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

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Background—The pharmacological stress agents adenosine and dipyridamole are contraindicated in asthma patients because of the risk of adenosine receptor-mediated bronchospasm. Binodenoson, a selective adenosine A2A receptor agonist, produces maximal coronary hyperemia during pharmacological stress testing yet has a low affinity for the adenosine A1, A2B, and A3 receptors that are probably 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-blinded phase and a placebo-controlled, double-blinded phase conducted in healthy, young adults with documented mild, intermittent, asthma. In the single-blinded phase, 3 sequential cohorts of 8 subjects received intravenous binodenoson (0.5, 1.0, and 1.5 μg/kg). In the double-blinded phase, commenced after medical review of results from the single-blinded phase, subjects were randomly assigned 2:1 to either binodenoson 1.5 μg/kg (n=41) or placebo (n=22). The primary end point was clinically significant bronchoconstriction, defined as a decrease in forced expiratory volume in 1 second of ≥20% from the preinjection measure. Secondary safety end points were changes from preinjection measure in forced expiratory volume in 1 second, forced vital capacity, and forced expiratory flow during the middle 50% of the forced vital capacity; 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. (Circ Cardiovasc Imaging. 2009; 2:492-498.)

Key Words: binodenoson • pharmacological stress • bronchoconstriction • asthma

Approximately half the myocardial perfusion imaging (MPI) procedures performed in the United States are conducted using pharmacological 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 pharmacological 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 (eg, 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 atioventricular 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

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administer, and is diagnostically less accurate than adenosine or dipyridamole. 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.

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The bronchoconstrictor responses to adenosine observed in patients with obstructive airway diseases are believed to result from adenosine A2B receptor–mediated mast cell degranulation and bronchial smooth muscle contraction. If activation of the A2B 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 A2A than for the A2B receptor in in vitro assays, 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 inducing bronchoconstriction in healthy adult volunteers with mild, intermittent asthma.

Table 1. Subject Demographics

<table>
<thead>
<tr>
<th></th>
<th>Single-Blinded Phase</th>
<th></th>
<th>Double-Blinded Phase</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Binodenoson</td>
<td></td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total (n=24)</td>
<td>0.5 μg/kg (n=8)</td>
<td>1.0 μg/kg (n=8)</td>
<td>1.5 μg/kg (n=8)</td>
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<tr>
<td>Age, y</td>
<td>Mean±SD</td>
<td>27.9±7.7</td>
<td>27.4±8.7</td>
<td>27.1±8.3</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>18–46</td>
<td>18–45</td>
<td>20–46</td>
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<tr>
<td>Sex, %</td>
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<td>63</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>42</td>
<td>25</td>
<td>38</td>
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<td>Race, %</td>
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<td>75</td>
<td>100</td>
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<td>0</td>
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<tr>
<td></td>
<td>Other</td>
<td>4</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>Mean±SD</td>
<td>25.4±4.3</td>
<td>24.6±3.3</td>
<td>26.7±2.8</td>
</tr>
<tr>
<td>Baseline FEV₁, % predicted</td>
<td>Mean±SD</td>
<td>90.5±8.6</td>
<td>91.5±11.9</td>
<td>90.6±7.7</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>80–119</td>
<td>81–119</td>
<td>80–102</td>
</tr>
</tbody>
</table>

*Significantly lower than placebo, P<0.05.

Methods

Study End Points

The primary end point was clinically significant bronchoconstriction, defined as a decrease in forced expiratory volume in 1 second (FEV₁) of ≥20% from the preinjection measure. Secondary safety end points were the changes from the preinjection measure in FEV₁, forced vital capacity (FVC), and forced expiratory flow during the middle 50% of the FVC (FEF₂₅–₇₅%), changes in vital signs and pulse oximetry, and adverse events.

Subjects

Subjects ≥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 FEV₁≥12%) after 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 ≤18 mg/mL. 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. 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. 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, a seated systolic blood pressure (SBP) <100 mm Hg or >140 mm Hg, seated diastolic blood pressure (DBP) <60 mm Hg or >90 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-blinded (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-blinded phase in which subjects were randomly assigned 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-blinded 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 before progressing to the next higher dose and before commencing the double-blinded phase. Subjects (n=63) enrolled in the double-blinded phase of the study were randomly assigned 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-blinded 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 preinjection measure for the second and third 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 preinjection 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 after the third intravenous 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-blinded portion of the study, treatment group demographics were compared with ANOVA and a Cochran-Mantel-Haenszel test. A comparison of change from the preinjection measure for each PFT at each time point between the third injection of placebo and binodenoson (1.5 μg/kg) was performed using an ANOVA model controlling for the preinjection measure value. All values are expressed as mean±SE. Treatment comparisons of the percent changes from the preinjection measure for FEV₁, FVC, and FEF₂₅%–₇₅% were performed using Student t test. Descriptive post hoc t tests were performed on changes from the preinjection measure (last measurement before dose) in vital signs after the third injection. Fisher exact test was used to compare the incidence of AEs for treatments after the third injection. Probability values were 2-sided and unadjusted; those ≤0.05 were considered significant.

**Results**

**Subject Demographics**

Eighty-seven subjects qualified for treatment (Table 1). In the single-blinded phase of the study, all subjects completed assigned treatments. The majority of subjects (58%) were male and white (88%), and body mass index and mean baseline FEV₁ percent predicted values were similar between cohorts. In the double-blinded phase, 2 subjects randomly assigned to receive binodenoson were not treated beyond the initial placebo injection: 1 for an abnormal ECG and 1 for an FEV₁ <80% predicted; 1 subject randomly assigned 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-blinded phase were female (78%) and white (87%), and the mean baseline FEV₁ percent 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 preinjection measure) in any subject in the single- or double-blinded phases.

No clinically significant changes over time in mean FEV₁, percent predicted, mean FEF₂₅%–₇₅%, or mean FVC (Figure 1) occurred after 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-blinded phase. In the double-blinded phase of the trial, no bronchoconstriction or clinically significant individual changes in FEV₁ (Figure 2), mean FEV₁, percent 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 preinjection measure PFTs were small; no statistically significant differences between the binodenoson group and the placebo group in changes or percent changes from the preinjection measure were observed for any PFT at any time point (Table 2 for change results).

The largest observed decreases from preinjection FEV₁ were 11% in 1 subject 5 minutes after binodenoson 0.5 μg/kg in the single-blinded phase and 16% in 1 subject 15 minutes after placebo in the double-blinded 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 (±SE) SBP, DBP, HR, or pulse oximetry in any of the subjects in the single- or double-blinded phases of the study (Figure 4, 5).

In the single-blinded phase, binodenoson doses of 1.0 μg/kg and 1.5 μg/kg increased mean SBP compared with the preinjection 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 bpm (all P<0.001, t test), respectively, versus the preinjection measure (Figure 4B). One of 8 subjects treated with 1.5 μg/kg binodenoson had transient (3 minutes) increases in SBP ≥150 mm Hg (from 122 at the preinjection measure to 154 mm Hg) and HR ≥120 (from 74 to 121 bpm). Pulse oximetry remained unaltered after all treatments (Figure 4B).

In the double-blinded 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 bpm versus the preinjection measure 3 and 13 minutes after injection, respectively (both P<0.001, t test, Figure 5B). Two of 39 binodenoson-treated subjects had transient elevations in SBP ≥150 mm Hg (from 142 at the preinjection measure to 150 mm Hg and from 132 to 160 mm Hg), and HR increased to ≥120 bpm from the preinjection measure to 3 minutes after binodenoson in 6 of 39 subjects (86 to 124 bpm, 81 to 132 bpm, 86 to 125 bpm, 68 to 130 bpm, 87 to 122 bpm, 78 to 120 bpm). Increases in HR were not consistently associated with decreases in BP. Pulse oximetry remained unaltered after all treatments (Figure 5B).
Adverse Events
In the single-blinded phase of the study, none of the 24 subjects had 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 1 AE after injections of 0.5, 1.0, or 1.5 μg/kg binodenoson, respectively (not significantly different, \( P = 0.191 \), Fisher 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-blinded phase, the overall incidence of AEs was higher after binodenoson compared with placebo (\( P < 0.01 \), Fisher exact test). No placebo group subjects had AEs after the first or second injections, and 4 subjects (19%) reported AEs after the third placebo injection. In the binodenoson group, 1 subject reported an AE after placebo, 2 after the hypersensitivity test dose of 0.1 μg/kg, and 27 (69%) after 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-blinded phase after 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 pharmacological stressors, adenosine and dipyridamole, are contraindicated because of their propensity to cause bronchoconstriction. Adenosine must also be used with caution in patients with obstructive lung disease not associated with bronchoconstriction (eg, emphysema, bronchitis). Although dobutamine does not provoke bronchospasm, it is poorly tolerated, technically more difficult to administer, and diagnostically less accurate than the vasodilator PS agents. Although contraindicated, adenosine is occasionally administered alone to patients with mild asthma who are well controlled and who are not actively wheezing. 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. 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. 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 mark-
edly lower affinity for the A2B receptors that degranulate mast cells and constrict bronchiolar smooth muscle. It failed to produce bronchoconstriction in an allergic sheep model. 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 nonasthmatic populations and are similar to those produced by adenosine. Studies in intact rats suggest that adenosine A2A receptor agonists may increase HR via direct and indirect mechanisms, although these results have not been confirmed in humans.

Because the potential for a selective adenosine A2A agonist to evoke bronchoconstriction was unknown before 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 β2-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-blinded phase was initiated only after gaining confidence that binodenoson was unlikely to provoke bronchoconstriction at the highest dose tested in the single-blinded phase, 1.5 μg/kg. The effects of binodenoson were monitored over a 90-minute period to allow detection of possible drug effects on pulmonary function, BP, HR, ECG 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 chronic obstructive pulmonary disease.

Limitations
The volunteers in this study do not represent the target population of subjects referred for pharmacological stress myocardial perfusion imaging, who are older, have known or suspected coronary artery disease, and have more comorbidities, sometimes including more severe asthma and chronic obstructive pulmonary disease. A pulmonary event occurring in <8% of subjects may not have been detected in the small population enrolled in this study.

Sources of Funding
This study was funded by King Pharmaceuticals Research and Development, Cary, NC.

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 3. Treatment-Emergent Adverse Events Occurring in >1 Subject After Third Injection in the Double-Blinded Phase

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (n=21)*</th>
<th>Binodenoson, 1.5 μg/kg (n=39)†</th>
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<tbody>
<tr>
<td>Subjects with any event after third injection</td>
<td>4 (19)</td>
<td>27 (69)‡</td>
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<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>
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<td>6 (15)</td>
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<tr>
<td>Nausea</td>
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<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>

* One subject in the placebo group was randomly assigned but not treated.
† Two subjects in the binodenoson group were randomly assigned but not treated.
‡ The incidence of AEs was higher after binodenoson compared with placebo (P<0.01, Fisher exact test).

Figure 5. Mean (±SE) SBP and DBP (A) and O2 saturation and HR (B) in subjects in the double-blinded 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.


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**CLINICAL PERSPECTIVE**

The first-generation coronary vasodilator pharmacological stress agents adenosine and dipyridamole are contraindicated in patients with asthma because of their propensity to cause bronchoconstriction. Such patients complete a dobutamine-stress test or are referred directly for diagnostic angiography. Binodenoson is a highly selective agonist at the adenosine A$_{2A}$ receptor, and its safety profile and bronchospasticity have been confirmed in a patient with severe asthma, the selective adenosine A$_{2A}$ receptor agonist binodenoson may provide a safer alternative to current pharmacological stress agents or direct referral to angiography.
Safety of Binodenoson, a Selective Adenosine A2A Receptor Agonist Vasodilator Pharmacological Stress Agent, in Healthy Subjects With Mild Intermittent Asthma


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