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MONOGRAPH

# LESOGABERAN

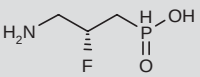
Rec INN

*$GABA_B$ Receptor Agonist*
*Treatment of Gastroesophageal Reflux Disease*

AZD-3355

3-Amino-2(*R*)-fluoropropylphosphinic acid

InChI: 1S/C3H9FNO2P/c4-3(1-5)2-8(6)7/h3,8H,1-2,5H2,(H,6,7)/t3-/m1/s1




$C_3H_9FNO_2P$
Mol wt: 141.0812
CAS: 344413-67-8
CAS: 344413-63-4 (racemate)
CAS: 344413-68-9 ([*S*]-enantiomer)
EN: 306369

**SUMMARY**

*Gastroesophageal reflux disease (GERD) is a highly prevalent medical disorder. Most patients require chronic medical therapy and proton pump inhibitors (PPIs) are the mainstay of treatment. Some patients, however, have persistent symptoms of reflux despite PPI therapy. A medication to treat the major pathophysiologic event that causes reflux, transient lower esophageal sphincter relaxations (TLESRs), could improve reflux symptoms and potentially reduce complications of persistent acid reflux. Baclofen, a $GABA_B$ receptor agonist, has been shown to reduce TLESRs and acid reflux in both healthy volunteers and patients with GERD. Central nervous system (CNS) side effects limited its use in clinical practice. Lesogaberan is a novel, peripherally acting, $GABA_B$ receptor agonist with limited CNS side effects that decreases TLESRs, reduces the number of acid reflux events and improves acid exposure time in the distal esophagus. This monograph will review the pharmacology, preclinical and clinical data, and discuss the safety of this new compound.*

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*Synthesis prepared by R. Pandian, J. Bolòs, R. Castañer. Thomson Reuters, Provença 388, 08025 Barcelona, Spain.

**SYNTHESIS***

Lesogaberan is prepared as follows:

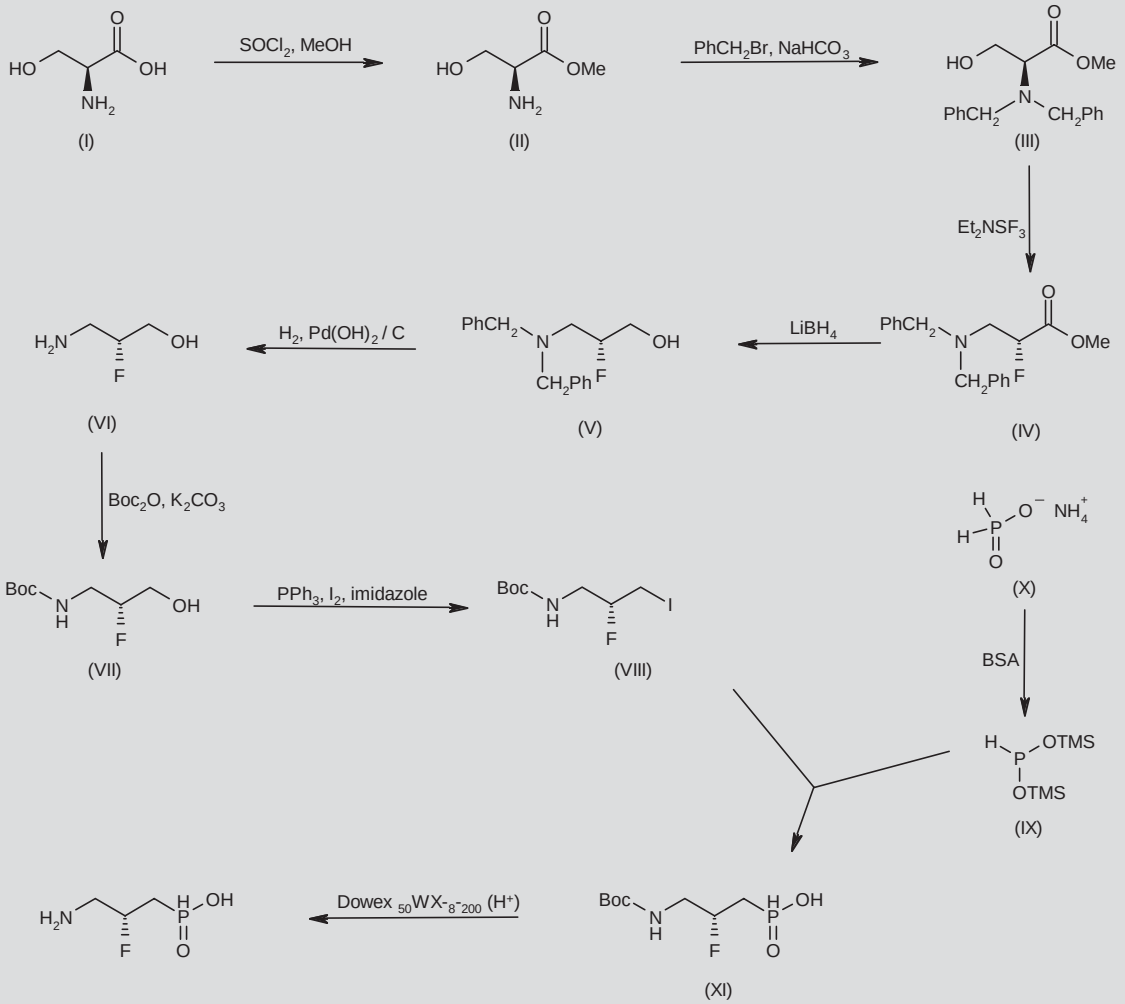
Esterification of L-serine (I) using $SOCl_2$ in MeOH, followed by alkylation of the resulting amino ester (II) with benzyl bromide and $NaHCO_3$ in DMSO/THF affords *N,N*-dibenzyl-L-serine methyl ester (III), which by subsequent treatment with diethylaminosulfur trifluoride in THF gives rise to the rearranged fluoro amine (IV) (1). After reduction of the ester (IV) to the primary alcohol (V) using $LiBH_4$ in THF, the *N*-benzyl groups are removed by catalytic hydrogenation over $Pd(OH)_2/C$ in EtOH to provide 3-amino-2(*R*)-fluoro-1-propanol (VI). Amine (VI) is protected with $Boc_2O$ and $K_2CO_3$ in $H_2O$/dioxane to yield the *t*-butyl carbamate (VII), which is iodinated to compound (VIII) by means of $I_2$ and $PPh_3$ in the presence of imidazole in $CH_2Cl_2$. Condensation of *N*-Boc-2(*R*)-fluoro-3-iodopropylamine (VIII) with bis(trimethylsilyl)phosphonite (IX) –generated from ammonium hypophosphite (X) and BSA– in $CH_2Cl_2$ gives the *N*-Boc-aminophosphinic acid (XI), which is finally deprotected by passage through an acidic ion exchange resin (1-3). Scheme 1.

**BACKGROUND**

Gastroesophageal reflux disease (GERD) is a highly prevalent disorder with weekly prevalence rates ranging from 10-20% in the Western world to 10.3-11.9% in South America (4-7). The prevalence of GERD is lower in Asia and the Middle East, with rates of 2.5-6.8% (8, 9). The lower reported prevalence of GERD in patients from Asia and the Middle East likely reflects a combination of diet, social, cultural, genetic and environmental factors.

Current treatment options for GERD include lifestyle modifications, acid suppression and surgery. Although commonly employed, lifestyle modifications are unlikely to help patients with anything more than mild, intermittent symptoms. Anti-reflux surgery can be effective if patients are carefully selected. However, many patients are concerned about the risks of surgery, and are also disappointed with the fact that many patients are placed back on proton pump inhibitor (PPI) therapy within 5 years after undergoing anti-reflux surgery (10). The mainstay of treatment for acid reflux thus remains acid suppression using PPIs. As a class, these agents have been shown to be dramatically superior to other agents (i.e., histamine $H_2$ receptor antagonists) at healing esophagitis and are generally quite

**Scheme 1.** Synthesis of Lesogaberan




effective at improving symptoms of acid reflux (11). However, not all patients respond to PPI therapy. In fact, an ever-increasing number of referrals to gastroenterologists are for the treatment of "PPI non-responders". Failure to respond to a PPI can occur for a variety of reasons (i.e., misdiagnosis, overlapping diagnoses, incorrect medication use, incorrect dosing). However, other patients have persistent symptoms of acid reflux despite using a PPI properly. Since acid reflux is not a disease of excess acid production, but instead occurs due to the reflux of gastric contents (primarily acid and pepsin) into the distal esophagus, then treatments that focus on the pathophysiologic events that cause reflux may provide better treatment options for patients with GERD.

The most common pathophysiologic event responsible for GERD is transient lower esophageal sphincter relaxation (TLESR) (12). TLESRs are characterized by an abrupt decrease in LES pressure not associated with a swallow. Some researchers require a drop in LES pressure of at least 5 mmHg, although other researchers recognize that TLESRs can occur with a drop in LES pressure to gastric baseline, although the extent of LES pressure reduction may only be a few mmHg. In contrast to swallow-induced LES relaxation, TLESRs are always longer, and usually last more than 10 s, although some may be as long as 30-45 s. Gastric distention, mediated by mechanoreceptors in the fundus of the stomach, appears to be the major cause of TLESRs.

PPIs do not influence TLESR frequency or duration. Baclofen, a γ-aminobutyric acid $GABA_B$ receptor agonist used to treat muscle spasticity, significantly inhibits TLESRs in dogs (13). Subsequent studies demonstrated that baclofen decreased TLESR frequency

and improved symptoms of reflux in humans (14-16). It is thought that activation of $GABA_B$ receptors on vagal afferent terminals in the dorsal medulla and on gastric mechanoreceptors is responsible for the reduction in TLESRs (17-19). However, baclofen is associated with significant central nervous system (CNS) side effects (headache, nausea, sleepiness, dizziness), which has limited its use in reflux patients (20).

The initial success of baclofen, however, prompted further research and development of other $GABA_B$ agonists. Subsequently, significant efforts have focused on the development of peripherally restricted $GABA_B$ agonists that are devoid of the CNS side effects associated with baclofen. Lesogaberan (AZD-3355) is a novel peripherally acting $GABA_B$ receptor agonist with limited CNS activity that has been demonstrated to inhibit TLESRs in human and animal models. This article will review the pharmacology and pharmacokinetics of lesogaberan, and present preclinical and clinical data on the safety and efficacy of lesogaberan for the treatment of GERD.

## PRECLINICAL PHARMACOLOGY

In vitro studies have shown lesogaberan to tightly bind and efficiently agonize $GABA_B$ receptors ($K_i$ = 5.1 nM; mean $EC_{50}$ = 8.6 nM) (1, 21). Using an in vivo ferret model, lesogaberan was shown to dose-dependently reduce gastric vagal mechanoreceptor activity, which would be expected to reduce TLESRs (21). It has been shown to be preferentially deposited in regions lacking the blood–brain barrier in rats. The dose–response curve for lesogaberan is similar to peripherally acting GABA, suggesting that low-dose lesogaberan acts peripherally to reduce TLESRs. Low-dose lesogaberan has been shown to act at peripheral $GABA_B$ receptors, but at higher doses may have more central effects.

In an in vivo dog model, oral lesogaberan dose-dependently inhibited TLESRs with an $ED_{50}$ of approximately 7 µmol/kg. Increasing the dose to 100 µmol/kg resulted in near complete inhibition of TLESRs (90 ± 10%) (22). Repeated dosing over 14 days did not reduce the ability of lesogaberan to inhibit TLESRs. The authors concluded that the inhibitory effects of lesogaberan on TLESRs was reproducible and did not induce tolerance after once-daily dosing for 14 days.

Several in vitro and in vivo preclinical studies have been completed to evaluate the effects of lesogaberan. As lesogaberan was developed primarily as an alternative to baclofen (due to its extensive side effect profile), most of these studies directly compared lesogaberan to baclofen and GABA. These experiments examined not only the effects on TLESR and pH-metry, but also changes at the cellular level and potential side effects.

A study by Lehmann and colleagues in 2005 used murine and canine models to look directly at the effect of lesogaberan on TLESRs in vivo, as well as the selectivity of the drug in vitro (23). The authors found a decrease in TLESRs of about 60% at a dose of 14 µmol/kg in dogs. Interestingly, there was significant hypothermia at higher doses (1-8 mmol/kg) in mice. They also found that lesogaberan was more selective for the $GABA_B$ receptor in rat brain compared to baclofen by measuring receptor-mediated calcium release. This study confirmed that lesogaberan was a full agonist at the $GABA_B$ receptor and that the drug had potential for use as an anti-reflux medication.

A subsequent study several years later by Lehmann and colleagues used murine, ferret and canine models to look at several factors related to lesogaberan (24). In vitro experiments once again found that lesogaberan had high affinity and selectivity for $GABA_B$ receptors and was also more potent at the $GABA_B$ receptor compared to baclofen. In addition, lesogaberan was found to accumulate in neural cells of rats at a much higher level than baclofen. These novel findings illustrated the potential benefits of lesogaberan not only as a selective drug but also one with fewer (CNS) side effects, such as drowsiness, dizziness, headache, confusion and insomnia, due to sequestration in brain cells. Lastly, in contrast to previous studies, a reduction in TLESRs of about 90% was achieved at a dose of 300 µmol/kg, which was a vast improvement from previous experiments.

A more recent in vivo study in dogs (25) found a decrease in the number of reflux episodes and acid exposure time when comparing lesogaberan (7 µmol/kg) to baclofen and controls. The mean number of reflux episodes per 24-h period was 4.6 for the lesogaberan group compared to 6.4 for the baclofen group and 10.7 for the control group ($P < 0.0001$). Acid exposure time was 23.6 min total in the lesogaberan group compared to 35.4 min in the baclofen group and 51.2 min in the control group ($P < 0.0001$). The success of lesogaberan in these in vitro and in vivo models appeared clear and set the stage for clinical trials.

## PHARMACOKINETICS AND METABOLISM

Boeckxstaens and colleagues (26) evaluated the pharmacokinetics of lesogaberan 0.8 mg/kg compared with baclofen in healthy males (N = 21). Lesogaberan was rapidly absorbed with a median $t_{max}$ of 1.0 h. The geometric mean value for $C_{max}$ was 1.60 µmol/L and the $AUC_t$ was 6.47 µmol·h/L. Baclofen was also rapidly absorbed with a median $t_{max}$ of 1.5 h. The geometric mean value for $C_{max}$ was 2.29 µmol/L and the $AUC_t$ was 9.61 µmol·h/L.

Niazi and colleagues (27) evaluated the pharmacokinetic interaction between lesogaberan and esomeprazole in healthy volunteers (N = 28) in an open-label, randomized, crossover study following oral dosing. Modified-release lesogaberan (150 mg) twice daily was compared with esomeprazole (40 mg) daily and a combination of twice-daily lesogaberan (150 mg) and once-daily esomeprazole (40 mg). No clinically significant changes were noted in the $AUC_{0-24}$ for lesogaberan alone (35.0 h·µM) compared with the combination of lesogaberan with esomeprazole (32.3 h·µM). The $C_{max}$ for lesogaberan alone (4.66 µM) was not meaningfully different than when combined with esomeprazole (4.23 µM). The $t_{max}$ was 3 h in both the lesogaberan group and the combination group. The $t_{1/2}$ was 6.2 h in the lesogaberan-only group and 6.6 h in the combined group. Similarly, no clinically meaningful differences were noted for oral clearance between lesogaberan alone and when combined with esomeprazole (30.4 L/h vs. 32.9 L/h). Additionally, only minor changes were noted in the pharmacokinetics of esomeprazole when combined with lesogaberan.

Fransson et al. (28), studied the effects of food ingestion on the bioavailability of lesogaberan in healthy volunteers (N = 60). A randomized, open-label, crossover study was used to evaluate lesogaberan (100 mg) as an oral solution or a modified-release capsule with a dissolution rate of 50% at 4 h, or a modified-release capsule

with a dissolution rate of 100% at 4 h. Fasting $t_{max}$ was 1 h for the solution and 5 h for the modified-release 50% capsule. The $t_{max}$ for the modified-release 100% capsule was 3 h. Food ingestion moderately increased the $t_{max}$ value for the solution (1.8 h) and the 50% modified-release capsule (5 h), but not for the 100% modified-release capsule. The $t_{1/2}$, $C_{max}$ and AUC of the capsules were not substantially different during fasting and postprandially.

## SAFETY

In a single-blind, placebo-controlled, randomized, crossover phase I study in 24 healthy men, 21 of whom completed the study (mean age = 27 years; mean body mass index [BMI] = 23.7 kg/m$^2$), a single oral dose of lesogaberan (0.8 mg/kg) was generally well tolerated (26). No serious adverse events were reported and no participant ended the study prematurely due to side effects. The authors reported that vital signs, laboratory values and electrocardiograms (ECGs) were not changed. Adverse events (AEs) attributable to the study medication were more common with baclofen (40 mg p.o. single dose; 15 patients) than with either lesogaberan (8 patients) or placebo (8 patients). The three most common side effects were transient paresthesias (4 patients), somnolence (3 patients) and abdominal pain (2 patients). Paresthesias were generally rated as mild to moderate in intensity, occurred 1-63 min after oral administration and resolved within 3-60 min.

In a study designed to assess the impact of food on the bioavailability of lesogaberan, 60 healthy males (mean age = 27.3 years; mean weight = 77.1 kg) received two separate 100-mg doses of lesogaberan separated by 5-7 days (28). No serious AEs were reported. The most common AEs were headache (n = 11), transient paresthesias (n = 10) and increased urine output (n = 8).

To evaluate possible interactions between lesogaberan and a PPI, 30 healthy males (mean age = 23 years) were treated with 150 mg p.o. twice daily lesogaberan or 40 mg p.o. once daily esomeprazole, or both agents, for 7 days (27). No severe AEs were reported. The most common AE was paresthesia in five patients on lesogaberan alone and in four volunteers treated with lesogaberan and esomeprazole together.

In one of the largest studies published to date involving GERD patients –27 patients (16 men; mean age = 51.6 years; mean BMI = 25.9 kg/m$^2$) enrolled in a double-blind, placebo-controlled, crossover study– the number of AEs was similar in patients taking lesogaberan (65 mg p.o. b.i.d.) or placebo. Paresthesias (five events) and dizziness (three events) were more common in the lesogaberan group than in the placebo group (three and one event, respectively) (29). Headache was reported more frequently in the placebo group (11 events) compared to the lesogaberan group (8 events). Three patients reported flushing in the lesogaberan group compared to one in the placebo group. No serious AEs were reported in either group.

The efficacy of lesogaberan at relieving persistent symptoms of reflux despite PPI therapy was evaluated in a prospective, randomized, placebo-controlled study in 232 patients (30). In this study, the most common AE in the lesogaberan group was diarrhea (11% vs. 3% on placebo). Other reported AEs in the lesogaberan group were paresthesias (8%), nausea (7%) and fatigue (6%) (5%, 3% and 6%, respectively, on placebo).

## CLINICAL STUDIES

Several clinical studies have examined various aspects of lesogaberan use, including dosage, TLESRs, reflux events and symptom improvement. Some of these studies are still ongoing (see clinicaltrials.gov); only two studies have been published to date and these are reviewed below.

The first published study, by Boeckxstaens and colleagues (26), was a single blind, placebo-controlled, randomized, crossover phase I study comparing lesogaberan (0.8 mg/kg), baclofen (40 mg) and placebo. Twenty-four healthy males were enrolled and 21 completed the study. All subjects received single doses of each drug and placebo with each trial period separated by a washout period of at least 7 days. Manometric and pH-metric data were collected in the 4 h following the dose. All subjects received a meal 45 min after the drug or placebo. Analysis found a decrease of 36% in the mean number of TLESRs from 13 (placebo) to 8.3 and 6.8, respectively, with lesogaberan and baclofen (geometric mean ratio [GMR] = 0.64 and confidence interval [CI] = 0.51-0.82 for lesogaberan; GMR = 0.53 and CI = 0.41-0.67 for baclofen). LES pressure was also significantly increased by 39% with lesogaberan compared to placebo (GMR = 1.39 and CI = 1.18-1.64). In addition, lesogaberan reduced the number of reflux episodes during the three episodes after the meal with a mean reduction of 1.6 episodes (CI = 0.34-2.9). There was a similar number of swallows with lesogaberan and placebo (69.5 and 66.3, respectively); baclofen had a reduced number of swallows by a mean of 10.4 compared to placebo (CI = –1.8 to –19.0). Similar numbers of nervous system side effects were reported after lesogaberan (7/21) and placebo administration (6/22), but baclofen had nearly twice as many (14/22). In this first human trial, lesogaberan's effect appeared to translate well from the previous animal models. The effect on TLESRs was not as dramatic as some of the preclinical studies, but the authors noted that increasing doses of lesogaberan were needed in animal models to produce a 90% reduction. Importantly, the decreased side effect profile was once again evident, as was an increase in the LES pressure, which had not been described previously.

The second study, also by Boeckxstaens and colleagues, was a randomized, double-blind, placebo-controlled, crossover phase IIa study comparing lesogaberan and placebo (29). This study focused on patients with a history of GERD who were symptomatic despite PPI therapy. A total of 27 patients were enrolled (16 male, 11 female). Patients were randomized to receive three doses of lesogaberan or matching placebo in the morning and evening on day 1 and in the morning on day 2. After a washout period of 5-28 days, they crossed over to the opposite treatment arm. Ambulatory impedance-pH recording was performed over the 24 h following the first treatment dose on day 1. On the second day, the catheter was replaced with a manometric impedance-pH catheter which was utilized to record for the 4 h following the third treatment dose. Analysis found a decrease of 25% in the mean number of TLESRs from 15.5 with placebo to 11.6 with lesogaberan (GMR = 0.75; CI = 0.60-0.93). LES pressure was increased by 28% with lesogaberan (GMR = 1.28; CI = 1.05-1.57). The number of reflux episodes decreased by 35% compared with placebo (arithmetic mean difference = –22; CI = –28 to –15) over the first 24 h. The effects were more pronounced for acid reflux episodes than for either weakly acidic or weakly alkaline

episodes. Esophageal acid exposure time was also reduced with lesogaberan compared to placebo (1.2% and 3.0%, respectively), as was acid clearance time when supine (69.8 and 143.3 s, respectively). The total number of reflux episodes related to reflux was 33 with lesogaberan and 57 with placebo ($P = 0.092$). The number of reported AEs was similar with lesogaberan (n = 18) and placebo (n = 20). The number of spontaneous swallows was also similar.

The largest published study to date evaluating the efficacy of lesogaberan at relieving persistent symptoms of reflux despite PPI therapy was a double-blind, randomized, prospective, multicenter study in 232 patients (30). Male and female adult patients (aged 18-70 years) with persistent GERD symptoms despite at least 6 weeks of PPI therapy were eligible for study inclusion as long as they had at least 3 days of heartburn or regurgitation in the 7 days before study initiation. Patients continued their same PPI but were randomized to receive either twice-daily lesogaberan (65 mg) or placebo. The primary efficacy endpoint was the presence of at most one 24-h period of reflux during the last 7 days of treatment. Using this strict endpoint, 16% of patients treated with lesogaberan responded to treatment compared to 8% treated with placebo ($P = 0.026$). A post hoc analysis using a less strict endpoint of "not more than very mild intensity of heartburn or regurgitation during the last 7 days of treatment" led to an increased response rate in those treated with lesogaberan (34%) compared to those treated with placebo (15%; *P* value not provided).

While published clinical data are still somewhat sparse at this time, the results appear promising. TLESRs are clearly reduced across preclinical and clinical studies. More importantly, reflux episodes and acid exposure time are also decreased and this appears to be resulting in a trend towards symptom improvement. These results are more even impressive in the setting of a tolerable side effect profile. Future studies will be important to determine the optimal dose and the best use for lesogaberan and its long-term outcomes.

## DRUG INTERACTIONS

Little data are currently available regarding potential drug interactions. In the one published study to date evaluating the efficacy and safety of lesogaberan used in conjunction with a PPI, no apparent interactions were noted. Based on limited data available from baclofen studies, with the obvious inherent limitations of this type of analysis, it seems likely that lesogaberan will be able to be used safely with other commonly used medications in a reflux population. Theoretically, baclofen can be associated with muscle hypotonia and hypotension when used in conjunction with tricyclic antidepressants and monoamine oxidase inhibitors, respectively, and thus future studies of lesogaberan will need to observe patients carefully for these possible side effects. In addition, future trials of lesogaberan will need to evaluate possible drug interactions with patients who are on oral contraceptives, clopidogrel, coumadin, serotonin reuptake inhibitors, phenytoin and commonly used antibiotics.

## SOURCE

AstraZeneca (GB).

## DISCLOSURES

In the last two years, Dr. Lacy has received research support from the NIH as a coinvestigator for the Functional Dyspepsia Treatment Trial, and an investigator-initiated, unrestricted educational research grant from AstraZeneca to assess the effects of intraduodenal fat on acid reflux. Dr. Crowell and Dr. Chehade state no conflicts of interest.

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