textsubscript{25\%-75\%}), changes in vital signs and pulse oximetry, and adverse events.

\textbf{Subjects}

Subjects $\geq 18$ years of age and weighing $<159$ kg were recruited by 7 allergy/pulmonology specialists from their patient populations. Subjects eligible for enrollment had a history of asthma that was confirmed by reversal of bronchoconstriction (increase in FEV\textsubscript{1}}
≥ 12%) following either 2 puffs of albuterol from a metered dose inhaler or 2.5 mg of albuterol solution by nebulizer, or by eliciting a positive challenge (20% decrease in FEV₁) to a methacholine dose of < 8 mg/mL.(16) Subjects must have had mild, intermittent asthma as defined by National Institutes of Health criteria: FEV₁ or peak expiratory flow (PEF) ≥ 80% predicted, PEF variability < 20%, daytime symptoms occurring ≤ 2 days per week, nighttime symptoms occurring ≤ 2 nights per month, brief exacerbations controlled with short-acting inhaled β₂-agonists alone, and no symptoms and normal PEF values between exacerbations.(17) None of the subjects required chronic asthma medications. Subjects must have been able to perform reproducible pulmonary function tests (PFTs), and to refrain from ingestion of caffeine for ≥ 24 hours and inhalation of β₂-agonists for ≥ 6 hours, must have been nonsmokers ≥ 1 year, and have a smoking history ≤ 10 pack-years. Subjects must have been in good health without a history of renal or liver disease, hypertension, diabetes, or any known illness that might interfere with study assessments, and must have had a very low or low likelihood of coronary artery disease as determined by the American College of Cardiology/American Heart Association guidelines for stress testing.(18) Subjects were excluded who had a clinical exacerbation of asthma requiring emergency treatment or hospitalization within 6 months of the study, a history of allergic reaction to adenosine or dipyridamole, had seated systolic blood pressure (SBP) < 100 mm Hg or > 140 mm Hg, seated diastolic blood pressure (DBP) < 60 mm Hg or > 90 mm Hg, seated heart rate (HR) > 95 beats per minute, or were pregnant or lactating. The study was approved by each center’s local institutional review board, and all subjects provided written informed consent.

Study Design

This study was a multicenter, 2-phase trial composed of a nonrandomized, dose-escalating, 3-cohort, single-blind (subjects blinded) phase in which all subjects received binodenoson that was conducted from December 2003 to November 2004. This was followed
by a randomized double-blind phase in which subjects were randomized 2:1 to receive binodenoson or placebo. Binodenoson and placebo were administered to seated subjects as three 30-second bolus intravenous injections, separated by ≥ 90 minutes.

In the single-blind phase, the first injection was placebo and the second was binodenoson 0.1 μg/kg (to detect potential hypersensitivity reactions). The third injection administered in cohorts 1, 2, and 3 (n = 8 for each dose) was binodenoson 0.5, 1.0, or 1.5 μg/kg, respectively. The investigators and the study medical officer reviewed all data from lower doses prior to progressing to the next higher dose, and prior to commencing the double-blind phase. Subjects (n = 63) enrolled in the double-blind phase of the study were randomized 2:1 to receive a bolus injection of placebo, a binodenoson hypersensitivity challenge dose (0.1 μg/kg), and binodenoson, 1.5 μg/kg (binodenoson group, n = 41), or 3 bolus injections of placebo (placebo group, n = 22).

Subject Assessments

In both the open-label and the double-blind phases, seated PFTs were conducted before the first injection, at 15 and 90 minutes after the first and second injections, and at 5, 15, 45, and 90 minutes after the third injection. As PFTs and vital signs may vary over time, the 90-minute PFT and vital signs values from the previous injection served as the pre-injection measure for the 2nd and 3rd injections in all subjects.

If the best effort FEV₁ was ≤ 75% of predicted value after the first injection (placebo), the subject was discontinued from the study. If the FEV₁ of a subject decreased by ≥ 20% from the pre-injection measure after any dose of binodenoson, all dosing was to be suspended pending medical review, and the study terminated if the bronchoconstrictor response was determined to be related to binodenoson. Vital signs were measured immediately before each PFT at approximately 13 and 88 minutes after each of the first 2 injections, and at approximately 3, 13, 43, and 88 minutes following the third IV injection. Rescue medications, including β₂-agonists,
injectable epinephrine, and intravenous steroids were available as needed. Spontaneously reported adverse events (AEs) and their intensity were recorded.

**Statistical Analyses**

For the double-blind portion of the study, treatment group demographics were compared with analysis of variance and a Cochran-Mantel-Haenszel test. A comparison of change from the pre-injection measure for each PFT at each time point between the third injection of placebo and binodenoson (1.5 μg/kg) was performed using an analysis of covariance model controlling for the pre-injection measure value. All values are expressed as mean ± standard error (SE). Treatment comparisons of the percent changes from the pre-injection measure for FEV₁, FVC, and FEF₂₅%-₇₅% were performed using Student’s t test. Descriptive post hoc t-tests were performed on changes from the pre-injection measure (last measurement prior to dose) in vital signs after the 3ʳᵈ injection. Fisher’s exact test was used to compare the incidence of AEs for treatments after the 3ʳᵈ injection. P values were two-sided and unadjusted; those ≤ 0.05 were considered significant.

**RESULTS**

**Subject Demographics**

Eighty-seven subjects qualified for treatment (Table 1). In the single-blind phase of the study, all subjects completed assigned treatments. The majority of subjects (58%) were male and white (88%), and BMI and mean baseline FEV₁, % predicted values were similar between cohorts. In the double-blind phase, two subjects randomized to receive binodenoson were not treated beyond the initial placebo injection: one for an abnormal electrocardiogram, and one for an FEV₁ < 80% predicted; one subject randomized to the placebo group was not treated beyond the initial placebo injection because of disqualifying PEF variability on 3 of 7 days preceding treatment. The majority of subjects in the double-blind phase were female (78%) and white.
(87%), and the mean baseline FEV₁, % predicted value was significantly lower in the binodenoson group (88.3%) than in the placebo group (92.8%). No subjects discontinued from the study because of asthma exacerbations or other adverse events.

**Pulmonary Function Tests**

Binodenoson did not produce clinically significant bronchoconstriction (defined as ≥ 20% decrease in FEV₁ from the pre-injection measure) in any subject in the single- or double-blind phases.

No clinically significant changes over time in mean FEV₁, % predicted, mean FEF₂₅%-₇₅%, or mean FVC (Figure 1) occurred following injection of placebo, the 0.1 μg/kg binodenoson hypersensitivity test dose and binodenoson doses of 0.5, 1.0, or 1.5 μg/kg in any of the 24 subjects treated in the single-blind phase. In the double-blind phase of the trial, no bronchoconstriction or clinically significant individual changes in FEV₁ (Figure 2), mean FEV₁, % predicted, mean FEF₂₅%-₇₅%, or mean FVC were observed in subjects who received 3 placebo injections (placebo group), or placebo, and the 0.1 μg/kg binodenoson hypersensitivity test dose and 1.5 μg/kg binodenoson (binodenoson group) (Figure 3). Mean changes from the pre-injection measure PFTs were small; no statistically significant differences between the binodenoson group and the placebo group in changes or percent changes from the pre-injection measure were observed for any PFT at any time point (Table 2 for change results). The largest observed decreases from pre-injection FEV₁ were 11% in one subject 5 min after binodenoson 0.5 μg/kg in the single-blind phase, and 16% in one subject 15 min after placebo in the double-blind phase.
Vital Signs and Pulse Oximetry

Neither the placebo injections nor the binodenoson hypersensitivity test dose (0.1 μg/kg) had clinically significant effects on mean (± standard error [SE]) SBP, DBP, HR or pulse oximetry in any of the subjects in the single- or double-blind phases of the study (Figures 4, 5).

In the single-blind phase, binodenoson doses of 1.0 μg/kg and 1.5 μg/kg increased mean SBP compared to the pre-injection measure at 3 minutes after administration by 13.3 ± 3.1 and 13.6 ± 4.0 mm Hg (both p < 0.05, t-test), respectively, and the 1.5 μg/kg dose increased mean DBP at 3 minutes by 4.9 ± 2.0 mm Hg (p < 0.05, t-test) (Figure 4A). Binodenoson doses of 0.5, 1.0, and 1.5 μg/kg increased mean HR 3 minutes after injection by 16.4 ± 2.7, 25.4 ± 2.6, and 31.5 ± 3.0 beats/min (all p < 0.001, t-test), respectively, vs. the pre-injection measure (Figure 4B). One of 8 subjects treated with 1.5 μg/kg binodenoson experienced transient (3 minutes) increases in SBP ≥ 150 mmHg (from 122 at the pre-injection measure to 154 mmHg) and HR ≥ 120 (from 74 to 121 beats/minute). Pulse oximetry remained unaltered following all treatments (Figure 4B).

In the double-blind phase, the 1.5 μg/kg binodenoson dose was associated with a transient (3 minutes) increase in mean SBP (8.6 ± 1.5 mm Hg, p< 0.001, t-test) and a slight decrease in mean DBP (3.7 ± 1.5 mm Hg, p < 0.05, t-test, Figure 5A). Mean HR increased by 32.9 ± 1.8 and 12.0 ± 1.6 beats/minute vs. the pre-injection measure 3 and 13 minutes after injection, respectively (both p< 0.001, t-test, Figure 5B). Two of 39 binodenoson-treated subjects experienced transient elevations in SBP ≥ 150 mmHg (from 142 at the pre-injection measure to 150 mmHg, and from 132 to 160 mmHg, both at 3 minutes). Heart rate increased to ≥ 120 beats/minute from the pre-injection measure to 3 minutes after binodenoson in 6/39 subjects: (86 to 124 beats/min, 81 to 132 beats/min, 86 to 125 beats/min, 68 to 130 beats/min, 87 to 122 beats/min, 78 to 120 beats/min). Increases in heart rate were not consistently associated with decreases in BP. Pulse oximetry remained unaltered following all treatments (Figure 5B).
Adverse Events

In the single-blind phase of the study, none of the 24 subjects experienced an AE after receiving placebo or the binodenoson 0.1 μg/kg hypersensitivity test dose, and 2 (25%), 4 (50%), and 6 (75%) subjects reported at least one AE following injection of 0.5, 1.0, or 1.5 μg/kg binodenoson, respectively (not significantly different, p=0.191, Fisher’s exact test). The most common treatment-emergent AEs were flushing (n = 4, 50%), sinus tachycardia (n = 3, 38%), and nausea (n = 3, 38%). All AEs were mild or moderate in intensity, transient, and required no intervention.

In the double-blind phase, the overall incidence of AEs was higher following binodenoson compared to placebo (p<0.01, Fisher’s exact test). No placebo group subjects experienced AEs following the first or second injections, and 4 subjects (19%) reported AEs following the third placebo injection. In the binodenoson group, 1 subject reported an AE following placebo, 2 following the hypersensitivity test dose of 0.1 μg/kg, and 27 (69%) following injection of the 1.5-μg/kg dose of binodenoson (significantly different from placebo, p<0.01). The most common AEs experienced by > 1 subject in either group in the double-blind phase following the third injection are listed in Table 3.

DISCUSSION

Patients with asthma present unique challenges when referred for PS MPI procedures, as the 2 most commonly used pharmacologic stressors, adenosine and dipyridamole, are contraindicated because of their propensity to cause bronchoconstriction (2). Adenosine must also be used with caution in patients with obstructive lung disease not associated with bronchoconstriction (e.g., emphysema, bronchitis) (3). While dobutamine does not provoke bronchospasm, it is poorly tolerated, technically more difficult to administer, and diagnostically
less accurate than the vasodilator PS agents (2,11). Although contraindicated, adenosine is occasionally administered alone to patients with mild asthma who are well controlled and who are not actively wheezing (19,20). Adenosine PS MPI procedures have also been completed safely in mild asthmatics pretreated with inhaled β2-receptor agonist bronchodilators with or without concomitant low-level exercise (21,22). However, the safety of inducing stress with adenosine with such interventions has not been tested in patients with moderate to severe asthma. Even with these precautions, asthmatics have a higher risk of bronchospasm than nonasthmatics, and administering bronchodilators and monitoring pulmonary function obviously complicates and prolongs the imaging procedure. Therefore, patients being evaluated for coronary disease with uncertain or unstable asthma or moderate to severe chronic obstructive pulmonary disease are often referred for a dobutamine-stress MPI test or cardiac catheterization (23). A vasodilator PS agent that can be administered to these patients, and that is safer, better tolerated, easier to use, and diagnostically more accurate than dobutamine is clearly needed.

Binodenoson is a potent agonist at the adenosine A2A receptors that mediate coronary vasodilatation, but has markedly lower affinity for the A2B receptors that degranulate mast cells and constrict bronchiolar smooth muscle (6,12,13). It failed to produce bronchoconstriction in an allergic sheep model (13). In the present study, binodenoson produced no bronchoconstriction or other detectable changes in pulmonary function parameters and was well tolerated. Nearly all adverse events were mild or moderate in intensity, and resolved without sequelae or intervention. The magnitude and duration of the transient, dose-related tachycardia, modest changes in BP, and the nature and intensity of the AEs associated with the 1.5 μg/kg bolus binodenoson dose were consistent with those reported previously in non-asthmatic populations, and are similar to those produced by adenosine (8,9,14). Increases in HR were not consistently associated with decreases in BP, and thus do not appear to be a purely reflexive response (14,15). Studies in intact rats suggest that adenosine A2A receptor agonists may increase HR via
direct and indirect mechanisms (24,25), although these results have not been confirmed in humans.

Because the potential for a selective adenosine A\textsubscript{2A} agonist to evoke bronchoconstriction was unknown prior to this study, binodenoson was first cautiously administered to this small population of otherwise healthy adults whose mild, intermittent asthmatic symptoms were controlled by short-acting inhaled \( \beta_2 \)-agonists alone. The study design provided for a thorough medical review of the responses to each binodenoson dose before the next higher dose was administered. The double-blind phase was initiated only after gaining confidence that binodenoson was unlikely to provoke bronchoconstriction at the highest dose tested in the single-blind phase, 1.5 \( \mu \text{g/kg} \). The effects of binodenoson were monitored over a 90-min period to allow detection of possible drug effects on pulmonary function, BP, HR, electrocardiogram responses, and subject tolerability for the approximate time of a typical PS MPI procedure.

The safety of binodenoson in these otherwise healthy, mildly asthmatic subjects encourages assessment of its safety in subjects with more severe asthma and COPD.

Limitations

The volunteers in this study do not represent the target population of subjects referred for pharmacologic stress myocardial perfusion imaging, who are older, have known or suspected CAD, and have more comorbidities, sometimes including more severe asthma and COPD. A pulmonary event occurring in fewer than 8% of subjects may not have been detected in the small population enrolled in this study.

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Conflicts of Interest Disclosures: Drs. Murray, Weiler, Schwartz, Busse, Katial, Lockey, and McFadden, and their institutions received support from King Pharmaceuticals to conduct the study. Mr. Pixton and Dr. Barrett were employees of King Pharmaceuticals.
REFERENCES


### Table 1. Subject Demographics

<table>
<thead>
<tr>
<th></th>
<th>Single-blind phase</th>
<th>Double-blind phase</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (N = 24)</td>
<td>Binodenoson</td>
<td>Total (N = 63)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.5 μg/kg (n = 8)</td>
<td>1.0 μg/kg (n = 8)</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>Mean ± SD</td>
<td>27.9 ± 7.7</td>
<td>27.4 ± 8.7</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>18 – 46</td>
<td>18 - 45</td>
</tr>
<tr>
<td><strong>Sex, %</strong></td>
<td>Male</td>
<td>58</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>42</td>
<td>25</td>
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<tr>
<td><strong>Race, %</strong></td>
<td>White</td>
<td>88</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>Black</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td><strong>Body mass index, kg/m²</strong></td>
<td>Mean ± SD</td>
<td>25.4 ± 4.3</td>
<td>24.6 ± 3.3</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>19.3 – 37.6</td>
<td>19.4 - 28.8</td>
</tr>
<tr>
<td><strong>Baseline FEV₁, % predicted</strong></td>
<td>Mean ±SD</td>
<td>90.5 ± 8.6</td>
<td>91.5 ± 11.9</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>80 - 119</td>
<td>81 - 119</td>
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</tbody>
</table>

FEV₁ = Forced expiratory volume in 1 second; SD = Standard deviation.

Significantly lower than placebo, *P* <0.05.
Table 2. Mean Changes from the Pre-injection Measure (SD) in Pulmonary Function Tests after the Third Injection in the Double-blind Phase

<table>
<thead>
<tr>
<th>Assessment Time</th>
<th>Placebo (n = 21)</th>
<th>1.5 μg/kg (n = 39)</th>
<th>P-value&lt;sup&gt;a&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; (L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 minutes</td>
<td>-0.06 (0.11)</td>
<td>0.00 (0.12)</td>
<td>0.075</td>
</tr>
<tr>
<td>15 minutes</td>
<td>-0.01 (0.10)</td>
<td>-0.01 (0.09)</td>
<td>0.808</td>
</tr>
<tr>
<td>45 minutes</td>
<td>0.02 (0.08)</td>
<td>0.00 (0.12)</td>
<td>0.637</td>
</tr>
<tr>
<td>90 minutes</td>
<td>0.02 (0.09)</td>
<td>0.04 (0.12)</td>
<td>0.391</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; (% predicted)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 minutes</td>
<td>-1.4 (3.3)</td>
<td>0.1 (3.3)</td>
<td>0.089</td>
</tr>
<tr>
<td>15 minutes</td>
<td>0.0 (2.6)</td>
<td>-0.3 (2.6)</td>
<td>0.831</td>
</tr>
<tr>
<td>45 minutes</td>
<td>0.5 (2.7)</td>
<td>0.1 (3.3)</td>
<td>0.630</td>
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<tr>
<td>90 minutes</td>
<td>0.4 (2.5)</td>
<td>1.1 (3.2)</td>
<td>0.482</td>
</tr>
<tr>
<td>FEF&lt;sub&gt;25-75%&lt;/sub&gt;</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>5 minutes</td>
<td>-0.05 (0.16)</td>
<td>-0.05 (0.23)</td>
<td>0.782</td>
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<tr>
<td>15 minutes</td>
<td>-0.04 (0.20)</td>
<td>-0.04 (0.19)</td>
<td>0.935</td>
</tr>
<tr>
<td>45 minutes</td>
<td>0.05 (0.18)</td>
<td>-0.03 (0.24)</td>
<td>0.128</td>
</tr>
<tr>
<td>90 minutes</td>
<td>-0.01 (0.25)</td>
<td>-0.04 (0.25)</td>
<td>0.505</td>
</tr>
<tr>
<td>FVC (L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 minutes</td>
<td>-0.05 (0.13)</td>
<td>0.00 (0.16)</td>
<td>0.243</td>
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<tr>
<td>15 minutes</td>
<td>0.02 (0.09)</td>
<td>-0.02 (0.13)</td>
<td>0.238</td>
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<tr>
<td>45 minutes</td>
<td>0.02 (0.11)</td>
<td>-0.01 (0.16)</td>
<td>0.469</td>
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<tr>
<td>90 minutes</td>
<td>0.04 (0.10)</td>
<td>0.07 (0.16)</td>
<td>0.384</td>
</tr>
</tbody>
</table>

FEV<sub>1</sub> = Forced expiratory volume in 1 second; FEF<sub>25-75%</sub> = Forced expiratory flow during the middle 50% of the FVC; FVC = Forced vital capacity; SD = Standard deviation.<sup>a</sup>From analysis of covariance model adjusted for baseline value.
Table 3. Treatment-Emergent Adverse Events Occurring in >1 Subject Following Third Injection in the Double-blind Phase

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (n = 21)</th>
<th>Binodenoson, 1.5 μg/kg (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with any event after third injection</td>
<td>4 (19)</td>
<td>27 (69)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>0</td>
<td>12 (31)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>6 (15)</td>
</tr>
<tr>
<td>Flushing</td>
<td>0</td>
<td>6 (15)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Sinus tachycardia</td>
<td>0</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>0</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (5)</td>
<td>2 (5)</td>
</tr>
</tbody>
</table>

1: 1 subject in the placebo group was randomized but not treated.
2: 2 subjects in the binodenoson group were randomized but not treated.
3: The incidence of AEs was higher following binodenoson compared to placebo (p<0.01, Fisher’s exact test).
FIGURE LEGENDS

Figure 1: Mean (±SE) FEV₁, % predicted (Panel A); FEF₂₅%-₇₅% (Panel B); and FVC (Panel C) in subjects in the single-blind phase. Injection 1=placebo; Injection 2= hypersensitivity test dose of binodenoson, 0.1 μg/kg; Injection 3=binodenoson, 0.5, 1.0, or 1.5 μg/kg. Injections administered at bold arrows.

Figure 2: Individual subject FEV₁ at the pre-injection measure and 5 minutes after IV bolus injection of binodenoson, 1.5 μg/kg (Panel A, N=39) or placebo (Panel B, N=21) in the double-blind phase.

Figure 3: Mean (±SE) FEV₁, % predicted (Panel A); FEF₂₅%-₇₅% (Panel B); and FVC (Panel C) in subjects in the double-blind phase. Placebo group: 3 placebo injections; binodenoson group: Injection 1=Placebo; Injection 2= hypersensitivity test dose of binodenoson, 0.1 μg/kg; Injection 3=binodenoson, 1.5 μg/kg. Injections administered at bold arrows.

Figure 4: Mean (±SE) SBP and DBP (Panel A) and O₂ saturation and HR (Panel B) in subjects in the single-blind phase. Injection 1=Placebo; Injection 2= hypersensitivity test dose of binodenoson, 0.1 μg/kg; Injection 3=binodenoson, 0.5, 1.0, or 1.5 μg/kg. Injections administered at bold arrows. Vital signs were measured immediately before each PFT test. *p<0.05, **p<0.001

Figure 5: Mean (±SE) SBP and DBP (Panel A) and O₂ saturation and HR (Panel B) in subjects in the double-blind phase. Placebo group: 3 placebo injections; binodenoson group: Injection 1=Placebo; Injection 2= hypersensitivity test dose of binodenoson, 0.1 μg/kg; Injection 3=binodenoson, 1.5 μg/kg. Injections administered at bold arrows. * p<0.05, **p<0.001
Safety of Binodenoson, a Selective Adenosine A2A Receptor Agonist Vasodilator Pharmacologic Stress Agent, in Healthy Subjects with Mild, Intermittent Asthma


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