Telotristat Ethyl, a Tryptophan Hydroxylase Inhibitor for the Treatment of Carcinoid Syndrome

Kulke, et al

DATA SUPPLEMENT

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SUPPLEMENTAL METHODS

Study Design

This study was designed by the academic investigators in collaboration with the representatives of the sponsor, Lexicon Pharmaceuticals, Inc. All the authors contributed to the interpretation of data and the subsequent writing, reviewing, and revision of the manuscript. All the authors vouch for the accuracy and completeness of the reported data and attest that the study conformed to the protocol and statistical analysis plan.

Additional Inclusion/Exclusion Criteria

Patients with urinary 5-hydroxyindoleacetic acid (u5-HIAA) levels above and below the upper limit of normal (ULN; ≤0–15 mg/24 hours) and those with unknown values at baseline were allowed to participate in this study. One patient was classified as u5-HIAA levels >ULN with a value <15 mg/24 hours because a different lab assay with a lower ULN value (≤12 mg/24 hours) was used. Hepatic laboratory values at screening that excluded participation in the study were alanine transaminase (ALT) or aspartate transaminase (AST) ≥5.5 x ULN if the patient had a documented history of hepatic metastases, or ≥2.5 x ULN if not; total bilirubin >1.5 x ULN (unless the patient had a documented history of Gilbert's syndrome); alkaline phosphatase (ALP) ≥5 x ULN if total bilirubin was >ULN (no upper limit on the ALP value if total bilirubin was ≤ULN); and serum creatinine ≥1.5 x ULN.

Patient Randomization

A SAS-generated randomization schedule was generated by INC Research, LLC. Randomization was centralized and stratified by baseline u5-HIAA levels (≤ULN, >ULN, or unknown/uninterpretable). Patients who did not complete the study were not replaced. One patient was originally randomly assigned to telotristat ethyl 500 mg, but due to bruising found upon physical exam (day 1), this patient did not meet the eligibility criteria and the

randomization visit was terminated prior to the patient receiving any study drug. A few days later, this patient was subsequently rescreened, re-enrolled, and randomly assigned a second time to telotristat ethyl 250 mg, triggering a new patient number. The analysis of efficacy and safety of included this patient in the telotristat ethyl 250 mg arm because this was the only treatment administered. Analyses of this patient in the telotristat ethyl 500 mg arm (while never receiving this dosage) or being simultaneously in two study arms (250 mg and 500 mg) were not performed.

Administration of Study Medication

During week 1, dosing was blindly titrated, and patients in the telotristat ethyl groups received 1 telotristat ethyl 250 mg tablet plus 1 placebo tablet 3 times/day (tid); patients in the placebo group received 2 placebo tablets tid. The dosage of telotristat ethyl was escalated to 500 mg tid in the assigned group for the subsequent 11 weeks. In crossover patients, a similar dose titration occurred at the start of the open-label extension (week 13). Patients were instructed to take their assigned study medication with food, tid, spaced approximately 6 hours apart. The minimum allowable somatostatin analog (SSA) dose was octreotide long-acting release (LAR) 30 mg or lanreotide depot 120 mg every 3–4 weeks, except when not tolerated, in which case patients could enter the study at the highest tolerated dose. Compliance with study medication was based on a pill count at each scheduled visit, and patients were deemed compliant if they maintained ≥75% compliance as assessed in both the double blind and open-label extension (OLE) portions of the study.

Screening Period and Scheduled Assessments

Patients receiving stable-dose SSA therapy every 4 weeks entered a screening period of up to 28 days and returned for study visits at weeks 1, 2, 6, 8, and 12. Patients receiving stable-dose SSA therapy every 3 weeks entered a screening period of up to 21 days and returned for study

visits at weeks 1, 3, 6, 9, and 12. Patients on an infusion pump had at least 3 weeks of screening data. The timing of the first dose of study drug was intended to coincide with the patient's regular SSA injection. Following the screening period, patients not meeting the eligibility criteria outlined in the study protocol were excluded from study participation. Patient disposition throughout the study period is outlined in the CONSORT diagram (Fig 1).

Additional Efficacy Assessments

Patients were asked to record the number of cutaneous flushing episodes, abdominal pain/discomfort, stool consistency, frequency and dose of subcutaneous injections of rescue short-acting octreotide, and the urgency to defecate in their daily electronic diaries. Abdominal pain was determined from patient daily diaries in which they were asked to record any abdominal pain on an 11-point scale, from 0 indicating "no pain" and 10 indicating "worst pain ever experienced." Overall and domain scores of the responses to the EORTC QLQ-C30 paper questionnaire were averaged across all time points and at each study visit. Patients were asked to record a description of the average stool consistency for bowel movements (BMs) on the basis of the Bristol Stool Form Scale.[1] The sense of urgency to defecate was evaluated by the answer to the following question: "Have you felt or experienced a sense of urgency or immediate need to pass stool today?"

Additional Safety Assessments

Additional safety assessments included electrocardiograms, assessed at week 12 in the double-blind period and week 48/end of study in the OLE, and symptom-oriented physical assessments every 3–4 weeks. Intensity of adverse events was evaluated by the investigators using 1 of the 3 severity grades as follows: mild – aware of event but easily tolerated; moderate – discomfort enough to cause interference with usual activity; and severe – patient incapacitated or unable to work or perform usual activities.

Pharmacokinetic Analysis

The PK objective was to identify intrinsic and extrinsic factors contributing to variability in telotristat ethyl and LP-778902 exposure, including but not limited to, age, sex, race, body mass index (BMI), renal impairment, and hepatic impairment. Blood samples for the purpose of determining trough levels of telotristat ethyl and LP-778902 (active metabolite) concentrations in plasma. Samples were collected Baseline and weeks 6, 12, 18, 24, 32 (4-week SSA assessment only), 36 (3-week SSA administration only), and 48. Efforts were to be made to schedule these visits in the morning with instructions to the patient to arrive in a fasted state and not to take study drug before the blood was drawn. Additional samples were collected from a subset of patients over a 6-hour timeframe at Baseline and weeks 12, 24, and 48. All available plasma concentration data for telotristat ethyl and LP-778902 were used, where possible, for conducting noncompartmental PK analysis and the population PK modeling.

Statistical Analyses

The statistical testing paradigm determined whether 1 or more telotristat ethyl groups differed from placebo. A Bonferroni multiple comparison procedure with added restriction on the hierarchical testing of the primary and secondary efficacy endpoints within each treatment comparison, applied to the Wilcoxon rank-sum test (WRS), was used to control the overall study Type 1 error rate at 0.05. This was effectively done by setting the (local) family-wise Type 1 error to 0.05 for each endpoint tested and with equally weighted tests, using a per-comparison Type 1 error of 0.025. The latter error rate was used to derive the sample size for the primary endpoint, along with an estimated effect size of –1.5; power was set to 96% in order to detect this difference and effect sizes as small as –0.56 BMs/day. Other assumptions to derive the sample size included a common standard deviation of 1.0 BMs/day and an incidence rate of 20% for early termination. This yielded a sample size of 35 patients per treatment group, or 105 total. This plan was for the number of patients on a stable dose of octreotide therapy at study

entry. At the time, octreotide was the only SSA approved in the United States for patients with neuroendocrine tumors. Randomization was stratified by baseline u5-HIAA level. Hence, the total number of randomized patients was a random variable. Randomly permuted blocks of a fixed size were generated within each stratum of u5-HIAA (normal, elevated, or unknown) to ensure balance among treatment groups.

Efficacy analyses.

The primary analysis of the primary and secondary efficacy endpoints used a two-sample, blocked WRS test. The Hodges–Lehmann estimator was used as a nonparametric measure of treatment effect for each telotristat ethyl versus placebo comparison. For the location shift parameter, 95% and 97.5% confidence limits were estimated; the latter limits reflected use of the Bonferroni testing procedure in controlling for multiplicity. Supplemental analyses were used to assess the impact of distributional assumptions and other baseline variables on the testing and estimation of treatment effects for the primary efficacy endpoint. For all variables measured as counts, a generalized linear model based on a negative binomial process was used. Other supplemental analyses used a mixed-measures repeated model and yielded tests/estimates for treatment comparisons at week 12 (changes in u5-HIAA) or averaged over the 12 weeks (change in abdominal pain). For endpoints other than those listed as the primary and secondary efficacy measures, binomial variables assessing the proportion of patients with a certain outcome were examined with logistic regression supplemented by Pearson's chi square statistic. A blocked WRS test was used for variables measuring the proportion of days or weeks with a certain outcome supplemented by a generalized linear mixed model. All other variables measured on either an ordinal or continuous scale were evaluated using the blocked WRS test and Hodges–Lehmann estimators, supplemented by a mixed model with repeated measures. As previously mentioned, a Bonferroni-based multiple comparison procedure imposing a hierarchical testing strategy controlled the Type I error for the overall study at $\alpha=0.05$. This procedure was applied to test the 2 telotristat ethyl versus placebo comparisons across 1

primary and 3 secondary efficacy endpoints. Within each treatment comparison, the following order was applied: primary endpoint, u5-HIAA, flushing, and abdominal pain. Testing was at $\alpha=0.025$ for each treatment group comparison per endpoint, reflecting a local family-wise Type I error rate = 0.05. Only treatment comparisons achieving statistical significance for all prior endpoints were tested. Once statistical significance was not achieved, testing stopped within that treatment comparison.

All statistical analyses were performed by Lexicon Pharmaceuticals, Inc. or its designees (i.e., contract research organizations) using SAS® (SAS Institute, Inc. Cary, NC, USA) statistical software version 9.3 or higher.

SUPPLEMENTAL RESULTS

Additional Safety Results

Depression cases.

At study entry, 25 (18.5%) patients reported a history of depression, and 8 of 10 (80%) and 5 of 9 (56%) patients in the telotristat ethyl 250 mg and 500 mg groups, respectively, and 2 of 6 (33%) patients in the placebo group were receiving treatment for depression. Of the 3 patients who reported depression in the placebo group while on study, all cases were mild and resolved during the study, and 1 was considered possibly related to study treatment. Additional factors that could have contributed to the reported depression in the placebo group were the recent loss of a spouse for 1 patient and concomitant atenolol treatment in another. In the telotristat ethyl 250 mg group, the single reported depression case was moderate and resolved during the study; disease progression was a potential contributing factor in this case. Of the 6 patients who reported depression in the telotristat ethyl 500 mg group, all cases were mild, and 1 persisted after study completion. Additional factors that could have contributed to the reported depression in this treatment group were 1) underlying depression (2 patients; 1 with concomitant bisoprolol treatment and 1 whose condition resolved with refill of bupropion) or anxiety (2 patients; 1 with increasing abdominal pain and 1 with a close family member was battling terminal cancer), 2) concomitant metoprolol (1 patient), and 3) use of beta blockers (1 patient).

Deaths.

Three deaths in the placebo group occurred in the setting of advanced disease. In the telotristat ethyl 250 mg group, the only death occurred in a female patient (73 years old) with metastatic pancreatic NET who developed cholestasis and disseminated intravascular coagulation. The only death in the telotristat ethyl 500 mg group occurred in a female (60 years old) who had been recently hospitalized for confusion related to pain medication, diarrhea, and dehydration and received a new long-acting opioid medication at discharge. She was found unresponsive 5 days later, and resuscitation was unsuccessful.

Pharmacokinetic Data Analysis

The model of u5-HIAA was a linear model as shown below:

$$u5HIAA_{ij} = Baseline_i + SLP_i \times Cmax,ss_{ij}$$

Where:

$u5HIAA_{ij}$ is the model-predicted u5-HIAA in the *i*th patient at the *j*th exposure;

$Baseline_i$ is the model-predicted baseline for the *i*th individual; SLP_i is an estimated parameter (slope) relating u5-HIAA concentration to individual estimates of *Cmax,ss*; and

$Cmax,ss_{ij}$ is the individual model-predicted *Cmax* of the telotristat ethyl active metabolite at steady state.

The model of BM frequency was an inhibitory *Emax* time-course model as shown below:

$$Emax_i = -1.055 - 0.0004744 \times Cmax_{ij}$$

$$T50_i = 3.741 - 0.0008894 \times Cmax_{ij}$$

$$\text{Weekly BM} = 5.27 + (Emax_i \times Week_{ij})/(T50_i + \text{Week}_{ij})$$

Where:

$Cmax_{ij}$ is the maximum predicted concentration of the telotristat ethyl active metabolite in the *i*th subject at the *j*th week;

Emax is the maximum reduction in BM;

$Emax_i$ is the model-predicted maximum effect for the *i*th subject;

$T50_i$ is the model-predicted time to 50% of the maximum effect for the *i*th subject; and

$Week_{ij}$ is the week corresponding to the bowel movement measurement in the *i*th subject at the *j*th week.

REFERENCES

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