Poster C-22

Safety Analysis of Patients With Neuroendocrine Tumors Receiving Concomitant Treatment With Telotristat Ethyl and Everolimus in Phase 3 TELEPATH Study

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Abstract

Background: Telotristat ethyl (TE) is a tryptophan-hydroxylase 1 (TPH1) inhibitor approved for treatment of carcinoid syndrome diarrhea (CSD) in combination with somatostatin analogues (SSAs) in adults inadequately controlled with SSAs alone.

Methods: Subjects who participated in one of two Phase 2 (NCT00853047, NCT01104415) or two Phase 3 trials (NCT01677910, NCT02063659) investigating safety and efficacy of TE for treatment of CSD were eligible to enroll after completion of the trial into the "Expanded Treatment for Patients With Carcinoid Syndrome Symptoms (TELEPATH)" study (NCT02026063). The primary objective of TELEPATH was to evaluate long-term safety and tolerability of orally administered TE. Patients received treatment with SSAs and TE 500 mg tid, and concomitant antitumor therapies were allowed. We report data on serious treatment-emergent adverse events (TEAEs) observed in 12 patients participating in the TELEPATH study who received concomitant treatment with SSA, TE, and everolimus (EVE).

Results: A total of 12 patients (8 women and 4 men, median age 68 years, range 47 to 82 years) enrolled in TELEPATH (data cut-off date 23 December 2016) and received treatment with EVE at multiple dose levels (2.5, 5, 7.5, and 10 mg). 25 serious TEAEs were reported for 9/12 patients and led to treatment discontinuation in 2 patients. Almost all reported TEAEs (24/25) were considered not-related to treatment, and 1 TEAE was considered to be unlikely related to treatment. Serious TEAEs occurring in >1 patient were abdominal pain and diarrhea. The most common system organ class (SOC) term reported was "gastrointestinal disorders," with 7 TEAEs (28%). The reported serious TEAEs were severe in 52% (13/25) of cases, moderate in 40% (10/25 cases), and mild in 8% (2/25) cases).

Conclusion: Post hoc review of safety in 12 patients treated concomitantly with SSAs, TE, and EVE in the TELEPATH study suggests that the safety profile of the combination is consistent with the known safety profiles of each of the approved therapies.

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Background

- Telotristat ethyl (TE), a small-molecule tryptophan-hydroxylase 1 (TPH) inhibitor that decreases levels of 5-HT and 5HIAA, is approved in the United States and Europe for the treatment of adults with carcinoid system diarrhea inadequately controlled by somatostatin analogue (SSA) therapy.[1-5]
- 5-HT plays an important role in cellular proliferation and angiogenesis, and high levels of 5HIAA and 5-HT are associated with poor prognosis in cancer patients.[6-9]
- Everolimus (EVE), an inhibitor of mammalian target of rapamycin (mTOR), is approved to treat adults with progressive NETs of pancreatic origin, and progressive, well-differentiated, non-functional NETs of gastrointestinal or lung origin that are unresectable, locally advanced, or metastatic.[10]
- The most common adverse events (incidence ≥ 30%) associated with EVE treatment of NET patients are: stomatitis, infections, rash, fatigue, diarrhea, edema, abdominal pain, nausea, fever, asthenia, cough, headache, and decreased appetite.[10]
- This study presents preliminary results from a sub-analysis assessing the safety of patients with NETs who received TE in combination with EVE in the Phase 3 TELEPATH study.

1. Pavel ME, et al. *Endocr Relat Cancer*. 2018;25:309-322. 2. Kulke MH, et al. *J Clin Oncol*. 2017;35(1):14-23. 3. Xermelo® (telotristat ethyl) [prescribing information]. Lexicon Pharmaceuticals, Inc.: The Woodlands, TX; February 2017. 4. U.S. Food & Drug Administration. FDA approves Xermelo for carcinoid syndrome diarrhea. Available at: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm544035.htm. Accessed July 30, 2018. 5. European Medicines Agency. Xermelo. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003937/human_med_002168.jsp&mid=WC0b01ac058001d124. Accessed July 30, 2018. 6. Drozdov I, et al. *Cancer.* 2009; 115(21):4934-4945. 7. Sarrouilhe D, et al. *Curr Mol Med.* 2015;15:62-77. 8. van der Horst-Schrivers AN, et al. *Eur J Cancer.* 2007;43(18):2651-2657. 9. Xia Y, et al. *J Clin Lab Anal.* 2017;32(2):e22263. 10. Afinitor® (everolimus) [prescribing information]. Novartis Pharmaceuticals Corp.: East Hanover, NJ; April 2018.

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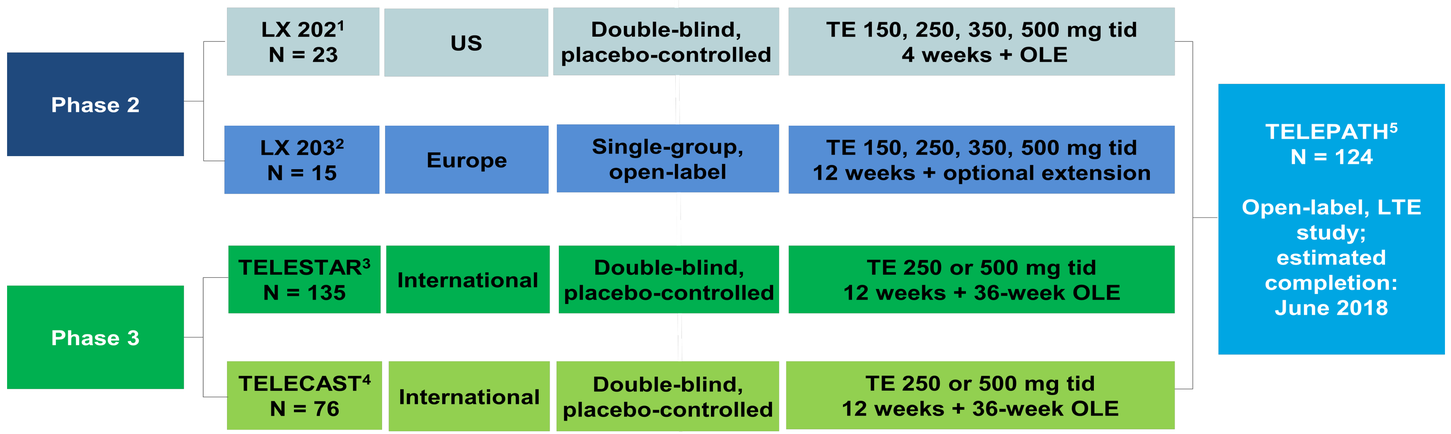
Methods

- CS patients (n = 12) were treated with TE and concomitant EVE (Figure 1 and Table 1).
- Length of treatment with TE at time of TELEPATH enrollment ranged from 36 weeks to 3.9 years.
- The long-term safety of TE was examined, including causes of hospitalization and death. Disease progression was assessed by reviewing adverse events (AEs).
- The data cut-off date was 23 December 2016.

Figure 1: Study Overview



1. Clinicaltrials.gov. NCT00853047. Available at: https://clinicaltrials.gov/ct2/show/NCT00853047. Accessed July 31, 2018. 2. Clinicaltrials.gov. NCT01104415. Available at: https://clinicaltrials.gov/ct2/show/NCT01104415. Accessed July 31, 2018. 3. Clinicaltrials.gov. NCT01677910. Available at: https://clinicaltrials.gov/ct2/show/NCT01677910. Accessed July 31, 2018. 4. Clinicaltrials.gov. NCT02063659. Available at: https://clinicaltrials.gov/ct2/show/NCT02063659. Accessed July 31, 2018. 5. Clinicaltrials.gov. NCT02026063. Available at: https://clinicaltrials.gov/ct2/show/NCT02026063. Accessed July 31, 2018.

Abbreviations: TE, telotristat ethyl; TPH, tryptophan hydroxylase.

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Table 1: Summary of Key Inclusion and Exclusion Criteria

Trial	Inclusion criteria	Exclusion criteria
LX 202[1]	• ≥ 4 BM/day • Receiving stable-dose SSAs	• KPS ≤ 70% • Previous use of TPH inhibitor
LX 203[2]	• ≥ 4 BM/day	• KPS ≤ 70%
TELESTAR[3]	• ≥ 4 BM/day • Receiving stable-dose SSAs	• KPS ≤ 60% • Previous treatment with TE
TELECAST[4]	• < 4 BM/day if on SSAs • If not on SSAs, ≥ 1 sign or symptom of CS	• KPS ≤ 60%
TELEPATH[5]	• Ongoing participation in LX 202, LX 203, TELESTAR, or TELECAST	• Major protocol violation or safety concern from LX 202, LX 203, TELESTAR, or TELECAST

1. Clinicaltrials.gov. NCT00853047. Available at: https://clinicaltrials.gov/ct2/show/NCT00853047. Accessed July 31, 2018. 2. Clinicaltrials.gov. NCT01104415. Available at: https://clinicaltrials.gov/ct2/show/NCT01104415. Accessed July 31, 2018.
3. Clinicaltrials.gov. NCT01677910. Available at: https://clinicaltrials.gov/ct2/show/NCT01677910. Accessed July 31, 2018. 4. Clinicaltrials.gov. NCT02063659. Available at: https://clinicaltrials.gov/ct2/show/NCT02063659. Accessed July 31, 2018.
5. Clinicaltrials.gov. NCT02026063. Available at: https://clinicaltrials.gov/ct2/show/NCT02026063. Accessed July 31, 2018.

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Results

- A total of 12 patients were treated with TE and concomitant EVE and SSAs in TELEPATH (Table 2).
- Patients were treated with EVE at multiple dose levels (2.5, 5, 7.5, and 10 mg.)

Table 2: Summary of Patient Demographics and Selected CS-related Medical History

Patient characteristics	N = 12
Median age, years (range)	68 (47–82)
Male, n (%)	4 (33.3)
Medical history, n (%)[a]	
Carcinoid heart disease[b]	11 (91.7)
Malnutrition	5 (41.7)
Fatigue	5 (41.7)
Weight decreased	2 (16.7)
Ascites	1 (8.3)

[a]Terms as reported by investigators. [b]Includes the preferred terms tricuspid valve incompetence, mitral valve incompetence, carcinoid heart disease, tricuspid valve replacement, carcinoid syndrome, aortic valve incompetence, pulmonary valve incompetence, pulmonary valve replacement, heart valve incompetence, heart valve replacement, tricuspid valve disease, cardiac valve disease, aortic valve disease, aortic valve stenosis, tricuspid valve stenosis, and mitral valve repair.

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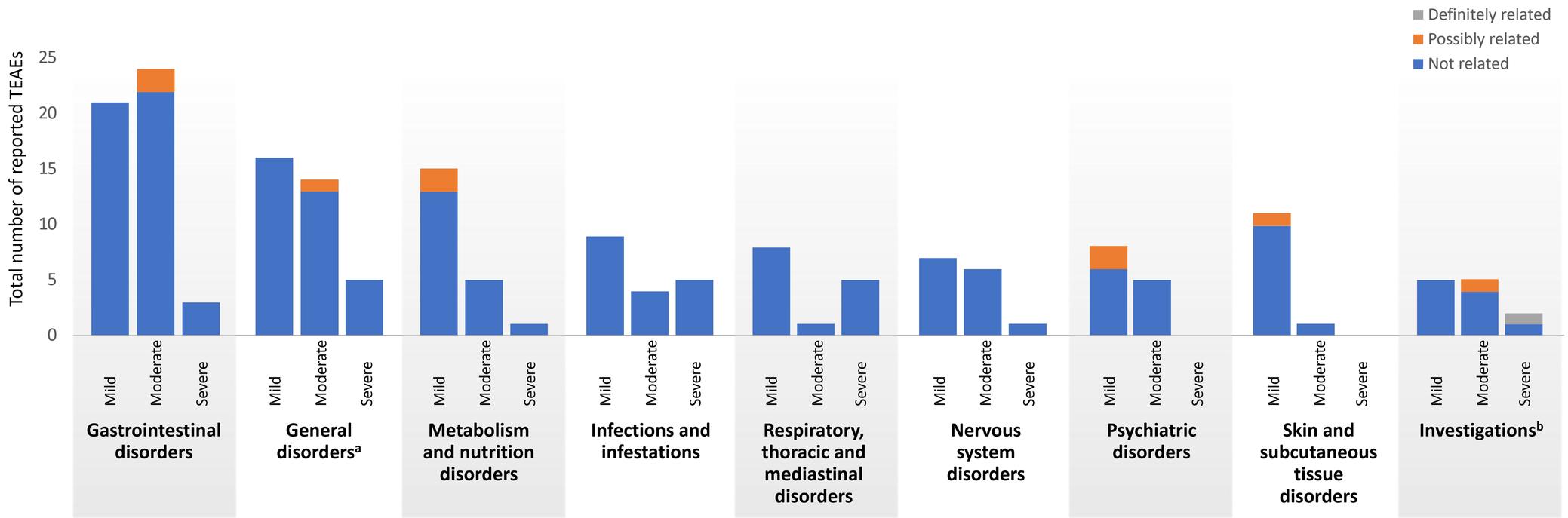
Results

Figure 2: TEAEs Experienced >10 Times in the Total Cohort by System Organ Class, Severity, and Treatment Relatedness



[a]Includes the preferred terms disease progression, general physical health deterioration, pyrexia, death, asthenia, complication of device insertion, fatigue, multi-organ failure, and pain. [b]Includes the preferred terms blood magnesium decreased, cardiac murmur, coagulation time prolonged, C-reactive protein increased, electrocardiogram QT prolonged, hepatic enzyme increased, skin turgor decreased, weight decreased, white blood cell count increased.

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Table 3: Moderate and Severe TEAEs Experienced by Each Patient During Concomitant Treatment

Patient	TE + EVE treatment duration, days	Adverse events (*severity*)	Patient	TE + EVE treatment duration, days	Adverse events (*severity*)
0001-010	15	• Constipation (*moderate*)	0601-005	41	• Fatigue (*moderate*) • Mucosal inflammation (*moderate*) • Pyrexia (*moderate*) • Vomiting (*severe*)
0101-005	20	• Abdominal pain lower (*moderate*) • Diarrhea (*moderate*) • Small intestinal obstruction (*moderate*)	0802-003	11	• None reported
0106-002	136	• Edema peripheral (*moderate*) • Hypomagnesemia (*moderate*) • Hyperglycemia (*severe*)	1201-002	Unknown	• None reported
0108-004	35	• Esophageal stenosis (*moderate*)	2704-501	407	• Abdominal pain (*moderate*) • Diarrhea (*moderate*) • Edema peripheral (*moderate*) • Pyrexia (*moderate*) • Respiratory tract infection (*moderate*) • Asthenia (*moderate and severe*)
0601-001	168	• Edema peripheral (*moderate*) • Diarrhea (*severe*) • General health deterioration (*severe*)			

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Table 3: Moderate and Severe TEAEs Experienced by Each Patient During Concomitant Treatment (continued)

Patient	TE + EVE treatment duration, days	Adverse events (*severity*)	
0108-003	Treatment ongoing	• Carcinoid tumor (*severe*)	
0108-007	Treatment ongoing	• Brain malformation (*moderate*) • Hemorrhage (*moderate*) • Hypotension (*moderate*) • Ileus (*moderate*) • Mental status changes (*moderate*) • Wound infection (*moderate*) • Acute hepatic failure (*severe*) • Anastomotic leak (*severe*) • Aspiration (*severe*) • Carcinoid crisis (*severe*) • Cardiac arrest (*severe*) • Cardiomyopathy (*severe*) • Coagulation time prolonged (*severe*) • Colitis ischemic (*severe*)	• Emphysema (*severe*) • Ileostomy (*severe*) • Leukopenia (*severe*) • Neutropenia (*severe*) • Non-cardiac chest pain (*severe*) • Pelvic abscess (*severe*) • Pleural effusion (*severe*) • Presyncope (*severe*) • Pyrexia (*severe*) • Renal failure acute (*severe*) • Respiratory failure (*severe*) • Sepsis (*severe*) • Septic shock (*severe*) • Tachycardia (*severe*)
0201-501	Treatment ongoing	• None reported	

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Results

- Most serious TEAEs (24/25) were classified by investigators as not related to study treatment; 1/25 serious TEAEs (*Campylobacter* gastroenteritis infection) was classified as unlikely related to treatment (Table 4).
- Serious TEAEs led to treatment discontinuation in 2 patients.
- There were no serious TEAEs that led to death.
- The following serious TEAEs of interest were reported once:
  - Ascites
  - Constipation
  - Intestinal obstruction
  - Pyrexia
  - Decreased appetite

Table 4: Serious TEAEs[a] Experienced >1 Time in the Total Cohort by System Organ Class and Severity

System organ class, preferred term, n (%)	Mild	Moderate	Severe	Total
Total serious TEAEs	2 (8)	10 (40)	13 (52)	25 (100)
Gastrointestinal disorders	2 (8)	3 (12)	2 (8)	7 (28)
Abdominal pain	1 (4)	0	1 (4)	2 (8)
Diarrhea	1 (4)	1 (4)	0	2 (8)
General disorders and administration site conditions[b]	0	2 (8)	1 (4)	3 (12)
General physical health deterioration	0	1 (4)	1 (4)	2 (8)
Infections and infestations	0	0	3 (12)	3 (12)
Nervous system disorders	0	2 (8)	0	2 (8)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)[c]	0	0	2 (8)	2 (8)

[a]Leading to hospitalization and/or death. [b]Includes the preferred terms disease progression, general physical health deterioration, pyrexia, death, asthenia, complication of device insertion, fatigue, multi-organ failure, and pain. [c]Includes preferred terms related to tumor progression.

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Summary & Conclusions

- The majority of TEAEs were mild or moderate and classified by investigators as not related to study treatment.
- Serious TEAEs led to treatment discontinuation in 2 patients.
- There were no serious TEAEs that led to death.
- Preliminary review of the safety of TE with concomitant EVE and SSAs in 12 patients suggests that the safety profile of the combination is consistent with the known safety profiles of each of the approved therapies.

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Acknowledgments

We thank the patients and investigators for participating in the study. We thank Rebecca Bigelow from Truposha, LLC (Publication Practice Counsel™) with funding from Lexicon Pharmaceuticals, Inc., for writing assistance in the preparation of this poster. TELEPATH was sponsored by Lexicon Pharmaceuticals, Inc.

Disclosures

RP-O, PB, SJ, ET, PT, and PL: employees of Lexicon Pharmaceuticals, Inc.

Presented at the NANETS 2018 Annual Symposium; October 4-6, 2018; Seattle, WA. **Address correspondence to:**

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