Survival and Clinical Outcomes with Telotristat Ethyl in Patients with Carcinoid Syndrome

**Purpose:** The TELEACE study showed reductions in tumor size in patients with neuroendocrine tumors, receiving telotristat ethyl in US clinical practice. Here, we report progression-free survival, time to tumor progression, changes in carcinoid syndrome symptoms, and indicators of overall health.

**Patients and Methods:** This was a retrospective, single-arm, pre-post medical chart review of patients with locally advanced or metastatic neuroendocrine tumors and documented carcinoid syndrome receiving telotristat ethyl for at least 6 months. Patients with poorly differentiated tumors, mixed tumor types or conflicting clinical trial enrollment were excluded. Descriptive statistics, Kaplan–Meier and chi-square tests were used to evaluate PFS, tumor progression, changes in symptoms, body weight and ECOG performance status before and after telotristat ethyl initiation. Subgroup analyses were conducted in patients with the same pre- and post-telotristat ethyl background treatment.

**Results:** Anonymized data for 200 patients were provided by 114 physicians; patients received telotristat ethyl for a median of 9 months. Median time to tumor progression was 39.8 months (IQR, 18.7–39.8); most had no tumor progression at 6 (92%) and 12 months (87%). Median progression-free survival was 23.7 months (17.8–39.8); most had progression-free survival at 6 (90%) and 12 months (80%). Results were consistent in the subgroup of 65 patients with the same pre/post background treatment. Nearly all patients had improved carcinoid syndrome symptoms, stable or improved weight and ECOG performance status.

**Conclusion:** Patients showed improvements in clinical outcomes and indicators of overall health following treatment with telotristat ethyl in this exploratory pilot study, consistent with previously observed reductions in tumor size.

**Keywords:** neuroendocrine tumors, carcinoid syndrome, telotristat ethyl, survival

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**Introduction**

Elevated systemic serotonin has proliferative effects on bladder cancer cells in culture and is associated with increased 1-year mortality in patients with NETs and the carcinoid syndrome (CS).\(^1\)\(^2\) The tryptophan hydroxylase enzyme TPH1 is a rate-limiting step in serotonin synthesis along with decarboxylase\(^3\) and has been associated with tumor size and tumor growth in animal models.\(^4\)\(^5\)\(^6\)

Telotristat ethyl (TE, Xermelo™, Lexicon Pharmaceuticals, Inc., The Woodlands, TX, USA) is a TPH inhibitor that reduces peripheral serotonin production and is approved for the treatment of carcinoid syndrome diarrhea (CSD) in combination with a somatostatin analog (SSA) for adults with NETs whose CSD is inadequately controlled by SSA therapy.\(^6\) TE has demonstrated improvement in CSD and CS symptoms in clinical trials\(^8\)\(^10\) and real-world clinical practice studies.\(^11\)\(^12\)
Considering the mechanism of TE therapeutic activity and its indication for use with an SSA, it would be of interest to understand the potential impact of TE treatment on tumor growth and clinical outcomes in the clinical practice setting. The SSAs lanreotide (Somatuline® Depot, Ipsen Biopharmaceuticals, Inc., Cambridge, MA, USA) and long-acting octreotide (Sandostatin® LAR Depot, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA) have shown therapeutic effect on tumor progression and survival, supporting their use in first-lineNET treatment. Lanreotide showed significantly improved progression-free survival (PFS) compared with placebo in the pivotal CLARINET trial after 24 months (65% vs 33%, respectively). Primary findings from the pivotal PROMID trial for octreotide showed significantly longer time to tumor progression with long-acting octreotide compared with placebo (14.3 vs 6 months; HR, 0.34; 95% CI, 0.20–0.59) and more patients with stable disease after 6 months (66.7% vs 37.2%). Though tumor progression endpoints have been correlated with overall survival (OS), long-term findings from PROMID have not shown a difference in OS compared with placebo.

The TELEACE retrospective medical chart review pilot study has shown a reduction in tumor size among patients with NETs receiving TE in US clinical practice. Longitudinal analysis showed an 8.5% reduction in tumor size associated with TE and independent of other NET treatments with or without SSA therapy. Here we report prespecified secondary clinical outcomes measured alongside changes in tumor size from the TELEACE study, including time to tumor progression, PFS, CS symptoms, and indicators of overall health for patients with NETs.

**Patients and Methods**

**Design and Patients**

TELEACE is a retrospective, single arm, pre-post physician panel-based medical chart review of patients with NETs receiving TE for at least 6 months. The design and methods of the TELEACE study have been reported previously. Adults with unresectable locally advanced or metastatic NETs and evidence of CS documented in their medical chart were eligible for inclusion if they had received TE for at least 6 months and had any additional CS and NET treatment information available for at least 6 months after TE initiation or until death. The presence of CS was based on the participating physician’s assessment of information contained in the medical charts. Participating physicians were recruited by a professional recruiting organization (Dynata, Plano, TX, USA) and had to have treated at least one eligible patient with TE in the past 12 months in order to participate. Eligible records had to have documented tumor size and tumor response assessments before and after TE initiation, including at least two radiological scans in the 12 months before TE and at least one scan after TE initiation. Patients with a histologically poorly differentiated NET based on grade (G3) or Ki67 index >20%, mixed tumor types according to physician notes, or documented enrollment in any clinical trial during the 6 months after TE initiation were excluded.

Patients’ medical records remained anonymized throughout the study, and the physicians and the study sponsor remained blinded to the other’s identity. The New England Independent Review Board reviewed the study protocol and electronic case report form and determined the study to be exempt from IRB review due to the retrospective observational nature, with a waiver of participant consent for records research. The study was conducted in compliance with the principles set forth by the Declaration of Helsinki and further actions were taken to ensure patient privacy and confidentiality. A randomization scheme was implemented during chart abstraction where a random sequence of letters was generated to determine the selection of each medical chart for review; the letters were not retained or recorded. An automatically generated date shift (addition or subtraction of a randomly generated number of days) was assigned to each patient to further preserve the de-identification of collected data.

**Outcomes**

Time to tumor progression was defined as the time from TE initiation to the first documented tumor progression in the medical chart. Patients who did not experience tumor progression were censored at their last radiological scan. PFS was defined as the time from TE initiation to tumor progression or death. Patients who did not experience tumor progression or death were censored at last follow-up. Physician-assessed changes in body weight, Eastern Cooperative Oncology Group (ECOG) Performance Status, and CS symptoms including diarrhea, flushing, abdominal pain, nausea and ascites were abstracted from medical charts before and after TE initiation.

**Statistical Analysis**

Sample size and power calculation details for the primary endpoint have been reported previously. In order to evaluate the effect of TE treatment on secondary clinical
Table 1 Demographic and Clinical Characteristics

| Characteristic, n (%) Unless Noted | Patients (n = 200) |
|-----------------------------------|-------------------|
| Age at TE initiation, mean (SD)   | 60.6 (10.2)       |
| Male                              | 113 (57)          |
| Race                              |                   |
| White                             | 148 (74)          |
| Black or African American         | 35 (18)           |
| Asian                             | 13 (7)            |
| Native American or American Indian| 3 (2)             |
| Unknown/not sure                  | 3 (2)             |
| Ethnicity                         |                   |
| Hispanic                          | 24 (12)           |
| Non-Hispanic                      | 176 (88)          |
| NET histologic differentiation    |                   |
| Well differentiated               | 122 (61)          |
| Moderately differentiated         | 78 (39)           |
| Primary site of tumor             |                   |
| Pancreas                          | 52 (26)           |
| Small bowel                       | 35 (18)           |
| Lung, bronchus, larynx, trachea, other respiratory organs | 19 (10) |
| Stomach                           | 16 (8)            |
| Jejunum                           | 16 (8)            |
| Duodenum                          | 13 (7)            |
| Ileum                             | 13 (7)            |
| Appendix                           | 9 (5)             |
| Colon                             | 8 (4)             |
| NET of unknown primary origin     | 8 (4)             |
| Small bowel mesentery             | 7 (4)             |
| Cecum                             | 3 (2)             |
| Rectum                            | 1 (1)             |
| ECOG Performance Status prior to TE initiation |                   |
| 0                                 | 61 (31)           |
| 1                                 | 111 (56)          |
| 2                                 | 26 (13)           |
| Unknown/not sure                  | 2 (1)             |
| Patients receiving SSA treatment  |                   |
| Octracetide, long-acting          | 66 (69)           |
| Lanreotide                        | 28 (29)           |
| Octracetide, short-acting or rescue| 5 (5)        |
| Pasireotide                       | 0                 |
| Patients receiving non-SSA NET treatment |           |
| Before TE, (n=35)                 | 12 (34)           |
| Liver-directed therapy (non-surgical) | 9 (17)    |
| Surgery                           | 13 (34)           |
| Chemotherapy                      | 15 (29)           |
| Targeted therapy                  | 13 (25)           |
| Interferon                        | 5 (10)            |
| Other therapy†                     | 2 (6)             |
| After TE, (n=52)                  | 6 (17)            |
| ECOG Status before TE initiation  |                   |
| None                              |                   |
| 1                                 | 1                 |
| 2                                 | 2                 |
| 3                                 | 1                 |

Notes: Percentages may not sum to 100% due to multiple treatments per patient or due to rounding; †Other therapies included peptide-receptor radionuclide therapy (Lu-177), external beam radiation, and peptide-receptor radionuclide therapy (yttrium-90).

Table 2 Time to Tumor Progression and Progression-Free Survival (Overall Population)

| Outcome | Events | Patients at Risk | Patients Without Outcome (%) |
|---------|--------|------------------|------------------------------|
| Tumor progression |        |                  |                              |
| 6 months | 12     | 83               | 92%                          |
| 12 months| 16     | 34               | 87%                          |
| 18 months| 18     | 13               | 78%                          |
| Progression-free survival |        |                  |                              |
| 6 months | 16     | 83               | 90%                          |
| 12 months| 23     | 34               | 80%                          |
| 18 months| 25     | 13               | 72%                          |

Note: Kaplan-Meier method estimated time to tumor progression and progression-free survival in the post-TE period.

Table 3 Time to Tumor Progression and Progression-Free Survival (Treatment Subgroup, n=65)

| Outcome | Events | Patients at Risk | Patients Without Outcome (%) |
|---------|--------|------------------|------------------------------|
| Tumor progression |        |                  |                              |
| 6 months | 0      | 27               | 100%                         |
| 12 months| 2      | 7                | 90%                          |
| 18 months| 2      | 5                | 90%                          |
| Progression-free survival |        |                  |                              |
| 6 months | 1      | 27               | 97%                          |
| 12 months| 3      | 7                | 88%                          |
| 18 months| 3      | 5                | 88%                          |

Note: Kaplan-Meier method estimated time to tumor progression and progression-free survival in the post-TE period.

Results

One hundred and fourteen physicians, predominantly oncologists (98%) from community practices (62%),

outcomes, analyses were conducted in the overall population and in a subgroup of patients who had the same documented non-TE NET treatment before and after TE initiation. Descriptive statistics summarized patient demographic and clinical characteristics, and changes in body weight and ECOG Performance Status after TE treatment initiation. Kaplan-Meier analyses estimated median time to tumor progression and median PFS. Chi-square test evaluated changes in documented CS symptoms (improved vs same/worsened) before and after TE initiation. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NET, neuroendocrine tumor; SD, standard deviation; SSA, somatostatin analog; TE, telotristat ethyl.
provided anonymized, abstracted medical record data. Data were provided from a median of 1.0 (IQR, 1–2) individual patient charts per physician.

Of the 200 study patients, most had a gastrointestinal primary tumor site and well-differentiated NETs (both 61%; Table 1). Patients received TE for a median of 9 months, and 82% were still receiving TE at the time of data collection. Sixty-five patients comprised a subgroup of those with the same NET treatment in the pre- and post-TE periods, with a median 7.7 months of TE treatment. This group was analyzed separately as well because of the potential to investigate the pure effect of TE therapy alone.

### Time to Tumor Progression and Progression-Free Survival

The median time to tumor progression in the overall population was 39.8 months (IQR: 18.7, 39.8; Table 2). The majority of patients had no tumor progression at 6 months (92%), 12 months (87%) and 18 months (78%) after TE initiation. The median PFS was nearly 2 years at the time of data collection (23.7 months; IQR: 17.8, 39.8). Most patients had PFS at 6 months (90%), 12 months (80%) and 18 months (72%) after TE initiation. Results for PFS and time to tumor progression in the subgroup of patients with the same NET and CS background treatments

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### Figure 1

Changes in CS symptoms during the post-TE treatment period. (A) Overall population (n=200). (B) Same NET treatment subgroup (n=65).

**Note:** *P* values are for differences between the proportions of patients with improved vs no change or worsened symptoms.

**Abbreviations:** CS, carcinoid syndrome; NET, neuroendocrine tumor; TE, telotristat ethyl.
(n=65) were slightly more favorable but generally consistent with those of the overall population (Table 3).

Changes in CS Symptoms, Body Weight and ECOG Performance Status

The majority of patients had improved CS symptoms in the post-TE period, both in the overall population and in the subgroup of patients with the same NET treatment before and after TE (shown in Figure 1). Body weight and ECOG Performance Status were improved or unchanged for most patients in both the overall population and the same NET treatment subgroup (shown in Figure 2).

Discussion

This report presents the secondary clinical outcomes from the TELEACE study, which has shown reductions in tumor size with TE independent of background NET treatment.17 We observed positive outcomes related to tumor progression and PFS along with improved clinical outcomes in patients with advanced NETs receiving TE in US clinical practice. Most patients had no tumor progression and had PFS through 18 months of follow-up after starting TE. Patients showed significant improvements in CS symptoms and clinical indicators of overall health after an average of 12 months of TE treatment. Findings were consistent for the overall population and a subgroup of patients with the same NET treatments before and after TE initiation, to ascertain the effect of TE treatment alone. At the time of TE initiation, the majority of patients were classified as having stable or improving tumor status by physician assessment, which was consistent with the expected use of TE in clinical practice.17,18 Our finding that TE may have antiproliferative effects and improve clinical outcomes is notable in this setting.

Improvements in CS symptoms and health indicators were consistent with those from other real-world studies of TE.11,12,19 The TELEPRO real-world study showed improvements in CS symptoms through 3 months of TE treatment, including improvements among those with a relatively low burden of CSD (<3 daily bowel movements).11,19 The RELAX registry showed 75% of patients to have maintained or gained weight after 6 months of TE treatment (22% reported weight gain).12 We observed weight maintenance or gain in 86% of patients (28% weight gain) over an average of 12 months of TE treatment in the overall TELEACE population.

The TELEACE study was a retrospective observational study that was not limited to the strict patient eligibility criteria of experimental trials, but could not account for unmeasured variables. The retrospective, non-randomized design may have been affected by potential biases including measurement error, non-random missing data, and external validity. There was no comparator group in this study, though subgroup analyses controlling for background NET and CS treatment showed consistent results with those of the overall cohort. The randomization scheme applied during the chart abstraction process was implemented to enhance external validity and reduce potential confounding. The pre-post design of this study reduced the potential for confounding and eliminated the challenge of selecting an appropriate control group. TE use was observed in a variety of NETs beyond those

![Figure 2 Changes in health indicators during the post-TE treatment period. (A) Body weight. (B) ECOG Performance Status.](https://www.dovepress.com/)

**Note:** ECOG Performance Status was unknown for one patient (not shown).

**Abbreviations:** ECOG, Eastern Cooperative Oncology Group; NET, neuroendocrine tumor; TE, telotristat etyl.
typically associated with CS. It should also be noted that, to date, limited in vitro studies have yet to support our clinical findings. Data extraction from electronic medical records did not provide a full view of clinical practice patterns, including SSA or TE treatment, and was limited to charts with documented radiological scan reports. Complete patient data may not have been available in all medical records. Self-selection bias may have been present among participating physicians. The proportion of eligible charts submitted by each physician was unknown, which may have contributed to selection bias; however, this bias was minimized with the implementation of the patient randomization scheme.

**Conclusion**

Telotristat ethyl treatment showed improvements in CS symptoms through an average of 12 months of treatment, and improvements in body weight maintenance or gain, an important indicator of overall health for patients with NETs. Preliminary findings related to tumor progression and PFS are encouraging for larger, prospective controlled trials to further investigate survival and clinical outcomes from TPH inhibition with TE.

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**Disclosure**

DCM, EL and MAM served as consultants for the study design and conduct and were compensated for their time and effort from Lexicon. DCM served as the chair emeritus for NANETS without compensation; reports personal fees from Curium, and Crinetics. He also reports grants from Wren. LH, ITI and MSD are employees of Analysis Group which received funding for data collection and analysis from Lexicon. LH also reports grants from Novartis, Pfizer, Taiho, Epizyme, and Takeda, outside the submitted work. VNJ, KS, SG and PL were employees of Lexicon Pharmaceuticals, Inc., the study sponsor. The authors report no other conflicts of interest in this work.

**References**

1. Siddiqui EJ, Shabbir MA, Mikhailidis DP, et al. The effect of serotonin and serotonin antagonists on bladder cancer cell proliferation. *BJU Int*. 2006;97:634–639. doi:10.1111/j.1464-410X.2006.06056.x

2. Joish VN, Shah S, Tierce JC, et al. Serotonin levels and 1-year mortality in patients with neuroendocrine tumors: a systematic review and meta-analysis. *Future Oncol*. 2019;15:1397–1406. doi:10.2217/fon-2018-0960

3. Diksic M, Young SN. Study of the brain serotonergic system with labeled alpha-methyl-L-tryptophan. *J Neurochem*. 2001;78:1185–1200.

4. Huang L, Mellor AL. Metabolic control of tumor progression and anti-tumor activity. *Curr Opin Oncol*. 2014;26:92–99. doi:10.1097/CCO.000000000000035

5. Jiang S-H, Li J, Zhang Z-G. Increased serotonin signaling contributes to the Warburg Effect in pancreatic tumor cells under metabolic stress and promotes growth of pancreatic tumors in mice. *Gastroenterol*. 2017;153:277–291. doi:10.1053/j.gastro.2017.03.008

6. Gautam J, Banskota S, Regmi SC, et al. Tryptophan hydroxylase 1 and 5-HT7 receptor preferentially expressed in triple-negative breast cancer promote cancer progression through autocrine serotonin signaling. *Mol Cancer*. 2016;15:75. doi:10.1186/s12943-016-0559-6

7. Matthes S, Bader M. Peripheral serotonin synthesis as a new drug target. *Trends Pharmacol Sci*. 2018;39:560–572. doi:10.1016/j.tips.2018.03.004

8. Lexicon Pharmaceuticals, Inc. XermeLO® (telotristat ethyl) Prescribing Information. 2017. Available from: https://www.xerme-lo.com/Media/Default/pdfs/Product_Info_telotristat_ethyl.pdf

Accessed August 11, 2020.

9. Kulkhe MH, Hörsch D, Caplin ME, et al. Telotristat ethyl, a tryptophan hydroxylase inhibitor for the treatment of carcinoid syndrome. *J Clin Oncol*. 2017;35:14–23. doi:10.1200/JCO.2016.69.2780

10. Pavel ME, Gross DJ, Benavent M, et al. Telotristat ethyl in carcinoid syndrome: safety and efficacy in the TELECAST phase 3 trial. *Endocr Rel Cancer*. 2018;25:309–322. doi:10.1530/ERC-17-0455

11. Strosberg J, Joish VN, Giacalone S, et al. TELEPRO: patient-reported carcinoid syndrome symptom improvement following initiation of telotristat ethyl in the real world. * Oncologist*. 2019;24:1446–1452. doi:10.1634/theoncologist.2018-0921

12. Price MA, Joish VN, Schwartz S, et al. XERMELO patient registry: improvements in clinical outcomes, patient satisfaction, and weight with telotristat ethyl in the real-world. In: Annual Symposium of the North American Neuroendocrine Tumor Society; October 3–5, 2019; Boston, Massachusetts. Paper no. ID77.

13. Caplin ME, Pavel M, Ruszniewski P. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *New Engl J Med*. 2014;371:1556–1557. doi:10.1056/NEJMoa1316158

14. Rinke A, Müller HH, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol*. 2009;27:4656–4663. doi:10.1200/JCO.2009.22.8510

15. Ter-Minassian M, Zhang S, Brooks NV, et al. Association between tumor progression endpoints and overall survival in patients with advanced neuroendocrine tumors. *Oncologist*. 2017;22:165–172. doi:10.1634/theoncologist.2016-0175

16. Rinke A, Wittenberg M, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors (PROMID): results of long-term survival. *Neuroendocrinology*. 2017;104:26–32. doi:10.1159/000443612
17. Morse MA, Liu E, Joish VN, et al. Exploring telotristat ethyl's antiproliferative effects in patients with carcinoid syndrome (TELEACE): a real-world observational study. *J Clin Oncol*. 2020;38:618.

18. Morse MA, Liu E, Joish VN, et al. Antiproliferative effects of telotristat ethyl in patients with neuroendocrine tumors: the TELEACE real-world chart review study. *Cancer Manag Res*. 2020;12:6607–6614. doi:10.2147/CMAR.S261257

19. Benson AB, Strosberg J, Joish VN, et al. Clinical benefits of telotristat ethyl in patients with neuroendocrine tumors and low bowel movement frequency: an observational patient-reported outcomes study. *Pancreas*. 2020;49:408–412.

20. Herrera-Martinez AD, Feelders RA, Van den Dungen R, et al. Effect of the tryptophan hydroxylase inhibitor telotristat on growth and serotonin secretion in 2D and 3D cultured pancreatic neuroendocrine tumor cells. *Neuroendocrinology*. 2020;110(5):351–363. doi:10.1159/000502200