Pasireotide LAR in Metastatic Carcinoid Tumors: a Randomized Phase I Study

Edward. M. Wolin,[1] Larry Kvols,[2] Shereen Ezzat,[3] Walter I. Kocha,[4] Brigitte Weisshaar,[5] Ke Hu,[6] Pharis Mohideen,[6] Eric Van Cutsem[7]

[1]Cedars-Sinai Cancer Center, Los Angeles, CA; [2]H. Lee Moffitt Cancer Center, Tampa, FL; [3]Ontario Cancer Institute, University of Toronto, Toronto, ON, Canada; [4]London Regional Cancer Centre, London, ON, Canada; [5]Novartis Pharma AG, Basel, Switzerland; [6]Novartis Pharmaceuticals Corporation, East Hanover, NJ; [7]Digestive Oncology unit, University Hospital Gasthuisberg, Leuven, Belgium

Background

- Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are slow growing tumors that have often metastasized by the time of diagnosis. The majority of GEP-NETs are carcinoid tumors whose syndrome is caused by the hypersecretion of biogenic amines, peptides and polypeptides responsible for the principal symptoms of diarrhea and flushing.
- The symptoms of carcinoid tumors are commonly treated with the somatostatin analogues octreotide and lanreotide, which have a high binding affinity for the somatostatin receptor subtype sst_2, and moderate affinity for sst_5. While most patients respond initially to treatment with these analogues, as many as 50% may experience tachyphylaxis after 12–18 months.[1]
- Pasireotide is a novel multi-receptor ligand somatostatin analogue with high binding affinity for $sst_{1,2,3}$ and sst_5. Compared with octreotide, pasireotide has 30-, 5- and 40-fold higher affinity for $sst_{1,3}$ and sst_5, respectively, and a slightly lower affinity for sst_2.[2]
- Twice-daily subcutaneous pasireotide 600–900 µg bid demonstrated efficacy in controlling diarrhea and flushing in a Phase II study (B2202) of patients with metastatic carcinoid tumors refractory or resistant to Sandostatin LAR.[3]
- Based on the encouraging results from studies of subcutaneous pasireotide, a long-acting-release (LAR) formulation of pasireotide, administered once every 28 days, has been developed. In a Phase I study of pasireotide LAR in healthy volunteers, pasireotide LAR was well tolerated at single doses of up to 60 mg, and the formulation was predicted to be suitable for a monthly dosing interval in patients.
- A Phase I study (C2110) was initiated to evaluate the pharmacokinetics and tolerability profiles of intramuscular depot injections of pasireotide LAR 20, 40 and 60 mg every 28 days in patients with metastatic carcinoid tumors. Preliminary 3-month results from this study are presented here.

Methods

Patients

- Adult patients (≥18 years) with biopsy-proven, histopathologically confirmed metastatic carcinoid tumors of the digestive system, and elevated chromogranin A (CgA) and/or 5-hydroxyindole acetic acid (5-HIAA) levels were included.
- Patients had symptoms of metastatic carcinoid tumors that were refractory or resistant to available somatostatin analogues (i.e octreotide or lanreotide).
- There were no minimum entry criteria for the frequency of bowel movements or flushing episodes, as this study was not designed to assess the efficacy of pasireotide LAR.

Study design

- This was a Phase I, randomized, open-label, multicenter study.
- Following an initial dose of subcutaneous pasireotide 300 µg to assess tolerability, patients received intratmuscular depot injections of pasireotide LAR 20, 40 or 60 mg every 28 days on days 0, 28 and 56. Safety and tolerability assessments were performed at regular intervals during 3 months of pasireotide LAR therapy. Blood samples for the pharmacokinetic analyses were collected throughout the pasireotide LAR treatment period.
- The primary objectives of the study were to evaluate the pharmacokinetic and safety/tolerability profiles of pasireotide LAR 20, 40 and 60 mg administered every 28 days in patients with metastatic carcinoid tumors.

Results

Patient baseline characteristics

- A total of 42 patients with metastatic carcinoid tumors were enrolled in the study (Table 1) and received pasireotide LAR.

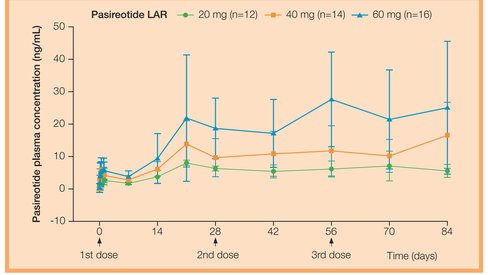
Table1. Baseline characteristics of patients with metastatic carcinoid tumors enrolled in study C2110

	Pasireotide LAR 20 mg (n=12)	Pasireotide LAR 40 mg (n=14)	Pasireotide LAR 60 mg (n=16)	Total (n=42)
Mean age, years (range)	56 (39-83)	59 (39-77)	63 (49-80)	60 (39-83)
Sex, n(%)				
Male	9 (75)	6 (43)	7 (44)	22 (52)
Female	3 (25)	8 (57)	9 (56)	20 (48)
Race, n(%)				
Caucasian	10 (83)	13 (93)	16 (100)	39 (93)
Black	1 (8)	0	0	1 (2)
Asian	1 (8)	0	0	1 (2)
Native American	0	1 (7)	0	1 (2)

Pharmacokinetics

- Mean (± SD) pasireotide plasma concentration versus time profiles for the three pasireotide LAR dose levels are shown in Figure 1.
- The pharmacokinetics of pasireotide LAR 20, 40 and 60 mg in patients with metastatic carcinoid tumors are approximately linear, with steady state being achieved after three injections. The trough pasireotide plasma concentrations on day 84 ($C_{trough,d84}$) were 5.6 ± 2.0, 16.6 ± 10.2 and 25.0 ± 20.5 ng/mL for the 20, 40 and 60 mg dose levels, respectively. The accumulation ratio ($C_{trough,d84}$/ $C_{trough,d28}$) was 20–80%. The exposure to pasireotide in patients with carcinoid tumors is approximately twice that in healthy volunteers.
- Pasireotide plasma concentrations at steady state achieved with monthly administration of pasireotide LAR 40 mg and 60 mg were in a range similar to those achieved with twice-daily administration of subcutaneous pasireotide 600 µg and 900 µg bid, respectively.

Figure 1. Mean (SD) pasireotide plasma concentration versus time profiles following three injections of pasireotide LAR 20, 40 or 60 mg every 28 days in patients with metastatic carcinoid tumors (n=42)



Safety and tolerability

- Pasireotide LAR was generally well tolerated, with 25 of the 42 patients (60%) reporting at least one adverse event (Table 2), most of which were mild.

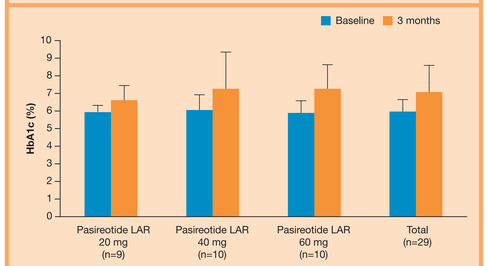
Table 2. Adverse events with a suspected study-drug relationship

System organ class	Pasireotide LAR 20 mg (n=12) n (%)	Pasireotide LAR 40 mg (n=14) n (%)	Pasireotide LAR 60 mg (n=16) n (%)	Total (n=42) n (%)
Any	6 (50)	10 (71)	9 (56)	25 (60)
Gastrointestinal disorders	3 (25)	4 (29)	2 (13)	9 (21)
Metabolism and nutrition disorders	2 (17)	5 (36)	5 (31)	12 (29)
General disorders and administration-site conditions	2 (17)	3 (21)	3 (19)	8 (19)
Nervous system disorders[a]	0	1 (7)	0	1 (2)
Skin and subcutaneous tissue disorders[b]	0	0	1 (6)	1 (2)
Vascular disorders[c]	0	2 (14)	0	2 (5)
Investigations[d]	1 (8)	0	2 (13)	3 (7)
Musculoskeletal and connective tissue disorders[e]	1 (8)	1 (7)	0	2 (5)
Renal and urinary disorders[f]	0	0	2 (13)	2 (5)
Cardiac disorders[g]	0	1 (7)	0	1 (2)
Psychiatric disorders[h]	0	0	1 (6)	1 (2)
Hepatobiliary disorders[i]	0	1 (7)	0	1 (2)

[a]Headache; [b]alopecia; [c]flushing, hypotension; [d]increased creatine phosphokinase, increased creatinine, increased blood glucose, decreased hemoglobin, decreased WBC count; [e]muscle spasm; [f]nocturia, polyuria; [g]palpitations; [h]altered mood; [i]cholelithiasis

- The most common adverse events with a suspected study-drug relationship were gastrointestinal disorders (eg. diarrhea [5%], nausea [5%] and steatorrhea [5%]), general disorders/administration-site conditions (eg. injection-site reaction [5%] and asthenia [5%]) and metabolism and nutrition disorders (eg. hyperglycemia [12%], type 2 diabetes mellitus [7%] and worsening of type 2 diabetes mellitus [12%]).
- In all patients with both baseline and 3-month HbA1c (glycosylated hemoglobin) measurements (n=29), HbA1c increased from a mean 5.96% at baseline to 7.06% at month 3 (Figure 2).

Figure 2. Glycosylated hemoglobin (HbA1c) at baseline and at 3 months in patients with metastatic carcinoid tumors who received pasireotide LAR 20, 40 and 60 mg every 28 days[1]

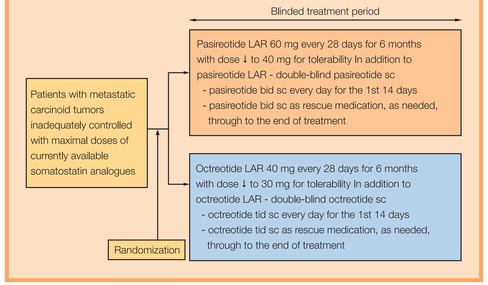


[1]Only patients with HbA1c results at baseline and at month 3 are reported

Discussion

- Pasireotide LAR 20, 40 and 60 mg at monthly dosing intervals were generally well tolerated in patients with metastatic carcinoid tumors. The safety profile of pasireotide LAR was similar to that of pasireotide sc bid, with no unexpected adverse events reported.
- Pasireotide LAR showed approximately linear pharmacokinetics in patients. A steady state was achieved after three monthly injections. Pasireotide concentrations at steady state achieved with pasireotide LAR 40 and 60 mg per month at monthly dosing intervals were similar to those achieved with pasireotide 600 and 900 µg sc bid, respectively, where clinical efficacy (symptom control with complete and partial response) was observed in a Phase II study (B2202) in approximately 30% of patients resistant or refractory to Sandostatin LAR.
- Based on the encouraging results from the Phase II study (B2202) and on the PK and safety results from the current Phase I study of pasireotide LAR, a Phase III study (C2303) of pasireotide LAR has been initiated (Figure 3). This Phase III clinical trial is a randomized, blinded, multicenter, efficacy and safety study of pasireotide LAR versus octreotide LAR in patients with metastatic carcinoid tumors whose disease-related symptoms are inadequately controlled by currently available somatostatin analogues.

Figure 3. Study design for a Phase III, randomized, blinded, multicenter, efficacy and safety study (C2303) of pasireotide LAR versus octreotide LAR in patients with metastatic carcinoid tumors



Conclusions

- Pasireotide is a promising treatment for patients with symptoms of carcinoid tumors. The availability of a long-acting release formulation of pasireotide will provide the patient and clinician with a safe and convenient treatment option, particularly for patients inadequately controlled with maximal doses of currently available somatostatin analogues.
- Pasireotide LAR was generally well tolerated and had a similar safety profile to that of the subcutaneous formulation. The most common adverse events with a suspected study-drug relationship were gastrointestinal disorders, general disorders/administration-site conditions and metabolism and nutrition disorders.
- The pharmacokinetics of pasireotide LAR 20, 40 and 60 mg every 28 days were approximately linear, with steady-state concentrations achieved after three injections.
- Results from the Phase III study will help determine the role of pasireotide LAR in the treatment of patients with metastatic carcinoid tumors.

References

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