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LONG-TERM TREATMENT WITH PEGVISOMANT AS MONOTHERAPY IN PATIENTS WITH ACROMEGALY: EXPERIENCE FROM ACROSTUDY

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Abstract

Objective—To evaluate use of pegvisomant, a GH receptor antagonist, as monotherapy in ACROSTUDY, a global safety surveillance study set in 14 countries (373 sites).

Methods—A descriptive analysis of safety, magnetic resonance imaging (MRI) reading and treatment outcomes in 710 subjects who received at least one pegvisomant dose as monotherapy during and up to 5 years follow-up in ACROSTUDY.

Results—Subjects received 5.4 yr. (mean) of pegvisomant and were followed in ACROSTUDY 3.8 yr. (mean). A total of 1255 adverse events were reported in 345 subjects (48.6%). Serious adverse events were reported in 133 (18.7%) subjects including 22 deaths, none of which were attributed to pegvisomant use. Of 670 (94%) subjects with at least one liver function test reported in ACROSTUDY, 8 (1.2%) had reported increases in transaminases > 3X ULN. No liver failure was reported. Based on central MRI reading, 12 of 542 subjects (2.2%) had a confirmed increase or increase/decrease in tumor size. Injection-site reactions were reported in 2.3%. At 5 years of therapy, IGF-1 level was reported normal in 67.5% (mean dose 17.2 mg/day) and elevated in 29.9% (mean dose 19.8 mg/day). Subjects on 20 mg per day or more rose from 36% at 3 years to 41% at 5 years of therapy.

Conclusions—ACROSTUDY data indicate that pegvisomant used as sole medical therapy is safe and effective medical treatment for acromegaly. The reported low incidence of pituitary tumor size increase and liver enzyme elevations are reassuring and support the positive benefit–risk of pegvisomant therapy.

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Keywords

acromegaly; pegvisomant; ACROSTUDY; clinical trial

INTRODUCTION

Current treatment for acromegaly includes surgery, radiotherapy, and/or medical therapy. Transsphenoidal surgery cures only 60% of patients (1,2) and radiotherapy has a slow onset of effect and may lead to hypopituitarism (3–5). Currently available medical therapies are dopaminergic agonists, somatostatin analogues and a growth hormone (GH) receptor antagonist – pegvisomant (Somavert®). Dopaminergic agonists rarely normalize IGF-1 levels and have side effects that may be limiting (6). Long-acting somatostatin analogues achieve biochemical control in 28–60% of patients (7–10).

Pegvisomant was approved in the United States in early 2003 and subsequently in Europe in 2004. Initial pivotal studies with pegvisomant provided short-term efficacy and safety data (11,12). Clinical symptoms were significantly improved and serum IGF-1 concentrations normalized in nearly all patients. Additional post –marketing information has been collected as part of ACROSTUDY (13,14).

ACROSTUDY, which included 1867 subjects from 14 countries enrolled between 2004 and December 4, 2012, is designed to capture safety and treatment outcomes in subjects with acromegaly treated with pegvisomant as used in routine clinical practice (“real-world”). As a Phase IV non-interventional safety surveillance study, it provides valuable long term follow up of a large number of subjects and an opportunity to look at data otherwise not obtainable from smaller-scale, controlled clinical trials.

A prior interim analysis of the entire ACROSTUDY cohort included data on subjects who received pegvisomant alone and those subjects who received pegvisomant together with other medical therapies (15). However, to date, no long-term data on pegvisomant as monotherapy are available. The long term benefits and risks of a drug may not be clear unless monotherapy results are presented. Therefore, in order to better define the “real world”, long-term safety and treatment outcomes of pegvisomant when used as the sole acromegaly medical therapy, we present in the current report the data collected in ACROSTUDY from subjects receiving pegvisomant monotherapy.

MATERIAL AND METHODS

Study Design

ACROSTUDY is an open-label, global, non-interventional, post marketing surveillance study open to subjects with acromegaly treated with pegvisomant. (15). Baseline is defined as start of pegvisomant treatment regardless of enrollment in ACROSTUDY. All recorded study data are collected as part of patient routine clinical care; i.e. no additional diagnostic or monitoring procedures are undertaken for the study as described previously (16,17). Timing of visits, pegvisomant dose and dose titration are at each treating physician/ investigator’s discretion. Safety monitoring, per the protocol suggests pituitary imaging at 6

and 12 months and then yearly and liver test evaluations and serum IGF-1 levels every 6 months after pegvisomant start. IGF-1 concentrations were reported as locally analyzed and referred to the local reference ranges. Data reported in this paper reflect a data cut on December 4, 2012.

Study Subject Inclusion/Exclusion Criteria

Subjects who received at least one dose of pegvisomant at, prescribed as monotherapy up to 5 years of follow-up in ACROSTUDY were included. Subjects on somatostatin analogs and/or dopamine agonists in combination with pegvisomant were excluded. Subjects who discontinued either somatostatin analogs or dopamine agonists at the time of the start of pegvisomant were included. Only subjects > 18 years of age at ACROSTUDY enrollment were included. Other inclusion and exclusion criteria were the same as for ACROSTUDY (15). The ACROSTUDY data reported here were collected in compliance with, and consistent with, the most recent version of the Declaration of Helsinki. In addition, all applicable local laws and regulatory requirements in the countries involved were adhered to. Local ethical approval was obtained for all participating centers, and all subjects provided written informed consent ACROSTUDY enrollment.

PARAMETERS ASSESSED

Safety was evaluated by adverse events (AEs) and laboratory data reported by investigators. AE was considered any untoward medical occurrence reported while the patient was in ACROSTUDY; the event need not be causally related to pegvisomant. Serious AEs (SAEs) were defined as AEs that were fatal or life threatening, required hospitalization, or prolongation of existing hospitalization, resulted in *in utero* exposure or permanent or serious disability/incapacity. AEs were coded and frequencies displayed according to the *Medical Dictionary for Regulatory Activities* (http://www.meddra.org/). Events and comorbidities that occurred prior to ACROSTUDY entry, even for patients on pegvisomant prior to ACROSTUDY, were considered part of medical history and recorded in the database as such. Worsening of a preexisting condition during ACROSTUDY was reported as an AE.

CENTRAL MAGNETIC RESONANCE IMAGING (MRI) READING

The ACROSTUDY protocol suggested the local MRI to be conducted with the same imaging technique and equipment. T1-weighted spin-echo (or fast spin echo) sagittal and coronal images before and after gadolinium, and T2-weighted fast spin-echo coronal images were recommended. All available images for a subject were sent for central review only if the local radiologist's reading reported a significant change (a decrease or an increase) in pituitary tumor size, regardless of whether or not the change was assessed as clinically important. Images depicting the tumor in comparable sections were selected. Sections depicting the infundibulum were used in most cases. A manual segmentation of the carotid arteries, sellar contents, normal pituitary, and adenoma was performed and volume changes assessed. By central reading, a significant change in pituitary tumor size was defined as a change in the largest diameter of more than 3 mm. For macroadenomas an additional

criterion of increase or decrease in tumor volume of greater than 20% was used to define a change, as previously described (18).

STATISTICAL ANALYSES

Data were analyzed descriptively. Cross-sectional data were analyzed from baseline (defined as start of pegvisomant treatment, regardless of when ACROSTUDY enrollment occurred) up to 5 years of pegvisomant therapy. Frequencies and percent were calculated for categorical variables. Percent was taken out of a total number of subjects with an observed measure of interest at the specified time point (cross-sectional summary) or over a specified time frame (incidence calculation). Tumor volume change response are: Increased, Decreased, Increased and Decreased, or Unchanged. Liver function abnormalities were identified from two data sources, reports of adverse events and abnormal laboratory investigations. Liver enzyme increases were defined as > 3-fold elevations in at least one test ALT (alanine aminotransferase), AST (aspartate aminotransferase). IGF-1 concentration was categorized either as normal (within upper and lower normal limits for the local laboratory reference values), > 1.2 X ULN (upper limit of normal), or < LLN (lower limit of normal) at each year of follow up. Data were analyzed by years from pegvisomant start and included mean pegvisomant daily dose (mg/day). Doses administered less frequently than daily were recalculated to mg/day. In addition, 155 subjects in whom yearly longitudinal IGF-1 data were available from start of pegvisomant to 5 years of follow-up (longitudinal group) were analyzed separately and similarly.

RESULTS

The study population consisted of the 710 subjects; 348 (49%) males and 362 (51%) females, of whom 93.2% were Caucasian, 0.8% Black, 0.3% Oriental, 0.1% Hispanic, 0.7% Asian and 2.3% other ethnicities from 14 countries (Figure 1). The country-specific proportion of subjects receiving monotherapy relative to the total number of subjects ranged from 7% to 85% and among countries with at least 100 subjects enrolled, ranged from 20% in the Netherlands to 54% in the USA. Acromegaly was diagnosed at 42 ± 13 years of age (mean +/− standard deviation) (range 1.7 – 82 yr.): 13 subjects were < 18 years, when diagnosed with gigantism, and 68 were ≥ 60 years at diagnosis. The majority, 624 (87.9%), had sporadic acromegaly, but 5.1% had acromegaly and a familial syndrome. Acromegaly was diagnosed for 8.5 ± 8.5 years prior to starting pegvisomant.

Nearly all subjects had received other acromegaly therapy before beginning pegvisomant (Figure 2); 333 (46.9%) had prior surgery and medical therapy, and 183 (25.8%) had a combination of surgery, medical and radiation therapy. Nearly all, 611 (87.2%), had prior other medical therapy, and of these, 63.6% had received somatostatin analogs, 33.8% both somatostatin analogs and dopamine agonists and 2.6% dopamine agonists only. The remaining 37 subjects (5.2%) had no previous treatment.

At least one co-morbidity was reported prior starting pegvisomant in 613 (86.3%) subjects with hypertension, diabetes mellitus, osteoarthritis, sleep apnea, thyroid tumors and colon tumors being most common (Table 1). The following deficiencies were reported: FSH/LH in

82/237 (34.6%), ACTH 59/223 (26.5%), TSH 68/257 (26.5%), and prolactin 10/238 (4.2%), ADH 1/167(0.6%). Pegvisomant was initiated at a mean age of 50.9 ± 13.5 years. After starting pegvisomant and before ACROSTUDY enrollment 19 subjects underwent pituitary surgery and 47 subjects underwent radiation therapy.

ADVERSE EVENTS

Prior to ACROSTUDY, subjects received 570 ± 613 days (mean) of pegvisomant, were then followed 4.3 ± 1.8 years (mean) (range 0.4 – 8.5 yrs.) in ACROSTUDY for a total of 5.4 ± 2.7 years (mean) (range 0–11 yrs.) of pegvisomant therapy.

Overall, 1255 AEs were reported in 345 (48.6%) subjects and SAEs in 133 (18.7%) subjects including 22 deaths, none considered treatment related (Table 2). The most common SAEs were pituitary tumor increase or recurrence, metastatic tumor and cardiovascular events (Table 3). SAEs reported by the investigator as treatment related and leading to drug withdrawal were 2 events of pituitary tumor recurrence, 1 event of increased transaminases and increased hepatic enzymes and one event of hypersensitivity reaction. Other non-serious adverse events resulting in drug withdrawal or reduction in drug dose are reported in Table 4.

LIVER FUNCTION TESTS

At pegvisomant start, ALT was normal in 329 and > 3X ULN in 3, and AST was normal in 347 subjects. Liver related AEs were reported in 30 subjects; 16 instances of increased transaminases, 5 elevations in liver enzymes, 9 abnormalities of ALT, 1 of AST, and 1 rise in GGTP. 670 (94%) subjects had at least one liver function test reported during ACROSTUDY and 8/670 (1.2%) had reported increases in transaminases > 3X ULN. Pegvisomant dose ranged from 10 to 40 mg in these subjects of whom 3 had drug withdrawn and 5 did not. The increases were reported as not recovered in 4, recovered in 3 and unknown in 1.

PITUITARY TUMOR SIZE

Pituitary tumor size assessed locally was reported at least once in 542 subjects (Table 5). The follow up MRI was done after 2.66 ± 2.2 years (mean) (range 0.5–10 yr.), which represents 1443 person-years of MRI observation on pegvisomant monotherapy. Local MRI reading reported a change in 114 subjects and central reading was accomplished in 47 of them (Table 5). Central reading of 17 of the 28 with a locally reported increase confirmed an increase in 7, reclassified 8 as no change and 1 as an increase and decrease. Central reading of 4 of the 10 with a locally reported increase/decrease reclassified 2 as an increase and 2 as no change.

GLUCOSE HOMEOSTASIS

There were 26 glucose-related AEs that occurred in 23 subjects. These included 13 patients with worsening of pre-existing diabetes mellitus including 1 patient with 2 adverse events and 1 patient with 3 adverse events. Two patients had new onset impaired fasting glucose, 6

patients had new onset diabetes mellitus and there were 1 instance each of diabetic retinopathy and nephropathy occurring in patients with pre-existing diabetes mellitus.

INJECTION SITE REACTIONS

There were 16 (2.3%) subjects with 19 adverse events related to administration site issues. Investigators categorized these as lipodystrophy or lipohypertrophy (n=8), pruritus (n=1), injection site irritation (n=1), reaction (n=4), or condition (3), skin reaction (n=1) and injection site hematoma (n=1).

TREATMENT OUTCOMES

At 5 years of pegvisomant therapy, 67.5% of subjects achieved IGF-1 level normalization while 29.9% still had an elevated IGF-1 and 2.6% had IGF-1 levels below the lower limit of normal (Figure 3). Mean pegvisomant doses were higher in subjects with persistently elevated IGF-1 levels, average 19.8 mg per day at 5 years vs. 17.2 mg/day in those with normal IGF-1 levels. Mean pegvisomant dose in the elevated IGF-1 group increased by 1 mg per day from years 3 to 5 of therapy. The percentage of subjects on 20 mg or more per day changed from 36% at year 3 to 41% at year 5 of therapy. At the start of pegvisomant 673 (94.8%) of subjects were on daily injections. Dosing regimen was similar in follow up; among subjects whose dose frequency was recorded at 5 years, 91% were on daily dosing, 2.4% on 2–6 times per week, 1.4 % on weekly and 3.7% on some other regimen.

Subjects in the longitudinal group (n=155) received pegvisomant for a total of 7.5 years (mean) (range 1 to 9.9 yr.) and was similar to the overall cohort with respect to demographics, age of diagnosis, years of acromegaly and therapy prior to pegvisomant. In this group, 15.5% had a normal IGF-1 at baseline (the start of pegvisomant), 63.8% were normalized at 1 year and 65.8% were normalized at 5 years of pegvisomant therapy (Figure 4). The course of IGF-1 changes from baseline through 5 years in ACROSTUDY is shown in Figure 5. Most patients who had a normal IGF-1 at baseline or by year 1 remained normal at 5 years. However, some patients (n=25) became elevated at year 5 after having normalized at 1 year and various other patterns of IGF-1 status occurred.

DISCUSSION

This analysis aimed to evaluate the long-term safety and treatment outcomes of pegvisomant used as monotherapy for acromegaly in ACROSTUDY. Prior reports presented the data in subjects receiving pegvisomant alone together with those pegvisomant in combination with the drugs, the latter being a substantial portion of the ACROSTUDY cohort. Given the rarity of acromegaly, initial placebo-controlled randomized trials of pegvisomant monotherapy were relatively small and short term (11,12). Therefore, this large, long-term post approval safety surveillance study provides additional opportunities to verify initial data, ensure capture of rare adverse events and give insight into the performance of pegvisomant in a variety of clinical practice settings.

This analysis examined safety of pegvisomant monotherapy with regard to parameters identified from earlier studies as warranting continued re-assessment (12). One such

parameter is liver enzyme changes. The current analysis finds a low rate of liver function test abnormalities for pegvisomant monotherapy Many subjects, however, began pegvisomant prior to enrollment into ACROSTUDY so this figure could under-represent the transient LFT abnormalities shown previously to be more likely early in therapy (12). In ACROSTUDY overall liver enzyme abnormalities were reported in 2.5%, potentially reflecting a greater propensity for these with combination therapy of pegvisomant and somatostatin analogues (13,15,19,20). Another AE of interest were local reactions to the injection, these also occurred at low rate.

Another important goal of long-term safety surveillance in ACROSTUDY has been the monitoring of pituitary tumor size. Considering just the centrally read MRIs, 12 were confirmed to have an increase or increase/decrease in tumor size However, a limitation of this analysis is that substantial portion of the locally read MRIs reporting an increase in tumor size were not re-evaluated centrally so these changes could not be confirmed or disputed with a central reading. In addition, local reading cannot be used alone to establish the expected percentage of tumors that increase in size because studies have shown that about half of those initially reported to be increased locally are found to not be on central reading (18). Despite the limitations inherent in a surveillance study, this estimate of tumor enlargement rate on monotherapy is reassuringly low and similar to that reported in the overall ACROSTUDY that included subjects on combination therapy as well as detailed studies specifically examining tumor size on pegvisomant (18,21). Risk factors for tumor enlargement suggested by prior studies include documented tumor growth before starting pegvisomant, withdrawal of somatostatin analog therapy that previously produced tumor shrinkage (21–23) and no prior radiotherapy (23–28). The rates of tumor growth on pegvisomant alone are in line with tumor changes seen with other forms of medical therapy (10).

ACROSTUDY also aimed to monitor long-term biochemical control with pegvisomant, specifically IGF-1 normalization. The rate of IGF-I normalization observed in our study was similar to that reported for the entire ACROSTUDY cohort (15), a figure which represents IGF-1 normalization of both pegvisomant monotherapy and combination therapy groups.

This analysis confirms prior reports from the overall ACROSTUDY that IGF-1 normalization rate on pegvisomant monotherapy when used in clinical practice appears to be lower than expected based on initial trials (13) reporting normalization in 89% with 12 weeks and 97% with 12 months or more of therapy (11,12). Based on these data and the known mechanism of action of pegvisomant nearly all subjects were expected to achieve IGF-1 normalization if sufficient doses are administered. Reporting of efficacy based on IGF-1 normalization at any time point in early clinical trials could be an important reason for the apparent efficacy difference between those trials and this report. Whether treatment compliance played an additional role in the different efficacy observed in this vs. earlier reports is unknown because treatment compliance was not assessed.

One noticeable explanation for these disparities, as previously reported for ACROSTUDY (13) as well as the German ACROSTUDY (29), is that dose up-titration may not be maximal in subjects with persistently elevated IGF-1 levels. The reason for this observation

is unknown, but guidelines for acromegaly therapy recommend titration to achieve an IGF-1 within the reference range, and many physicians will titrate to an IGF-1 below a SDS of +1. The data with monotherapy demonstrate a rise in the proportion of subjects receiving higher doses of pegvisomant over time, longitudinally and cross-sectionally, and higher doses in patients with persistently elevated IGF-1 levels. Inconvenience of dosing beyond 20 mg, which requires 2 injections per day could be a factor limiting escalation. In our longitudinal subgroup analysis, 25% of subjects did normalize, but subsequently had a rise in IGF-1 potentially reflecting an initial wash out from prior somatostatin analog use or a waning of compliance. The proportion of normalized patients increased over time, parallel to the pegvisomant dose, suggesting that tachyphylaxis does not appear to play a role. No center in ACROSTUDY has reported tachyphylaxis, to date. A limitation of our analysis is the fact that central IGF-I levels were available only in some subjects, which necessitated that efficacy be based on local IGF-1 measurements for which the reliability is not known.

Although ACROSTUDY data provide important insight into the outcome of pegvisomant use in clinical practice, the study's population may be skewed to patients with the most severe acromegaly. In both the US and Europe pegvisomant is generally indicated for patients failing other therapy. In the US it is approved for patients with an inadequate response to surgery and/or radiation therapy and/or other medical therapies, or for whom these are not appropriate. In Europe, pegvisomant is approved for patients with an inadequate response to surgery and/or radiation therapy and in whom somatostatin analogues did not normalize IGF-1 or was not tolerated. We found that most subjects on pegvisomant monotherapy in ACROSTUDY failed prior therapies confirming that it is used in clinical practice for those with the most difficult to treat disease. Interestingly, pegvisomant is currently being given as monotherapy in only 37.5% of ACROSTUDY patients whereas, earlier in ACROSTUDY about 2/3 of subjects were receiving monotherapy. Whether this change in practice patterns reflects increasing comfort with the use of combination therapy or the entry of more complex patients into ACROSTUDY is not known. Interestingly, also, the proportion of subjects receiving monotherapy vs. combination therapy varies considerably between countries. The percentage of ACROSTUDY participants using pegvisomant as monotherapy seems somewhat more common in the US compared to most European countries, potentially reflecting the pegvisomant indication in Europe only in unresponsive or intolerant subjects to other medical therapies. ACROSTUDY's design provides a window into how the drug performs in clinical use, but this is also a setting subject to considerably less consistency in parameters such as patient compliance and physician practice patterns. In particular, the scope of data entered into the ACROSTUDY database varies at the clinician's discretion thus limiting that available for analysis and its uniformity. The fact that the study did not provide dose escalation guidelines, but left this to each clinician could have contributed to the less than maximal dose escalation in subjects with persistently elevated IGF-1 levels even after years of therapy.

In conclusion, this study confirms earlier smaller reports that pegvisomant monotherapy is safe and effective treatment for acromegaly with 67.5% of patients achieving a normal IGF-1 level by 5 years of therapy. The rate of liver function abnormalities is very low as is the rate of pituitary tumor growth on pegvisomant monotherapy.

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Abbreviations

ACTH	Adrenocorticotropic hormone
ADH	anti-diuretic hormone
AE	adverse events
ALT	alanine aminotransferase
AST	aspartate aminotransferase
DM	Diabetes Mellitus
FSH	Follicle stimulating hormone
GGT	gamma-glutamine transferase
GH	growth hormone
HbA1C	Hemoglobin A1C
IGF-1	Insulin like growth factor 1
LFT	liver function tests
LH	Luteinizing hormone
LLN	lower limit of normal
MI	Myocardial infarction
MRI	magnetic resonance imaging
SAE	Serious adverse events
SDS	Standard deviation score
TSH	thyroid stimulating hormone
ULN	upper limit of normal

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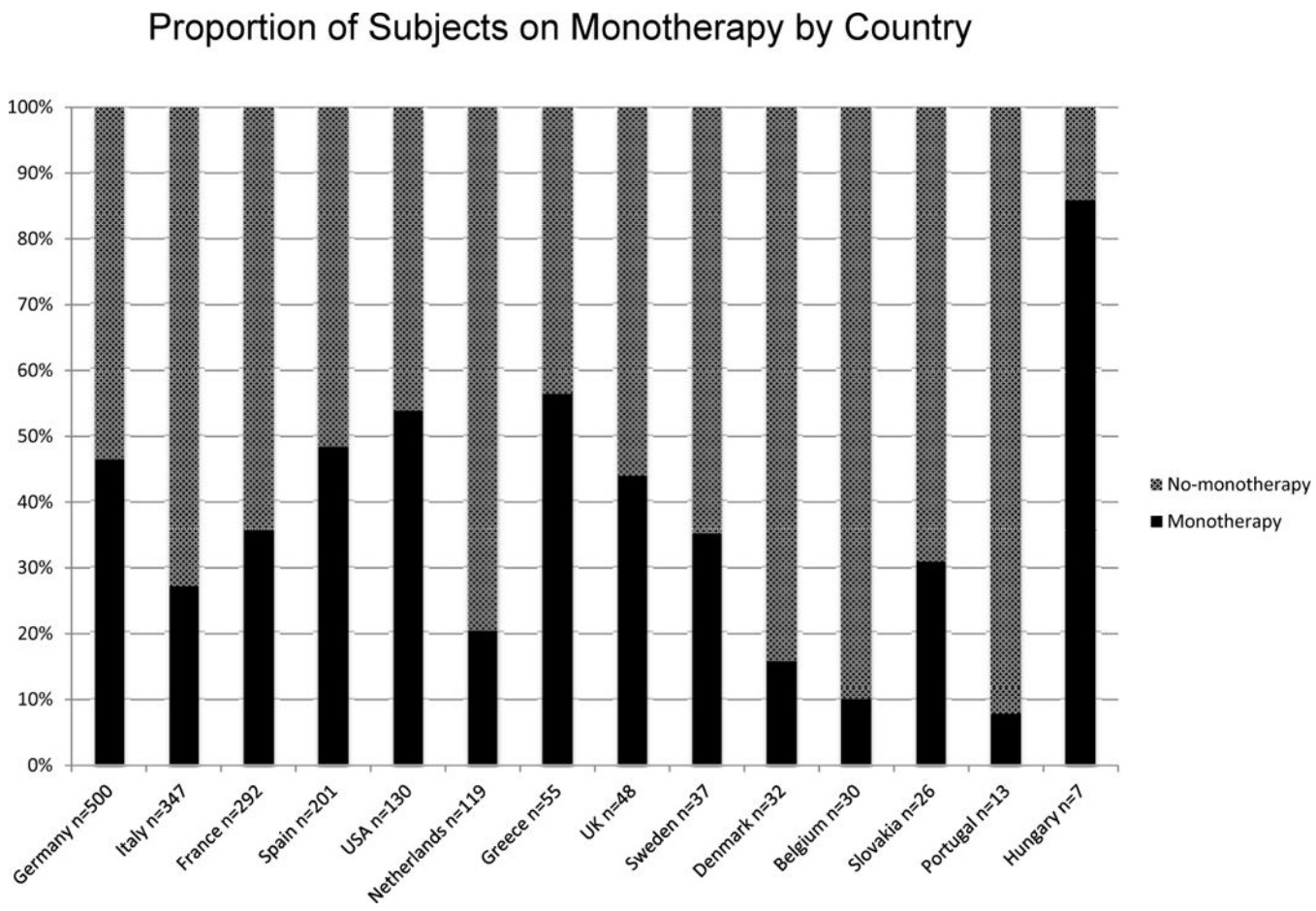


Figure 1.

Proportion of subjects on pegvisomant monotherapy in each country in ACROSTUDY (n=total number of subjects in ACROTSTUDY by country).

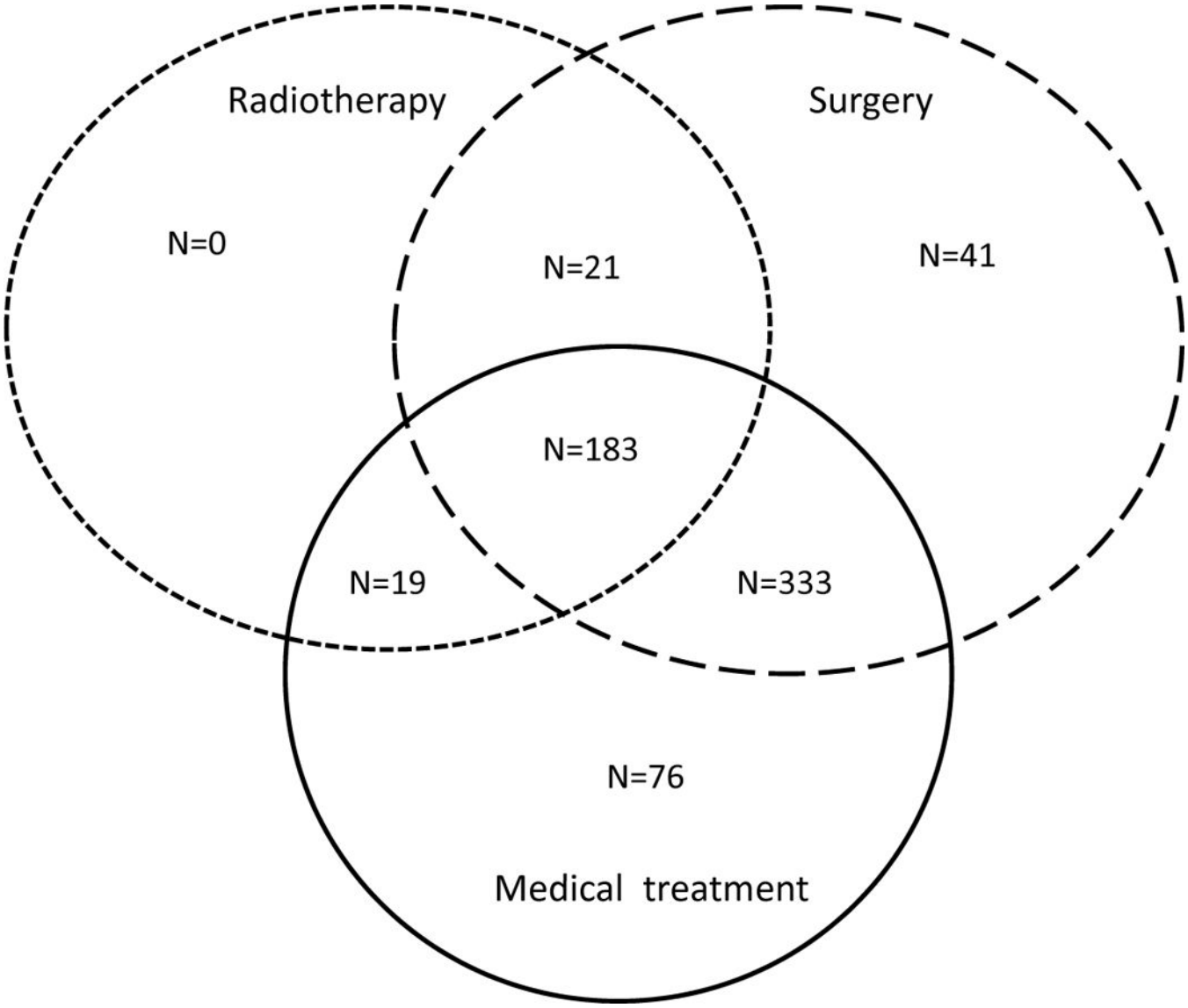


Figure 2.

Acromegaly therapies prior to pegvisomant in 710 patients receiving pegvisomant monotherapy in ACROSTUDY. N=number of subjects who received each therapy or a combination of each type therapy.

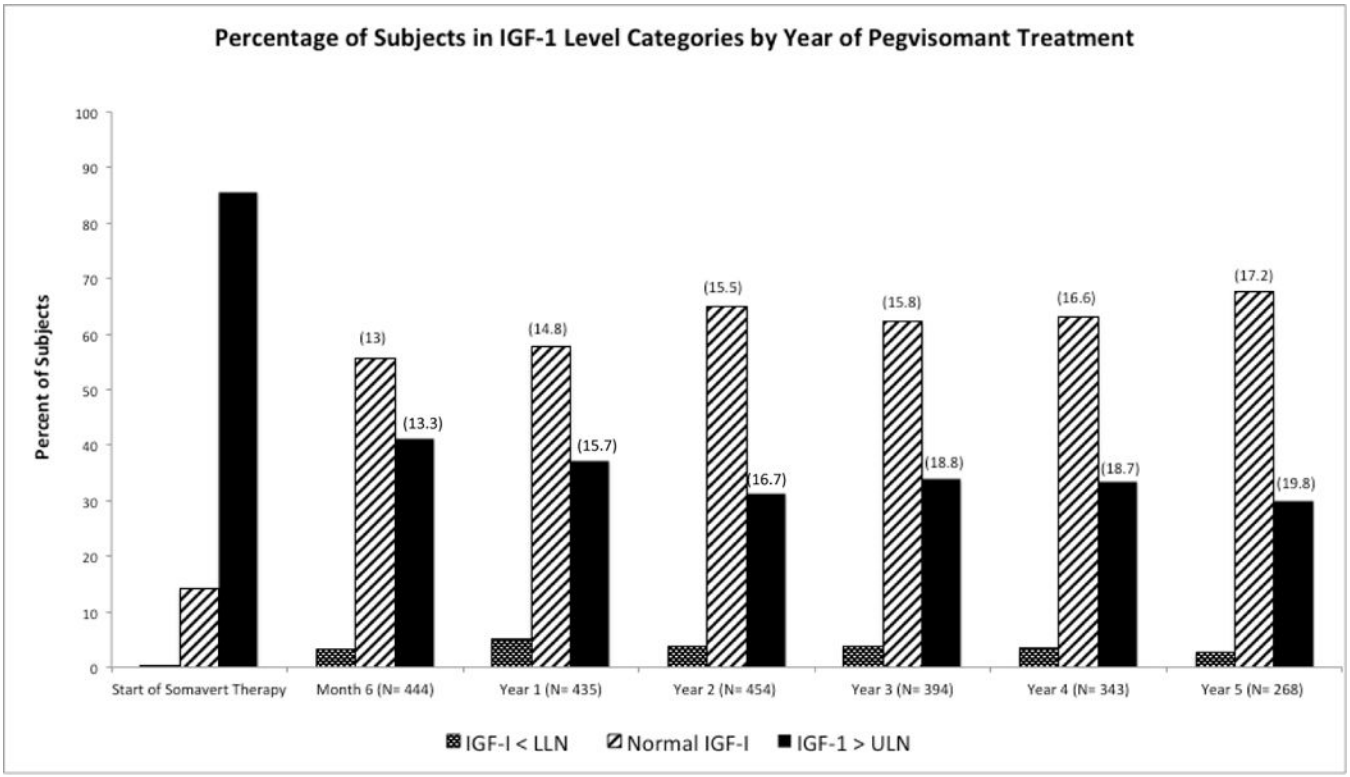


Figure 3.

Cross sectional data showing the percentage of subjects in IGF-1 categories at each year of pegvisomant monotherapy. Mean pegvisomant doses (mg/day) are shown above the bars.

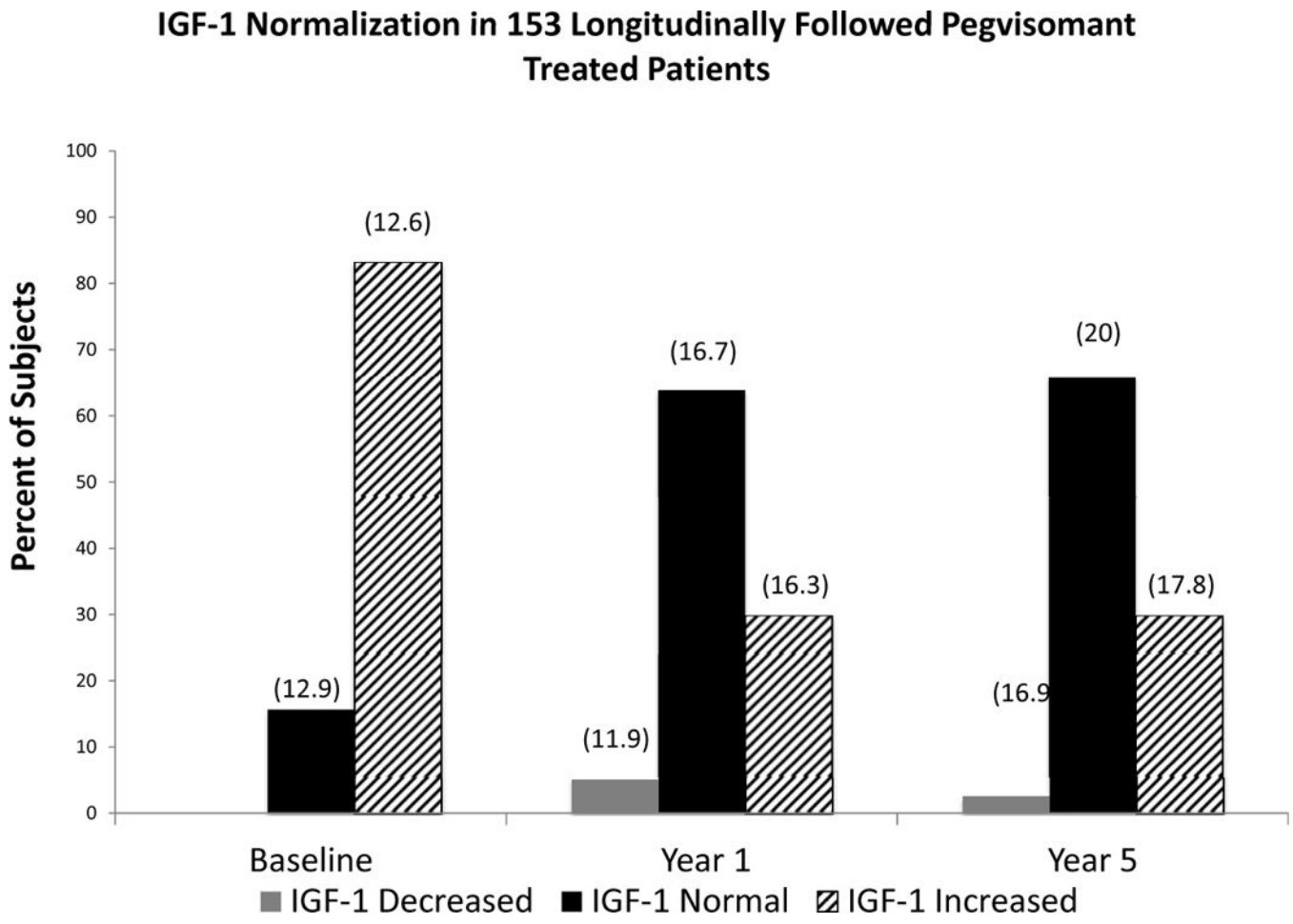
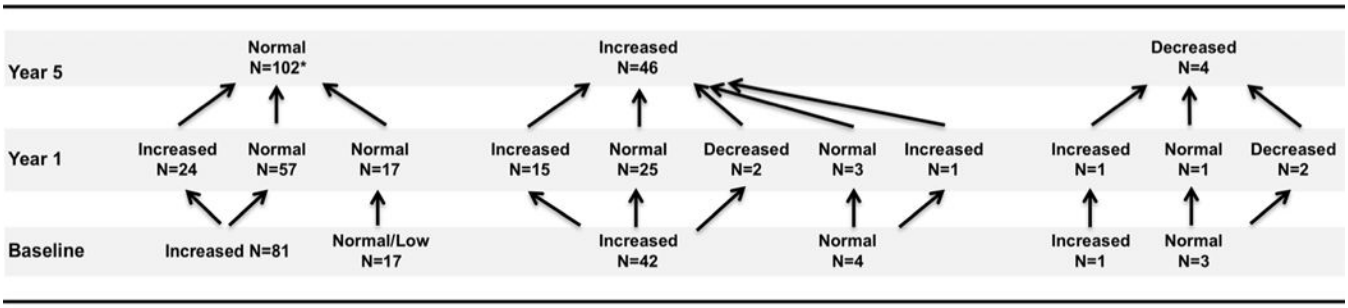


Figure 4.

IGF-1 normalization in 155 longitudinally followed pegvisomant treated patients. Mean pegvisomant doses (mg/day) are shown above the bars.



* 4 Subjects in the Normal IGF-1 at 5 year group had missing data at Baseline or 1 year. 3 additional subjects had missing datapoints at one of the 3 time points.

Figure 5.

Longitudinal Course of IGF-1 Levels in the 155 Subjects Followed over Time from Baseline to Year 1 and to Year 5 of Follow up in ACROSTUDY

Table 1

Comorbidities at the start of pegvisomant in 710 subjects

	Number (%)
Total Number of Subjects with Comorbidities	613 (86.3)
Metabolic/Endocrine	239 (33.0)
Diabetes mellitus	202 (33.0)
Goiter	37 (6)
Cardiovascular	341 (55.6)
Hypertension	326 (53.2)
Arrhythmia	37 (6.0)
Coronary heart disease	33 (5.4)
Cardiomyopathy	24 (3.9)
Myocardial infarction	14 (2.3)
Coronary angioplasty with or without stent	13 (2.1)
Coronary artery bypass surgery	10 (1.6)
Cerebrovascular	20 (3.3)
Transient ischemic attack	11 (1.8)
Infarction	3 (0.5)
Hemorrhage	1 (0.2)
Other cerebrovascular disease	5 (0.8)
Respiratory	170 (27.7)
Sleep apnea	131 (21.4)
Other respiratory disease	45 (7.3)
COPD	25 (4.1)
Musculoskeletal	216 (35.2)
Osteoarthritis	155 (25.3)
Surgery for Carpal Tunnel Syndrome	75 (12.2)
Other surgery for musculoskeletal disease	30 (4.9)
Osteoporosis	17 (2.8)
Tumors	278 (45.4)
Thyroid	139 (22.7)
Colon	108 (17.6)
Breast	28 (4.6)
Prostate	16 (2.6)
Skin	11 (1.8)
Lung	2 (0.3)
Other	85 (13.9)
Liver/Gallbladder	85 (13.9)
Hepatic disease	44 (7.2)
Surgery for gallstones	29 (4.7)
Current gallstones	22 (3.6)
Subjects with other comorbidity	325 (53.0)

	Number (%)
Other comorbidities	844

Table 2

Adverse Events and Serious Adverse Events during Pegvisomant Monotherapy in Acrostudy

	All Cause n (%)	Treatment Related n (%)
Subjects Evaluable for Adverse Events	710	710
Number of Adverse Events	1255	172
Patients with Adverse Events	345 (48.6)	106 (15)
Patients with Serious Adverse Events	133 (18.7)	12(1.7)
Subjects with Dose Reduced Due to Serious Adverse Events	1 (0.1)	0
Subjects with Drug Withdrawn (temporarily or permanently or delayed) due to Serious Adverse Events	39 (5.5)	5 (0.7)
Subjects discontinued treatment due to death	22(3)	0
Causes of Death (Age/gender)		
Ventricular fibrillation (48/M)	Death (62/M)	
Cardiac failure (66/M)	General physical health deterioration (84/F)	
Acute MI (69/M)	Gastric cancer (60/M)	
Sudden cardiac death (77/M)	Metastasis (63/F)	
Cardiac aneurysm (34/F)	Metastases Adenocarcinoma (49/M)	
Hemorrhagic stroke (34/M)	Esophageal carcinoma (lung metastases) (75/F)	
GI Bleeding (79/M)	Malignant melanoma (79/F)	
Acute pancreatitis (72/M)	Pulmonary edema (52/F)	
Death (65/F)	Sudden Death (75/F)	
Unknown Reason (76/F)	Aortic Aneurysm Rupture/Allergic Reaction to Allopurinol (70/F)	
Hypophagia (72/M)	Ictus (66/F)	

Table 3

All Adverse Events Reported in Acrostudy in Subjects on Pegvisomant

Subjects with Adverse Events		**345**
Administration site		41
Blood Disorders		12
Cardiac Disorders		45
Ear/Labyrnth		4
Endocrine	HbA1c increase	7
	Diabetes Mellitus	5
	Blood glucose increase	4
	Diabetes Mellitus poor control	3
	Impaired fasting glucose	2
	Type 2 DM	2
	Treatment Related DM	2
	Diabetic retinopathy	1
	Nephropathy	1
Hypopituitary		1
Eye Disorders		12
Gastrointestinal		60
	Polyp	10
	Abdominal pain	5
	Gastritis	5
	Nausea	4
	Diarrhea	4
Hepatobiliary		20
	Cholelithiasis	6
	Cholestasis	3
Immune System		4
Infection		19
Injuries		19
Vascular		42
	Hypertension	21

Table 4

Adverse Events Associated with Drug Withdrawal or Dose Reductions

	Relationship to Pegvisomant	
	Unrelated	**Related**
Non-Serious Adverse Events Associated with Drug Withdrawals		
Skin lesion		1
LFT increase		3
Renal failure		1
IGF-1 normal	6	1
Unknown	2	
Pituitary surgery	2	
Arthralgia	1	
Nausea	1	
Non-Serious Adverse Events Associated with Temporary Drug Withdrawals or		
IGF-1 normal	6	4
Discomfort		1
Headache		1
Cholecystitis	1	
Patient Request	1	
Cell Death	1	
Fatigue	1	
Vitamin D deficiency	1	
Serious Adverse Events Associated with Drug Withdrawal (other than death)		
Malignancy/Metastatic Cancer	5	
Pituitary Tumor Size Increase or Recurrent/removal	5	2
Elevated liver enzymes		1
Adrenal Gland Tumor		1
Hypersensitivity reaction		1
Cholecystitis	1	
Coronary Artery Disease	1	
Diplopia	1	
Depression	1	
Possible Optic nerve problem	1	
Spine Surgery	1	
Pulmonary Embolism	1	
Pregnancy	2	
Lacunar infarction	1	
Ankle fracture	1	
Vertebroplasty	1	

Table 5

Summary of Pituitary Tumor Imaging Results During Somavert Therapy Local vs. Central MRI Readings

	Central Reading					
	Increased	Decreased	Increased and Decreased	No change	Insufficient data	Not done
	N=10	N=13	N=2	N=18	N=4	N=495
Local Reading						
Increased (n=28)	7	0	1	8	1	11
Decreased (n=76)	1	13	1	8	3	50
Both increased and decreased (n=10)	2	0	0	2	0	6
No change (n=428)*						428