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Three-year oral pantoprazole administration is effective for patients with Zollinger–Ellison syndrome and other hypersecretory conditions

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SUMMARY

Background—Zollinger–Ellison syndrome and idiopathic hypersecretion are gastrointestinal hypersecretory conditions requiring long-term maintenance.

Aims—The safety and efficacy data for short-term (6-month) treatment of Zollinger–Ellison syndrome and idiopathic hypersecretion with oral pantoprazole were previously published. This study extends the initial observations to 3 years.

Methods—The primary efficacy end point for this report was the control of gastric acid secretion in the last hour before the next dose of oral pantoprazole (acid output of <10 mmol/h; <5 mmol/h in subjects with prior acid-reducing surgery). Dose titration was permitted to a maximum of 240 mg per 24 h.

Results—Twenty-four subjects completed the study. The acid output of 28 of 34 subjects was controlled at initial enrolment. The mean acid output rates were <10 mmol/h throughout the 36 months of treatment for 90–100% of the patients. The majority of the patients were controlled with b.d. doses of 40 or 80 mg pantoprazole at 36 months (acid output was controlled in 24 of 24 subjects). Pantoprazole was generally well tolerated with minimal adverse events reported.

Conclusions—Maintenance oral pantoprazole therapy up to 3 years at dosages of 40–120 mg b.d. was effective and well tolerated in patients with Zollinger–Ellison syndrome and other hypersecretory conditions.

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INTRODUCTION

Zollinger–Ellison syndrome (ZES) is a rare and potentially life-threatening condition characterized by the presence of gastrinomas with resulting hypergastrinaemia. Hypergastrinaemia, in turn, results in uncontrolled gastric acid hypersecretion. Idiopathic hypersecretion (IH) results in gastric acid hypersecretion in patients in whom a gastrinoma tumour is not identified. In both clinical scenarios, patients are at risk for the development of peptic ulcer disease and its complications. In approximately 25–33% of cases, ZES is associated with other endocrine tumours as part of the multiple endocrine neoplasia syndrome type 1 (MEN-1).[1] Persistent hypergastrinaemia leads to profound and uncontrolled gastric acid hypersecretion, which, left untreated, causes peptic ulcers in the upper gastrointestinal (GI) tract that may bleed and/or perforate.[2-4] Approximately 30% of selected patients who undergo resection of their gastrinomas remain biochemically cured 5 years after surgery.[5] However, the majority of patients require life-long therapy for gastric acid hypersecretion, because they are unsuitable candidates for tumour resection, tumour resection fails to cure their disease, or the tumour cannot be located.[3,6-9] Patients with IH also require life-long therapy because tumour resection is not an option.[4, 10]

Numerous studies have demonstrated that protonpump inhibitors (PPIs) are both efficacious and well tolerated in patients with hypersecretory conditions;[3,6,11-15] consequently, they are currently the antisecretory agents of choice to control gastric acid hypersecretion. Maintenance therapy with oral omeprazole and lansoprazole has been shown to be effective in the long-term management of patients with gastric acid hypersecretory conditions.[11-15] A previous study demonstrated the efficacy of pantoprazole to control acid output (AO) in ZES and IH patients for up to 6 months.[16] The current study was a continuation of the previous study to evaluate the safety and efficacy of 3-year treatment with oral pantoprazole in patients with ZES and other hypersecretory conditions.

METHODS

This was an open-label, multicentre study lasting 36 months. All study subjects ($n = 35$) were patients with either sporadic ZES ($n = 21$), ZES with MEN-1 ($n = 5$), or IH ($n = 9$) who completed the previous 6-month study.[16] Individuals with total gastrectomies, other significant upper GI disorders (other than ZES or gastric hypersecretory conditions), upper GI bleeding, pyloric stenosis, or any clinically important medical condition were not eligible for the study. However, previous surgery, including partial gastrectomy, vagotomy and pyloroplasty, simple closure of a perforation, and tumour excision or chemotherapy in patients with gastrinomas, was allowed provided that the remaining acid hypersecretion required maintenance PPI therapy.

The diagnostic criteria for ZES included a basal AO of ≥15 mmol/h, an elevated fasting serum gastrin level (≥100 pg/mL) in the presence of gastric acid secretion, a positive provocative secretin stimulation test (an increase of ≥200 pg/mL postinjection), a positive histological diagnosis of gastrinoma, or a combination of these, as previously described.[17,18] The diagnosis of IH required a basal AO of ≥15 mmol/h (≥10 mmol/h for subjects who

previously had undergone gastric acid-reducing surgery) with a normal fasting serum gastrin level.[4,15]

Each study subject underwent a complete clinical evaluation within 5–14 days before study drug administration. The evaluation included recording of demographic details and medical history, a complete physical examination with vital signs, an upper endoscopic examination, 12-lead electrocardiography (ECG), chest X-ray and fasting laboratory evaluations including haematology, blood chemistry, serum gastrin level determinations, urinalysis, thyroid studies and serum pregnancy testing for female patients of childbearing age. In addition, physical examinations included non-mydriatic ophthalmic examinations, which were conducted at baseline and periodically during the first 3 months and at 6-month intervals thereafter.

All study subjects provided written informed consent, which was approved by the Institutional Review Boards at each of the six participating institutions.

Concomitant antacid therapy was permitted as follows: Magaldrate (Riopan, Wyeth Pharmaceuticals, Collegeville, PA, USA) could be taken as needed for symptomatic relief at any time but not within 8 h before any acid secretory studies. Other PPIs or histamine-2 receptor antagonists were prohibited throughout the study. Patients took their last dose of the previous PPI or other treatment regimen on study day –1. A baseline determination of acid secretion in the presence of prior maintenance antisecretory therapy was obtained in the last 1 h before the next planned dose of drug [i.e. hours 12 or 24 after the last dose in subjects receiving twice-daily (b.d.) or once-daily therapy, respectively], prior to the administration of pantoprazole.[12,15]

Oral pantoprazole was administered twice daily (b.d.) in all subjects. The majority of subjects started with a dosage of 40 mg b.d. Investigators at each centre had the option of starting their patients at higher dosages (80 mg b.d., or even 120 mg b.d.) based on the patient's previous treatment response. The dosage could be increased further if acid secretion was not controlled to a maximum of 240 mg/day [80 mg three times a day (t.d.s.) or 120 mg b.d.], as described earlier.[16] Subjects whose acid secretion could not be controlled by day 14 or with 240 mg/day of pantoprazole at any time were considered treatment failures and were withdrawn from the study. Adequate control of acid secretion was defined as an AO of ≤10 mmol/h an hour before the next dose in subjects with intact stomachs[3] or ≤5 mmol/h in subjects with prior acid-reducing surgery.[19] Dose reduction was allowed if continued control was demonstrated 2 weeks later. Complete physical examinations including measurement of vital signs and ophthalmologic and neurological examinations were conducted at 6-month intervals or whenever symptoms developed during the course of the study. Standard laboratory evaluations, determination of fasting serum gastrin levels, ECGs and upper endoscopies were performed at six-month intervals. Adverse events (AEs) were monitored throughout the study.

The primary efficacy end point for the current study was the number of patients with adequate control of AO at 36 months, as described above. The AO was determined 1 h before the administration of the next scheduled dose of pantoprazole at 6, 10 and 28 days, and thereafter every 3 months for the duration of the study. Mean AO rates were calculated

by summing each of the four 15-min AO measurements to provide an AO rate per hour. The AO was calculated using the following formula: mL/15 min · mmol/L · 60 min/h · L/1000 mL = mmol/0.25 h for each 15-min collection (mmol/0.25 h X 4 = mmol/h). The number of patients whose AO fell below the predefined mmol/h limit was averaged for each dose level and at each AO measurement period. The mean AO rates (mmol/h) are presented by dose and diagnostic group. No statistical analyses were performed. To consider pantoprazole as effective maintenance therapy for patients with gastric hypersecretory states, the proportion of study subjects with controlled acid secretion at 36 months was expected to equal or exceed that of the prior maintenance therapy at enrolment.

RESULTS

A total of 35 patients were initially enrolled in the study and assigned to pantoprazole dosages of 40 mg b.d. (n = 25), 80 mg b.d. (n = 8), or 120 mg b.d. (n = 2; Figure 1). Dosage groups were assigned based on dose at the 6-month visit. Once assigned, the dosage group was not changed even if there was a dosage adjustment. The maintenance dosage was increased from 40 to 80 mg b.d. in nine patients [<14 days (n = 3), 6–12 months (n = 3), 12–24 months (n = 2) and >24 months (n= 1)]. Two of these patients required dosages to be further increased to 120 mg b.d. at months 15 and 27. The dosage was increased from 80 to 120 mg b.d. in two patients and 80 mg t.d.s. in one patient. The dosage was also temporarily increased due to symptoms or non-compliance in two additional patients. The dose was decreased from 120 to 80 mg b.d. because of AEs in one patient. Most patients received pantoprazole regimens of 40 or 80 mg b.d. Six patients received 120 mg of pantoprazole b.d. and one patient received 80 mg t.d.s. Of the seven patients receiving maximum doses, six patients underwent dose escalations to reduce the AO below the threshold of 10 mmol/h. One patient began treatment with 120 mg b.d. and had the dosage reduced to 80 mg b.d. on day 11 because of AEs related to pantoprazole, but the AO was effectively controlled at the lower dosage. Of the six patients who received 120 mg b.d., four had sporadic ZES, one had ZES with MEN-1 and one had IH.

Twenty-five (72%) of the 35 patients were initially treated with 40 mg of pantoprazole b.d. By 36 months, one patient discontinued treatment and 11 of the 24 patients (46%) were maintained at that dosage. The remaining 12 (50%) of 24 patients received 80 mg b.d. and one patient (4%) received 120 mg b.d. to improve AO. Control of AO was achieved in all patients whose dosages were adjusted.

Twenty-four patients completed all 3 years of the study (40 mg b.d., n = 19; 80 mg b.d., n = 5). The 11 patients who withdrew from the study prior to the 3-year time point did so by month 6 (n = 2), month 12 (n = 2), month 24 (n = 4) and by month 36 (n = 3; Figure 1). Seven withdrawals occurred because of AEs, one for disease progression at month 27, two at the patients' request and one for a protocol violation. Regarding the patients who withdrew from the study because of AEs, a total of four patients in the 40 mg group withdrew - two because of sepsis, one because of cardiac arrest and one patient because of alcohol abuse. In the 80 mg group, one patient withdrew because of cardiac arrest and one because of anaemia. In the 120 mg group, one patient withdrew from the study because of cardiac arrest.

There were five deaths: three were due to sepsis and one was due to metastatic disease (metastatic gastrinoma and carcinoid syndrome). One other death was due to GI bleeding and sepsis from a perforated duodenal ulcer in a patient with metastatic gastrinoma whose dosage was decreased from 120 to 40 mg b.d. for unclear reasons 2 months earlier and missed the month 11 AO evaluation. None of these cases was felt by the investigator to be drug-related.

Baseline and demographic characteristics for all patients are presented by diagnostic group in Table 1. Of the 35 patients, 13 were women and 22 were men; 27 were younger than 65 years of age and eight were 65 years of age or older; 32 were white and three were black; 21 had sporadic ZES, five had ZES with MEN-1 and nine had IH. In addition, six patients had undergone a partial gastrectomy. Baseline and demographic characteristics for the 24 patients completing the study were similar to those initially enrolled (Table 1).

The number and percentage of patients in whom AO was controlled at enrolment after pantoprazole treatment by dosage and diagnosis for all patients and the 24 who completed the study are presented in Table 2. At month 6, 94% of the study patients responded to therapy. The overall response rate ranged between 93% and 100% from months 12 to 36. For the majority of patients, mean and median AO rates were <10 mmol/h throughout the 36 months of treatment with pantoprazole.

From month 6 to the end of the study, AO remained at ≤5 mmol/h for all patients when viewed by diagnosis (Figure 2) and dosage group (Figure 3), except for one patient (ZES with MEN-1) at month 18 (AO = 5.15 mmol/h) and one patient (dosage = 120 mg b.d.) at month 12 (AO = 6.18 mmol/h) respectively. Both of these patients had undergone prior acid-reducing surgery.

At least one AE was noted in all but two subjects during pantoprazole therapy, but most AEs were not considered to be drug-related. The most common treatment-emergent AEs were headaches in 17 patients (49%), diarrhoea in 15 patients (43%), nausea in 14 patients (40%), abdominal pain in 12 patients (34%), dyspepsia in 11 patients (31%) and vomiting in 11 patients (31%).

The incidence of headaches was similar across dosage treatment groups; 12 (48%) in 40 mg group, four (50%) in 80 mg group and one (50%) in 120 mg group. Generally, for other AEs the differences in the incidence of treatment emergent adverse events (TEAEs) followed a dose-response pattern. However, it should be noted that patients were not randomly assigned to dose groups and that patients with more severe symptomatic pathological hypersecretory conditions and multiple serious medical problems, who were more likely to have AEs, received higher doses. Thus, it cannot be concluded that the incidence of AE was dose-related.

During this 3-year study, there were five patient deaths (see above), 19 serious AEs (14 of which were previously reported) and seven patient discontinuations because of AEs.

Table 3 shows the 11 patients' reasons for discontinuation. There were no significant alterations in serum gastrin levels (ZES or IH) or laboratory abnormalities related to pantoprazole noted throughout the study.

The results of the non-mydriatic ophthalmic examinations for all 35 patients show sporadic changes from previous examinations for 11 patients. All of these events were considered to be mild to moderate in severity and not related to the study medication. There was no report of treatment-related ophthalmic or optic nerve complications.

DISCUSSION

The discovery of potent PPIs has dramatically improved the control of gastric acid hypersecretion in patients with conditions such as ZES and IH. Control of gastric acid secretion may be required even in patients with ZES after successful gastrinoma resection because of the enhanced parietal cell mass.[20] The purpose of this study was to investigate the safety and efficacy of pantoprazole for long-term maintenance (up to 3 years) and therefore extend our previous 6-month observations at dosages required to maintain AO control in ZES.[16] These safety data are particularly relevant given the long-term treatment with PPIs in patients with gastro-oesophageal reflux disease. All of the patients enrolled were previously treated with either omeprazole or lansoprazole. In a preliminary study that investigated the ability of oral pantoprazole to control pentagastrin-stimulated acid secretion in healthy subjects we showed that a dose of 40 mg of pantoprazole resulted in the control of gastric acid secretion, defined as <10 mmol/h.[21] This study provided important prognostic information with regard to the dosage of pantoprazole that would be necessary to control AO in patients with ZES. Accordingly, the dosage of pantoprazole selected was 40 mg b.d. at study entry. The measurement of gastric AO at defined study points permitted dose escalation to control gastric acid secretion.

We found pantoprazole to be both effective and generally well tolerated in patients with ZES or IH. Of the 35 patients enrolled in the study, 24 patients (19 ZES patients, including five with MEN-1 and five IH patients) completed the 36-month study. For the majority of patients, mean and median AO rates were <10 mmol/h throughout the 36 months of treatment with pantoprazole. The AOs of the majority of patients were controlled with a dosage of 40 mg b.d. or 80 mg b.d. Only six patients (17%) throughout the study required 240 mg/day for AO control.

The drop out rate may appear high compared with previous studies,[6,10-12] but this may be due to the much longer duration of this study compared with the others. Most of the patients dropped out because of a desire to limit frequent monitoring and not because of treatment failure. Only one patient (120 mg group) dropped out of the study because of an unsatisfactory response regarding the control of gastric acid secretion. This patient was also in violation of the protocol as she was intermittently non-compliant. She was discontinued on day 858, despite AO values ≤5 mmol/h. The patient died of advanced pancreatic cancer, sepsis and congestive heart failure approximately 2 months after discontinuation.

The subjects who participated in this study are representative of the larger group of patients with gastric acid hypersecretory conditions. The study included both ZES and IH to reflect this group. Furthermore, inclusion of patients with MEN-1 ($n = 5$) as well as ZES patients with prior gastric acid-reducing surgery is particularly important because it has been established previously that gastric acid control is considerably more difficult in these patients.[6] Adjustment of the dosage of pantoprazole in this study paralleled other reports with omeprazole and lansoprazole and underscores the necessity of periodically measuring gastric AO in patients with hypersecretory conditions.[3, 6, 11-15] Although the rationale for dosage adjustments is not clear, in these studies it is presumed that the need for dosage adjustment is due to fluctuations in AO as a function of tumour burden or hypercalcaemia as observed in patients with MEN-1. Other potential reasons include fluctuations in the rate of gastric emptying and, hence, PPI absorption in the duodenum.

When we analysed our month 6 data[16] we observed that 94% of the study participants had controlled AOs (<10 mmol/h). From months 12 to 36, the rate of AO control ranged from 93% to 100%. More importantly, by the end of the study, the AOs of all of the patients were controlled with pantoprazole.

We chose a b.d. dose for convenience, balancing the needs for ongoing acid control with the ease of administration. The b.d. dosing has now become the de facto regimen of choice without clear data supporting it. It is hypothesized that the rationale for the use of b.d. doses in patients with hypersecretory conditions is that these patients have an increase in parietal cell mass and an increase in pump turnover.[22] These observations are supported by other studies in which the majority of ZES patients required b.d. doses of omeprazole or lansoprazole.[6,11,12,15,23,24] It has been previously reported[6] that, in some patients, dosages may be reduced with careful measurements of gastric acid secretion. This was accomplished in the current study.

Safety evaluations were performed at each study interval. Headache was the most frequent AE and the frequency was similar across dose groups. No serious AEs felt to be related to pantoprazole were noted. Furthermore, no episodes of anterior ischaemic optic neuropathy were reported in any of the study participants.

In conclusion, maintenance oral pantoprazole therapy at dosages of 80–240 mg/day for up to 36 months is effective and generally well tolerated for patients with pathological hypersecretory conditions including ZES, with and without MEN-1 and IH.

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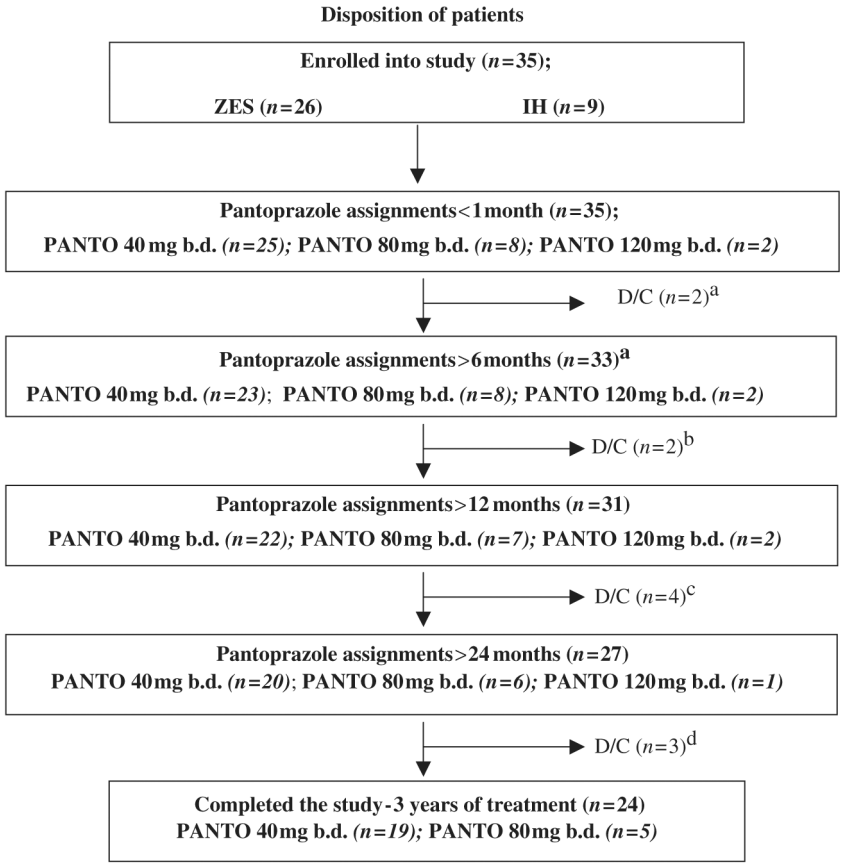

Figure 1.

Disposition of patients. ZES, Zollinger-Ellison syndrome; D/C, discontinuation; PANTO, pantoprazole; IH, idiopathic hypersecretion; D, died; b.d., twice a day. (a) Two patients discontinued because of adverse events on relative days 8 and 6. (b) Two patients discontinued because of adverse events on relative days 197 and 246 (D). (c) Four patients discontinued because of adverse events (n = 2, D), protocol violation (n = 1) and patient request (n = 1) before the end of year 2. (d) Three additional patients discontinued because of unsatisfactory response (n = 1, D), patient request (n = 1) and adverse event (n = 1) by the end of year 3. Dose assignments as per initial group assignment.

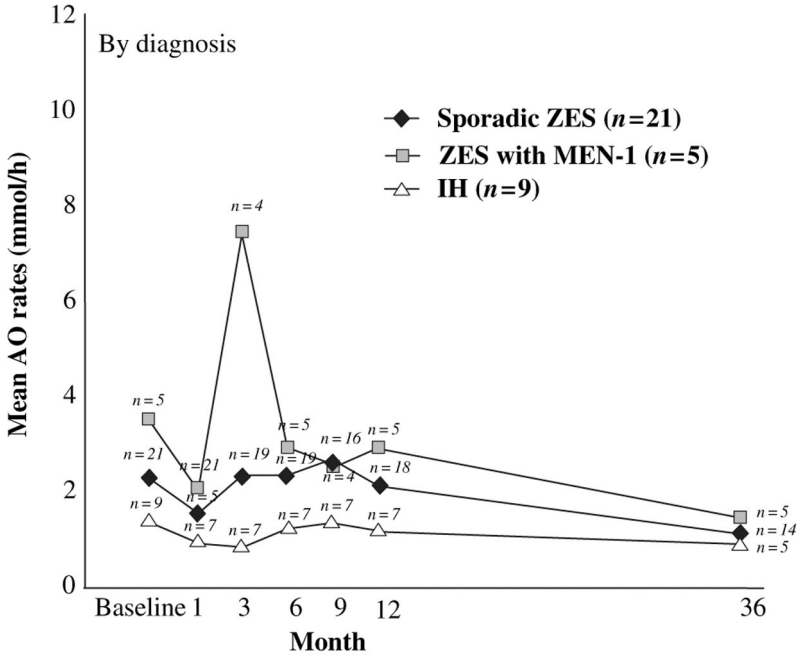

Figure 2.

Mean acid output (AO) over the 36-month treatment period presented by diagnosis. ZES, Zollinger-Ellison syndrome; IH, idiopathic hypersecretion; ZES with MEN-1, ZES with multiple endocrine neoplasia syndrome type 1.

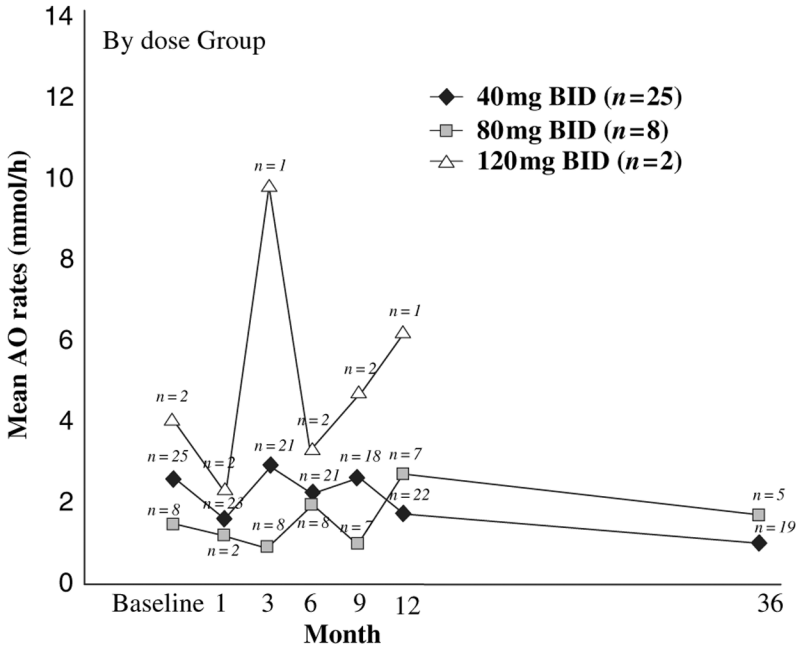

Figure 3.

Mean acid output (AO) over the 36-month treatment period presented by dose of pantoprazole given twice/day (b.d.) to the patient.

Table 1.

Demographic and baseline characteristics by diagnosis

Characteristic	IH (*n* = 9)	ZES (*n* = 21)	ZES with MEN-1 (*n* = 5)	Total (*n* = 35)	Completers (*n* = 24)
Age (years)					
Mean (range)	55.2 (35–74)	51.6 (30–73)	45.8 (32–59)	51.7 (30–74)	54.7 (32–74)
Age group, *n* (%; years)					
<65	6 (67)	16 (76)	5 (100)	27 (77)	18 (75)
≥65	3 (33)	5 (24)	0	8 (23)	6 (25)
Sex (male/female; *n*)	7/2	12/9	3/2	22/13	16/8
Ethnicity (white/black; *n*)	9/0	18/3	5/0	32/3	22/2
Height (cm)					
Mean ± s.d.	176.1 ± 8.4	172.9 ± 10.3	171.2 ± 11.6	173.4 ± 9.9	174.2 ± 10.4
Weight (kg)					
Mean ± s.d.	80.3 ± 15.4	84.2 ± 19.9	93.2 ± 6.4	84.5 ± 17.6	88.0 ± 18.5
Treatment, *n* (%)					
Pantoprazole, 40 mg b.d.	8 (89)	13 (62)	4 (80)	25 (71)	19 (79)
Pantoprazole, 80 mg b.d.	1 (11)	6 (29)	1 (20)	8 (23)	5 (21)
Pantoprazole, 120 mg b.d.	0	2 (9)	0	2 (6)	0
Partial gastrectomy, *n* (%)					
No	9 (100)	16 (76)	4 (80)	29 (83)	19 (79)
Yes	0	5 (24)	1 (20)	6 (17)	5 (21)
Completed study, *n* (%)					
No	4 (44)	7 (33)	0	11 (31)	
Yes	5 (56)	14 (67)	5 (100)	24 (69)	

Table 2.

Number (%) of patients with AO controlled at the indicated time points

	By dose group (mg b.d.)			By diagnosis			
AO collection (time point)	**40**	**80**	**120**	**Sporadic ZES**	**ZES with MEN-I**	**IH**	**Total**
Day 28	23/23 (100)	8/8 (100)	2/2 (100)	21/21 (100)	5/5 (100)	7/7 (100)	33/33 (100)
Month 3	21/23 (91.3)	8/8 (100)	1/2 (50)	19/21 (90.5)	4/5 (80.0)	7/7 (100)	30/33 (90.9)
6	21/23 (91.3)	8/8 (100)	2/2 (100)	19/21 (90.5)	5/5 (100)	7/7 (100)	31/33 (93.9)*
9	18/21 (85.7)	7/7 (100)	2/2 (100)	16/18 (88.9)	4/5 (80.0)	7/7 (100)	27/30 (90.0)
12	22/22† (100)	7/7 (100)	1/1 (100)	18/18 (100)	5/5 (100)	7/7 (100)	30/30 (100)
15	18/20 (90.0)	6/6 (100)	1/1 (100)	15/16 (93.8)	4/5 (80.0)	6/6† (100)	25/27 (92.6)
18	20/20 (100)	6/7† (85.7)	1/1 (100)	16/16 (100)	4/5 (80.0)	7/7 (100)	27/28 (96.4)
21	18/20 (90.0)	6/6 (100)	1/1 (100)	14/15 (93.3)	5/5 (100)	6/7 (85.7)	25/27 (92.6)
24	19/20 (95.0)	6/6 (100)	1/1 (100)	14/15 (93.3)	5/5 (100)	7/7 (100)	26/27 (96.3)
27	18/19 (94.7)	6/6 (100)	1/1 (100)	15/15 (100)	4/4† (100)	6/7 (85.7)	25/26 (96.2)
30	18/19 (94.7)	5/6 (83.3)	0	12/13† (92.3)	4/5 (80.0)	7/7 (100)	23/25 (92.0)
33	19/19 (100)	5/6 (83.3)	0	13/14 (92.9)	5/5 (100)	6/6 (100)	24/25 (96.0)
36	19/19 (100)	5/5 (100)	0	14/14 (100)	5/5 (100)	5/5 (100)	24/24 (100)

*One patient in the 120 mg b.d. group received 12 months of study medication, but the acid measurement was not performed at the 12-month evaluation.

†Denominator change reflects the number of patients who kept the assessment appointment and completed the 3-year study. IH, idiopathic hypersecretion; AO, acid output.

Table 3.

Number (%) of patients who discontinued by primary reason

	Pantoprazole (mg b.d.)		
Reason	**40 (*n* = 25)**	**80 (*n* = 8)**	**120 (*n* = 2)**
Total	6 (24)	3 (38)	2 (100)
Adverse event	4 (16) *	2 (25)	1 (50)
Patient request	1 (4)	1 (13)	0
Protocol violation	1 (4) *	0	0
Unsatisfactory control	0	0	1 (50)

* One patient discontinued treatment because of a protocol violation (non-compliance due to alcoholism), but the patient is accounted for in the adverse event (alcohol abuse) row as well.