HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LETAIRIS® safely and effectively. See full prescribing information for LETAIRIS.

Letairis (ambrisentan) tablets, for oral use
Initial U.S. Approval: 2007

WARNING: EMBRYO-FETAL TOXICITY
See full prescribing information for complete boxed warning.

- **Do not administer Letairis to a pregnant female because it may cause fetal harm (4.1, 5.1, 8.1).**
- **Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception (2.2, 8.3).**
- **For all female patients, Letairis is available only through a restricted program called the Letairis Risk Evaluation and Mitigation Strategy (REMS) (5.2).**

----------INDICATIONS AND USAGE----------
Letairis is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1):
- To improve exercise ability and delay clinical worsening.
- In combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability.

Studies establishing effectiveness included trials predominantly in patients with WHO Functional Class II–III symptoms and etiologies of idiopathic or heritable PAH (60%) or PAH associated with connective tissue diseases (34%) (1).

----------DOSAGE AND ADMINISTRATION----------
- Initiate treatment at 5 mg once daily (2.1).
- May be started with tadalafil (2.1).
- Titrate at 4-week intervals as needed and tolerated (2.1).
- Do not split, crush, or chew tablets (2.1).

----------DOSAGE FORMS AND STRENGTHS----------
Tablet: 5 mg and 10 mg (3)

----------CONTRAINDICATIONS----------
- Pregnancy (4.1)
- Idiopathic Pulmonary Fibrosis (4.2)

----------WARNINGS AND PRECAUTIONS----------
- Fluid retention may require intervention (5.3).
- If patients develop acute pulmonary edema during initiation of therapy with Letairis, consider underlying pulmonary veno-occlusive disease and discontinue treatment if necessary (5.4).
- Decreases in sperm count have been observed in patients taking endothelin receptor antagonists (5.5).
- Decreases in hemoglobin have been observed within the first few weeks; measure hemoglobin at initiation, at 1 month, and periodically thereafter (5.6).

----------ADVERSE REACTIONS----------
- Most common adverse reactions (>3% compared to placebo) are peripheral edema, nasal congestion, sinusitis, and flushing (6.1).
- When used in combination with tadalafil, most common adverse reactions (>5% compared with either monotherapy) are peripheral edema, headache, nasal congestion, cough, anemia, dyspepsia, and bronchitis (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at (1-800-445-3235, Option 3) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Cyclosporine increases ambrisentan exposure; limit ambrisentan dose to 5 mg once daily (7).

----------USE IN SPECIFIC POPULATIONS----------
- Breastfeeding: Choose Letairis or breastfeeding (8.2).
- Not recommended in patients with moderate or severe hepatic impairment (8.7).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2018

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FULL PRESCRIBING INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

Do not administer Letairis to a pregnant female because it may cause fetal harm. Letairis is very likely to produce serious birth defects if used by pregnant females, as this effect has been seen consistently when it is administered to animals *[see Contraindications (4.1), Warnings and Precautions (5.1), and Use in Specific Populations (8.1)].*

Exclude pregnancy before the initiation of treatment with Letairis. Females of reproductive potential must use acceptable methods of contraception during treatment with Letairis and for one month after treatment. Obtain monthly pregnancy tests during treatment and 1 month after discontinuation of treatment *[see Dosage and Administration (2.2) and Use in Specific Populations (8.3)]*.

Because of the risk of embryo-fetal toxicity, females can only receive Letairis through a restricted program called the Letairis REMS program *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

Letairis is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1):

- To improve exercise ability and delay clinical worsening.
- In combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability *[see Clinical Studies (14.2)].*

Studies establishing effectiveness included predominantly patients with WHO Functional Class II–III symptoms and etiologies of idiopathic or heritable PAH (60%) or PAH associated with connective tissue diseases (34%).

2 DOSAGE AND ADMINISTRATION

2.1 Adult Dosage

Initiate treatment at 5 mg once daily, with or without tadalafil 20 mg once daily. At 4-week intervals, either the dose of Letairis or tadalafil can be increased, as needed and tolerated, to Letairis 10 mg or tadalafil 40 mg.

Do not split, crush, or chew tablets.

2.2 Pregnancy Testing in Females of Reproductive Potential

Initiate treatment with Letairis in females of reproductive potential only after a negative pregnancy test. Obtain monthly pregnancy tests during treatment *[see Use in Specific Populations (8.3)].*

3 DOSAGE FORMS AND STRENGTHS

5 mg and 10 mg film-coated tablets for oral administration

- Each 5 mg tablet is square convex, pale pink, with “5” on one side and “GSI” on the other side.
- Each 10 mg tablet is oval convex, deep pink, with “10” on one side and “GSI” on the other side.

4 CONTRAINDICATIONS

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4.1 Pregnancy

Letairis may cause fetal harm when administered to a pregnant female. Letairis is contraindicated in females who are pregnant. Letairis was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Warnings and Precautions (5.1, 5.2) and Use in Specific Populations (8.1)]*.

4.2 Idiopathic Pulmonary Fibrosis

Letairis is contraindicated in patients with Idiopathic Pulmonary Fibrosis (IPF), including IPF patients with pulmonary hypertension (WHO Group 3) *[see Clinical Studies (14.4)].*

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-fetal Toxicity

Letairis may cause fetal harm when administered during pregnancy and is contraindicated for use in females who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, ensure use of acceptable contraceptive methods, and obtain monthly pregnancy tests *[see Dosage and Administration (2.2), and Use in Specific Populations (8.1, 8.3)]*.

Letairis is only available for females through a restricted program under a REMS *[see Warnings and Precautions (5.2)]*.

5.2 Letairis REMS Program

For all females, Letairis is available only through a restricted program called the Letairis REMS, because of the risk of embryo-fetal toxicity *[see Contraindications (4.1), Warnings and Precautions (5.1), and Use in Specific Populations (8.1, 8.3)].*

Notable requirements of the Letairis REMS program include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the Letairis REMS program prior to initiating Letairis. Male patients are not enrolled in the REMS.
    - Females of reproductive potential must comply with the pregnancy testing and contraception requirements *[see Use in Specific Populations (8.3)].*
- Pharmacies that dispense Letairis must be certified with the program and must dispense to female patients who are authorized to receive Letairis.

Further information is available at www.letairisrems.com or 1-866-664-5327.

5.3 Fluid Retention

Peripheral edema is a known class effect of endothelin receptor antagonists, and is also a clinical consequence of PAH and worsening PAH. In the placebo-controlled studies, there was an increased incidence of peripheral edema in patients treated with doses of 5 or 10 mg Letairis compared to placebo *[see Adverse Reactions (6.1)]*. Most edema was mild to moderate in severity.

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In addition, there have been postmarketing reports of fluid retention in patients with pulmonary hypertension, occurring within weeks after starting Letairis. Patients required intervention with a diuretic, fluid management, or, in some cases, hospitalization for decompensating heart failure.

If clinically significant fluid retention develops, with or without associated weight gain, further evaluation should be undertaken to determine the cause, such as Letairis or underlying heart failure, and the possible need for specific treatment or discontinuation of Letairis therapy.

Peripheral edema/fluid retention is more common with Letairis plus tadalafil than with Letairis or tadalafil alone.

5.4 Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)

If patients develop acute pulmonary edema during initiation of therapy with vasodilating agents such as Letairis, the possibility of PVOD should be considered, and if confirmed Letairis should be discontinued.

5.5 Decreased Sperm Counts

Decreased sperm counts have been observed in human and animal studies with another endothelin receptor antagonist and in animal fertility studies with ambrisentan. Letairis may have an adverse effect on spermatogenesis. Counsel patients about potential effects on fertility *[see Use in Specific Populations (8.6) and Nonclinical Toxicology (13.1)].*

5.6 Hematological Changes

Decreases in hemoglobin concentration and hematocrit have followed administration of other endothelin receptor antagonists and were observed in clinical studies with Letairis. These decreases were observed within the first few weeks of treatment with Letairis, and stabilized thereafter. The mean decrease in hemoglobin from baseline to end of treatment for those patients receiving Letairis in the 12-week placebo-controlled studies was 0.8 g/dL.

Marked decreases in hemoglobin (>15% decrease from baseline resulting in a value below the lower limit of normal) were observed in 7% of all patients receiving Letairis (and 10% of patients receiving 10 mg) compared to 4% of patients receiving placebo. The cause of the decrease in hemoglobin is unknown, but it does not appear to result from hemorrhage or hemolysis.

In the long-term open-label extension of the two pivotal clinical studies, mean decreases from baseline (ranging from 0.9 to 1.2 g/dL) in hemoglobin concentrations persisted for up to 4 years of treatment.

There have been postmarketing reports of decreases in hemoglobin concentration and hematocrit that have resulted in anemia requiring transfusion.

Measure hemoglobin prior to initiation of Letairis, at one month, and periodically thereafter. Initiation of Letairis therapy is not recommended for patients with clinically significant anemia. If a clinically significant decrease in hemoglobin is observed and other causes have been excluded, consider discontinuing Letairis.

6 ADVERSE REACTIONS

Clinically significant adverse reactions that appear in other sections of the labeling include:

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- Embryo-fetal Toxicity *[see Warnings and Precautions (5.1), Use in Specific Populations (8.1)]*
- Fluid Retention *[see Warnings and Precautions (5.3)]*
- Pulmonary Edema with PVOD *[see Warnings and Precautions (5.4)]*
- Decreased Sperm Count *[see Warnings and Precautions (5.5)]*
- Hematologic Changes *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Safety data for Letairis are presented from two 12-week, placebo-controlled studies (ARIES-1 and ARIES-2) in patients with pulmonary arterial hypertension (PAH), and one randomized, double-blind, active-controlled trial in 605 patients with PAH (AMBITION) comparing Letairis plus tadalafil to Letairis or tadalafil alone. The exposure to Letairis in these studies ranged from 1 day to 4 years (N=357 for at least 6 months and N=279 for at least 1 year).

In ARIES-1 and ARIES-2, a total of 261 patients received Letairis at doses of 2.5, 5, or 10 mg once daily and 132 patients received placebo. The adverse reactions that occurred in >3% more patients receiving Letairis than receiving placebo are shown in Table 1.

Table 1 Adverse Reactions with Placebo-Adjusted Rates >3% in ARIES-1 and ARIES-2

	Placebo (N=132)	**Letairis (N=261)**	
Adverse Reaction	**n (%)**	**n (%)**	**Placebo-adjusted (%)**
Peripheral edema	14 (11)	45 (17)	6
Nasal congestion	2 (2)	15 (6)	4
Sinusitis	0 (0)	8 (3)	3
Flushing	1 (1)	10 (4)	3

Most adverse drug reactions were mild to moderate and only nasal congestion was dose-dependent.

Few notable differences in the incidence of adverse reactions were observed for patients by age or sex. Peripheral edema was similar in younger patients (<65 years) receiving Letairis (14%; 29/205) or placebo (13%; 13/104), and was greater in elderly patients (≥65 years) receiving Letairis (29%; 16/56) compared to placebo (4%; 1/28). The results of such subgroup analyses must be interpreted cautiously.

The incidence of treatment discontinuations due to adverse events other than those related to PAH during the clinical trials in patients with PAH was similar for Letairis (2%; 5/261 patients) and placebo (2%; 3/132 patients). The incidence of patients with serious adverse events other than those related

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to PAH during the clinical trials in patients with PAH was similar for placebo (7%; 9/132 patients) and for Letairis (5%; 13/261 patients).

During 12-week controlled clinical trials, the incidence of aminotransferase elevations >3 x upper limit of normal (ULN) were 0% on Letairis and 2.3% on placebo. In practice, cases of hepatic injury should be carefully evaluated for cause.

Combination Use with Tadalafil

The mean exposure to Letairis + tadalafil in the AMBITION study was 78.7 weeks. The adverse reactions that occurred in >5% more patients receiving Letairis + tadalafil than receiving Letairis or tadalafil monotherapy in AMBITION are shown in Table 2.

Table 2 Adverse Reactions Reported More Commonly (>5%) on Letairis + Tadalafil than on Letairis or Tadalafil Monotherapy (ITT) in AMBITION

Adverse Reactions	Letairis + Tadalafil Combination Therapy (N=302) n (%)	Letairis Monotherapy (N=152) n (%)	Tadalafil Monotherapy (N=151) n (%)
Peripheral edema	135 (45%)	58 (38%)	43 (28%)
Headache	125 (41%)	51 (34%)	53 (35%)
Nasal congestion	58 (19%)	25 (16%)	17 (11%)
Cough	53 (18%)	20 (13%)	24 (16%)
Anemia	44 (15%)	11 (7%)	17 (11%)
Dyspepsia	32 (11%)	5 (3%)	18 (12%)
Bronchitis	31 (10%)	6 (4%)	13 (9%)

Peripheral edema was more frequent on combination therapy; however, there was no notable difference observed in the incidence of peripheral edema in elderly patients (≥65 years) versus younger patients (<65 years) on combination therapy (44% vs. 45%) or Letairis monotherapy (37% vs. 39%) in AMBITION.

Treatment discontinuations due to adverse events while on randomized treatment were similar across treatment groups: 16% for Letairis + tadalafil, 14% for Letairis alone, and 13% for tadalafil alone.

Use in Patients with Prior Endothelin Receptor Antagonist (ERA) Related Serum Liver Enzyme Abnormalities

In an uncontrolled, open-label study, 36 patients who had previously discontinued endothelin receptor antagonists (ERAs: bosentan, an investigational drug, or both) due to aminotransferase elevations >3 x ULN were treated with Letairis. Prior elevations were predominantly moderate, with 64% of the ALT elevations <5 x ULN, but 9 patients had elevations >8 x ULN. Eight patients had been re-challenged with bosentan and/or the investigational ERA and all eight had a recurrence of aminotransferase abnormalities that required discontinuation of ERA therapy. All patients had to have normal aminotransferase levels on entry to this study. Twenty-five of the 36 patients were also receiving prostanoid and/or phosphodiesterase type 5 (PDE5) inhibitor therapy. Two patients discontinued early (including one of the patients with a prior 8 x ULN elevation). Of the remaining 34 patients, one

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patient experienced a mild aminotransferase elevation at 12 weeks on Letairis 5 mg that resolved with decreasing the dosage to 2.5 mg, and that did not recur with later escalations to 10 mg. With a median follow-up of 13 months and with 50% of patients increasing the dose of Letairis to 10 mg, no patients were discontinued for aminotransferase elevations. While the uncontrolled study design does not provide information about what would have occurred with re-administration of previously used ERAs or show that Letairis led to fewer aminotransferase elevations than would have been seen with those drugs, the study indicates that Letairis may be tried in patients who have experienced asymptomatic aminotransferase elevations on other ERAs after aminotransferase levels have returned to normal.

6.2 Postmarketing Experience

The following adverse reactions were identified during post-approval use of Letairis. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to estimate reliably the frequency or to establish a causal relationship to drug exposure: anemia requiring transfusion *[see Warnings and Precautions (5.6)]* heart failure (associated with fluid retention), symptomatic hypotension, and hypersensitivity (e.g., angioedema, rash).

Elevations of liver aminotransferases (ALT, AST) have been reported with Letairis use; in most cases alternative causes of the liver injury could be identified (heart failure, hepatic congestion, hepatitis, alcohol use, hepatotoxic medications). Other endothelin receptor antagonists have been associated with elevations of aminotransferases, hepatotoxicity, and cases of liver failure *[see Adverse Reactions (6.1)].*

7 DRUG INTERACTIONS

Multiple dose coadministration of ambrisentan and cyclosporine resulted in an approximately 2-fold increase in ambrisentan exposure in healthy volunteers; therefore, limit the dose of ambrisentan to 5 mg once daily when coadministered with cyclosporine *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on data from animal reproduction studies, Letairis may cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy. There are limited data on Letairis use in pregnant women. In animal reproduction studies, Letairis was teratogenic in rats and rabbits at doses which resulted in exposures of 3.5 and 1.7 times, respectively, the human dose of 10 mg per day *[see Animal Data]*. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential hazard to a fetus *[see Contraindications (4.1), Warnings and Precautions (5.1)]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

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Data

Animal Data

Letairis was teratogenic at oral dosages of ≥15 mg/kg/day (AUC 51.7 h•µg/mL) in rats and ≥7 mg/kg/day (24.7 h•µg/mL) in rabbits; it was not studied at lower dosages. These dosages are of 3.5 and 1.7 times, respectively, the human dose of 10 mg per day (14.8 h•µg/mL) based on AUC. In both species, there were abnormalities of the lower jaw and hard and soft palate, malformation of the heart and great vessels, and failure of formation of the thymus and thyroid.

A preclinical study in rats has shown decreased survival of newborn pups (mid and high dosages) and effects on testicle size and fertility of pups (high dosage) following maternal treatment with ambrisentan from late gestation through weaning. The mid and high dosages were 51 x, and 170 x (on a mg/m^2 body surface area basis) the maximum oral human dose of 10 mg and an average adult body weight of 70 kg. These effects were absent at a maternal dosage 17 x the human dose based on mg/m^2.

8.2 Lactation

Risk Summary

It is not known whether ambrisentan is present in human milk. Because many drugs are present in human milk and because of the potential for serious adverse reactions in breastfed infants from Letairis, a decision should be made whether to discontinue breastfeeding or discontinue Letairis, taking into account the importance of the drug to the mother.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Female patients of reproductive potential must have a negative pregnancy test prior to initiation of treatment, monthly pregnancy test during treatment, and pregnancy test 1 month after stopping treatment with Letairis. Advise patients to contact their healthcare provider if they become pregnant or suspect they may be pregnant. Perform a pregnancy test if pregnancy is suspected for any reason. For positive pregnancy tests, counsel patient on the potential risk to the fetus and patient options *[see Boxed Warning and Dosage and Administration (2.2)].*

Contraception

Female patients of reproductive potential must use acceptable methods of contraception during treatment with Letairis and for 1 month after stopping treatment with Letairis. Patients may choose one highly effective form of contraception (intrauterine device [IUD], contraceptive implant, or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods). If a partner's vasectomy is the chosen method of contraception, a hormone or barrier method must be used along with this method. Counsel patients on pregnancy planning and prevention, including emergency contraception, or designate counseling by another healthcare provider trained in contraceptive counseling *[see Boxed Warning].*

Infertility

Males

In a 6-month study of another endothelin receptor antagonist, bosentan, 25 male patients with WHO functional class III and IV PAH and normal baseline sperm count were evaluated for effects on

testicular function. There was a decline in sperm count of at least 50% in 25% of the patients after 3 or 6 months of treatment with bosentan. One patient developed marked oligospermia at 3 months, and the sperm count remained low with 2 follow-up measurements over the subsequent 6 weeks. Bosentan was discontinued and after 2 months the sperm count had returned to baseline levels. In 22 patients who completed 6 months of treatment, sperm count remained within the normal range and no changes in sperm morphology, sperm motility, or hormone levels were observed. Based on these findings and preclinical data *[see Nonclinical Toxicology (13.1)]* from endothelin receptor antagonists, it cannot be excluded that endothelin receptor antagonists such as Letairis have an adverse effect on spermatogenesis. Counsel patients about the potential effects on fertility *[see Warnings and Precautions (5.5)]*.

8.4 Pediatric Use

Safety and effectiveness of Letairis in pediatric patients have not been established.

Juvenile Animal Data

In juvenile rats administered ambrisentan orally once daily during postnatal day 7 to 26, 36, or 62, a decrease in brain weight (−3% to −8%) with no morphologic or neurobehavioral changes occurred after breathing sounds, apnea, and hypoxia were observed, at exposures approximately 1.8 to 7.0 times human pediatric exposures at 10 mg, based on AUC.

8.5 Geriatric Use

In the two placebo-controlled clinical studies of Letairis, 21% of patients were ≥65 years old and 5% were ≥75 years old. The elderly (age ≥65 years) showed less improvement in walk distances with Letairis than younger patients did, but the results of such subgroup analyses must be interpreted cautiously. Peripheral edema was more common in the elderly than in younger patients.

8.6 Renal Impairment

The impact of renal impairment on the pharmacokinetics of ambrisentan has been examined using a population pharmacokinetic approach in PAH patients with creatinine clearances ranging between 20 and 150 mL/min. There was no significant impact of mild or moderate renal impairment on exposure to ambrisentan *[see Clinical Pharmacology (12.3)]*. Dose adjustment of Letairis in patients with mild or moderate renal impairment is therefore not required. There is no information on the exposure to ambrisentan in patients with severe renal impairment.

The impact of hemodialysis on the disposition of ambrisentan has not been investigated.

8.7 Hepatic Impairment

Pre-existing Hepatic Impairment

The influence of pre-existing hepatic impairment on the pharmacokinetics of ambrisentan has not been evaluated. Because there is in vitro and in vivo evidence of significant metabolic and biliary contribution to the elimination of ambrisentan, hepatic impairment might be expected to have significant effects on the pharmacokinetics of ambrisentan *[see Clinical Pharmacology (12.3)]*. Letairis is not recommended in patients with moderate or severe hepatic impairment. There is no information on the use of Letairis in patients with mild pre-existing impaired liver function; however, exposure to ambrisentan may be increased in these patients.

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Elevation of Liver Transaminases

Other endothelin receptor antagonists (ERAs) have been associated with aminotransferase (AST, ALT) elevations, hepatotoxicity, and cases of liver failure *[see Adverse Reactions (6.1, 6.2)]*. In patients who develop hepatic impairment after Letairis initiation, the cause of liver injury should be fully investigated. Discontinue Letairis if elevations of liver aminotransferases are >5 x ULN or if elevations are accompanied by bilirubin >2 x ULN, or by signs or symptoms of liver dysfunction and other causes are excluded.

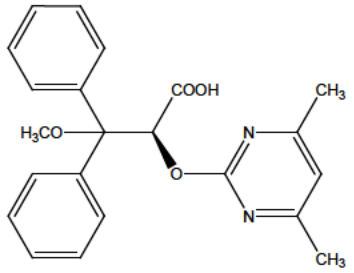
10 OVERDOSAGE

There is no experience with overdosage of Letairis. The highest single dose of Letairis administered to healthy volunteers was 100 mg, and the highest daily dose administered to patients with PAH was 10 mg once daily. In healthy volunteers, single doses of 50 mg and 100 mg (5 to 10 times the maximum recommended dose) were associated with headache, flushing, dizziness, nausea, and nasal congestion. Massive overdosage could potentially result in hypotension that may require intervention.

11 DESCRIPTION

Letairis is the brand name for ambrisentan, an endothelin receptor antagonist that is selective for the endothelin type-A (ET_A) receptor. The chemical name of ambrisentan is (+)-(2*S*)-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropanoic acid. It has a molecular formula of $C_{22}H_{22}N_2O_4$ and a molecular weight of 378.42. It contains a single chiral center determined to be the (*S*) configuration and has the following structural formula:

Figure 1 Ambrisentan Structural Formula



Ambrisentan is a white to off-white, crystalline solid. It is a carboxylic acid with a pKa of 4.0. Ambrisentan is practically insoluble in water and in aqueous solutions at low pH. Solubility increases in aqueous solutions at higher pH. In the solid state ambrisentan is very stable, is not hygroscopic, and is not light sensitive.

Letairis is available as 5 mg and 10 mg film-coated tablets for once daily oral administration. The tablets include the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate and microcrystalline cellulose. The tablets are film-coated with a coating material containing FD&C Red #40 aluminum lake, lecithin, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide. Each square, pale pink Letairis tablet contains 5 mg of ambrisentan. Each oval, deep pink Letairis tablet contains 10 mg of ambrisentan. Letairis tablets are unscored.

12 CLINICAL PHARMACOLOGY

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12.1 Mechanism of Action

Endothelin-1 (ET-1) is a potent autocrine and paracrine peptide. Two receptor subtypes, ET_A and ET_B, mediate the effects of ET-1 in the vascular smooth muscle and endothelium. The primary actions of ET_A are vasoconstriction and cell proliferation, while the predominant actions of ET_B are vasodilation, antiproliferation, and ET-1 clearance.

In patients with PAH, plasma ET-1 concentrations are increased as much as 10-fold and correlate with increased mean right atrial pressure and disease severity. ET-1 and ET-1 mRNA concentrations are increased as much as 9-fold in the lung tissue of patients with PAH, primarily in the endothelium of pulmonary arteries. These findings suggest that ET-1 may play a critical role in the pathogenesis and progression of PAH.

Ambrisentan is a high-affinity (K_i=0.011 nM) ET_A receptor antagonist with a high selectivity for the ET_A versus ET_B receptor (>4000-fold). The clinical impact of high selectivity for ET_A is not known.

12.2 Pharmacodynamics

Cardiac Electrophysiology

In a randomized, positive- and placebo-controlled, parallel-group study, healthy subjects received either Letairis 10 mg daily followed by a single dose of 40 mg, placebo followed by a single dose of moxifloxacin 400 mg, or placebo alone. Letairis 10 mg daily had no significant effect on the QTc interval. The 40 mg dose of Letairis increased mean QTc at t_{max} by 5 ms with an upper 95% confidence limit of 9 ms. For patients receiving Letairis 5–10 mg daily and not taking metabolic inhibitors, no significant QT prolongation is expected.

N-terminal pro-B-type natriuretic peptide (NT-proBNP)

In AMBITION *[see Clinical Studies (14.2)]*, the decrease in NT-proBNP in patients on Letairis plus tadalafil was observed early (Week 4) and was sustained, with a reduction of 63% on Letairis plus tadalafil, 50% on Letairis alone, and 41% on tadalafil alone at Week 24.

12.3 Pharmacokinetics

The pharmacokinetics of ambrisentan (S-ambrisentan) in healthy subjects is dose proportional. The absolute bioavailability of ambrisentan is not known. Ambrisentan is absorbed with peak concentrations occurring approximately 2 hours after oral administration in healthy subjects and PAH patients. Food does not affect its bioavailability. In vitro studies indicate that ambrisentan is a substrate of P-gp. Ambrisentan is highly bound to plasma proteins (99%). The elimination of ambrisentan is predominantly by non-renal pathways, but the relative contributions of metabolism and biliary elimination have not been well characterized. In plasma, the AUC of 4-hydroxymethyl ambrisentan accounts for approximately 4% relative to parent ambrisentan AUC. The in vivo inversion of S-ambrisentan to R-ambrisentan is negligible. The mean oral clearance of ambrisentan is 38 mL/min and 19 mL/min in healthy subjects and in PAH patients, respectively. Although ambrisentan has a 15-hour terminal half-life, the mean trough concentration of ambrisentan at steady-state is about 15% of the mean peak concentration and the accumulation factor is about 1.2 after long-term daily dosing, indicating that the effective half-life of ambrisentan is about 9 hours.

Reference ID: 4357178

Drug Interactions

In Vitro Studies

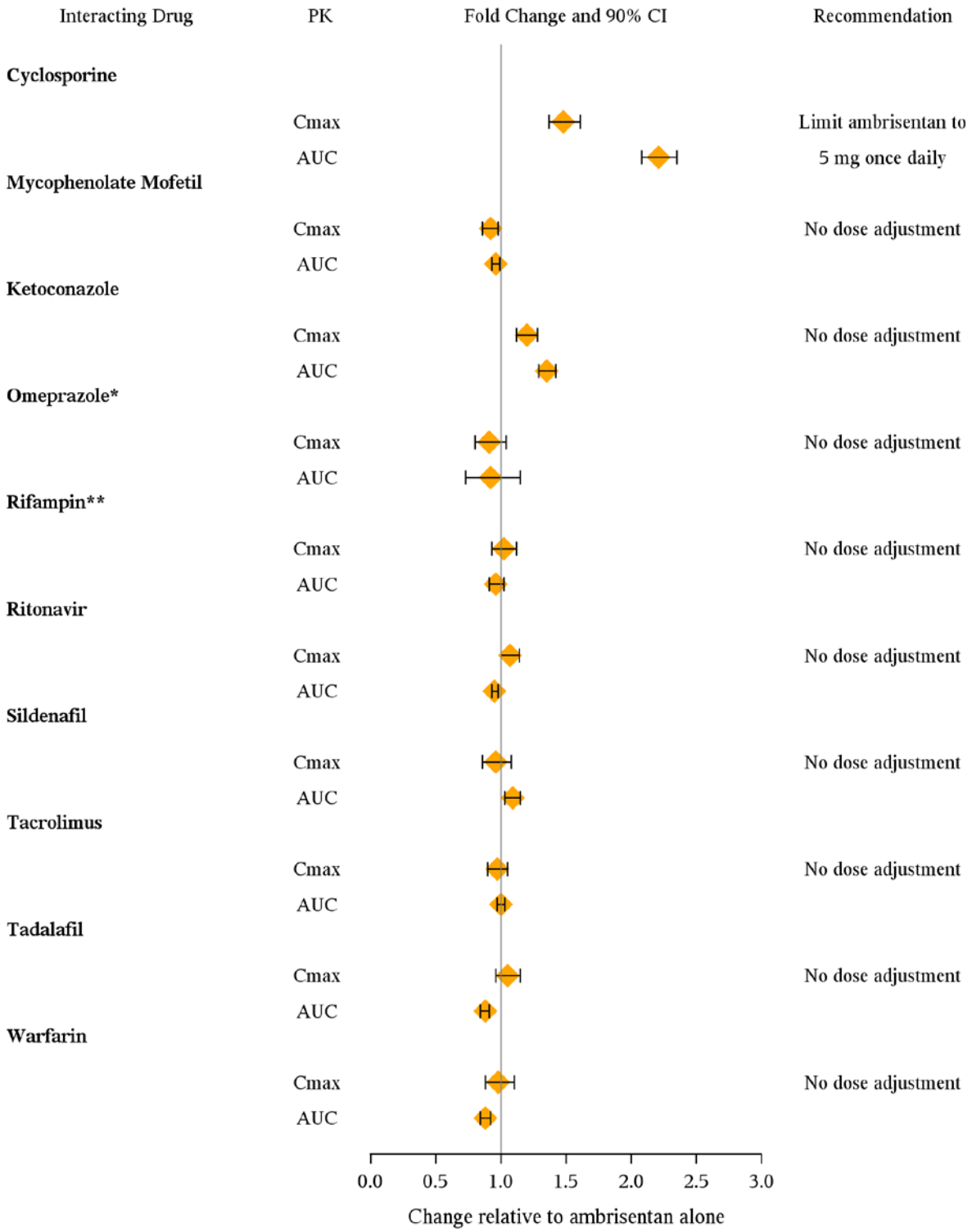
Studies with human liver tissue indicate that ambrisentan is metabolized by CYP3A, CYP2C19, and uridine 5'-diphosphate glucuronosyltransferases (UGTs) 1A9S, 2B7S, and 1A3S. In vitro studies suggest that ambrisentan is a substrate of the Organic Anion Transporting Polypeptides OATP1B1 and OATP1B3, and P-glycoprotein (P-gp). Drug interactions might be expected because of these factors; however, a clinically relevant interaction has been demonstrated only with cyclosporine *[see Drug Interactions (7)]*. In vitro studies found ambrisentan to have little to no inhibition of human hepatic transporters. Ambrisentan demonstrated weak dose-dependent inhibition of OATP1B1, OATP1B3, and NTCP (IC_{50} of 47 µM, 45 µM, and approximately 100 µM, respectively) and no transporter-specific inhibition of BSEP, BRCP, P-gp, or MRP2. Ambrisentan does not inhibit or induce drug metabolizing enzymes at clinically relevant concentrations.

In Vivo Studies

The effects of other drugs on ambrisentan pharmacokinetics and the effects of ambrisentan on the exposure to other drugs are shown in Figure 2 and Figure 3, respectively.

Reference ID: 4357178

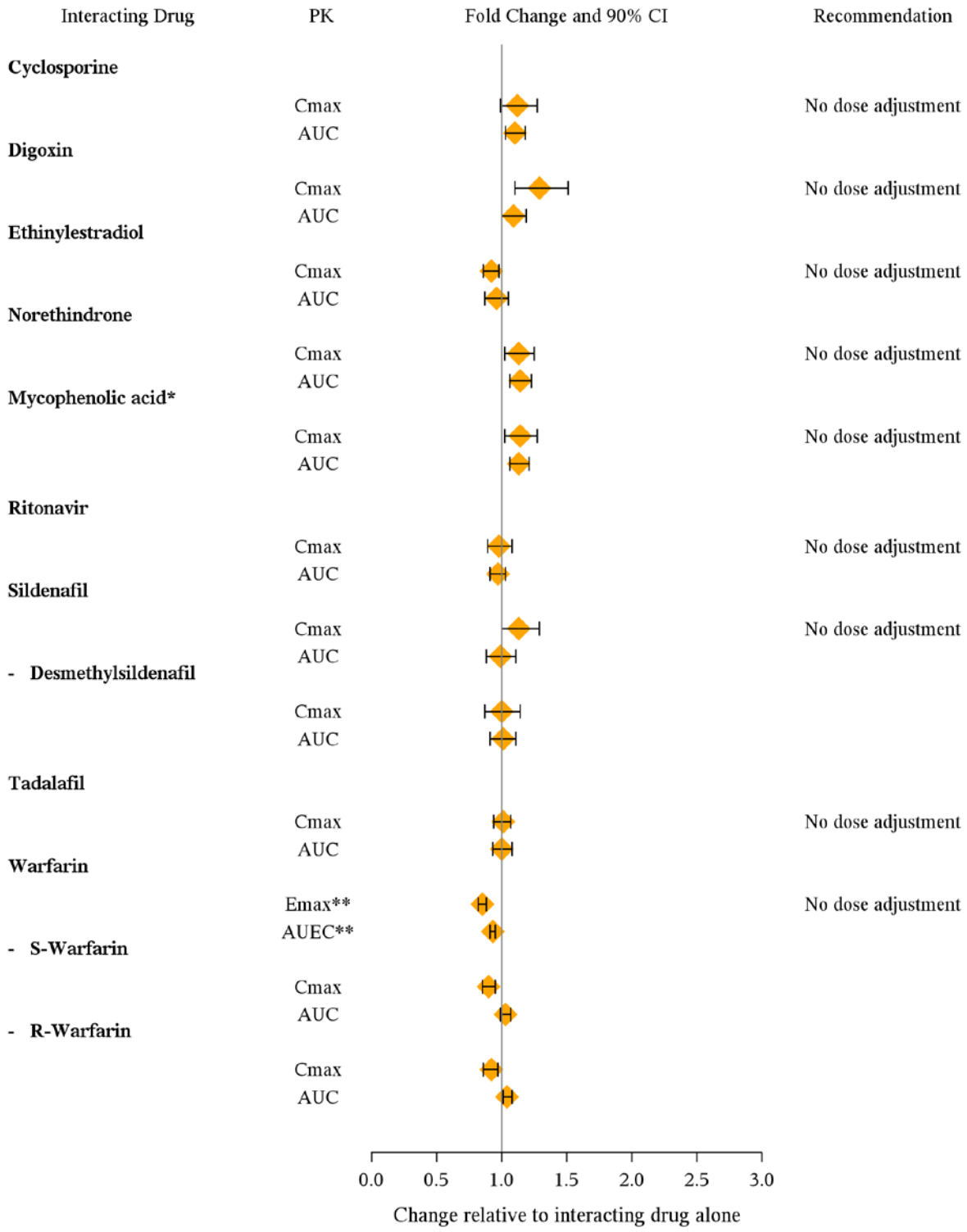
Figure 2 Effects of Other Drugs on Ambrisentan Pharmacokinetics



* Omeprazole: based on population pharmacokinetic analysis in PAH patients

** Rifampin: AUC and C_{max} were measured at steady-state. On Day 3 of coadministration a transient 2-fold increase in AUC was noted that was no longer evident by Day 7. Day 7 results are presented.

Figure 3 Effects of Ambrisentan on Other Drugs



* Active metabolite of mycophenolate mofetil

** GMR (95% CI) for INR

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Oral carcinogenicity studies of up to two years duration were conducted at starting doses of 10, 30, and 60 mg/kg/day in rats (8 to 48 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) and at 50, 150, and 250 mg/kg/day in mice (28 to 140 times the MRHD). In the rat study, the high- and mid-dose male and female groups had their doses lowered to 40 and 20 mg/kg/day, respectively, in week 51 because of effects on survival. The high-dose males and females were taken off drug completely in weeks 69 and 93, respectively. The only evidence of ambrisentan-related carcinogenicity was a positive trend in male rats, for the combined incidence of benign basal cell tumor and basal cell carcinoma of skin/subcutis in the mid-dose group (high-dose group excluded from analysis), and the occurrence of mammary fibroadenomas in males in the high-dose group. In the mouse study, high-dose male and female groups had their doses lowered to 150 mg/kg/day in week 39 and were taken off drug completely in week 96 (males) or week 76 (females). In mice, ambrisentan was not associated with excess tumors in any dosed group.

Positive findings of clastogenicity were detected, at drug concentrations producing moderate to high toxicity, in the chromosome aberration assay in cultured human lymphocytes. There was no evidence for genetic toxicity of ambrisentan when tested in vitro in bacteria (Ames test) or in vivo in rats (micronucleus assay, unscheduled DNA synthesis assay).

The development of testicular tubular atrophy and impaired fertility has been linked to the chronic administration of endothelin receptor antagonists in rodents. Testicular tubular degeneration was observed in rats treated with ambrisentan for two years at doses ≥10 mg/kg/day (8-fold MRHD). Increased incidences of testicular findings were also observed in mice treated for two years at doses ≥50 mg/kg/day (28-fold MRHD). Effects on sperm count, sperm morphology, mating performance, and fertility were observed in fertility studies in which male rats were treated with ambrisentan at oral doses of 300 mg/kg/day (236-fold MRHD). At doses of ≥10 mg/kg/day, observations of testicular histopathology in the absence of fertility and sperm effects were also present.

14 CLINICAL STUDIES

14.1 Pulmonary Arterial Hypertension (PAH)

Two 12-week, randomized, double-blind, placebo-controlled, multicenter studies were conducted in 393 patients with PAH (WHO Group 1). The two studies were identical in design except for the doses of Letairis and the geographic region of the investigational sites. ARIES-1 compared once-daily doses of 5 mg and 10 mg Letairis to placebo, while ARIES-2 compared once-daily doses of 2.5 mg and 5 mg Letairis to placebo. In both studies, Letairis or placebo was added to current therapy, which could have included a combination of anticoagulants, diuretics, calcium channel blockers, or digoxin, but not epoprostenol, treprostinil, iloprost, bosentan, or sildenafil. The primary study endpoint was 6-minute walk distance. In addition, clinical worsening, WHO functional class, dyspnea, and SF-36® Health Survey were assessed.

Patients had idiopathic or heritable PAH (64%) or PAH associated with connective tissue diseases (32%), HIV infection (3%), or anorexigen use (1%). There were no patients with PAH associated with congenital heart disease.

Patients had WHO functional class I (2%), II (38%), III (55%), or IV (5%) symptoms at baseline. The mean age of patients was 50 years, 79% of patients were female, and 77% were Caucasian.

Reference ID: 4357178

Submaximal Exercise Ability

Results of the 6-minute walk distance at 12 weeks for the ARIES-1 and ARIES-2 studies are shown in Table 3 and Figure 4.

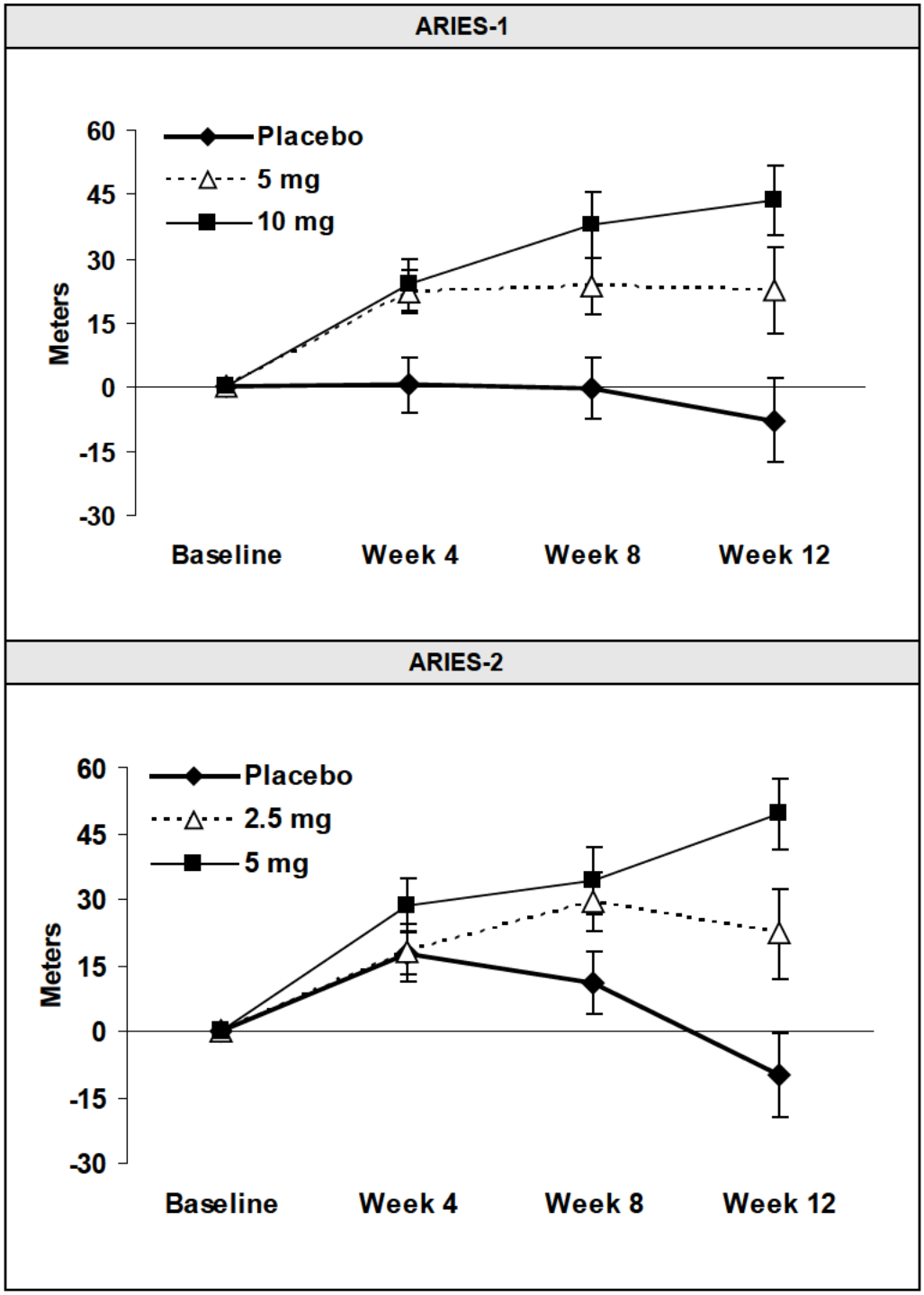
Table 3 Changes from Baseline in 6-Minute Walk Distance (meters) (ARIES-1 and ARIES-2)

	ARIES-1			ARIES-2		
	Placebo (N=67)	**5 mg (N=67)**	**10 mg (N=67)**	**Placebo (N=65)**	**2.5 mg (N=64)**	**5 mg (N=63)**
Baseline	342 ± 73	340 ± 77	342 ± 78	343 ± 86	347 ± 84	355 ± 84
Mean change from baseline	-8 ± 79	23 ± 83	44 ± 63	-10 ± 94	22 ± 83	49 ± 75
Placebo-adjusted mean change from baseline	_	31	51	_	32	59
Placebo-adjusted median change from baseline	_	27	39	_	30	45
p-value[a]	_	0.008	<0.001	_	0.022	<0.001

Mean ± standard deviation

a p-values are Wilcoxon rank sum test comparisons of Letairis to placebo at Week 12 stratified by idiopathic or heritable PAH and non-idiopathic, non-heritable PAH patients

Figure 4 Mean Change in 6-Minute Walk Distance (ARIES-1 and ARIES-2)



Mean change from baseline in 6-minute walk distance in the placebo and Letairis groups.
Values are expressed as mean ± standard error of the mean.

In both studies, treatment with Letairis resulted in a significant improvement in 6-minute walk distance for each dose of Letairis and the improvements increased with dose. An increase in 6-minute walk distance was observed after 4 weeks of treatment with Letairis, with a dose-response observed after 12 weeks of treatment. Improvements in walk distance with Letairis were smaller for elderly patients (age ≥65) than younger patients and for patients with secondary PAH than for patients with idiopathic or heritable PAH. The results of such subgroup analyses must be interpreted cautiously.

Reference ID: 4357178

Clinical Worsening

Time to clinical worsening of PAH was defined as the first occurrence of death, lung transplantation, hospitalization for PAH, atrial septostomy, study withdrawal due to the addition of other PAH therapeutic agents, or study withdrawal due to early escape. Early escape was defined as meeting two or more of the following criteria: a 20% decrease in the 6-minute walk distance; an increase in WHO functional class; worsening right ventricular failure; rapidly progressing cardiogenic, hepatic, or renal failure; or refractory systolic hypotension. The clinical worsening events during the 12-week treatment period of the Letairis clinical trials are shown in Table 4 and Figure 5.

Table 4 Time to Clinical Worsening (ARIES-1 and ARIES-2)

	ARIES-1		**ARIES-2**	
	Placebo (N=67)	**Letairis (N=134)**	**Placebo (N=65)**	**Letairis (N=127)**
Clinical worsening, no. (%)	7 (10%)	4 (3%)	13 (22%)	8 (6%)
Hazard ratio	_	0.28	_	0.30
p-value, Log-rank test	_	0.030	_	0.005

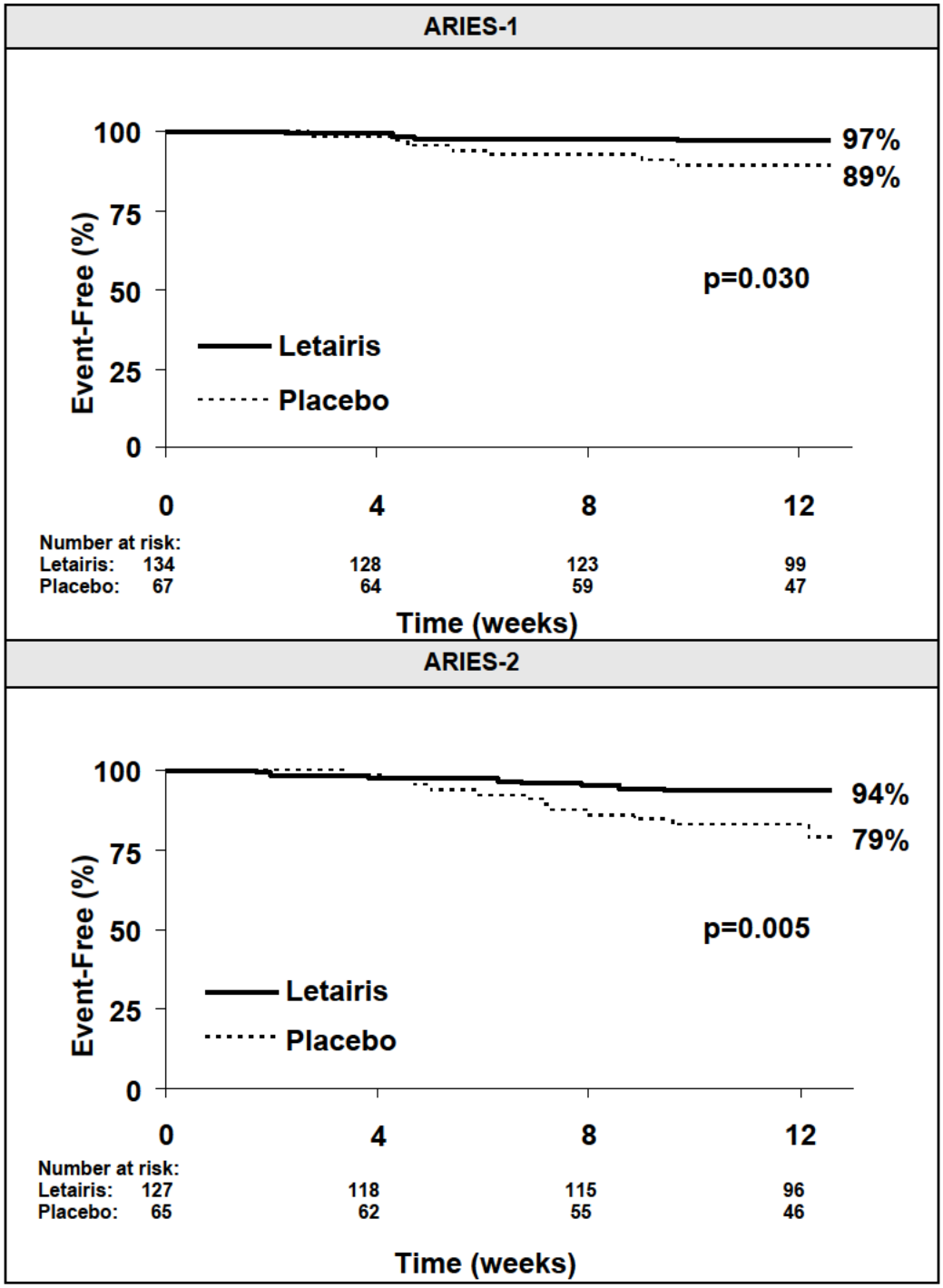
Intention-to-treat population.

Note: Patients may have had more than one reason for clinical worsening.

Nominal p-values

There was a significant delay in the time to clinical worsening for patients receiving Letairis compared to placebo. Results in subgroups such as the elderly were also favorable.

Figure 5 Time to Clinical Worsening (ARIES-1 and ARIES-2)



Time from randomization to clinical worsening with Kaplan-Meier estimates of the proportions of patients without events in ARIES-1 and ARIES-2.

p-values shown are the log-rank comparisons of Letairis to placebo stratified by idiopathic or heritable PAH and non-idiopathic, non-heritable PAH patients.

14.2 Combination Treatment of PAH

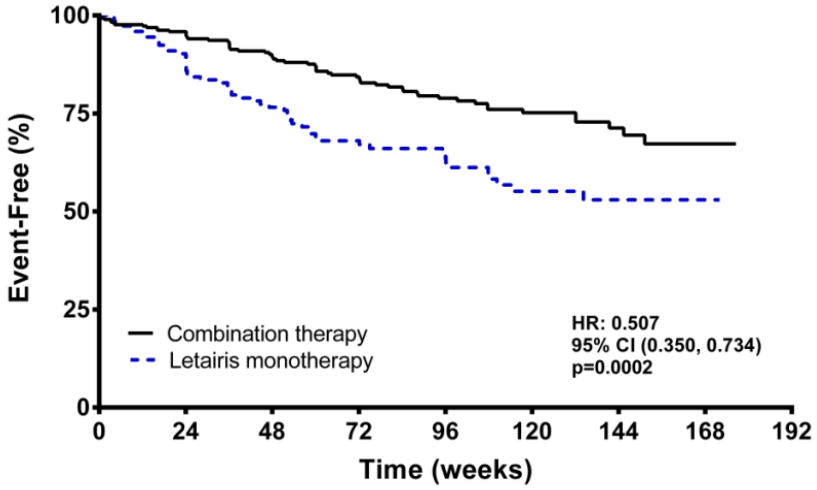
In a randomized, double-blind, active-controlled trial (AMBITION), 605 patients with WHO Functional Class II or III PAH were randomized 2:1:1 to once daily Letairis plus tadalafil or to Letairis or tadalafil alone. Treatment was initiated with Letairis 5 mg and tadalafil 20 mg. If tolerated, tadalafil was increased to 40 mg at 4 weeks and Letairis was increased to 10 mg at 8 weeks.

The primary endpoint was time to first occurrence of (a) death, (b) hospitalization for worsening PAH, (c) >15% decrease from baseline in 6MWD combined with WHO Functional Class III or IV symptoms sustained over 14 days (short term clinical worsening), or (d) reduction in 6MWD sustained over 14 days combined with WHO Functional Class III or IV symptoms sustained over 6 months (inadequate long term clinical response).

Patients had idiopathic PAH (55%), heritable PAH (3%), or PAH associated with connective tissue diseases, congenital heart disease, stable HIV infection, or drugs or toxins (APAH, 43%). Median time from diagnosis to first study drug administration was 25 days. Approximately 32% and 68% of patients were in WHO Functional Class II and III, respectively. The mean patient age was 55.7 years (34% were ≥65 years old). Most patients were white (90%) and female (76%); 45% were North American.

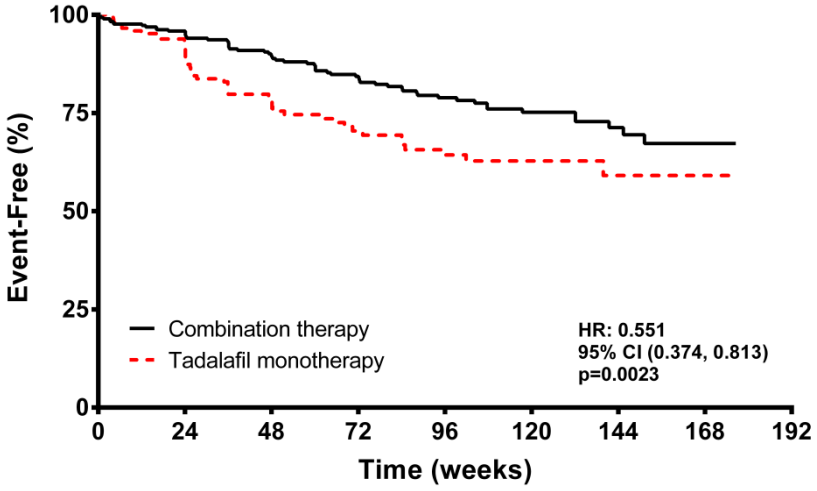
Principal results are shown in Figures 6 and 7.

Figure 6 Time to Primary Endpoint Event (AMBITION)



Number at risk:

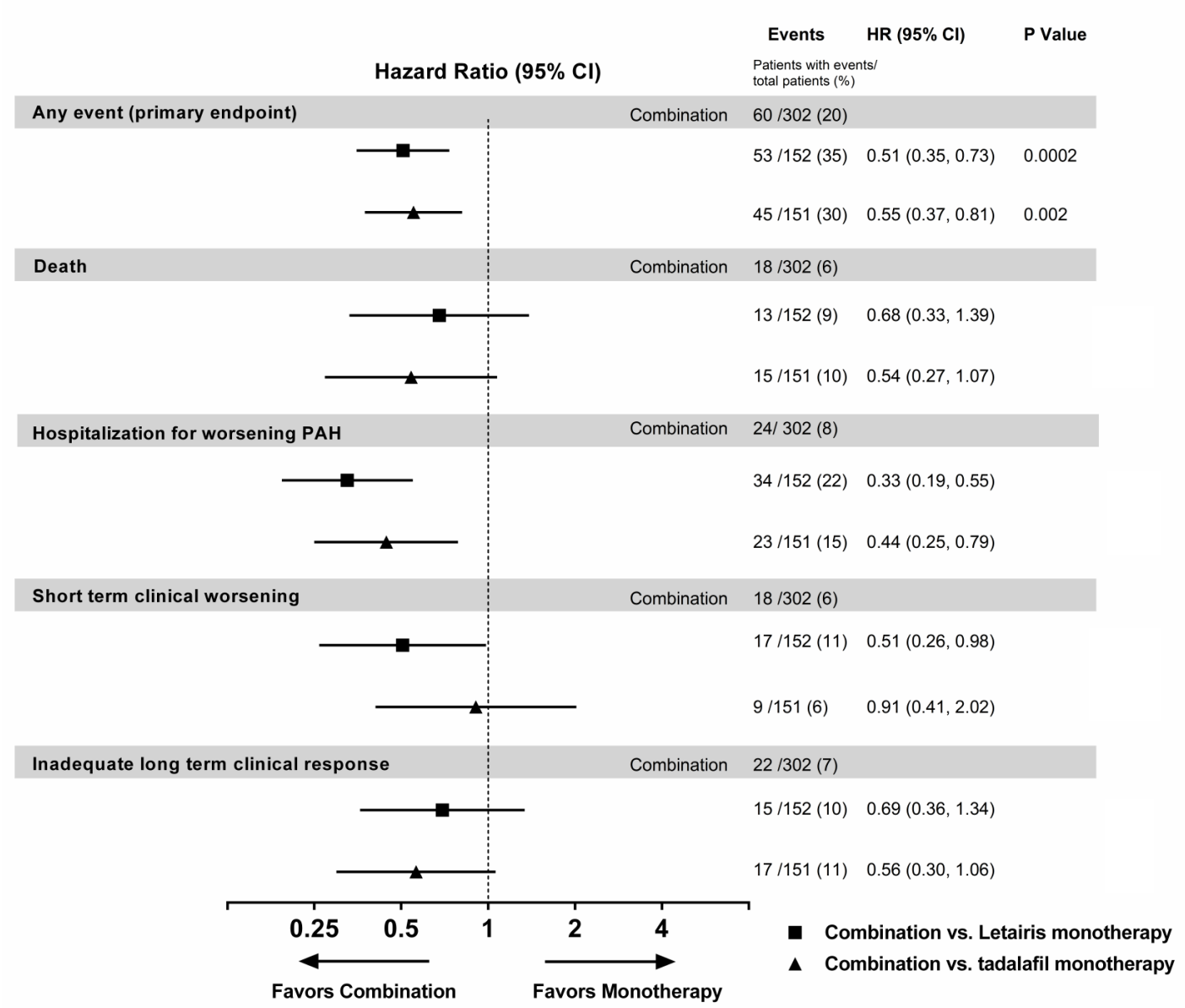
Combination:	302	270	217	170	126	85	45	9
Letairis monotherapy:	152	123	96	71	53	30	17	3



Number at risk:

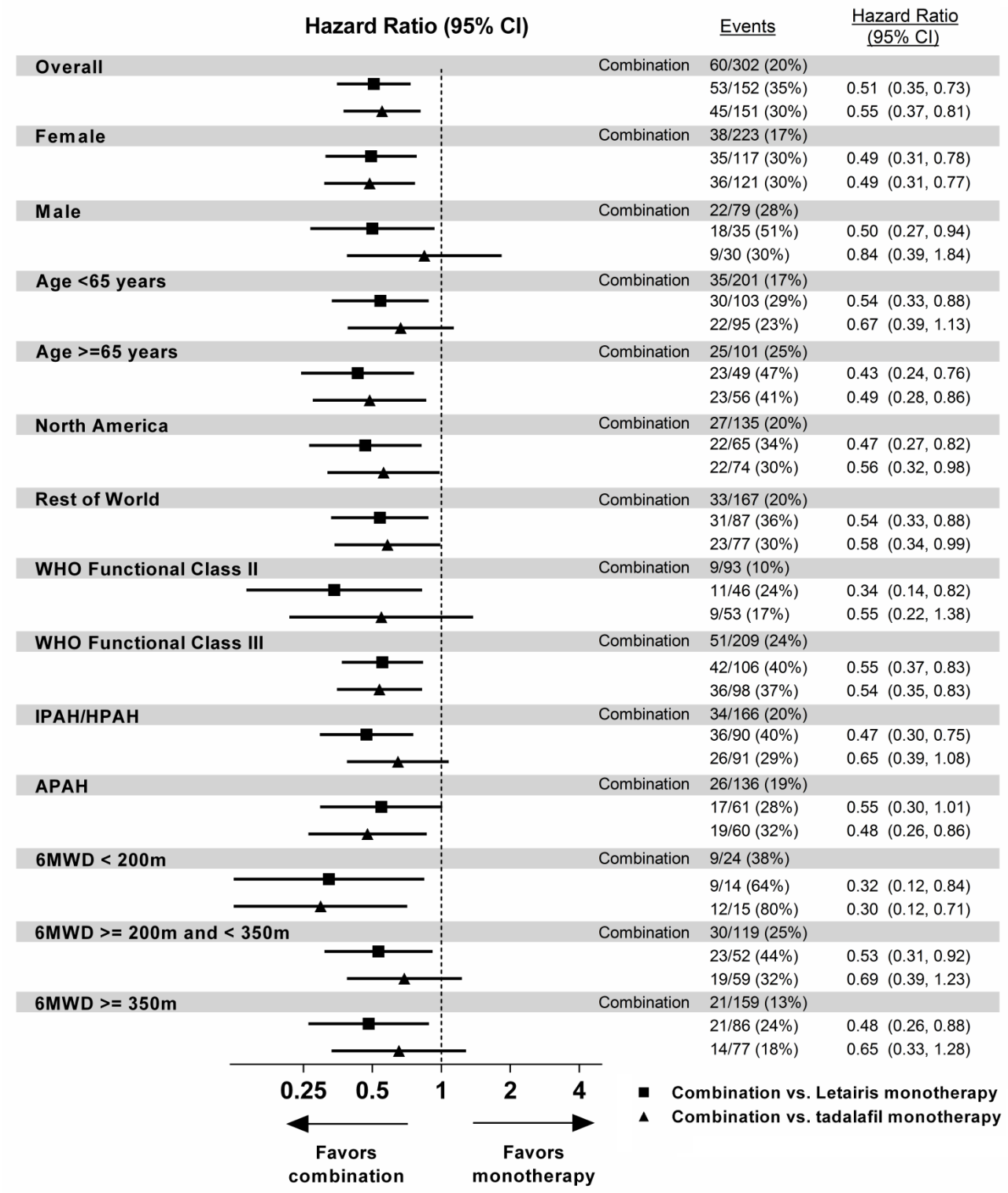
Combination:	302	270	217	170	126	85	45	9
Tadalafil monotherapy:	151	128	92	65	48	33	15	3

Figure 7 Primary Endpoint Events and First Occurrences of Each Component at Any Time (AMBITION)



The treatment effect of Letairis plus tadalafil compared with individual monotherapy on time to first primary endpoint event was consistent across subgroups. (Figure 8).

Figure 8 Primary Endpoint by Subgroups (AMBITION)



Note: The figure above presents effects in various subgroups all of which are baseline characteristics and all of which were pre-specified, if not the groupings. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over interpreted.

Reference ID: 4357178

Exercise Ability

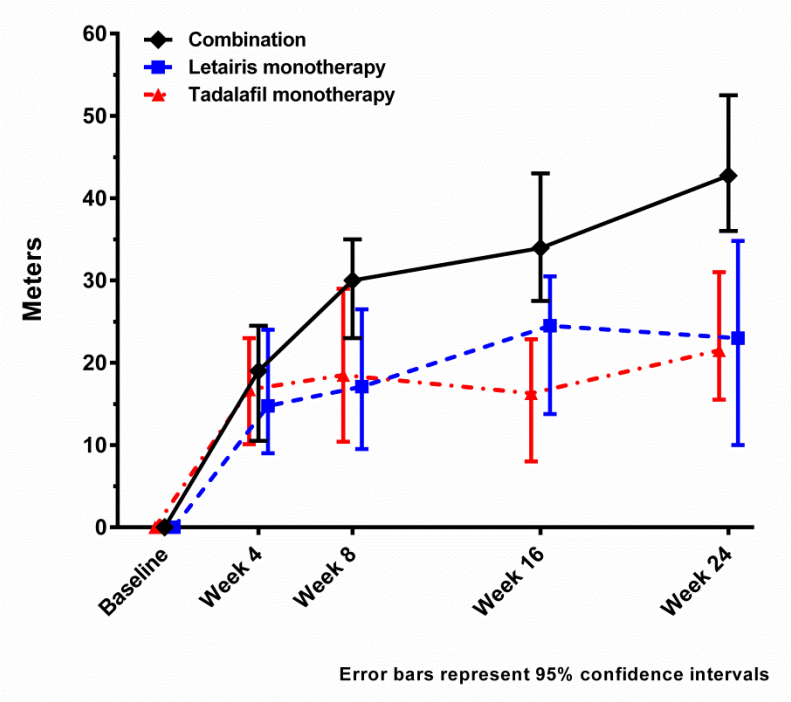
Results of the 6MWD at 24 weeks for the AMBITION study are shown in Table 5 and Figure 9.

Table 5 6-Minute Walk Distance at Week 24 (meters)[a] (AMBITION)

	Letairis + Tadalafil (N=302)	Letairis Monotherapy (N=152)	Tadalafil Monotherapy (N=151)
Baseline (median)	356	366	352
Change from baseline (median)	43	23	22
Median difference from Letairis + Tadalafil (95% CI)		24 (11, 37)	20 (8, 32)
P-Value		0.0004	0.0016

a Missing values at Week 24 were imputed using Worst Rank scores for patients with an adjudicated clinical failure event of death or hospitalization, and Last Observed Carried Forward otherwise.

Figure 9 Median Change in 6-Minute Walk Distance (meters) in AMBITION



14.3 Long-term Treatment of PAH

In long-term follow-up of patients who were treated with Letairis (2.5 mg, 5 mg, or 10 mg once daily) in the two pivotal studies and their open-label extension (N=383), Kaplan-Meier estimates of survival at 1, 2, and 3 years were 93%, 85%, and 79%, respectively. Of the patients who remained on Letairis for up to 3 years, the majority received no other treatment for PAH. These uncontrolled observations do not allow comparison with a group not given Letairis and cannot be used to determine the long-term effect of Letairis on mortality.

14.4 Adverse Effects in Idiopathic Pulmonary Fibrosis (IPF)

A randomized controlled study in patients with IPF, with or without pulmonary hypertension (WHO Group 3), compared Letairis (N=329) to placebo (N=163). The study was terminated after 34 weeks for lack of efficacy, and was found to demonstrate a greater risk of disease progression or death on Letairis. More patients taking Letairis died (8% vs. 4%), had a respiratory hospitalization (13% vs. 6%), and had a decrease in FVC/DLCO (17% vs. 12%) *[see Contraindications (4.2)]*.

16 HOW SUPPLIED/STORAGE AND HANDLING

Letairis film-coated tablets are supplied as follows:

Tablet Strength	Package Configuration	NDC No.	Description of Tablet; Debossed on Tablet; Size
5 mg	30 count blister	61958-0801-2	Square convex; pale pink; "5" on side 1 and "GSI" on side 2; 6.6 mm Square
	30 count bottle	61958-0801-1	
	10 count blister	61958-0801-3	
	10 count bottle	61958-0801-5	
10 mg	30 count blister	61958-0802-2	Oval convex; deep pink; "10" on side 1 and "GSI" on side 2; 9.8 mm x 4.9 mm Oval
	30 count bottle	61958-0802-1	
	10 count blister	61958-0802-3	
	10 count bottle	61958-0802-5	

Store at 25° C (77° F); excursions permitted to 15–30° C (59–86° F) *[see USP controlled room temperature]*. Store Letairis in its original packaging.

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Medication Guide).

Embryo-fetal Toxicity

Instruct patients on the risk of fetal harm when Letairis is used in pregnancy *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]*. Female patients must enroll in the Letairis REMS program. Instruct females of reproductive potential to immediately contact their physician if they suspect they may be pregnant.

Letairis REMS Program

For female patients, Letairis is only available through a restricted program called the Letairis REMS *[see Contraindications (4.1), Warnings and Precautions (5.2)]*. Male patients are not enrolled in the Letairis REMS.

Inform female patients (and their guardians, if applicable) of the following notable requirements:

- All female patients must sign an enrollment form.
- Advise female patients of reproductive potential that they must comply with the pregnancy testing and contraception requirements *[see Use in Specific Populations (8.3)]*.

- Educate and counsel females of reproductive potential on the use of emergency contraception in the event of unprotected sex or known or suspected contraceptive failure.
- Advise pre-pubertal females to report any changes in their reproductive status immediately to their prescriber.

Review the Letairis Medication Guide and REMS educational material with female patients.

A limited number of pharmacies are certified to dispense Letairis. Therefore, provide patients with the telephone number and website for information on how to obtain the product.

Hepatic Effects

Advise patients of the symptoms of potential liver injury and instruct them to report any of these symptoms to their physician.

Hematological Change

Advise patients of the importance of hemoglobin testing.

Other Risks Associated with Letairis

Instruct patients that the risks associated with Letairis also include the following:

- Decreases in sperm count
- Fluid overload

Administration

Advise patients not to split, crush, or chew tablets.

Gilead Sciences, Inc., Foster City, CA 94404

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MARY R SOUTHWORTH
11/30/2018