Transcript Details

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Protecting Patients from COPD Exacerbations

Announcer:
Welcome to ReachMD. This medical industry feature, titled Protecting Patients From COPD Exacerbations is sponsored by AstraZeneca. This program is intended for health care providers.

Presenting is Danielle Dolan.

Hello, my name is Danielle Dolan, and I'm a respiratory clinical science liaison with AstraZeneca. I was a nurse practitioner for about 20 years, practicing most of my time in hospitals and nursing homes. I lost my grandfather way too early to chronic obstructive pulmonary disease, or COPD, and he was among the many patients who I loved and cared for during my years as a clinician. Helping providers to ease the burden for their COPD patients is something near and dear to my heart after witnessing the pain that many patients with COPD endure.

AstraZeneca's commitment to put patients first, and to work with caregivers like you to ease this burden, makes me proud to be part of this organization and excited to be here today to talk about AstraZeneca's inhaled respiratory product, BREZTRI Aerosphere (budesonide, glycopyrrolate, and formoterol fumarate).

During today's presentation, we are going to explore COPD exacerbations and their profound impact on patients and disease progression. I will also share information with you about BREZTRI Aerosphere, including the clinical development program that was used to acquire approval from the FDA for BREZTRI Aerosphere in the United States. And finally, I'll spend some time talking about the dosing and administration of BREZTRI.

Let's start by discussing COPD exacerbations and their impact on disease progression. COPD exacerbations are events that many patients with COPD may experience at some point in their journey, and these COPD exacerbations can be classified into different severities: mild, moderate, or severe. A mild exacerbation is one that is treated with short-acting, beta2-adrenergic agonists, or short-acting muscarinic antagonists only. A moderate exacerbation is one that is treated with short-acting beta2-adrenergic agonists or short-acting muscarinic antagonists with the addition of antibiotics and/or oral corticosteroids. And finally, a severe exacerbation is one that requires hospitalization or for the patient to go to the emergency department for treatment.

The effects of COPD exacerbations may be devastating, and they can be multi- faceted. One in particular is around lung function. One study from 2018 showed that, after a moderate exacerbation, patients with COPD may not fully recover lung function that is lost. The study was a post hoc analysis performed on data from 317 patients in the WISDOM trial, which was a multinational, randomized, double-blind study in patients with severe to very severe COPD. In the study, lung function was characterized before, during, and after a moderate or severe COPD exacerbation, with patients taking daily spirometric measurements at home.

In fact, some patients did not recover to pre-exacerbation levels by 8 weeks after the start of the first moderate exacerbation. So, if you look at the weeks leading up to a patient's first moderate exacerbation, their lung function slowly starts to creep downward until the exacerbation hits. At that point, the lung function declines more rapidly. As lung function recovers after the exacerbation, it doesn't fully return back to baseline levels 8 weeks after the exacerbation.

It's also important to look at the potential effects of severe exacerbations, as a study showed that severe exacerbations were associated with increased mortality. In the study, which evaluated the natural history of COPD after the first severe exacerbation, a large cohort of patients presenting with their first-ever hospitalization for COPD was identified from the health insurance program of the province of Québec, Canada. Severe exacerbations were defined as hospitalization with a primary discharge diagnosis of COPD. Cumulative

mortality was assessed in over 73,000 patients, from the time of their first- ever hospitalization for a COPD exacerbation over about an 18-year follow- up period.

In this study, fifty percent of patients died within 3.6 years after the first COPD exacerbation requiring hospitalization. Think about that. Half of the patients who had their first severe exacerbation requiring hospitalization were dead within approximately 3-1/2 years.

But aside from the potentially devastating effects that exacerbations have been shown to have on lung function and mortality, the damage can go beyond the lungs.

A case-series study conducted in 25,857 patients showed an increased risk of cardiovascular complications such as myocardial infarction and stroke. The study assessed the magnitude and timing of the risk of myocardial infarction and stroke following a COPD exacerbation from those entered in The Health Improvement Network database in England and Wales over a 2-year period. In the study, moderate exacerbations were defined by prescription of oral steroids, except fludrocortisone, and prescription of preselected oral antibiotics commonly used in treating exacerbations. In the days following a moderate COPD exacerbation, patients with COPD were at about a 2.3-fold higher risk of myocardial infarction within 5 days. The risk returned to baseline over time. In addition, they had a 40% increase in their risk of stroke within 10 days. This result was not significant.

Patients with COPD need protection from the dangers associated with exacerbations. I'm sure that after hearing some of these statistics, that it would be no surprise to you if I told you that chronic lower respiratory diseases, of which COPD is a major component, were found to be the fourth leading cause of death in the United States. This was behind cardiovascular diseases, cancers, and accidents.

In fact, one study showed that patients with COPD who experienced a moderate exacerbation were at a 21% increased risk of a future COPD hospitalization, and this was after just one moderate exacerbation. This study was a UK population- based study of ~100,000 patients with COPD, with up to 10 years of follow- up. The analysis compared patients with 1 moderate acute exacerbation of COPD with those who had none.

Another study showed that patients who had cardiovascular disease or multiple risk factors for cardiovascular disease were at a 10-fold increased risk of a cardiovascular event in the first month after a COPD hospitalization. This was a post hoc analysis of the multinational SUMMIT trial with 16,485 patients to determine whether the risk for cardiovascular events increases after a moderate or severe COPD exacerbation. The analysis was performed in patients with COPD who had cardiovascular disease or multiple risk factors for cardiovascular disease in the first 30 days following the onset of an acute exacerbation.

And finally, as I mentioned earlier, 1 in 2 patients or half the patients - died in just over 3 ½ years after their first COPD hospitalization due to a severe exacerbation.

As a reminder, this was from a cohort study that evaluated severe COPD exacerbations and their association with mortality in 73,106 patients with their first severe COPD exacerbation requiring hospitalization in the health insurance program of the province of Québec, Canada.

Now that we've had time to review some of the burdens of COPD exacerbations as well as the disease progression, I'd like to discuss the clinical efficacy of BREZTRI Aerosphere.

BREZTRI Aerosphere is indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease, or COPD. BREZTRI Aerosphere is not indicated for the relief of acute bronchospasm, or for the treatment of asthma.

Please see the Full Prescribing Information, including Patient Information, available at www.breztrihcp.com.

BREZTRI is contraindicated in patients who have a hypersensitivity to budesonide, glycopyrrolate, formoterol fumarate, or product excipients.

BREZTRI is not indicated for treatment of asthma. Long-acting beta2-adrenergic agonist (LABA) monotherapy for asthma is associated with an increased risk of asthma-related death. These findings are considered a class effect of LABA monotherapy. When a LABA is used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone. Available data do not suggest an increased risk of death with use of LABA in patients with COPD.

The remainder of the important safety information will be presented later in the program.

Now that we've reviewed some of the important safety information, let’s talk about the components of BREZTRI. BREZTRI is a fixed-dose, triple therapy, which includes budesonide, an inhaled corticosteroid with anti-inflammatory properties, as well as 2

bronchodilators, glycopyrrolate, which is a long-acting antimuscarinic agent or LAMA, and formoterol fumarate, which is a long-acting beta2-adrenergic agonist or LABA.

BREZTRI was approved by the FDA for maintenance treatment of COPD, and it was studied in patients with moderate to very severe COPD regardless of exacerbation history. In fact, the clinical development program, which was used to seek approval by the FDA, consisted of two pivotal studies.

The first is ETHOS or Study 1. ETHOS was a randomized, double-blind, multicenter, parallel-group trial. ETHOS was a 52-week trial, and in this trial, the patient population was required to have a history of at least one moderate or severe exacerbation in the previous year. If a patient's postbronchodilator FEV1 was <50% of predicted normal, then the requirement was ≥1 moderate or severe exacerbation, and for a patient with FEV1 ≥50% of predicted normal, the requirement was ≥2 moderate or ≥1 severe exacerbation.

The second trial was KRONOS or Study 2. KRONOS was a randomized, double- blind, multicenter, parallel-group trial. In this 24-week study, the patient population was not required to have a moderate or severe exacerbation in the previous year. Postbronchodilator FEV1 was required to be <80% and ≥25% of predicted normal.

Let's take a few moments and spend some time talking about Study 1, called ETHOS.

Patients enrolled in the ETHOS trial had COPD with a history of moderate or severe exacerbations in the previous year. This was a randomized, double-blind, multi- center, parallel-group trial. It was 52 weeks in length and evaluated the efficacy and safety of BREZTRI in symptomatic patients with moderate to very severe COPD with a history of 1 or more exacerbations in the previous year. The study consisted of over 8,500 patients. Patients were required to be between 40 and 80-years of age, with significant airflow obstruction as quantified by having a postbronchodilator FEV1/FVC ratio of less than 0.7, and a postbronchodilator FEV1 ranging from 25% to 65% of predicted normal. Patients were required to be symptomatic while receiving at least two inhaled maintenance therapies for COPD for at least six weeks before screening.

Once patients were screened, they were randomized into one of four treatment arms. The first is the dose approved by the FDA in the United States, which is BREZTRI consisting of budesonide 320 micrograms, glycopyrrolate 18 micrograms, and formoterol fumarate 9.6 micrograms administered twice a day. In the second arm, triple therapy containing half the dose of the ICS was assessed. Now, this is not an approved dose in the United States, and we will not be discussing this arm as we move forward with this presentation. The third arm in the trial included a LAMA/LABA consisting of glycopyrrolate 18 micrograms and formoterol fumarate 9.6 micrograms, while the fourth arm included an ICS/LABA consisting of budesonide 320 micrograms and formoterol fumarate 9.6 micrograms. All treatments were administered via a single aerosphere inhaler, and the primary endpoint for this trial was annual rate of moderate or severe COPD exacerbations.

Now, let's take a look at the patients who were enrolled in the ETHOS trial. The modified intent-to-treat population included all patients who underwent randomization, received any amount of trial treatment, and had post randomization data obtained before discontinuation of treatment. The patients had a mean age of approximately 65 years, the majority of them were male, and white. Over 40% of the patients were current smokers. And as I mentioned before, all the patients had a history of moderate or severe exacerbations in the previous year. Approximately 43% of patients had less than or equal to one exacerbation in the previous year, and approximately 57% of patients had greater than or equal to two in the previous year. Patients in the ETHOS trial also had their eosinophil levels measured. And we see here that approximately 60% of the patients had eosinophil counts of greater than 150. These patients were severely airflow-obstructed with a post-albuterol FEV1 of approximately 43% to 44% predicted. Approximately 70% of the patients fall into the severe to very severe category. About 30% of the patients showed reversibility. Bronchodilator reversibility was defined as an increase in FEV1 of at least 12% and at least 200 mL after administration of albuterol. About eighty percent of the patients were using ICS at screening. These patients were all symptomatic, with CAT scores just over 19. Scores on the COPD Assessment Test range from 0 to 40, with higher scores indicating more symptoms; the minimum clinically important difference in score is 2 points.

Let's consider the results of the ETHOS trial. Again, our primary endpoint was the annual rate of moderate or severe COPD exacerbations. In the trial, moderate exacerbations were defined as those leading to treatment with systemic corticosteroids and/or antibiotics, and severe exacerbations were defined as those resulting in hospitalization or death. BREZTRI significantly reduced the rate of moderate or severe exacerbations versus dual therapies. Over the 52 weeks, BREZTRI demonstrated a statistically significant reduction in the rate of moderate or severe exacerbations by 24% compared to LAMA/LABA arm with a *P*-value of less than 0.0001. There was a 13% reduction when compared to the ICS/LABA arm, with a *P*-value of 0.0027, also statistically significant.

When looking at exacerbations over 52-weeks, the model-estimated annual rate of moderate or severe exacerbations was 1.08 for the BREZTRI group, 1.42 for the LAMA/LABA group, and 1.24 for the ICS/LABA group. This was assessed in the modified intent-to-treat population.

Next is one of our secondary endpoints, which was rate of hospitalizations for severe exacerbations versus dual therapies. And over the 52 weeks, BREZTRI demonstrated a reduction in the rate of severe exacerbations by 20% compared to the ICS/LABA-containing arm with a *P*-value equal to 0.02. The analysis was conducted based on a Type-1 error control plan. When compared to the LAMA/LABA arm, there was a 16% reduction with a *P*-value of 0.09.

And again, the model-estimated annual rate of severe exacerbations, was 0.13 for the BREZTRI group, 0.15 for the LAMA/LABA group, and 0.16 for the ICS/LABA group. This was assessed in the modified ntent-to- treat population.

A secondary endpoint looked at time to all-cause mortality. The analysis of time to death from any cause over 52 weeks was performed in the intent-to-treat population with the use of treatment policy estimand, which included all observed data from the patients regardless of whether they continued to receive their assigned treatment. And over the 52 weeks, a difference was observed in time to all-cause mortality. These results were observational in nature; any comparisons between treatment arms should be interpreted with caution.

Looking at the safety profile in ETHOS, the most common adverse reactions occurring at an incidence of at least 2% of patients and more common in the BREZTRI arm compared to LAMA/LABA or ICS/LABA were upper respiratory tract infection, pneumonia, back pain, and oral candidiasis.

So, now let's shift gears and talk about our second trial, which was the KRONOS trial. The KRONOS trial was a lung function study in which the majority of patients did not have a history of exacerbations in the previous year.

KRONOS was a randomized, double-blind, parallel-group trial. It was 24 weeks in length and evaluated the efficacy and safety of BREZTRI in symptomatic patients with moderate to very severe COPD. There were just over 1,900 patients enrolled in this trial. They did not have a requirement for moderate or severe exacerbations in the previous year. They were required to be 40 to 80-years of age, with a post- bronchodilator FEV1 of greater than or equal to 25% to less than 80% of predicted normal. These patients in the KRONOS trial also were symptomatic while receiving two or more inhaled maintenance therapies for at least six weeks before screening.

Upon screening, they were then randomized into one of four arms. First is the FDA- approved 320/18/9.6 microgram dose of BREZTRI. The second, the LAMA/LABA arm with glycopyrrolate [18 micrograms] and formoterol fumarate [9.6 micrograms.] The third, the ICS/LABA arm with budesonide [320 micrograms] and formoterol fumarate [9.6 micrograms.] Now, there was a fourth arm included in this trial, which was an open-label arm consisting of budesonide and formoterol in the form of a dry powder inhaler. This arm was a requirement for some regulatory agencies outside of the US. However, as this product is not available in the US, we will not be discussing it further in this program.

The KRONOS trial had two primary endpoints. The first primary endpoint was FEV1 area under the curve, 0 to 4 hours at week 24 compared to budesonide and formoterol fumarate. And the second was a change from baseline in morning pre- dose trough FEV1 at Week 24 compared to the LAMA/LABA arm of glycopyrrolate and formoterol fumarate.

Let's take a look at the patients who were in the KRONOS trial. The modified intent-to-treat population included all patients with post randomization data obtained before discontinuation of treatment. Patients had a mean age of approximately 65 years, predominantly male, and a large portion were white or Asian. As I mentioned earlier, this was an international trial that included a large portion of patients from China and Japan. About 40% of the patients were current smokers. And again, exacerbation history was not a requirement; in fact, almost three-quarters of the patients did not have a history of moderate or severe exacerbations in the previous 12 months, approximately 18% with a history of 1 and approximately 7% of patients with greater than or equal to two moderate or severe exacerbations in the previous year.

Patients in the KRONOS trial also had their eosinophil counts measured, with the breakdown being approximately half-and-half between patients who had counts of less than 150, compared to those who had greater than or equal to 150. These patients were also airflow compromised, with a post-bronchodilator FEV1 of about 50% predicted. About 43% to 45% of the patients showed reversibility. In KRONOS, reversible was defined as improvement in FEV1 after salbutamol administration, compared with before salbutamol administration, of 12% or more and 200 mL or more. And again, these patients were symptomatic, [with] CAT scores of over 18.

So, what were the results of the KRONOS trial? There were two primary endpoints in this trial, both looked at differences in lung function at 24 weeks. BREZTRI demonstrated a significant improvement of 116 mL in FEV1 area under the curve, from 0 to 4 hours, compared to ICS/LABA. This result had a P-value of less than 0.0001. In addition, BREZTRI also demonstrated a 13 mL improvement in the mean change from baseline in morning pre-dose trough FEV1 versus LAMA/LABA, with a P- value equal to 0.2375.

One of the secondary endpoints in KRONOS was the rate of moderate or severe exacerbations. The definition of moderate and severe exacerbations was the same in KRONOS as in ETHOS, namely, moderate exacerbations were defined as those leading to treatment with systemic corticosteroids and/or antibiotics, and severe exacerbations were defined as those resulting in

hospitalization or death. And what we saw here was that BREZTRI demonstrated a 52% reduction compared to the LAMA/ LABA arm, with an unadjusted P-value of less than 0.0001. There was an 18% reduction when compared to the ICS/LABA arm, with a P-value equal to 0.2792. And keep in mind, KRONOS was the population of patients who did not have to have an exacerbation requirement.

Model-estimated rate of moderate or severe exacerbations per year was 0.46 for the BREZTRI arm, 0.95 for the LAMA/LABA arm, and 0.56 for the ICS/LABA arm. An “other endpoint” was the rate of severe exacerbations, and there was a difference in the rate of severe exacerbations observed in the KRONOS trial. The model estimated annual rate of severe COPD exacerbation was 0.05 for the BREZTRI arm and the ICS/LABA arm, and 0.13 for the LAMA/LABA arm. These results are observational in nature; any comparisons between treatment arms should be interpreted with caution.

Let’s talk about the safety profile that was observed in KRONOS. The most common adverse events occurring at an incidence of at least 2% included nasopharyngitis, upper respiratory tract infection, worsening of COPD, and bronchitis.

So, let's review the summary of the clinical trials. BREZTRI showed the power to protect and prevent exacerbations to help patients breathe better and reduce overall symptoms.

The power to protect was demonstrated in our ETHOS trial, in which patients were required to have a history of moderate or severe exacerbations. BREZTRI significantly reduced moderate or severe exacerbations versus LAMA/LABA and versus ICS/LABA. In fact, the rate of severe exacerbations was significantly reduced by 20% versus ICS/LABA and by 16% versus LAMA/LABA.

The power to prevent was demonstrated in KRONOS, where the majority of the patients did not have a history of exacerbations in the last year. BREZTRI demonstrated a significant improvement in lung function looking at FEV1 area under the curve, 0 to 4 hours, versus ICS/LABA, and improved mean change from baseline in morning pre-dose trough FEV1 versus LAMA/LABA. We also saw the rate of moderate or severe exacerbations being reduced by 52% versus the LAMA/LABA arm, and 18% versus the ICS/LABA-containing arm.

And lastly, in trials totaling more than 10,000 patients, of which 2783 patients with COPD received at least 1 dose of BREZTRI 320/18/9.6 micrograms, BREZTRI had a safety profile comparable with LAMA/LABA and ICS/LABA.

Let’s talk about the dosing and administration of BREZTRI. BREZTRI is administered as two inhalations, twice a day. Each oral inhalation delivers 160 micrograms of budesonide, 9 micrograms of glycopyrrolate, and 4.8 micrograms of formoterol fumarate. BREZTRI should be given in the morning and administered again in the evening. You should advise patients not to take more than two inhalations twice daily. After each inhalation, patients should rinse their mouth out with water, without swallowing this water.

Thank you for your time and your participation today. Please keep listening for additional important safety Information. I hope the data I shared today will be part of your decision to choose BREZTRI to protect and prevent for your appropriate patients with COPD.

Announcer:

IMPORTANT SAFETY INFORMATION

BREZTRI is contraindicated in patients who have a hypersensitivity to budesonide, glycopyrrolate, formoterol fumarate, or product excipients

BREZTRI is not indicated for treatment of asthma. Long-acting beta2- adrenergic agonist (LABA) monotherapy for asthma is associated with an increased risk of asthma-related death. These findings are considered a class effect of LABA monotherapy. When a LABA is used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone. Available data do not suggest an increased risk of death with use of LABA in patients with COPD

BREZTRI should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition

BREZTRI is NOT a rescue inhaler. Do NOT use to relieve acute symptoms; treat with an inhaled short-acting beta2-agonist

BREZTRI should not be used more often than recommended; at higher doses than recommended; or in combination with LABA-containing medicines, due to risk of overdose. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs

Oropharyngeal candidiasis has occurred in patients treated with orally inhaled drug products containing budesonide. Advise patients to rinse their mouths with water without swallowing after inhalation

Lower respiratory tract infections, including pneumonia, have been reported following ICS. Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbations frequently overlap

Due to possible immunosuppression, potential worsening of infections could occur. Use with caution. A more serious or fatal course of chickenpox or measles can occur in susceptible patients

Particular care is needed for patients transferred from systemic corticosteroids to ICS because deaths due to adrenal insufficiency have occurred in patients during and after transfer. Taper patients slowly from systemic corticosteroids if transferring to BREZTRI

Hypercorticism and adrenal suppression may occur with regular or very high dosage in susceptible individuals. If such changes occur, consider appropriate therapy

Caution should be exercised when considering the coadministration of BREZTRI with long-term ketoconazole and other known strong CYP3A4 Inhibitors. Adverse effects related to increased systemic exposure to budesonide may occur

If paradoxical bronchospasm occurs, discontinue BREZTRI immediately and institute alternative therapy

Anaphylaxis and other hypersensitivity reactions (eg, angioedema, urticaria or rash) have been reported. Discontinue and consider alternative therapy

Use caution in patients with cardiovascular disorders, especially coronary insufficiency, as formoterol fumarate can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles

Decreases in bone mineral density have been observed with long-term administration of ICS. Assess initially and periodically thereafter in patients at high risk for decreased bone mineral content

Glaucoma and cataracts may occur with long-term use of ICS. Worsening of narrow- angle glaucoma may occur, so use with caution. Consider referral to an ophthalmologist in patients who develop ocular symptoms or use BREZTRI long term. Instruct patients to contact a healthcare provider immediately if symptoms occur

Worsening of urinary retention may occur. Use with caution in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to contact a healthcare provider immediately if symptoms occur

Use caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis or unusually responsive to sympathomimetic amines

Be alert to hypokalemia or hyperglycemia

Most common adverse reactions in a 52-week trial (incidence ≥ 2%) were upper respiratory tract infection (5.7%), pneumonia (4.6%), back pain (3.1%), oral candidiasis (3.0%), influenza (2.9%), muscle spasms (2.8%), urinary tract infection (2.7%), cough (2.7%), sinusitis (2.6%), and diarrhea (2.1%). In a 24-week trial, adverse reactions (incidence ≥ 2%) were dysphonia (3.3%) and muscle spasms (3.3%)

BREZTRI should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors and tricyclic antidepressants, as these may potentiate the effect of formoterol fumarate on the cardiovascular system

BREZTRI should be administered with caution to patients being treated with:

- Strong cytochrome P450 3A4 inhibitors (may cause systemic corticosteroid effects)
- Adrenergic drugs (may potentiate effects of formoterol fumarate)
- Xanthine derivatives, steroids, or non-potassium sparing diuretics (may potentiate hypokalemia and/or ECG changes)
- Beta-blockers (may block bronchodilatory effects of beta-agonists and produce severe bronchospasm)
- Anticholinergic-containing drugs (may interact additively). Avoid use with BREZTRI

Use BREZTRI with caution in patients with hepatic impairment, as budesonide and formoterol fumarate systemic exposure may increase. Patients with severe hepatic disease should be closely monitored

Danelle Dolan:
AstraZeneca is committed to conducting business with the highest standards of integrity and professionalism. If you have any questions or comments, please contact us at 1-800-236-9933.

Announcer:
This program was sponsored by AstraZeneca. If you missed any part of this discussion, and to learn more about other programs focusing on COPD exacerbations, visit ReachMD.com. This is ReachMD. Be part of the knowledge.