The Efficacy and Safety of Pasireotide (SOM230) in the Treatment of Patients With Metastatic Neuroendocrine Tumors (NET) Refractory or Resistant to Octreotide LAR

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BACKGROUND

- Currently, octreotide and lanreotide are the mainstay of therapy for the symptomatic relief of patients with neuroendocrine tumors (NET). Of the somatostatin receptor subtypes (sst_{1-5}), octreotide and lanreotide have a high affinity for sst_2 and a modest affinity for sst_5.[1] However, multiple sst expression is observed in NET.[2]
- Although octreotide LAR therapy effectively reduces the symptoms of carcinoid syndrome in the majority of patients,[3] some patients experience an escape from response within months to several years of treatment.[4] Mechanisms by which this desensitization may occur include sst_2 internalization and downregulation on tumor cells, overexpression of other somatostatin receptor subtypes,[5] or other unknown mechanisms.
- Targeting multiple somatostatin receptor subtypes in NET may provide an effective treatment for the relief of symptoms in patients who are unresponsive or no longer responsive to the currently available somatostatin analogues.
- Pasireotide (SOM230) is a novel multi-receptor targeted somatostatin analogue that exhibits a high binding affinity to four of the five somatostatin receptor subtypes ($sst_{1,2,3}$ and sst_5) and higher binding affinity than octreotide for $sst_{1,3}$ and sst_5.[6,7] Because of this multi-receptor binding profile, pasireotide may offer symptom reduction in patients who are unresponsive or no longer responsive to octreotide LAR therapy.
- This poster presents results from a Phase II, open-label, multicenter study designed to assess the efficacy and safety of pasireotide in patients with metastatic NET whose symptoms were refractory or resistant to octreotide LAR therapy.

METHODS

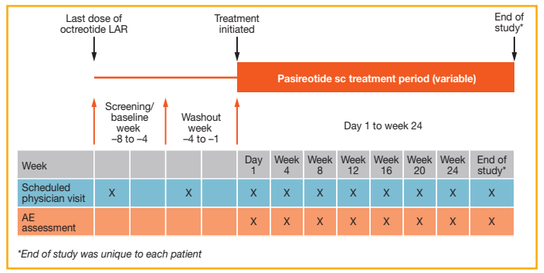
Study Population

- Eligible patients were aged ≥18 years and had histopathologically and biochemically confirmed metastatic NET that were considered refractory or resistant to octreotide LAR treatment. Patients were required to have elevated urinary 5-hydroxyindole acetic acid (5-HIAA) and/or serum CgA levels, one or more measurable lesions (excluding bone) and a Karnofsky Performance status of at least 60.
- Inadequate control of disease with octreotide LAR therapy was based on the symptoms of carcinoid syndrome (diarrhea and/or flushing), defined as a mean of ≥4 bowel movements per day and/or ≥2 episodes of flushing per day for at least 2 weeks during the 28-day period following the last dose of octreotide LAR.

Study Design

- This was a Phase II, open-label, multicenter study (Figure 1).
- The primary efficacy outcome was symptom control (diarrhea, flushing) over 15 consecutive days at a fixed dose. Secondary objectives included safety/tolerability, tumor response and pharmacokinetics (PK).
- After a washout period, patients self-administered pasireotide sc 150 µg twice daily (bid) for 3 days.
- If at least partial symptom control was not achieved, the dose of pasireotide was escalated by 150 µg per dose up to a limit of 900 µg per dose (1800 µg daily). Dose increases up to 1200 µg bid could also be administered based on evidence of therapeutic benefit. If unacceptable toxicity (Common Toxicity Criteria [CTC] grade 3 or higher) occurred, a dose reduction of 150 µg bid was performed.
- Patients could continue to receive pasireotide as long as control was maintained without unacceptable toxicity or disease progression. As such, end of study was unique to each patient.

Figure 1. Study Design*



*End of study was unique to each patient

Assessments

- Pasireotide was considered effective if 30% of the patients experienced at least partial symptom control on a constant dose for 15 consecutive days. Outcome definitions are included in Table 1.

Table 1. Definitions of Primary Efficacy Outcomes

Outcome	Definition
Partial symptom control	An average of <4 bowel movements/day, with no more than six bowel movements on any given day, and an average of less than two episodes of flushing per day
Complete symptom control	An average of ≤3 bowel movements/day for at least 3 consecutive days, with no more than three episodes on any given day, and no episodes of flushing
Partial treatment success	Partial symptom control during 15 consecutive days of treatment at a constant dose level, but without reaching complete symptom control over the same time period, no more than a 10% increase in biochemical parameters above baseline, and no significant clinical signs of disease progression, as adjudicated by the investigator
Complete treatment success	Complete symptom control during 15 consecutive days of treatment at a constant dose level, no more than a 10% increase in biochemical parameters (serum CgA and urinary 5-HIAA) above baseline and no clinical signs of disease progression as adjudicated by the investigator
Treatment failure	Failure to obtain partial or complete treatment success over any consecutive 15-day period at a constant dose level

- Tumor responses were measured by CT or MRI at baseline and every 3 months, and were assessed using the Response Evaluation Criteria In Solid Tumors (RECIST). Serum CgA and urinary 5-HIAA were obtained at baseline and monthly thereafter.
- Safety and tolerability assessments consisted of reporting all adverse events and serious adverse events, with severity graded according to CTC (grades 1–4). Safety assessments included regular monitoring of hematology, blood chemistry, vital signs, physical condition, ECG evaluations and body weight.
- Plasma samples were collected for PK assessments after 4 weeks of treatment with pasireotide sc 150–1200 µg bid. Blood samples were taken at time 0 (pre-dose), 0.5, 1, 2, 3, 4 and 6 hours after morning administration of pasireotide.

Statistical Methods

- The total planned sample size was a minimum of 36 patients. The sample size was chosen based on the assumption of a proportion of success of 0.3 and an approximate width of 0.3 for a two-sided 95% confidence interval.
- Summary statistics were provided for the primary and secondary endpoints. No formal statistical comparisons were performed for this study.

RESULTS

- A total of 53 patients were enrolled in the study, of whom 45 received pasireotide and were included in the safety analysis, and 44 were evaluable for efficacy (Table 2). One patient was excluded from the efficacy analyzable population because no post-baseline efficacy assessments were completed.
- Of the 45 patients to receive pasireotide treatment, 11 discontinued because of adverse events. The median treatment duration was 12.7 weeks (89 days).

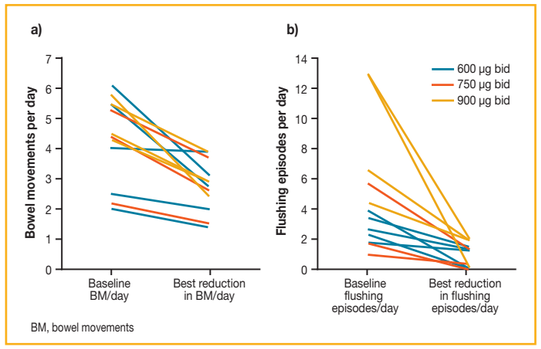
Table 2. Demographic Characteristics of the Safety (n=45) and Efficacy (n=44) Populations

Variable	Safety population	Efficacy population
Mean age, years (range)	61 (40–83)	61 (40–83)
Gender, n (%)		
Males	25 (56)	25 (57)
Females	20 (44)	19 (43)
Race, n (%)		
Caucasian	44 (98)	43 (98)
Asian	1 (2)	1 (2)
Location of primary tumor, n (%)		
Small intestine	36 (80)	36 (82)
Colon	1 (2)	1 (2)
Cecum	1 (2)	0
Peritoneum	1 (2)	1 (2)
Lung	1 (2)	1 (2)
Other	5 (11)	5 (11)

Symptom Control with Pasireotide

- Of the 44 patients included in the efficacy analyzable population, 12 (27%) had complete or partial symptom control over 15 days of treatment with pasireotide.
- Three (7%) of these patients achieved complete control of symptoms (two of whom received pasireotide 600 µg bid and one who received 900 µg bid), and nine (20%) achieved partial symptom control in response to treatment (three patients each received pasireotide 600, 750 or 900 µg bid).
- For the 12 patients who showed complete or partial symptom control, the mean (± SD) number of daily bowel movements were reduced from 4.3 ± 1.4 at baseline to 2.8 ± 0.8 post-pasireotide treatment, and mean (± SD) daily flushing episodes declined from 4.9 ± 4.1 at baseline to 1.0 ± 0.8 post treatment (Figure 2).
- The mean duration of complete and partial symptom control was 43.7 days (range 26–58) and 72.0 days (range 15–244), respectively.
- When assessing the number of patients with complete treatment success, partial treatment success and treatment failure, one (2.3%) patient achieved complete treatment success and four (9.1%) patients achieved partial treatment success. The remaining 39 (88.6%) patients were classified as treatment failures.

Figure 2. Clinical Symptom Responses Following Pasireotide Treatment in Responding Patients: (a) Best Reductions in the Number of Bowel Movements Per Day from Baseline; and (b) Best Reductions in the Number of Flushings Per Day From Baseline. Patients Received Pasireotide sc 600, 750 or 900 µg bid



BM, bowel movements

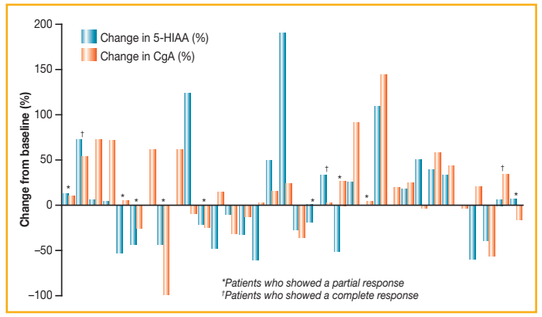
Tumor Response

- Overall tumor response based on RECIST following treatment with pasireotide was assessed in 23 of the 44 patients.
- At 6 months, 57% (13/23) of patients had stable disease and 43% (10/23) of patients had progressive disease.
- There were no complete or partial tumor responses observed.

Biochemical Marker Data

- Figure 3 shows the percent changes from baseline in urinary 5-HIAA and serum CgA levels for each patient in whom this was measured. Partial and complete responders (based on symptom control) are indicated.

Figure 3. The Percentage Change from Baseline Urinary 5-HIAA and Serum CgA in Patients With a Complete or Partial Symptom Control by Individual Patient



Safety and Tolerability

- Forty-four of the 45 patients (98%) included in the safety population experienced one or more adverse event, with 36 patients (80%) considered to have study drug-related adverse events (Table 3).

Table 3. Adverse Events with a Suspected Study Drug Relationship of Any CTC Grade

Adverse event	n (%)
Nausea	12 (26.7)
Abdominal pain	9 (20.0)
Weight decrease	9 (20.0)
Hyperglycemia	7 (15.6)
Diabetes mellitus	4 (8.9)
Dysgeusia	4 (8.9)
Flatulence	4 (8.9)
Fatigue	4 (8.9)
Asthenia	3 (6.7)
Vertigo	3 (6.7)
Diarrhea	3 (6.7)
Headache	3 (6.7)

- Most adverse events were of mild or moderate intensity (CTC grades 1 [36%] and 2 [24%]). Fourteen patients (31%) experienced serious adverse events, however only one of these events was suspected to be study drug related; this patient had a CTC grade 4 increase in lipase, which resolved spontaneously and no action was taken.
- One patient died during the study because of tumor progression that was not considered study drug related.
- Weight loss occurred in 19 patients (42%) during the study, with nine of the cases (20%) considered related to pasireotide. Maximum weight loss occurred within 4–6 months of treatment with pasireotide, with a stabilization of effect after approximately 6 months. There was no apparent relationship between weight loss and pasireotide dose.
- Three of four patients who experienced an adverse event of worsening diabetic symptoms had a medical history of active diabetes mellitus, and three of the seven patients who experienced hyperglycemia had a history of active hyperglycemia at baseline. One additional patient who experienced an adverse event of hyperglycemia had a history of diabetes mellitus at baseline.
- For the majority of patients, the effect on fasting blood glucose was transient as a result of adjustments to the dose of pasireotide and appropriate antidiabetic management.

Pharmacokinetics

- Thirty-five of the 37 patients with available PK plasma samples were analyzed; one patient was excluded because of early discontinuation from the study and one patient was excluded because of missing pre-dose plasma PK samples.
- Pharmacokinetic exposures of pasireotide showed large inter-patient variability. Pasireotide was absorbed rapidly (t_{max} within 1 hour after administration). In patients administered pasireotide sc 600, 750 and 900 µg bid, the mean values of C_{min} were 9.9, 10.0 and 13.5 ng/mL, and mean values of C_{max} were 26.4, 31.6 and 40.6 ng/mL, respectively (Figure 4, Table 4).

Further Investigation

- A randomized Phase III study to compare the efficacy of pasireotide LAR versus octreotide LAR is ongoing in patients with metastatic carcinoid tumors whose disease-related symptoms are inadequately controlled by conventional doses of somatostatin analogues (Figure 5).

Figure 4. Plasma Concentration Versus Time Profiles of Pasireotide Following 4 Weeks of Multiple bid Pasireotide Dosing

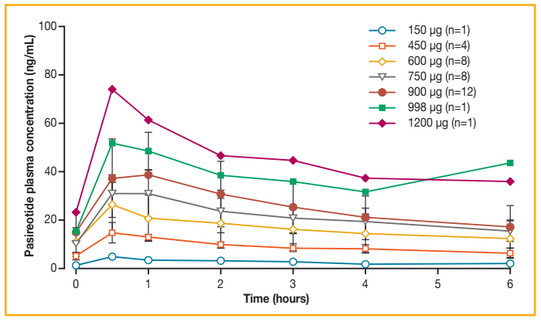
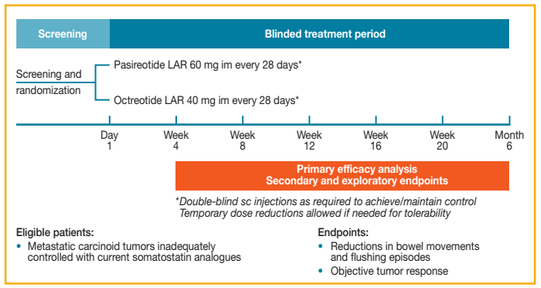


Table 4. Pharmacokinetic Parameters of Pasireotide sc Following 4 Weeks Multiple bid Dosing

Dose (µg)	N	t_{max} (h)	C_{max} (ng/mL)	C_{min} (ng/mL)	$AUC_{0\text{-}6\ h}$ (h•ng/mL)
150	1	0.50	4.7	1.4	15.0
450	4	0.79 (0.50–1.00)	15.2 ± 3.9	5.1 ± 1.6	58.4 ± 9.3
600	8	0.50 (0–0.50)	26.4 ± 12.2	9.9 ± 6.4	105 ± 53
750	8	0.75 (0.50–1.17)	31.6 ± 9.8	10.0 ± 4.0	128 ± 36
900	12	1.00 (0.50–3.00)	40.6 ± 17.8	13.5 ± 7.1	155 ± 66
998	1	0.52	51.9	15.2	231
1200	1	0.50	73.8	23.3	278

Data for C_{min}, C_{max} and $AUC_{0\text{-}6\ h}$ are expressed as mean ± SD. Data for t_{max} are expressed as median (min–max)

Figure 5. Study Design of an Ongoing Phase III Trial of Pasireotide LAR Versus Octreotide LAR in Patients with Symptomatic Carcinoid Tumors



*Double-blind sc injections as required to achieve/maintain control
Temporary dose reductions allowed if needed for tolerability

Eligible patients:
- Metastatic carcinoid tumors inadequately controlled with current somatostatin analogues

Endpoints:
- Reductions in bowel movements and flushing episodes
- Objective tumor response

DISCUSSION AND CONCLUSIONS

- **Pasireotide sc 600–900 µg bid controlled the symptoms of diarrhea and flushing in 27% of patients with metastatic NET unresponsive or no longer responsive to octreotide LAR therapy.**
- **Pasireotide treatment resulted in stable disease in 57% of patients at 6 months, which is a significant achievement in patients with metastatic NET and carcinoid syndrome who are refractory or resistant to octreotide LAR.**
- **Pasireotide demonstrated a similar tolerability profile to that of currently available somatostatin analogues, with most adverse events being mild or moderate and gastrointestinal in nature.**
- **Pharmacokinetic exposures of pasireotide sc 150–1200 mg bid appeared to be approximately dose proportional.**
- **These results demonstrate that pasireotide is a potential treatment option for patients with the symptoms of carcinoid syndrome who are resistant or refractory to octreotide LAR.**
- **A Phase III randomized study comparing pasireotide LAR with octreotide LAR in patients with metastatic NET is ongoing.**

References

1. Bruns C *et al. Ann N Y Acad Sci* 1994;733:138–146.
2. Hofland LJ & Lamberts SW. *Endocr Rev* 2003;24:28–47.
3. Rubin J *et al. J Clin Oncol* 1999;17:600–606.
4. Hofland LJ *et al. J Endocrinol Invest* 2005;28(11 Suppl):36–42.
5. Schmid HA & Schoeffter P. *Neuroendocrinology* 2004;80(Suppl 1):47–50.
6. Bruns C *et al. Eur J Endocrinol* 2002;146:707–716.
7. Schmid HA. *Mol Cell Endocrinol* 2008;286:69–74.

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