



Patient-reported outcomes in patients with acromegaly treated with pegvisomant in the ACROSTUDY extension: A real-world experience

Roberto Salvatori, Pietro Maffei, Susan M. Webb, Thierry Brue, Jane Loftus, Srinivas Rao Valluri, Roy Gomez, Michael P. Wajnrajch, Maria Fleseriu

► To cite this version:

Roberto Salvatori, Pietro Maffei, Susan M. Webb, Thierry Brue, Jane Loftus, et al.. Patient-reported outcomes in patients with acromegaly treated with pegvisomant in the ACROSTUDY extension: A real-world experience. *Pituitary*, 2022, 25 (3), pp.420-432. 10.1007/s11102-022-01206-2 . hal-03780362

HAL Id: hal-03780362

<https://amu.hal.science/hal-03780362>

Submitted on 14 Feb 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

**Patient-reported outcomes in patients with acromegaly treated with pegvisomant in the
ACROSTUDY extension: areal-world experience**

Roberto Salvatori, MD¹; Pietro Maffei, MD, PhD²; Susan M. Webb, MD³; Thierry Brue, MD, PhD⁴; Jane Loftus, MSc⁵; Srinivas Rao Valluri, PhD⁶; Roy Gomez MS, PhD⁷; Michael P Wajnrajch, MD, MPA⁶; Maria Fleseriu, MD⁸

¹Division of Endocrinology and Metabolism and Pituitary Center, Johns Hopkins University, School of Medicine, Baltimore, MD, USA; ²Department of Medicine (DIMED), University of Padua, Padua, Italy; ³IIB-Sant Pau and Department of Endocrinology/Medicine, Hospital Sant Pau, Universitat Autònoma de Barcelona, and Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBER-ER, Unit 747), ISCIII; Carrer de Sant Quintí 89, 08041-Barcelona, Spain; ⁴Assistance Publique-Hôpitaux de Marseille, Hôpital de la Conception, and Aix-Marseille Université, Marseille Medical Genetics, Marseille, France; ⁵Pfizer Ltd, Tadworth, United Kingdom; ⁶Pfizer, New York, NY, USA; ⁷Pfizer, Brussels, Belgium; ⁸Pituitary Center, Departments of Medicine (Division of Endocrinology, Diabetes, & Clinical Nutrition) and Neurological Surgery, Oregon Health & Science University, Portland, OR, USA.

Corresponding author:

Roberto Salvatori

Johns Hopkins University

Division of Endocrinology, Diabetes and Metabolism

1830 East Monument Street #333

Baltimore, MD 21287

Tel (410) 955-3921

Fax (410) 367-2042

Email: salvator@jhmi.edu

ABSTRACT

Purpose To report the effects of pegvisomant (PEGV) treatment on patient-reported outcomes in acromegaly patients.

Methods We conducted an extension study of an open-label, multinational, non-interventional study (ACROSTUDY) evaluating the long-term safety and efficacy of PEGV for acromegaly in routine clinical practice. Enrolled patients were rollover patients from ACROSTUDY, or treatment naïve/semi-naïve (NSN; no PEGV within 6 months of enrollment). Exploratory efficacy endpoints were changes in symptoms with the Patient-Assessed Acromegaly Symptom Questionnaire (PASQ) and quality of life with the Acromegaly Quality of Life questionnaire (AcroQoL). Results were analyzed in all patients, in NSN patient subgroup, and by diabetes status.

Results A total of 544 patients with acromegaly were enrolled, including 434 rollover subjects from ACROSTUDY and 110 NSN patients. Mean PEGV treatment duration was 7.8 years (range, 0–19.6 years). Overall, the majority of PASQ scores improved over time, but there was no significant difference between IGF-I controlled or uncontrolled groups. In the NSN subgroup, most PASQ and AcroQoL scores remained similar to baseline up to 2 years, regardless of IGF-I control. Patients with diabetes reported better PASQ scores over time with PEGV treatment, regardless of IGF-I control. IGF-I normalization increased from 10% of patients at baseline to more than 78% at year 10, with a mean daily PEGV dose of 18.7 mg.

Conclusion Overall, patients treated with PEGV had small improvements in PASQ. While IGF-I normalization increased with PEGV treatment, IGF-I control had no effects on PASQ and AcroQoL scores.

Keywords Acromegaly, Pegvisomant, ACROSTUDY, Patient-reported outcomes

Introduction

Acromegaly is caused by excess circulating growth hormone (GH) and insulin-like growth factor I (IGF-I), most often due to a GH-secreting pituitary adenoma [1]. Objective features of acromegaly may be subtle or severe, and can include excessive growth of hands and feet, coarsening of facial features, as well as prognathism [2, 3, 4]. Due to delayed detection, patients often have many complications at the time of diagnosis, including rheumatologic, cardiovascular, respiratory, neoplastic, neurological, and metabolic manifestations, which can negatively impact quality of life (QoL) [3, 5, 6]. Acromegaly treatment is multimodal, and may include surgery, medical therapy, radiation, or a combination of one or more of these treatments [7]. Medications include somatostatin receptor ligands (SRLs), dopamine agonists (DA), and the growth hormone receptor blocker, pegvisomant (PEGV), a pegylated GH receptor (GHR) antagonist. Goals of treatment include biochemical normalization, tumor control, prevention of complications, and normalization or improvement of QoL; however, several studies show that QoL is still impaired even when biochemical control is reached [6, 8, 9, 10].

PEGV binds to the human GHR and blocks signal transduction, resulting in a decline in circulating concentrations of IGF-I [11]. PEGV was approved by the European Medicines Agency (EMA) in 2002 [12] and by the US Food and Drug Administration (FDA) in 2003 [13]. Endocrine Society guidelines and consensus statements recommend using PEGV when patients have an inadequate response to surgery and/or radiation and fail to respond to other medical treatments, or as a primary therapy after failed surgery in selected patients [14, 15]. Clinical studies of PEGV have not reported any unexpected safety concerns, but found IGF-I normalization rates lower than those reported in initial clinical trials [16, 17], prompting the need for longer-term data in routine clinical practice.

ACROSTUDY was a non-randomized, open-label, multinational, non-interventional, post-authorization safety study (PASS) conducted to provide safety data for 1000 patients monitored over 5 years, as requested by the EMA. Initiated in 2004, the study monitored long-term safety and clinical outcomes; these data were submitted to the EMA in 2012, and in 2013 the EMA declared that the PASS commitment was fulfilled. However, the PASS study was voluntarily extended to follow-up a smaller patient subgroup, and to enroll a treatment naïve/semi-naïve to PEGV population of approximately 100 patients to analyze long-term safety as well as patient-reported outcomes (PROs) for health-related QoL.

This paper reports the effects of IGF-I control on treatment outcomes in terms of symptom scores on the Patient-Assessed Acromegaly Symptom Questionnaire (PASQ) and QoL on the Acromegaly Quality of Life questionnaire (AcroQoL) [18, 19] during long-term treatment with PEGV.

Methods and material

Study design

ACROSTUDY was an open-label, multinational, non-interventional study of the long-term safety and efficacy of PEGV used in the treatment of acromegaly in routine clinical practice. While the primary ACROSTUDY monitored long-term safety for at least 5 years, the current analysis, a voluntary long-term follow-up extension of the ACROSTUDY, was designed to include a subgroup of rollover patients (approximately 400), and a new subgroup of patients who were treatment naïve or semi-naïve (NSN; planned approximately 100). Both rollover and NSN subgroups formed the full analysis population (FAP); only patients in the newly enrolled NSN subgroup formed the NSN population.

ACROSTUDY was conducted in 15 countries (Austria, Belgium, Denmark, France, Germany, Greece, Hungary, Italy, Netherlands, Portugal, Slovakia, Spain, Sweden, UK, and the US), although not all countries were involved in the study extension (**Table 1**). The study was conducted according to the International Conference for Harmonisation Good Clinical Practices and in compliance with all legal and regulatory requirements of US, European, and international professional organizations. All patients (or informed legal representatives) gave written informed consent before study enrollment.

Inclusion criteria

ACROSTUDY primarily included adults (≥ 18 years) with acromegaly who were already receiving or began therapy with PEGV. All patients had undergone pituitary imaging within 6 months before enrollment. Pediatric patients could be enrolled in Europe but not in the US.

For the extension study, rollover patients continued treatment from the primary study after informed consent, and after verification of treatment compliance. NSN patients were defined, respectively, as never having received PEGV (naïve) or not being treated with PEGV during the 6 months before enrollment (semi-naïve); these patients began PEGV therapy during the study. Inclusion criteria for NSN patients were similar to those for rollover patients, except that these patients had to be enrolled within 5 days of the first dose of PEGV, and had to complete baseline evaluations (including PROs and laboratory tests) within 5 days of the first dose.

Exclusion criteria were discontinuation from the original ACROSTUDY, inability of patient (or representative) to understand the study and sign consent, recent (within 6 months) enrollment in another investigational drug trial for acromegaly, pregnancy or breastfeeding,

allergy to PEGV, or tumor complications (need for surgical tumor decompression, treatment for visual field loss, cranial nerve palsies, or intracranial hypertension).

Endpoints

Data collected from all patients in ACROSTUDY included acromegaly diagnosis, pituitary function, physical examination, previous and/or current therapies for acromegaly, PEGV dosage, IGF-I measurement, liver enzymes, adverse events, and concomitant medications/comorbidities. IGF-I was defined as normal, above the upper limit of normal (ULN), or below the lower limit of normal (LLN) for the laboratory used by each investigational site. Fasting blood glucose (elevated, >200 mg/dL) and glycosylated hemoglobin (HbA1c; elevated, >6.5%) were measured to determine diabetes status. IGF-I and HbA1c data were also analyzed separately for patients in the FAP, and the NSN subgroup.

Exploratory efficacy endpoints were changes in symptoms with the PASQ and QoL with the AcroQoL questionnaire. Paper questionnaires were autonomously completed by each patient. Responses were also analyzed by achievement of IGF-I normalization. The AcroQoL questionnaire was only administered during the extension and not during the primary ACROSTUDY.

The PASQ is an acromegaly-specific questionnaire that includes 6 questions evaluating headache, excessive sweating, joint pain, fatigue, soft-tissue swelling, and numbness or tingling in the extremities, as well as a total score [20, 21]. Each item was scored from 0 (no symptoms) to 8 (severe, incapacitating symptoms), and lower scores indicated improvement. A final question asked the patient to judge overall health status (scored 0–10). Absolute value and

change from baseline were analyzed at each visit (month 6, year 1, year 2, etc.) for patients in the FAP, the NSN subgroup, and by diabetes status.

AcroQoL includes 22 questions on 3 subscales denoted as Physical, Psychological/Appearance, and Psychological/Personal Relationship, plus a dimension for a global score [18]. The 22 items were scored on a Likert scale of 1-5 for occurrence frequency (1 = always; 2 = most of the time; 3 = sometimes; 4 = rarely; or 5 = never) or level of agreement (1 = completely agree; 2 = moderately agree; 3 = neither agree nor disagree; 4 = moderately disagree; or 5 = completely disagree). The subscales all had different point ranges, so they were standardized on a scale from 0 (worst QoL) to 100 (best QoL) before adding them together for the global score. A score <40 was considered severe impairment; ≥ 40 to <60 moderate impairment; and ≥ 60 mild or no impairment [22]. Absolute value and change from baseline were analyzed at each visit (month 6, year 1, year 2, etc.) for patients in the NSN subgroup, and by diabetes status. In contrast to the PASQ, an improvement in AcroQoL is denoted by an increase in score.

Statistical analyses

No formal sample size calculation was performed. Estimates of approximately 400 rollover patients and 100 NSN patients were judged sufficient to evaluate symptoms and QoL between patients who achieved or did not achieve normalization of IGF-I.

There were no pre-specified statistical tests of hypotheses in ACROSTUDY. Timing of outcome assessments was measured during visit time, which was at the discretion of the investigator (e.g., baseline, month 6, and yearly thereafter). Patients had different follow-up

durations depending on their enrollment status; rollover patients had >5 years of data, whereas NSN patients had a maximum of 3 years of data. Missing values were not imputed.

All statistics were descriptive, and any inferential statistics (e.g., P values) were considered exploratory. The effects of IGF-I control (normalized versus not normalized) were analyzed with a longitudinal repeated-measures model with control (yes/no) as a time-varying factor, visit window (e.g., month 6, year 1) as a continuous variable, and baseline measurement as covariate. No statistical analyses were performed for change from baseline at any timepoints.

For PASQ and AcroQoL, differences in the change from baseline for individual and total scores between IGF-I controlled and IGF-I uncontrolled status were calculated with 95% confidence interval (CI). The longitudinal repeated-measures model was used to summarize the effects of IGF-I control over time on these PROs.

Results

Patient disposition and characteristics

Patient disposition is shown in **Fig. 1**. Overall, the ACROSTUDY population included 2221 patients, of which 2090 had at least 5 years of follow-up including 1624 (77.7%) patients classified as non-active (i.e., terminated, exited, or died) and 466 (22.3%) patients classified as active. For this extension study, 434 of the 466 active patients were enrolled with 110 newly enrolled NSN patients (96 naïve and 14 semi-naïve) forming the FAP (n = 544). Overall, 450 (83%) patients completed the study, including 366 rollover patients and 84 NSN patients. Discontinuations for rollover (n = 68) versus NSN patients (n = 26), respectively, were due to treatment discontinuation (54.4% vs 61.5%), patient death (8.8% vs 0%), withdrawal of informed consent (1.5% vs 7.7%), and other reasons (35.3% vs 30.8%). PASQ results were

available for 203 FAP patients (37.3%), which included 84 patients (76.4%) from the NSN subgroup. AcroQoL results were available for 84 patients from the NSN subgroup.

Patient characteristics are summarized in **Table 1**. Overall, most patients were male (55.5%) and white (93.9%), with mean age of 42.8 years at acromegaly diagnosis. Patients began treatment at a mean age of 49.5 years and had a mean treatment duration of 7.8 years. Before the start of PEGV treatment, the majority of patients were on SRL (64.4%) or SRL/DA (30.9%). At the start of PEGV treatment, PEGV-alone was used in 45.6% of patients.

Patient-reported outcomes

PASQ

PASQ data were gathered from baseline to year 15 for the FAP and to year 3 for the NSN subgroup. Total scores and overall health status by IGF-I control, as well as individual scores for each sign and symptom of PASQ for FAP and NSN are presented in **Fig. 2**. For subjects in the FAP, mean total PASQ scores were 16.2 at baseline (n = 196), and improved to 11.7 by year 9 (n = 19); scores subsequently worsen afterwards but sample sizes were smaller. Mean overall health status scores were 4.1 at baseline (n = 201), and remained similar (4.1) up to year 10. After 9 years of treatment, improvements in mean scores from baseline were observed in 4 individual PASQ domains (excessive sweating [2.6 to 1.1], fatigue [3.5 to 2.4], soft tissue swelling [2.3 to 1.3], and numbness/tingling of limbs [2.2 to 1.6]).

When the FAP was analyzed by IGF-I control, mean total PASQ scores in the IGF-I-controlled group improved from 15.3 at baseline to 10.2 after 9 years of treatment, while mean scores in the uncontrolled IGF-I group improved from 16.2 to 15.0, respectively, (**Figure 2A**). Afterwards, sample sizes became smaller over time and scores changed widely. In the IGF-

I-controlled group, improvements from baseline to year 9 were observed in the headache (2.4 to 1.7), excessive sweating (2.5 to 1.2), fatigue (3.5 to 2.2) and numbness/tingling of limbs (1.9 to 0.8) domains; results remained similar over time in the other domains. In the uncontrolled IGF-I group, improvements from baseline to year 9 were observed in the excessive sweating (2.6 to 0.7), fatigue (3.5 to 2.8) and soft tissue swelling (2.5 to 1.7) domains; results worsened over time for the other domains. Overall, there were no significant differences between the two groups, but scores tended to be better with IGF-I control.

In NSN subjects, most of the PASQ scores remained similar over time. Mean total PASQ scores were 18.2 at baseline and 17.8 at year 2; and mean overall health status scores were 4.5 at baseline and year 2. Only the excessive sweating domain showed improvement from baseline to year 2 (3.1 to 2.3). When analyzed according to IGF-I control, the mean total PASQ score in patients with controlled IGF-I was 19.5 at baseline, which improved to 16.7 at year 2. Patients with uncontrolled IGF-I had a mean total PASQ score of 17.7 at baseline, which worsened to 19.9 at year 2. In patients with controlled IGF-I, three other PASQ domains showed improvements from baseline to year 2, including excessive sweating (3.0 to 2.1), joint pain (4.2 to 3.4), and fatigue (4.5 to 3.7); other domains had similar scores over time. In patients with uncontrolled IGF-I, mean scores for headache (2.4 to 3.5) and numbness/tingling of limbs (2.1 to 2.9) worsened at year 2 from baseline, while other domains had similar scores. Similar to the FAP, no significant differences between the controlled and uncontrolled IGF-I groups were observed for any of the PASQ domains, but patients with controlled IGF-I tended to have better results.

Patients with diabetes ($n = 48$) had higher total mean PASQ scores at baseline than those reported from the FAP (17.5 vs 16.2, respectively). Total mean PASQ scores in patients with

diabetes improved to 16.2 at year 1 (n = 33), 12.9 at year 2 (n = 21), and 10.8 at year 5 (n = 12); afterwards scores worsened but sample sizes were small. Mean overall health status scores also improved from 4.6 at baseline (n = 49), to 4.1 at year 1 (n = 33) and 3.3 at year 2 (n = 21). No significant differences were observed between IGF-I controlled and uncontrolled groups for patients with diabetes for any PASQ domains.

AcroQoL

Since the AcroQoL questionnaire was only administered to NSN patients, data were only available up to year 3; however, only year 2 data are presented as sample sizes at year 3 were small (higher scores indicating improvement).

Individual scores for each AcroQoL dimension and by level of IGF-I control, are presented in **Fig. 3**. Improvements occurred between baseline and 1 year for all AcroQoL dimensions, afterwards scores either remained similar or decreased up to year 2. For the IGF-I-controlled and uncontrolled groups, there was no significant differences between the AcroQoL scores over the course of the study.

For patients with diabetes, mean global AcroQoL scores were 56.1 at baseline (n = 26), 61.4 at month 6 (n = 18), and returned to baseline levels at year 1 (55.6; n = 20) and year 2 (58.7; n = 9); the small group numbers at years 1 and 2 make it difficult to draw conclusions. Again, no significant differences were observed between IGF-I controlled and uncontrolled groups over time for all four AcroQoL dimensions.

IGF-I Normalization

Results for IGF-I (normal, <LLN, >ULN) by mean daily PEGV dose from baseline to 15 years are presented in **Table 2** and **Fig. 4A**. Percentages of patients with normal IGF-I increased over time in the FAP and NSN subgroup. IGF-I normalization increased from 10.3% at baseline up to 78.6% at year 10 at a mean PEGV dose of 18.7 mg/day in the FAP; at year 10, about half of the patients were on PEGV alone (54.2%). Overall, IGF-I remained normal in >65% of patients from year 2 up to year 14 (range, 65.5% to 79.3%). In the NSN subgroup, patients with IGF-I normalization increased from 13.1% at baseline to 64.3% at year 2 at a mean PEGV dose of 14.8 mg/day.

Normal HbA1c levels (**Fig. 4B**) were consistently observed more often in patients with controlled IGF-I than in those with uncontrolled IGF-I over time (>82% vs >70%, respectively). In patients with controlled IGF-I, mean percent HbA1c levels was 6.1% at baseline and ranged from 5.7% to 6.6% over the course of the study. In those with uncontrolled IGF-I, mean percent HbA1c levels were 6.6% at baseline, and ranged from 5.9% to 8.2% over the course of the study. In the NSN subgroup, subjects with controlled IGF-I showed a mean percent HbA1c level of 5.8% at baseline, which remained the same at year 2; in IGF-I uncontrolled patients, HbA1c was 7.5% at baseline and improved to 6.5% at year 2.

Discussion

This long-term follow up of rollover patients and newly enrolled naïve/semi-naïve PEGV patients with acromegaly in ACROSTUDY evaluated patient-rated symptoms and health-related QoL measures.

The proportion of patients with normalized IGF-I increased throughout the study from 10% at baseline to 78% by year 10 in the FAP, and from 13% at baseline to 64% by year 2 in the

NSN subgroup, demonstrating a lack of tachyphylaxis. Numeric improvements in some of the PASQ scores were noted in the first 9 years in the FAP and in the first year in the NSN subgroup. AcroQoL scores remained similar to baseline by year 2 for the NSN subgroup. Overall, no significant differences were observed in PASQ and AcroQoL scores when stratified by IGF-I control; however, those with controlled IGF-I tended to have somewhat better scores, without reaching statistical significance. Patients with diabetes had improved total mean PASQ scores from baseline to year 5. AcroQoL scores remained stable from baseline to year 2 in patients with diabetes, which was not unexpected since AcroQoL does not include diabetes among the items evaluated. Finally, HbA1c improved over time with PEGV, despite not achieving IGF-I normalization, consistent with improved glucose metabolism previously reported in acromegaly patients [11, 23, 24].

While the correlation between PROs and laboratory evaluation requires more studies, we highlight the possibility that acromegaly symptoms and decreased HRQoL could persist even after achieving biochemical disease control. The role of complete or partial biochemical control on QoL score improvement has been previously studied in prospective clinical trials [25], but the impact of changes in a real-life study is less known. A recent large meta-analysis focused on QoL and PASQ showed that total PASQ score decreased by 2.3 points (95% CI, -1.3 to -3.3) and AcroQoL increased by 2.9 points (95% CI, 0.5 to 5.3) with treatment in 24 studies [26]. As expected, treatment-naïve patients saw a larger effect size compared with other patients. The authors suggested that, even if not validated, PASQ should be used in addition to biochemistry for monitoring patients, as was done in a subset of patients in ACROSTUDY as shown in the present report.

Commonly reported breakthrough symptoms of patients on chronic injectable SRLs were joint pain, fatigue, snoring, excessive sweating, and headaches despite biochemical control [27], and adding PEGV to SRLs or switching to PEGV has been shown in some studies to improve QoL. Here, we found that addition of PEGV (up to 9 years) improved PASQ scores in at least 4 of 6 domains, as well as the total score, while other domains and the overall score remained similar in IGF-I controlled patients. In IGF-I uncontrolled patients, 3 of the 6 PASQ domains had improvements, while scores worsened in the other 3 domains as well as the overall score. PASQ scores in patients with diabetes also improved with treatment over time.

Though treatment of acromegaly may affect QoL, biochemical control does not always correlate with degree of QoL impairments; QoL may still be impaired despite biochemical control [27, 28, 29, 30, 31]. Even with biochemical remission, patients treated with medical therapy have lower QoL compared with patients cured by surgery, which may possibly be related to their negative perception of having a persistent disease and/or still require chronic, life-long medication [9, 32, 33]. Several studies on how different types of medical therapy affect QoL have been published [18, 34, 35].

In this real-life international study, overall biochemical control (i.e., normal IGF-I) was achieved with PEGV in more than two-thirds of patients in the FAP and the NSN subgroup. Overall, the degree of control of IGF-I was lower than that reported in several controlled, clinical PEGV trials, likely representing the lack of adequate titration seen in the real-world setting. We cannot rule out that use of a higher PEGV dose, which may have further lowered IGF-I, could have further improved the QoL scores. Furthermore, some symptoms, especially joint pain, could be irreversible and could worsen despite biochemical normalization of acromegaly. Severity of the disease at baseline and long-term duration of the disease can also negatively impact recovery

of some subscale scores. Finally, it must be emphasized that alleviation of symptoms is not the only goal of acromegaly treatment, and that normalization of biochemical parameters has been shown to be associated with improvements of morbidity and mortality in these patients. Our PRO data from 84 treatment naïve/semi-naïve patients represents one of the largest PRO datasets (from baseline) in patients with acromegaly. The small improvements in PROs indicate that appropriately treating patients with PEGV does improve their QoL, as well as signs and symptoms, as shown by the observed positive trends.

Over the last several years, many other instruments have been developed to capture acromegaly disease activity and impact of treatment more holistically, including SAGIT [7], ACRODAT [20], and ACRO TSQ [36]. While biochemical control (i.e., controlled circulating IGF-I), is essential and should be the main focus of therapy [15, 37], it may not reflect normalization of IGF-I in all tissues, and this may be perceived as persistent morbidity by the patient. PROs should also play an important role to assess endpoints of therapy and further individualize treatment, and ideally should be part of the on-going clinical evaluation of the patient. However, as we have shown here, there are limitations in quantifying the improvement for whole groups with available questionnaires.

The strength of this study is that the data represent the real-life scenario of treating patients with acromegaly in routine clinical practice across many countries. Inherent limitations of this study include patient enrollment at variable times relative to initiation of PEGV treatment (except for those in the NSN subgroup), lack of uniform titration of the PEGV dose to normalize IGF-I in all patients, AcroQoL results being available only for the NSN subgroup, and lack of detailed medical history and severity of disease for all patients. Since some data were collected as part of routine practice, more systematic coordination of study data collection was lacking.

Finally, 5-fold more NSN patients withdrew from the study than rollover patients, which might be expected for newer than more experienced patients.

In summary, we have shown herein a large group of patients with acromegaly treated with PEGV (alone or in combination with other drugs) that when PRO improvements occurred, they were mostly in the first 10 years, with some symptoms of acromegaly improving in the IGF-I controlled subgroup, but others worsening/remaining similar despite IGF-I control. These data confirm that clinical evaluation and careful symptom assessment is an important aspect of the care of acromegaly patients, which should not be limited to measurement of biochemical parameters.

Declaration of interest

RS is an editor for Pituitary; **MF** and **TB** are on the Editorial Board of Pituitary. **RS** is a principal investigator with research support to Johns Hopkins University for clinical research studies with Crinetics, Novartis, and Chiasma and occasional scientific consultant for Ipsen and Recordati. **PM** has received honoraria as consultant/speaker, and is a principal investigator for research grants from CamurusAB, Ipsen, Novartis, Pfizer. **SMW** has received honoraria as consultant/speaker or is a principal investigator for research grants from: Pfizer, Novartis, Ipsen, Recordati, HRA, Crinetics and Corcept. **TB** has received honoraria as consultant/speaker, or is a principal investigator for research grants from: Pfizer SAS, Novartis Pharma SAS, Ipsen Pharma, Recordati, Merck-Serono, Sandoz, Novo-Nordisk, Advanz Pharma, and Corcept. **JL**, **MPW**, **SRV**, and **RG** are employees of Pfizer and are stockholders of Pfizer. **MF** is a principal investigator with research support at Oregon Health & Science University for clinical research studies with Crinetics, Novartis, Recordati, Chiasma, Ionis and occasional scientific consultant for Crinetics, Pfizer, Ipsen, Recordati, and Chiasma.

Funding

This study was sponsored by Pfizer. Editorial/medical writing support was provided by Hui Zhang, PhD and Dominique Verlaan, PhD, CMPP at Precise Publications, LLC and was funded by Pfizer.

Acknowledgements

The authors would like to thank all investigators, sub-investigators and study coordinators and patients for their participation and contributions to ACROSTUDY. This study was sponsored by

Pfizer Inc. The authors also want to acknowledge the medical writing assistance of Hui Zhang, PhD and Dominique Verlaan, PhD, CMPP of Precise Publications, LLC, which was supported by Pfizer Inc.

References

1. Melmed S. (2006) Medical progress: acromegaly. *N Engl J Med* 355(24):2558-2573.
2. Akirov A, Asa SL, Amer L, Shimon I, Ezzat S. (2019) The clinicopathological spectrum of acromegaly. *J Clin Med* 8(11):1962.
3. Vilar L, Vilar CF, Lyra R, Lyra R, Naves LA. (2017) Acromegaly: clinical features at diagnosis. *Pituitary* 20(1):22-32.
4. Melmed S. (2009) Acromegaly pathogenesis and treatment. *J Clin Invest* 119(11):3189-3202.
5. Maione L, Brue T, Beckers A, Delemer B, Petrossians P, Borson-Chazot F, Chabre O, Francois P, Bertherat J, Cortet-Rudelli C et al. (2017) Changes in the management and comorbidities of acromegaly over three decades: the French Acromegaly Registry. *Eur J Endocrinol* 176(5):645-655.
6. Gadelha MR, Kasuki L, Lim DST, Fleseriu M. (2019) Systemic complications of acromegaly and the impact of the current treatment landscape: an update. *Endocr Rev* 40(1):268-332.
7. Giustina A, Barkan A, Beckers A, Biermasz N, Biller BMK, Boguszewski C, Bolanowski M, Bonert V, Bronstein MD, Casanueva FF et al. (2019) A consensus on the diagnosis and treatment of acromegaly comorbidities: an update. *J Clin Endocrinol Metab* 105(4):dgz096.
8. Giustina A, Barkhoudarian G, Beckers A, Ben-Shlomo A, Biermasz N, Biller B, Boguszewski C, Bolanowski M, Bollerslev J, Bonert V et al. (2020) Multidisciplinary management of acromegaly: a consensus. *Rev Endocr Metab Disord* 21(4):667-678.

9. Crespo I, Valassi E, Webb SM. (2017) Update on quality of life in patients with acromegaly. *Pituitary* 20(1):185-188.
10. Fleseriu M, Biller BMK, Freda PU, Gadelha MR, Giustina A, Katznelson L, Molitch ME, Samson SL, Strasburger CJ, van der Lely AJ et al. (2021) A Pituitary Society update to acromegaly management guidelines. *Pituitary* 24(1):1-13.
11. Buchfelder M, van der Lely AJ, Biller BMK, Webb SM, Brue T, Strasburger CJ, Ghigo E, Camacho-Hubner C, Pan K, Lavenberg J et al. (2018) Long-term treatment with pegvisomant: observations from 2090 acromegaly patients in ACROSTUDY. *Eur J Endocrinol* 179(6):419-427.
12. SOMAVERT summary of product characteristics. *Pfizer*.
13. SOMAVERT (pegvisomant) for injection, for subcutaneous use Prescribing Information. *Pfizer*. New York, NY. 2013.
14. Katznelson L, Laws ER, Jr., Melmed S, Molitch ME, Murad MH, Utz A, Wass JA, Endocrine S. (2014) Acromegaly: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 99(11):3933-3951.
15. Melmed S, Bronstein MD, Chanson P, Klibanski A, Casanueva FF, Wass JAH, Strasburger CJ, Luger A, Clemmons DR, Giustina A. (2018) A consensus statement on acromegaly therapeutic outcomes. *Nat Rev Endocrinol* 14(9):552-561.
16. van der Lely AJ, Hutson RK, Trainer PJ, Besser GM, Barkan AL, Katznelson L, Klibanski A, Herman-Bonert V, Melmed S, Vance ML et al. (2001) Long-term treatment of acromegaly with pegvisomant, a growth hormone receptor antagonist. *Lancet* 358(9295):1754-1759.

17. Trainer PJ, Drake WM, Katznelson L, Freda PU, Herman-Bonert V, van der Lely AJ, Dimaraki EV, Stewart PM, Friend KE, Vance ML et al. (2000) Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant. *N Engl J Med* 342(16):1171-1177.
18. Badia X, Webb SM, Prieto L, Lara N. (2004) Acromegaly Quality of Life Questionnaire (AcroQoL). *Health Qual Life Outcomes* 2:13.
19. Webb SM, Prieto L, Badia X, Albareda M, Catala M, Gaztambide S, Lucas T, Paramo C, Pico A, Lucas A et al. (2002) Acromegaly Quality of Life Questionnaire (ACROQOL) a new health-related quality of life questionnaire for patients with acromegaly: development and psychometric properties. *Clin Endocrinol (Oxf)* 57(2):251-258.
20. Schreiber I, Buchfelder M, Droste M, Forssmann K, Mann K, Saller B, Strasburger CJ, German Pegvisomant I. (2007) Treatment of acromegaly with the GH receptor antagonist pegvisomant in clinical practice: safety and efficacy evaluation from the German Pegvisomant Observational Study. *Eur J Endocrinol* 156(1):75-82.
21. Sievers C, Brübach K, Saller B, Schneider HJ, Buchfelder M, Droste M, Mann K, Strasburger CJ, Stalla GK. (2010) Change of symptoms and perceived health in acromegalic patients on pegvisomant therapy: a retrospective cohort study within the German Pegvisomant Observational Study (GPOS). *Clin Endocrinol (Oxf)* 73(1):89-94.
22. van der Lely AJ, Gomez R, Pleil A, Badia X, Brue T, Buchfelder M, Burman P, Clemmons D, Ghigo E, Jorgensen JOL et al. (2017) Development of ACRODAT((R)), a new software medical device to assess disease activity in patients with acromegaly. *Pituitary* 20(6):692-701.

23. Feola T, Cozzolino A, Simonelli I, Sbardella E, Pozza C, Giannetta E, Gianfrilli D, Pasqualetti P, Lenzi A, Isidori AM. (2019) Pegvisomant improves glucose metabolism in acromegaly: a meta-analysis of prospective interventional studies. *J Clin Endocrinol Metab* 104(7):2892-2902.
24. Brue T, Lindberg A, Jan van der Lely A, Akerblad AC, Koltowska-Haggstrom M, Gomez R, Droste M, Hey-Hadavi J, Strasburger CJ, Camacho-Hubner C. (2019) Diabetes in patients with acromegaly treated with pegvisomant: observations from acrostudy. *Endocrine* 63(3):563-572.
25. Biermasz NR, van Thiel SW, Pereira AM, Hoftijzer HC, van Hemert AM, Smit JW, Romijn JA, Roelfsema F. (2004) Decreased quality of life in patients with acromegaly despite long-term cure of growth hormone excess. *J Clin Endocrinol Metab* 89(11):5369-5376.
26. Broersen LHA, Zamanipoor Najafabadi AH, Pereira AM, Dekkers OM, van Furth WR, Biermasz NR. (2021) Improvement in symptoms and health-related quality of life in acromegaly patients: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 106(2):577-587.
27. Webb SM. (2011) Pituitary tumors: coping with 'cured' pituitary tumors. *Nat Rev Endocrinol* 7(5):251-252.
28. Ben-Shlomo A, Sheppard MC, Stephens JM, Pulgar S, Melmed S. (2011) Clinical, quality of life, and economic value of acromegaly disease control. *Pituitary* 14(3):284-294.

29. Kyriakakis N, Lynch J, Gilbey SG, Webb SM, Murray RD. (2017) Impaired quality of life in patients with treated acromegaly despite long-term biochemically stable disease: results from a 5-years prospective study. *Clin Endocrinol (Oxf)* 86(6):806-815.
30. Tiemensma J, Kaptein AA, Pereira AM, Smit JW, Romijn JA, Biermasz NR. (2011) Affected illness perceptions and the association with impaired quality of life in patients with long-term remission of acromegaly. *J Clin Endocrinol Metab* 96(11):3550-3558.
31. Geraedts VJ, Andela CD, Stalla GK, Pereira AM, van Furth WR, Sievers C, Biermasz NR. (2017) Predictors of quality of life in acromegaly: no consensus on biochemical parameters. *Front Endocrinol (Lausanne)* 8:40.
32. Andela CD, Biermasz NR, Kaptein AA, Pereira AM, Tiemensma J. (2015) More concerns and stronger beliefs about the necessity of medication in patients with acromegaly are associated with negative illness perceptions and impairment in quality of life. *Growth Horm IGF Res* 25(5):219-226.
33. Yoshida K, Fukuoka H, Matsumoto R, Bando H, Suda K, Nishizawa H, Iguchi G, Ogawa W, Webb SM, Takahashi Y. (2015) The quality of life in acromegalic patients with biochemical remission by surgery alone is superior to that in those with pharmaceutical therapy without radiotherapy, using the newly developed Japanese version of the AcroQoL. *Pituitary* 18(6):876-883.
34. Webb SM, Badia X. (2016) Quality of life in acromegaly. *Neuroendocrinology* 103(1):106-111.
35. Caron PJ, Bevan JS, Petersenn S, Houchard A, Sert C, Webb SM, Group PI. (2016) Effects of lanreotide autogel primary therapy on symptoms and quality-of-life in acromegaly: data from the PRIMARYS study. *Pituitary* 19(2):149-157.

36. Fleseriu M, Fogelfeld L, Gordon MB, Sisco J, Colwell HH, Ludlam WH, Haviv A, Mathias SD. (2019) Development of a novel patient-reported measure for acromegaly: the Acro-TSQ. *Pituitary* 22(6):581-593.
37. Fleseriu M, Fogelfeld L, Gordon MB, Sisco J, Crosby RD, Ludlam WH, Haviv A, Mathias SD. (2020) An evaluation of the Acromegaly Treatment Satisfaction Questionnaire (Acro-TSQ) in adult patients with acromegaly, including correlations with other patient-reported outcome measures: data from two large multicenter international studies. *Pituitary* 23(4):347-358.

Figure Legend

Fig. 1 Patient disposition in the ACROSTUDY extension. *FAP* full analysis population

Fig. 2 Mean PASQ scores for (A) Total; (B) Headache; (C) Excessive sweating; (D) Joint pain; (E) Fatigue; (F) Soft tissue swelling; (G) Numbness/tingling of limbs; (H) Overall health status for the FAP and NSN subgroup. Each item is scored from 0 (no symptoms) to 8 (severe, incapacitating symptoms). Overall health status was scored from 0 to 10. *P*-value compared IGF-I controlled vs uncontrolled over time (up to 15 years for FAP and up to 3 years for NSN). *FAP* full analysis population (rollover and naïve/semi-naïve patients), *IGF-I* insulin-like growth factor I, *IGF-IC* IGF-I controlled, *IGF-IU* IGF-I uncontrolled, *NSN* naïve/semi-naïve analysis population, *LLN* lower limit of normal, *PASQ* Patient-Assessed Acromegaly Symptom Questionnaire

*Does not include subjects with IGF-I < LLN.^an = 35 for numbness/tingling of limbs and total; ^bn = 53 for numbness/tingling of limbs and total; ^cn = 57 for soft tissue swelling and total; ^dn = 42 for numbness/tingling of limbs and total; ^en = 31 for soft tissue swelling and total; ^fn = 17 for excessive sweating and total; ^gn = 12 for fatigue and total; ^hn = 163 for joint pain and numbness/tingling of limbs; n = 164 for soft tissue swelling; n = 160 for total; ⁱn = 50 for soft tissue swelling and numbness/tingling of limbs; n = 49 for total; ^jn = 201 for joint pain; n = 202 for soft tissue swelling; n = 199 for numbness/tingling of limbs; n = 196 for total; ^kn = 106 for soft tissue swelling; n = 103 for numbness/tingling of limbs; n = 102 for total; ^ln = 91 for soft tissue swelling and total; ^mn = 67 for numbness/tingling of limbs and total; ⁿn = 35 for soft tissue swelling and total; ^on = 24 for excessive sweating and total; ^pn = 14 for fatigue and total; ^qn = 24 for numbness/tingling of limbs and total; ^rn = 48 for numbness/tingling of limbs and total.

Fig. 3 Mean AcroQoL (A) Physical; (B) Psychological/appearance; (C) Psychological/personal relationship; and (D) Global scores by level of IGF-I control for the NSN population. AcroQoL subscales were standardized on a scale from 0 to 100 from worst to best QoL, so higher scores indicate improvement (a score <40 was considered severe impairment; ≥40 but <60 was moderate impairment; and ≥60 was mild or no impairment).

AcroQoL Acromegaly Quality of Life questionnaire, *IGF-I* insulin-like growth factor I, *NSN* naïve/semi-naïve analysis population

P-value compared IGF-I controlled vs uncontrolled over time.

Fig. 4 Normalization of (A) IGF-I and (B) HbA1c by IGF-I control with pegvisomant in the FAP and the NSN subgroup.

HbA1c hemoglobin A1c, *FAP* full analysis population, *IGF-I* insulin-like growth factor I, *IGF-I C* IGF-I controlled, *IGF-I U* IGF-I uncontrolled, *LLN* lower limit of normal, *NSN* naïve/semi-naïve analysis population, *ULN* upper limit of normal

Table 1 Patient characteristics

Characteristic	FAP (n = 544)	NSN subgroup (n = 110)
Sex, n (%)		
Male	302 (55.5)	59 (53.6)
Female	242 (44.5)	51 (46.4)
Country, n (%)		
Austria	13 (2.4)	5 (4.5)
Germany	124 (22.8)	12 (10.9)
Denmark	7 (1.3)	5 (4.5)
Italy	193 (35.5)	29 (26.4)
The Netherlands	49 (9.0)	9 (8.2)
Sweden	27 (5.0)	3 (2.7)
Slovakia	36 (6.6)	7 (6.4)
USA	95 (17.5)	40 (36.4)
Race/ethnicity, n (%)		
White	511 (93.9)	90 (81.8)
Black/African American	3 (0.6)	3 (2.7)
Asian	10 (1.8)	5 (4.5)
Hispanic	8 (1.5)	5 (4.5)
Other/missing	12 (2.2)	7 (6.4)
Age at acromegaly diagnosis, y*	543	109
Mean ± SD	42.8 ± 13.2	42.7 ± 14.8
Range	5.2-78.1	15.6-78.1
Age at treatment initiation, y		
Mean ± SD	49.5 ± 13.5	48.0 ± 15.3
Range	17.5-79.8	18.7-79.8
Weight at treatment initiation, kg*	412	101
Mean ± SD	88.2 ± 19.5	92.9 ± 21.8
Range	46.7-158.8	48.6-158.8
Pegvisomant treatment duration, y		
Mean ± SD	7.8 ± 4.5	2.0 ± 1.0
Range	0.0-19.6	0.0-5.5
Years in ACROSTUDY		
Mean ± SD	6.9 ± 3.4	2.2 ± 0.6
Range	1.3-13.9	1.3-3.6
Acromegaly medications before PEGV start, n (%)		
SRL	302 (64.4)	
SRL/DA	145 (30.9)	
DA	22 (4.7)	
Acromegaly medications at study start, n (%)		
PEGV	248 (45.6)	
PEGV/DA	25 (4.6)	
PEGV/SRL	231 (42.5)	
PEGV/DA/SRL	40 (7.4)	
Subjects with diabetes, n (%)	89 (16.4)	26 (23.6)

DA dopamine agonists, FAP full analysis population, NSN naïve/semi-naïve analysis population, PEGV pegvisomant, SD standard deviation, SRL somatostatin receptor ligands

*Sample sizes are given if different from totals in column heads.

Table 2 IGF-I status by study population and pegvisomant dose from baseline to year 2

Patient Group and Time Point	n	IGF-I <LLN		IGF-I Normal		IGF-I >ULN	
		n (%)	Mean daily dose \pm SD, mg	n (%)	Mean daily dose \pm SD, mg	n (%)	Mean daily dose \pm SD, mg
FAP							
Baseline	400	1 (0.3)	--	41 (10.3)	--	358 (89.5)	--
Month 6	320	8 (2.5)	10.6 \pm 1.8	163 (50.9)	12.4 \pm 4.8	149 (46.6)	11.9 \pm 8.1
Year 1	333	8 (2.4)	13.3 \pm 7.0	185 (55.6)	13.5 \pm 6.4	140 (42.0)	13.0 \pm 8.4
Year 2	315	5 (1.6)	16.6 \pm 6.2	209 (66.3)	14.7 \pm 6.7	101 (32.1)	15.1 \pm 8.9
Year 3	295	2 (0.7)	17.5 \pm 3.5	195 (66.1)	13.9 \pm 6.9	98 (33.2)	17.4 \pm 10.2
Year 4	293	5 (1.7)	17.0 \pm 12.1	192 (65.5)	15.8 \pm 8.0	96 (32.8)	17.2 \pm 9.5
Year 5	250	2 (0.8)	16.1 \pm 1.5	173 (69.2)	15.7 \pm 8.3	75 (30.0)	19.4 \pm 10.8
Year 6	228	0	0	168 (73.7)	16.3 \pm 9.4	60 (26.3)	20.3 \pm 10.8
Year 7	180	0	0	134 (74.4)	16.3 \pm 9.5	46 (25.6)	21.9 \pm 13.7
Year 8	151	1 (0.7)	25.0	113 (74.8)	16.4 \pm 9.5	37 (24.5)	22.0 \pm 14.9
Year 9	148	2 (1.4)	10.0 \pm 0.0	111 (75.0)	17.2 \pm 8.6	35 (23.6)	22.5 \pm 13.6
Year 10	112	1 (0.9)	4.3	88 (78.6)	18.7 \pm 9.5	23 (20.5)	19.3 \pm 11.3
Year 11	104	1 (1.0)	15.0	72 (69.2)	18.7 \pm 8.9	31 (29.8)	23.3 \pm 15.2
Year 12	75	3 (4.0)	16.7 \pm 5.8	56 (74.7)	17.9 \pm 9.3	16 (21.3)	23.5 \pm 13.9
Year 13	51	1 (2.0)	20.0	38 (74.5)	17.6 \pm 7.8	12 (23.5)	17.5 \pm 13.5
Year 14	29	0	0	23 (79.3)	18.9 \pm 10.2	6 (20.7)	12.2 \pm 12.2
Year 15	9	0	0	5 (55.6)	21.0 \pm 8.9	4 (44.4)	17.1 \pm 10.4
Naïve/Semi-Naïve (NSN) Subgroup							
Baseline	84	0	0	11 (13.1)	--	73 (86.9)	--
Month 6	64	1 (1.6)	10.0	32 (50.0)	13.0 \pm 6.2	31 (48.4)	12.7 \pm 14.0
Year 1	67	1 (1.5)	20.0	43 (64.2)	13.4 \pm 6.3	23 (34.3)	11.0 \pm 6.9
Year 2	42	2 (4.8)	12.9 \pm 10.1	27 (64.3)	14.8 \pm 6.7	13 (31.0)	10.4 \pm 7.5
Year 3	9	0	0	7 (77.8)	13.9 \pm 6.4	2 (22.2)	3.8 \pm 5.3

FAP full analysis population (rollover + naïve/semi-naïve patients), *IGF-I* insulin-like growth factor I, *LLN* lower limit of normal, *NA* not available, *ULN* upper limit of normal

Fig. 1

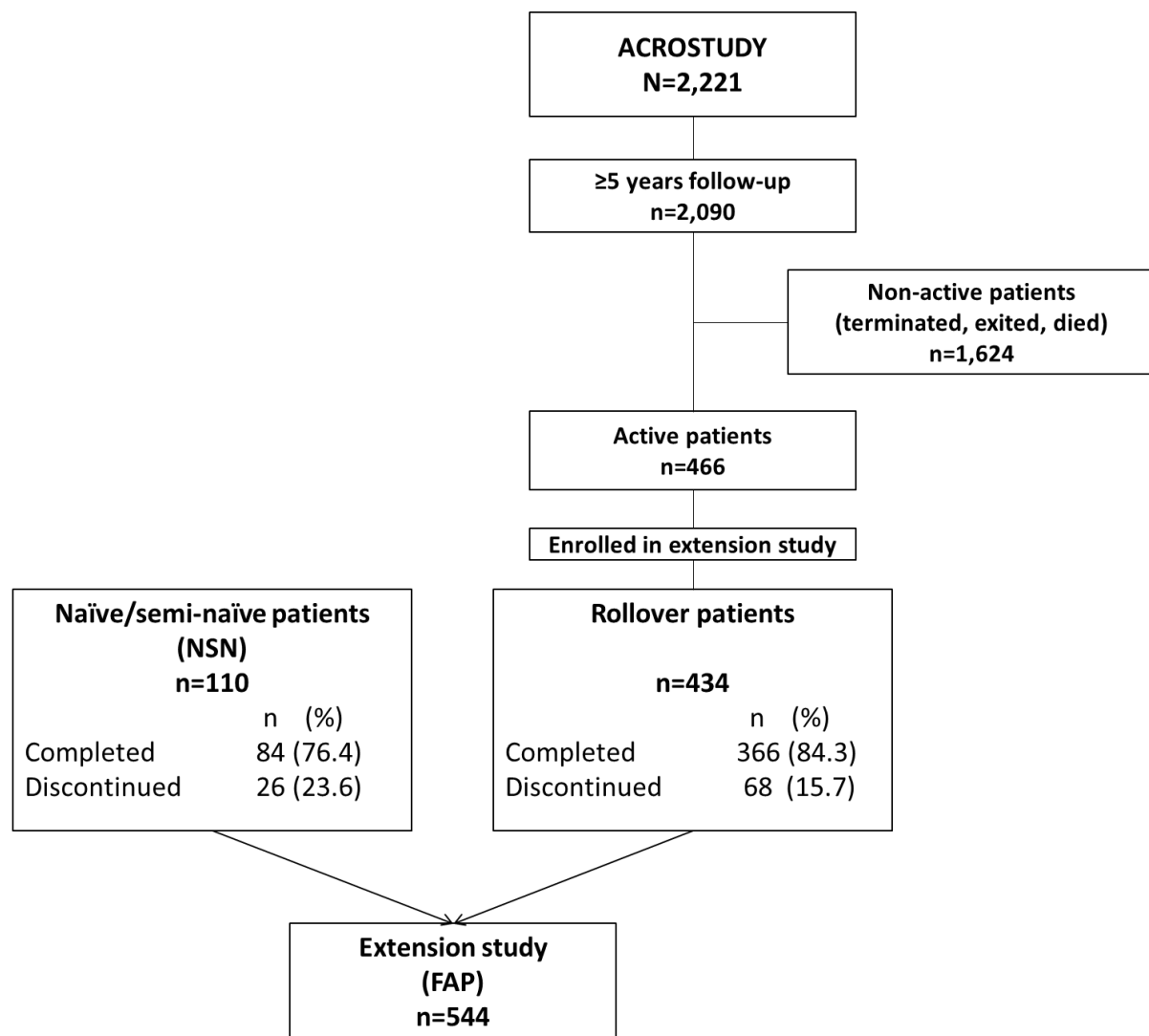
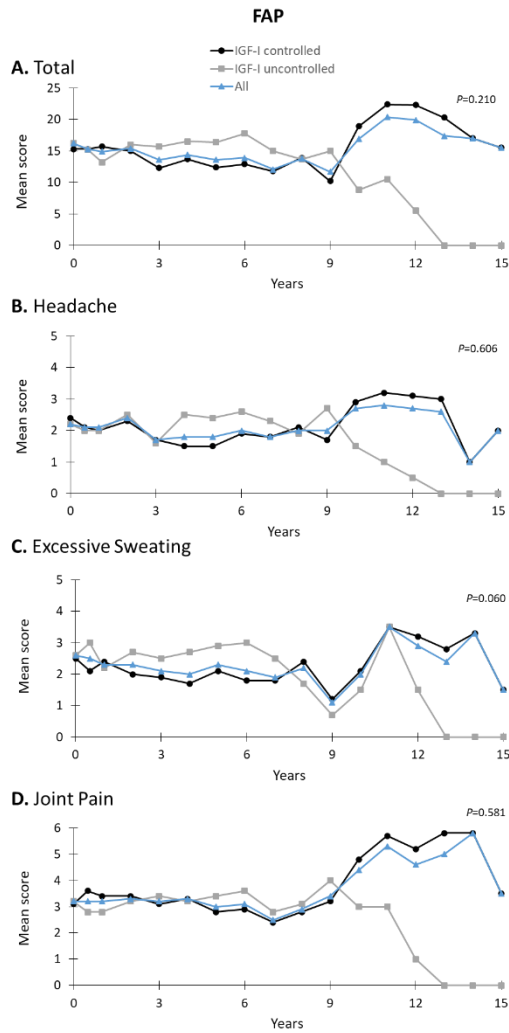


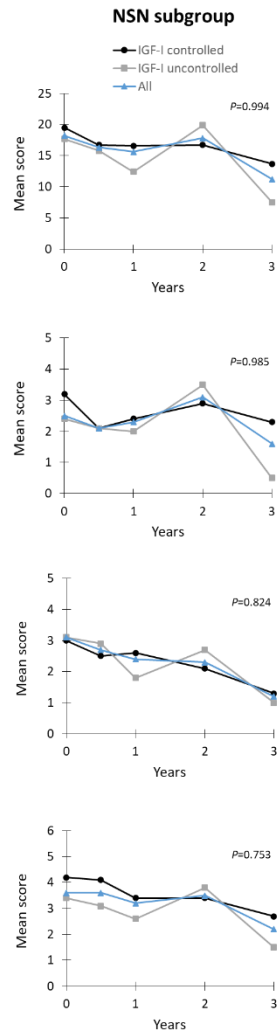
Fig. 2

Patient-Assessed Acromegaly Symptom Questionnaire (PASQ)



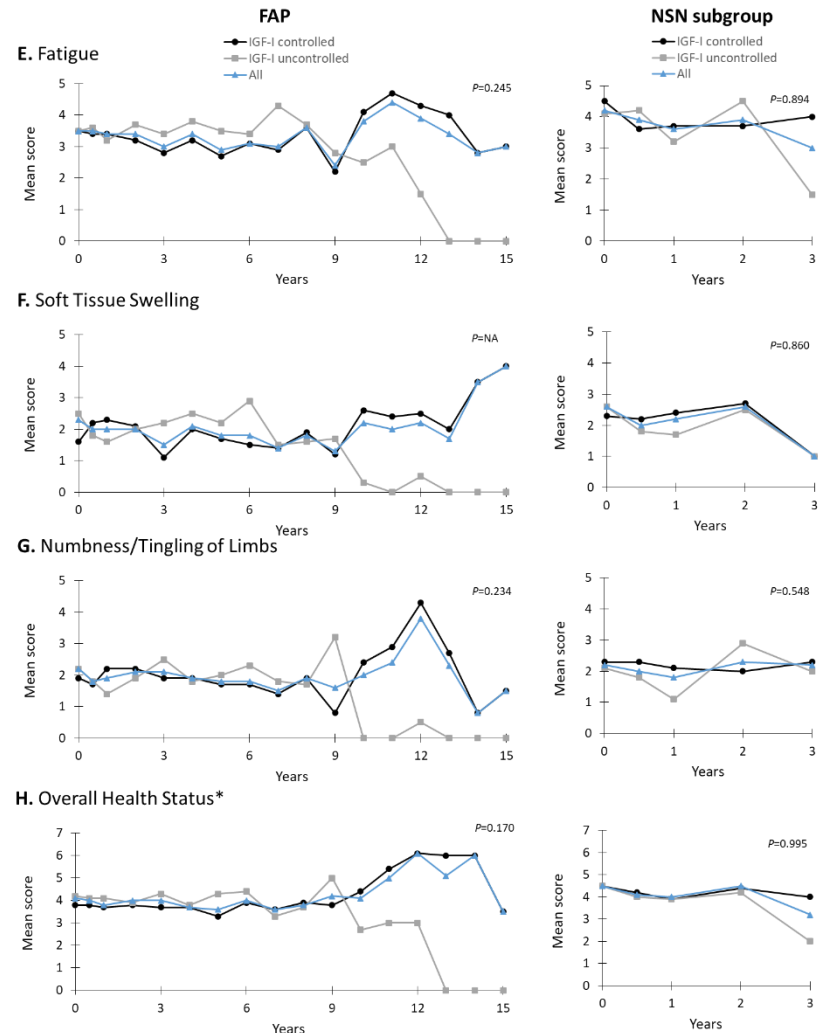
n for FAP PASQ scores†															
Years	0	0.5	1	2	3	4	5	6	7	8	9	10	11	12	13
IGF-IC, n	37 ^a	56 ^b	67	58 ^c	43 ^d	48	40	38	32 ^e	18 ^f	13	16	10	13 ^g	6
IGF-IU, n	165 ^h	51 ⁱ	42	34	25	17	17	10	4	7	6	4	2	2	1
All, n	203 ^j	107 ^k	110	92 ^l	68 ^m	65	57	48	36 ⁿ	25 ^o	19	20	12	15 ^p	7

†except overall health status



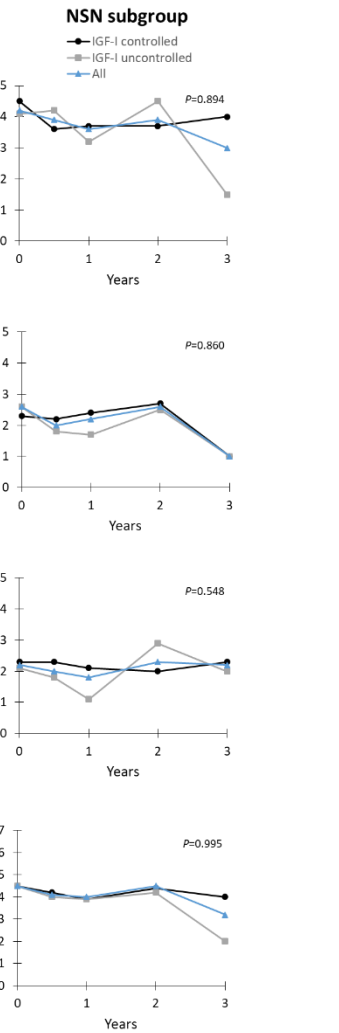
n for NSN subgroup PASQ scores†					
Years	0	0.5	1	2	3
IGF-IC, n	13	25 ^a	39	20	3
IGF-IU, n	70	24	17	11	2
All, n	84	49 ^b	57	31	5

†except overall health status



n for FAP PASQ Overall Health Status scores															
Years	0	0.5	1	2	3	4	5	6	7	8	9	10	11	12	13
IGF-IC, n	36	55	67	57	42	48	40	38	32	18	13	16	10	13	6
IGF-IU, n	163	48	36	31	24	16	16	10	4	7	6	3	2	1	1
All, n	201	105	110	91	67	65	57	48	36	25	19	20	12	15	7

†except overall health status



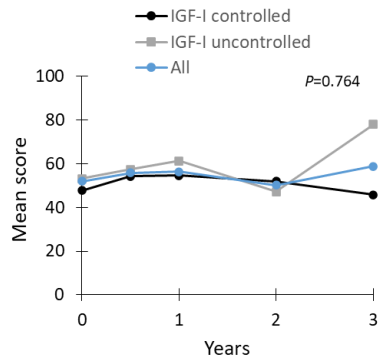
n for NSN subgroup PASQ Overall Health Status scores					
Years	0	0.5	1	2	3
IGF-IC, n	13	25	39	19	3
IGF-IU, n	69	23	16	9	2
All, n	84	49	57	30	5

†except overall health status

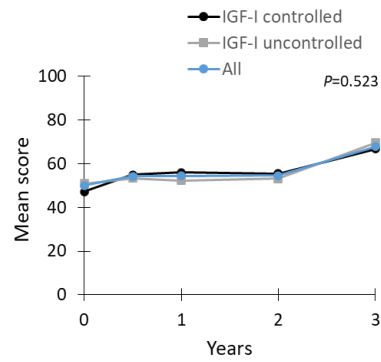
Fig. 3

Acromegaly Quality of Life questionnaire (AcroQoL)

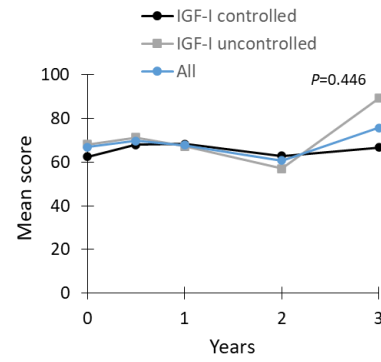
A. Physical Score



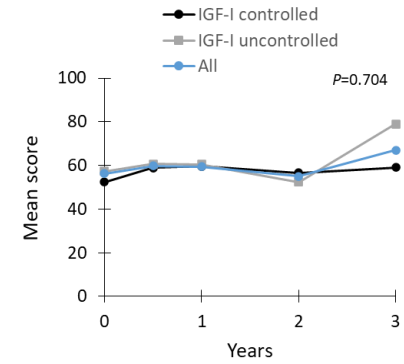
B. Psychological/Appearance Score



C. Psychological/Personal Relationship Score

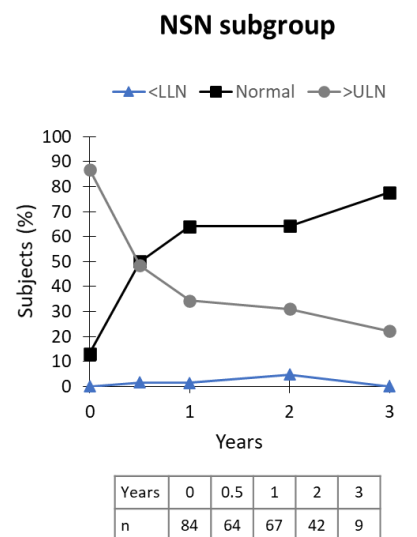
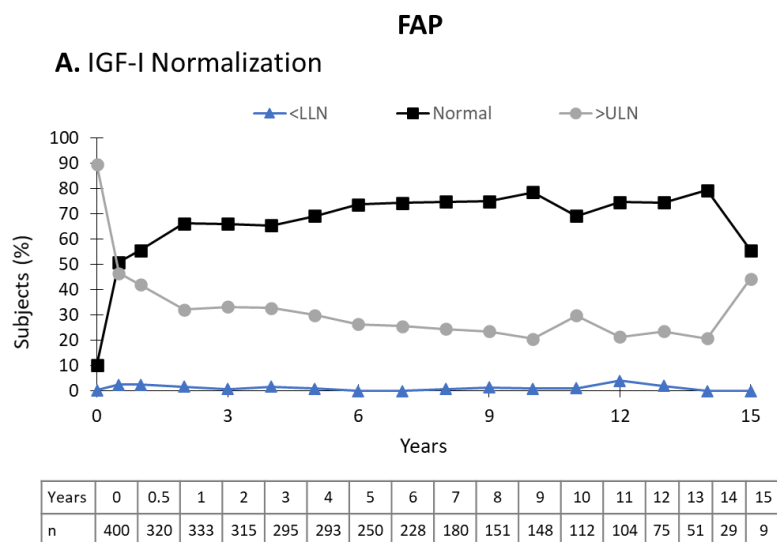


D. Global Score



n for NSN subgroup AcroQoL scores					
Years	0	0.5	1	2	3
IGF-IC, n	12	24	39	20	3
IGF-IU, n	71	24	18	11	2
All, n	84	48	58	31	5

Fig. 4



B. HbA1C Normalization by IGF-I Control

