

New somatostatin analogues

■ SOM-230 (pasireotide)

- High affinity to sst1, sst2, sst3 and sst5

Phase II study : Sc pasireotide 1200 mcg bd can control carcinoid syndrome symptoms, in 25% of non-responders to Octreotide LAR

Kvols et al, J Clin Oncol 2006

- Double-blinded randomized study for patients with carcinoid syndrome not responding to Octreotide LAR 30mg
Octreotide 40mg IM vs Pasireotide 60mg
IN PROGRESS

Telotristat Etriprate (LX1606) : a new drug candidate for carcinoid syndrome

Efficacy of Telotristat Etriprate in Refractory Carcinoid Syndrome: Preliminary Results of a Randomized, Placebo-controlled, Multicenter Study

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Lexicon

BACKGROUND

Carcinoid tumors are associated with excessive 5-HT secretion. High levels of circulating 5-HT are associated with the diarrhea and abdominal discomfort associated with carcinoid syndrome (CS).

Telotristat etripate (LX1606) is an orally delivered inhibitor of the rate-limiting enzyme in 5-HT synthesis, tryptophan hydroxylase-1 (TH1). Telotristat etripate has been shown to be effective in a study in healthy volunteers and in patients with CS. In this study, telotristat etripate was evaluated in a randomized, placebo-controlled, multicenter study in patients with refractory CS. The primary endpoint was the reduction in the number of daily bowel movements (BMs) compared to placebo over 14 days.

STUDY OVERVIEW

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in patients with refractory CS. Patients were randomized to receive either telotristat etripate (LX1606) or placebo over 14 days. The primary endpoint was the reduction in the number of daily BMs compared to placebo over 14 days. Secondary endpoints included the change in the number of daily BMs, the change in the number of daily BMs with adequate relief, and the change in the number of daily BMs with adequate relief and adequate relief.

STUDY DESIGN

The study was a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in patients with refractory CS. Patients were randomized to receive either telotristat etripate (LX1606) or placebo over 14 days. The primary endpoint was the reduction in the number of daily BMs compared to placebo over 14 days. Secondary endpoints included the change in the number of daily BMs, the change in the number of daily BMs with adequate relief, and the change in the number of daily BMs with adequate relief and adequate relief.

OBJECTIVES

Primary Objective:

- To evaluate the safety and efficacy of telotristat etripate compared to placebo in patients with refractory CS.

Secondary Objectives:

- To evaluate the efficacy of telotristat etripate in reducing the number of daily BMs compared to placebo in patients with refractory CS.
- To evaluate the efficacy of telotristat etripate in reducing the number of daily BMs with adequate relief compared to placebo in patients with refractory CS.
- To evaluate the efficacy of telotristat etripate in reducing the number of daily BMs with adequate relief and adequate relief compared to placebo in patients with refractory CS.

ASSESSMENTS

Efficacy:

- The primary efficacy measure was the reduction in the number of daily bowel movements (BMs) compared to placebo over 14 days.
- Secondary efficacy measures included the change in the number of daily BMs, the change in the number of daily BMs with adequate relief, and the change in the number of daily BMs with adequate relief and adequate relief.

Safety:

- The primary safety measure was the number of adverse events (AEs) compared to placebo over 14 days.
- Secondary safety measures included the number of AEs, the number of AEs leading to discontinuation, and the number of AEs leading to death.

PATIENT SELECTION/DEMOGRAPHICS

Eligibility Criteria:

- Patients with refractory CS who had not received telotristat etripate or placebo for at least 14 days.
- Patients who were unable to tolerate telotristat etripate or placebo for at least 14 days.
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Demographics:

Characteristic	Number of Patients
Total	100
Male	50
Female	50
Mean Age (SD)	58.5 (10.5)
Median Age (IQR)	57 (48-66)
Median Weight (IQR)	70 (58-82)
Median Height (IQR)	170 (160-180)
Median BMI (IQR)	24.5 (21.5-27.5)
Median Time Since Diagnosis (IQR)	10 (5-15)
Median Time Since Last Treatment (IQR)	10 (5-15)

RESPONDER DEFINITION

Primary Response:

- ≥30% reduction from baseline in the daily mean number of bowel movements per day (BM) over 14 days.

Secondary Response:

- ≥30% reduction from baseline in the number of daily BMs with adequate relief over 14 days.

Response Rate:

- The response rate was defined as the percentage of patients who had a primary or secondary response.

PRIMARY OUTCOMES

Outcome	Placebo (n=50)	Telotristat etripate (n=50)
Primary Response	10 (20%)	15 (30%)
Secondary Response	10 (20%)	15 (30%)
Response Rate	20 (40%)	30 (60%)

REDUCTION IN BM FREQUENCY

Change in BM Frequency (Mean)	Placebo (n=50)	100 mg (n=25)	200 mg (n=25)	300 mg (n=25)	400 mg (n=25)
Day 1	-0.1	-1.4	-1.2	-1.2	-1.2
Day 2	-0.1	-1.4	-1.2	-1.2	-1.2
Day 3	-0.1	-1.4	-1.2	-1.2	-1.2
Day 4	-0.1	-1.4	-1.2	-1.2	-1.2
Day 5	-0.1	-1.4	-1.2	-1.2	-1.2
Day 6	-0.1	-1.4	-1.2	-1.2	-1.2
Day 7	-0.1	-1.4	-1.2	-1.2	-1.2
Day 8	-0.1	-1.4	-1.2	-1.2	-1.2
Day 9	-0.1	-1.4	-1.2	-1.2	-1.2
Day 10	-0.1	-1.4	-1.2	-1.2	-1.2
Day 11	-0.1	-1.4	-1.2	-1.2	-1.2
Day 12	-0.1	-1.4	-1.2	-1.2	-1.2
Day 13	-0.1	-1.4	-1.2	-1.2	-1.2
Day 14	-0.1	-1.4	-1.2	-1.2	-1.2

ADEQUATE RELIEF

Outcome	Placebo (n=50)	100 mg (n=25)	200 mg (n=25)	300 mg (n=25)	400 mg (n=25)
Adequate Relief	10 (20%)	15 (30%)	15 (30%)	15 (30%)	15 (30%)

CHANGE IN u5-HIAA

Outcome	Placebo (n=50)	100 mg (n=25)	200 mg (n=25)	300 mg (n=25)	400 mg (n=25)
Change in u5-HIAA (Mean)	0.0	-0.5	-0.5	-0.5	-0.5

SAFETY

Telotristat etripate was well tolerated and adverse events in the study were mostly mild to moderate and similar to placebo. The most common adverse events were headache, dizziness, and constipation. There was no treatment-emergent serious adverse event assessed in this study. There was no treatment-emergent serious adverse event assessed in this study. There was no treatment-emergent serious adverse event assessed in this study.

CONCLUSIONS

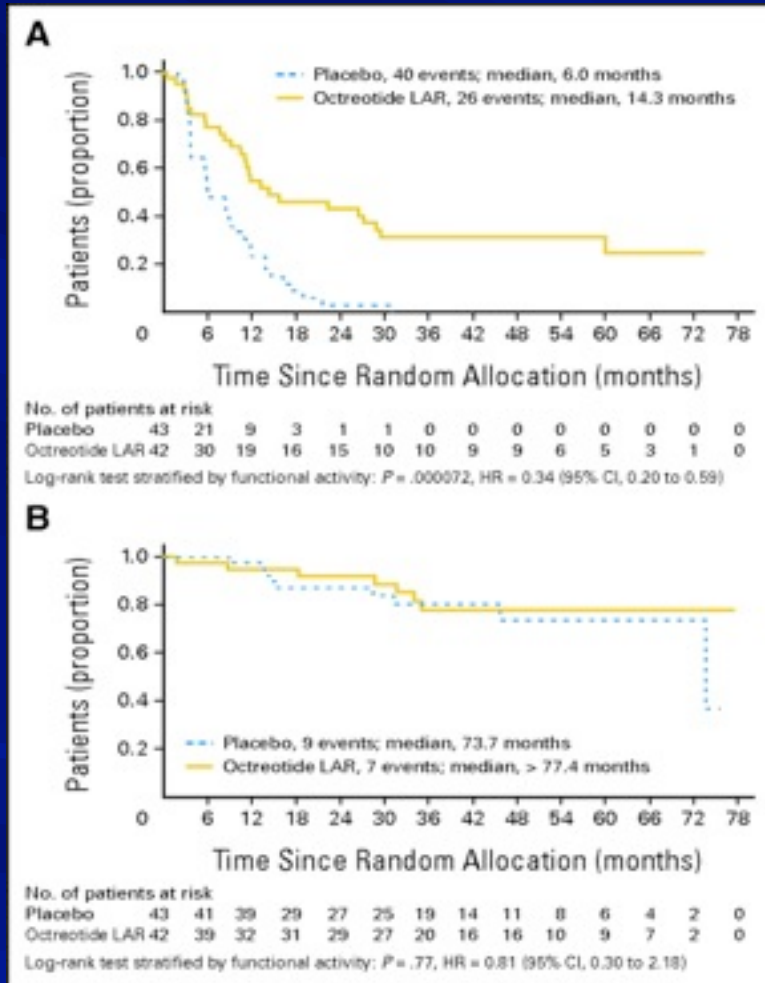
Telotristat etripate was well tolerated and achieved a statistically significant reduction in the number of daily BMs compared to placebo over 14 days. Telotristat etripate was well tolerated and achieved a statistically significant reduction in the number of daily BMs compared to placebo over 14 days.

- Inhibitor of tryptophan hydroxylase – reduces serotonin production
- Oral agent
- Well tolerated and achieved > 30% reduction of bowel movements from baseline

Control of tumor growth in cases of advanced disease

- Biological treatment (somatostatin analogues and/or interferon)
- Cytotoxic chemotherapy
- Hepatic arterial embolization or Chemoembolization
- Ablative therapies (i.e radiofrequency ablation)
- Radiotargeted therapy
- New treatments
- *No treatment but only active surveillance*

Placebo-Controlled, Double-Blind, Prospective, Randomized study of the effect of Octreotide LAR in the control of tumour growth in patients with metastatic neuroendocrine midgut tumours : A report from the PROMID study group



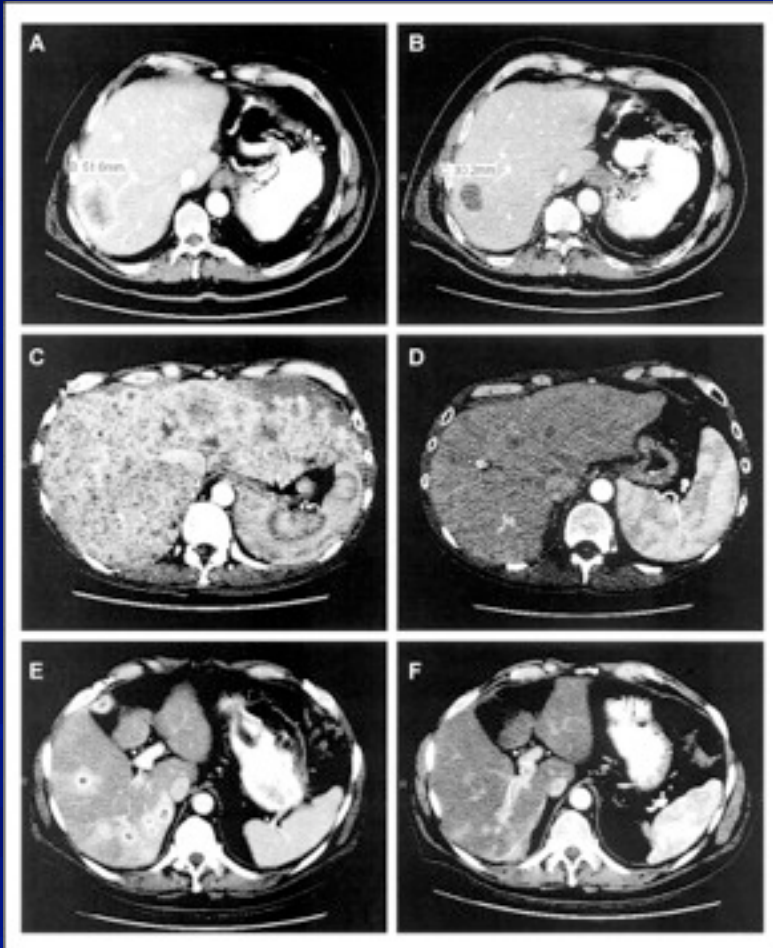
- Median time to progression in LAR group:
14.3 m vs 6 months in placebo
- After 6 m of treatment :
stable disease in 66.7% of LAR vs 37.2% of placebo
- Most favorable effect in patients with low-hepatic tumour load and resected primary tumour

Rinke A et al. JCO 2009;27:4656-4663

JOURNAL OF CLINICAL ONCOLOGY



Systemic Chemotherapy



- Streptozocin + 5FU regimens (+/- doxorubicin) for mod/well differentiated pancreatic neuroendocrine tumours 35-60% response rate.
- Small bowel carcinoids $\leq 15\%$ response.
- Cisplatin & Etoposide for poorly differentiated PETs ~60% response, but early relapse.

Kouvaraki, M. A. et al. J Clin Oncol 2004

Toumpanakis et al, Best Pract Res Clin End Metab 2007