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Long-term safety and efficacy of pegvisomant monotherapy for acromegaly: final data from the full ACROSTUDY cohort

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1 **Long-term safety and efficacy of pegvisomant monotherapy for acromegaly: final data**
2 **from the full ACROSTUDY cohort**

3

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36

37 **Declarations**

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45

46

47

48 **Abstract**

49 **Purpose:** ACROSTUDY was an international, non-interventional, cross-sectional study that
50 evaluated the long-term safety and treatment outcomes of pegvisomant treatment (monotherapy
51 or combination) in patients with acromegaly in “real-world” clinical practice. This study aimed to
52 characterize the long-term safety and efficacy of pegvisomant monotherapy in ACROSTUDY.

53 **Methods:** Patients with acromegaly aged >18 years (at ACROSTUDY enrollment) who had re-
54 ceived ≥ 1 dose of pegvisomant as monotherapy were included in the monotherapy cohort. Clini-
55 cal assessments included adverse events (AEs), comorbidities, pituitary imaging, liver function
56 tests, and insulin-like growth factor-1 (IGF-I) serum measurements.

57 **Results:** Patients with acromegaly ($N=1464$) received pegvisomant monotherapy for a median
58 (min, max) of 6.0 (0.0, 19.3) years and were followed in ACROSTUDY for a mean of 7.6 years.
59 The rates of AEs (all-causality) and serious AEs were 49% ($n=717/1464$) and 19.3%
60 ($n=282/1464$), respectively. The most common treatment-related AEs were IGF-I increased
61 (1.8%), lipohypertrophy (1.2%), transaminases increased (1.2%), and IGF-I decreased (1.1%).
62 There were 31 (2.1%) deaths and none were related to treatment. Magnetic resonance imaging
63 findings at study sites showed 7.2% ($n=90/1248$) of patients had increased tumor size, whereas
64 70.6% ($n=881/1248$) of patients had change in tumor size. At the last observation, the serum
65 IGF-I normalization rate was 62.3% ($n=756/1213$) and the median (min, max) daily pegvisomant
66 dose was 15.0 (0, 60) mg/day.

67 **Conclusions:** In this largest and longest real-world study of pegvisomant monotherapy in pa-
68 tients with acromegaly to date, pegvisomant demonstrated a favorable safety profile and was
69 effective at normalizing and maintaining IGF-I levels in the majority of patients.

70

71 **Keywords (4-6):** pegvisomant, acromegaly, monotherapy, safety, efficacy, IGF-I

72

73 **Introduction**

74 Acromegaly is a rare, chronic, and progressive endocrine disorder characterized by excess se-
75 cretion of growth hormone (GH) and insulin-like growth factor-1 (IGF-I), most commonly result-
76 ing from a GH-secreting pituitary adenoma ^{1,2}. Acromegaly is associated with multiple comorbid-
77 ities and complications, including cardiovascular, metabolic, respiratory, articular, and bone
78 complications ¹, resulting in impairment of quality of life and increased morbidity and mortality
79 rates, especially if untreated or sub-optimally treated ³.

80 The first-line treatment modality for acromegaly is trans-sphenoidal surgery, whereas
81 medical treatment and radiotherapy are generally considered as adjuvant (or second-line) and
82 third-line options, respectively, for patients not in remission postoperatively ⁴. Medical treat-
83 ments that can normalize IGF-I levels include somatostatin receptor ligands (SRLs), dopamine
84 agonists (DAs), and the GH receptor antagonist pegvisomant. Pegvisomant is a recombinant
85 GH analog that binds to the human GH receptor, thereby disrupting GH signal transduction and
86 lowering IGF-I levels. The efficacy, safety, and tolerability of pegvisomant was established in
87 previous prospective randomized clinical trials, with 87/90 (97%) patients achieving serum IGF-I
88 normalization in a long-term (up to 18 months) study ⁵. Pegvisomant was initially approved in
89 Europe in 2002 and in the United States in 2003 for the treatment of patients with inadequately
90 controlled acromegaly disease activity.

91 ACROSTUDY was a multi-country, non-randomized, open-label, non-interventional,
92 cross-sectional, post-authorization safety surveillance study initiated in 2004 at the request of
93 the European Medicines Agency (EMA). The objective of the study was to evaluate the long-
94 term safety and treatment outcomes of patients with acromegaly treated with pegvisomant in
95 “real-world” clinical practice. Data from the full international ACROSTUDY cohort ^{6,7}, country-
96 specific ACROSTUDY analyses ⁸⁻¹⁰, and other real-world studies ^{11,12}, have confirmed the safety
97 and efficacy of pegvisomant. The end-of-study report describing the full ACROSTUDY cohort

98 was recently published ¹³, reporting data from 2221 patients who received pegvisomant (in com-
99 bination or as monotherapy) for a median of 9.3 years and were followed for a median of 7.4
100 years. When combined with other treatments, such as SRLs, the independent effects of pegvi-
101 somant therapy are difficult to quantify. For instance, SRLs ¹⁴ and pegvisomant ¹⁵ exert oppos-
102 ing effects on glucose metabolism, which can confound efforts to characterize the safety and
103 efficacy of pegvisomant per se in patients receiving both of these medications.

104 To better understand the effects of pegvisomant alone, it is imperative to characterize
105 patients in ACROSTUDY who received pegvisomant monotherapy. Tritos et al. conducted an
106 analysis of data extracted from ACROSTUDY ¹⁶, which included 204 patients receiving pegviso-
107 mant as primary medical therapy or as adjunctive therapy, showing that pegvisomant monother-
108 apy normalized IGF-I in >75% of patients and had a favorable safety profile. An interim analysis
109 of ACROSTUDY performed in 2015 by Freda et al. focused primarily on the safety of pegviso-
110 mant in patients with acromegaly treated with pegvisomant monotherapy at that time ¹⁷. This
111 analysis of 710 patients who were followed for a mean of 3.8 years showed that the safety of
112 pegvisomant was consistent with that reported in previous, smaller studies and that 67.5% of
113 patients achieved normal IGF-I levels within 5 years of treatment ¹⁷.

114 In this study, we provide the final ACROSTUDY data to supplement the interim analysis
115 published by Freda et al. in 2015 ¹⁷. In this end-of-study report, we now present the final out-
116 comes specifically for patients receiving pegvisomant monotherapy from the full ACROSTUDY
117 cohort. The present study includes data from 1464 patients treated with pegvisomant monother-
118 apy for an average of 6.6 years, representing the largest and longest real-world clinical study of
119 pegvisomant monotherapy in patients with acromegaly to date.

120

121 **Methods**

122 **Study design and treatments**

123 A decade after its initiation, in 2014, ACROSTUDY was continued on a voluntary basis after
124 confirmation from the EMA that the safety requirement was satisfied. All study data were col-
125 lected as part of each patient's routine clinical care. The timing of patient visits and pegvisomant
126 dose and schedule, as well as dose titrations, were performed at the discretion of the treating
127 physician. This study was conducted in accordance with the Declaration of Helsinki and the ap-
128 plicable laws and regulations in each of the countries involved. Ethics approval was obtained for
129 all participating centers, and all patients provided written informed consent before enrollment
130 into the study. A detailed description of the study methodology can be found in previous publica-
131 tions ¹⁷⁻¹⁹, which reported the interim results up to December 2012 for the pegvisomant mono-
132 therapy cohort.

133

134 **Participants**

135 Patients were included in the monotherapy cohort if they were >18 years at enrollment into
136 ACROSTUDY and (1) had received ≥ 1 dose of pegvisomant prescribed as monotherapy without
137 concomitant SRLs or DA exposure, or (2) had discontinued SRLs or DAs at the beginning of
138 pegvisomant treatment (>28 days since the last dose of SRLs, >7 days since the last dose of
139 DA, and >7 days since the last dose of any other acromegaly therapy). Patients who received
140 SRLs and/or DAs in combination with pegvisomant within ACROSTUDY were excluded from the
141 monotherapy cohort. Additional inclusion and exclusion criteria are the same as for the full
142 ACROSTUDY cohort and were reported by van der Lely et al. ¹⁹.

143

144 **Study assessments**

145 Adverse events (AEs) were coded and summarized using the Medical Dictionary for Regulatory
146 Activities (version 20.1). Any comorbidities or events that occurred before a patient's enrollment
147 into ACROSTUDY were recorded in the database as part of their medical history; this was also

148 applied to patients who had received pegvisomant prior to being enrolled in ACROSTUDY. Se-
149 rum IGF-I levels were measured at baseline and liver function tests and serum IGF-I measure-
150 ments were performed every 6 months after initiation of pegvisomant treatment. Laboratory ab-
151 normalities were to be reported as AEs per investigator judgement or if they met pre-specified
152 criteria per protocol. Diabetes mellitus at baseline was defined using HbA1c and glucose levels
153 as well as the patient's medical history and concomitant medications. Evaluation of the effects of
154 IGF-I control on glucose homeostasis commenced in 2014, following extension of the study on a
155 voluntary basis.

156

157 **Central MRI reading**

158 A detailed description of the imaging methodology employed in ACROSTUDY is described in
159 Buchfelder et al.²⁰. Pituitary magnetic resonance imaging (MRI) was performed at baseline,
160 months 6 and 12, and then every 12 months. The ACROSTUDY protocol recommended that the
161 MRI at the study site (local MRI) be conducted using the same imaging technique and equip-
162 ment. T1-weighted spin-echo (or fast spin-echo) sagittal and coronal images (before and after
163 gadolinium) and T2-weighted fast spin-echo coronal images were recommended by the MRI
164 protocol. Pituitary tumor images were collected and reviewed locally and if a local radiologist de-
165 termined that an image showed significant changes in tumor size, all available images were
166 then requested to be assessed by a central reader; it should be noted that this was not a re-
167 quirement during the voluntary extension period. Based on central assessment, change in pitui-
168 tary adenoma size was considered substantial if there was a >3-mm change in the largest diam-
169 eter of the tumor. Central MRI assessment also considered increases in tumor size to be clini-
170 cally relevant based on radiological signs such as compression of visual pathways. For pituitary
171 macroadenomas, an additional criterion of >20% change (increase or decrease) in tumor vol-
172 ume was used to define a substantial change.

173

174 **Statistical analyses**

175 Statistical analyses were descriptive, and baseline was defined as the start of pegvisomant
176 treatment, irrespective of when enrollment into ACROSTUDY occurred. Change in tumor vol-
177 ume was categorized as (1) increased, (2) decreased, (3) increased and decreased, or (4) un-
178 changed. Serum IGF-I levels were categorized as normal (within upper and lower limits of nor-
179 mal based on the reference values for the local laboratory), $>1.3\times$ the upper limit of normal
180 (ULN), or less than the lower limit of normal (LLN) at each year of follow-up.

181

182 **Results**

183 **Participants and treatment**

184 Among the final ACROSTUDY cohort of 2221 patients, 1464 (65.9%) received pegvisomant
185 monotherapy, with an equal male-to-female ratio. The majority of the patients were from Ger-
186 many ($n=385$), Italy ($n=303$), France ($n=242$), Spain ($n=171$), and the United States ($n=158$)
187 (**Supplementary Table 1**).

188 The mean (standard deviation [SD]) age at acromegaly diagnosis was 42.2 (13.5) years,
189 and the mean (SD) age at which patients started pegvisomant treatment was 49.9 (13.9) years
190 (**Supplementary Table 1**). The mean (SD) time between diagnosis of acromegaly and the start
191 of pegvisomant treatment was 7.6 (8.1) years. Patients received pegvisomant monotherapy for
192 a median (min, max) duration of 6.0 (0.0, 19.3) years. A total of 18/1464 (1.2%) patients re-
193 ceived treatment for less than 30 days (~1 month) and 68 /1464 (4.6%) patients received treat-
194 ment for less than 90 days (~3 months). Most patients (86.5%) had at least one year of pegviso-
195 mant treatment. A total of 249 (17.0%) patients had no prior use of any other medical therapies,
196 whereas 1230 (84.0%) patients had received other forms of medical therapy (including SRLs or
197 DAs) prior to pegvisomant monotherapy. Almost half of the patients ($n=706$, 48.2%) had re-
198 ceived both surgery and medical therapy, and 23.3% ($n=341$) of patients had received surgery,

199 medical therapy, and radiotherapy (**Fig. 1**). The mean (SD) time between a patient's first pitui-
200 tary surgery and their first dose of pegvisomant was 7.1 (7.56) years. The mean (SD) time be-
201 tween receiving the first dose of SRL and the first dose of pegvisomant was 4.6 (4.60) years (in-
202 cluding the time between cessation of SRL and initiation of pegvisomant).

203 Most (89.0%) patients had ≥ 1 reported comorbidity before starting pegvisomant mono-
204 therapy (**Supplementary Table 2**). The most prevalent comorbidities ($\geq 15\%$ of patients) were
205 hypertension (52.0%), diabetes mellitus (31.5%), osteoarthritis (24.0%), sleep apnea (21.9%),
206 thyroid tumors (18.9%; majority were benign tumors), surgery for gallstones (17.6%), and colon
207 tumors (16.7%; including adenomatous polyps and other benign tumors, as well as adenocarci-
208 nomas). Pituitary hormone deficiencies included hypogonadotropic hypogonadism ($n=157/429$;
209 36.6%), adrenocorticotrophic hormone deficiency ($n=115/402$; 28.6%), thyroid-stimulating hor-
210 mone deficiency ($n=133/458$; 29.0%), and prolactin deficiency ($n=18/421$; 4.3%) (**Table 1**).

211

212 **Safety**

213 **Adverse events**

214 Almost half of the patients ($n=717$; 49.0%) reported an AE (all-causality), and the most common
215 AEs are described in **Table 2**. Treatment-related AEs were reported in 198 (13.5%) patients
216 (**Table 3**). The most commonly reported treatment-related AEs ($>0.5\%$ of patients) were IGF-I
217 increased (1.8%), lipohypertrophy (1.2%), transaminases increased (1.2%), IGF-I decreased
218 (1.1%), alanine aminotransferase increased (0.8%), and injection site reaction (0.6%). Serious
219 AEs (SAEs; all-causality) were reported in 282 (19.3%) patients, with 25 (1.7%) patients report-
220 ing SAEs that were considered treatment-related and 75 patients (5.1%) discontinuing treatment
221 due to an SAE (**Table 3**). There were 31 (2.1%) deaths in the study, and none were considered
222 related to treatment; causes of death are listed in **Supplementary Table 3**.

223

224 ***Serum liver function tests***

225 Of 1464 patients, 54 (3.7%) had aspartate aminotransferase/alanine aminotransferase
226 (AST/ALT) values that were >3× ULN during treatment with pegvisomant (**Supplementary Ta-**
227 **ble 4**). Of the 864 patients with normal baseline AST/ALT values, 30 (3.5%) had values that
228 rose to >3× ULN during treatment. Of the 68 patients who entered the study with an AST/ALT
229 value between 1 to 3× ULN, 9 (13.2%) had values that rose to >3× ULN. Of the 7 patients who
230 entered the study with an AST/ALT value >3× ULN, 2 (28.6%) had values that remained >3×
231 ULN.

232

233 ***Pituitary tumor size***

234 A total of 1438 patients were analyzed for pituitary imaging and, of these, 1248 (86.8%) had ≥1
235 post-baseline local pituitary MRI result reported (**Supplementary Table 5**). Based on the local
236 pituitary MRI results, 881 (70.6%) patients had no change in tumor size relative to the last ex-
237 amination or to the start of pegvisomant therapy. A total of 213 (17.1%) patients had a decrease
238 in tumor size, 90 (7.2%) patients had an increase in tumor size, and 64 (5.1%) patients had both
239 an increase and a decrease in tumor size (**Supplementary Table 5**). No SAEs related to tumor
240 size increase and leading to drug withdrawal or dose reduction were reported. The proportion of
241 patients in each category of tumor changes was similar between patients who had no prior ther-
242 apies and those who had prior therapies (increase or decrease: 34.1% vs. 29.0%; increase only:
243 7.0% vs. 7.4%; decrease only: 22.7% vs. 16.1%; both increase and decrease: 4.3% vs. 5.5%;
244 no change: 65.9% vs. 71.0%). The proportion of patients who had ≥1 change in tumor size (ei-
245 ther increase or decrease) was higher for patients who had radiotherapy after pegvisomant
246 (69.4%) compared with those who had radiotherapy before pegvisomant (44.0%) or had not had
247 any radiotherapy (43.3%) (**Supplementary Table 5**). Specifically, the subgroup that had radio-

248 therapy after pegvisomant treatment had a higher proportion of patients with a decrease in tu-
249 mor size or both an increase and decrease in tumor size compared with the other 2 subgroups
250 (**Supplementary Table 5**). A total of 636 patients had radiotherapy either before or after the
251 start of pegvisomant treatment; of these, 27 (4.2%) showed an increase in tumor size (no de-
252 creases in tumor size were observed in these patients).

253

254 **Glucose homeostasis**

255 The median glucose level at the start of pegvisomant therapy was 95.5 mg/dL (5.3 mmol/L) and
256 remained between 88 and 95 mg/dL (4.9-5.3 mmol/L) through to year 12 (**Supplementary Fig.**
257 **1**). Similarly, median HbA1c was 6.1% (43.2 mmol/mol) at the start of pegvisomant treatment
258 and remained between 5.8% and 5.9% (39.9-41.0 mmol/mol) through to year 12 (**Supplemen-**
259 **tary Fig. 1**) Of the 325 patients enrolled into the voluntary extension study period, only a small
260 number had fasting glucose levels >200 mg/dL (>11.1 mmol/L) at baseline ($n=6/325$; 1.8%),
261 year 1 ($n=1/325$; 0.3%), and year 2 ($n=1/325$; 0.3%). The number of patients with glycated he-
262 moglobin (HbA1c) levels >6.5% (>47.5 mmol/L) at baseline, year 1, and year 2 was 29/325
263 (8.9%), 16/325 (4.9%), and 25/325 (7.7%), respectively. Compared with baseline, the percent-
264 age of patients receiving treatments for diabetes mellitus decreased over the course of pegviso-
265 mant treatment (**Supplementary Fig. 2**). At the beginning of pegvisomant therapy, 31/1464
266 (2.1%) patients were receiving insulin, and by month 6 of treatment, 4/1464 (0.3%) patients
267 were receiving insulin. There were between 2 (0.1%) and 10 (0.7%) patients receiving insulin
268 per year from years 1 to 10 and from years 11 to 15 there were no patients receiving insulin
269 (**Supplementary Fig. 2**). A total of 212/1464 (14.5%) patients were receiving oral anti-diabetes
270 drugs at the beginning of pegvisomant therapy and after 6 months of treatment, 59/1464 (4.0%)
271 patients were receiving oral anti-diabetes drugs. From years 1 to 10, there were between 11
272 (0.8%) and 74 (5.1%) patients receiving oral anti-diabetes drugs in each year, and from years

273 11 to 15, there were 7 or fewer patients receiving oral anti-diabetes drugs (**Supplementary Fig.**
274 **2**).

275

276

277 **IGF-I levels**

278 Normal IGF-I levels were observed in 20/132 (15.2%) patients at the beginning of pegvisomant
279 treatment, in 367/716 (51.3%) patients after 6 months of treatment, and in 406/693 (58.6%) pa-
280 tients after 1 year of treatment (**Fig. 2A**). Between years 2 ($n=422/682$) and 6 ($n=244/346$), IGF-
281 I normalization rates increased from 61.9% to 70.5%. Normalization rates remained above 70%
282 between years 7 ($n=175/238$) and 14 ($n=9/11$), with the highest being 83.3% in years 10
283 ($n=90/108$) and 13 ($n=20/24$) (**Fig. 2A**). The normalization percentage at the last observation
284 ($n=756/1213$) was 62.3%. The percentage of patients who had IGF-I levels below the LLN was
285 <5% between the start of therapy and year 14 (**Fig. 2B**). In patients with normal IGF-I levels, the
286 mean (SD) daily dose of pegvisomant at month 6, year 5, year 10, and last observation was
287 12.9 (5.27) mg/day, 17.3 (8.39) mg/day, 17.3 (8.73) mg/day, and 16.2 (8.09) mg/day, respec-
288 tively (**Fig. 2A**); the median daily dose of pegvisomant was 10.0 mg/day at month 6 and was
289 15.0 mg/day from year 1 to year 10 and at last observation (doses ranged from 0 to 60.0
290 mg/day). In patients with IGF-I >ULN, the mean (SD) daily dose of pegvisomant at month 6,
291 year 5, year 10, and last observation was 13.8 (6.46) mg/day, 19.0 (11.49) mg/day, 16.5 (8.71)
292 mg/day, and 18.2 (10.04) mg/day, respectively; the median daily dose at the same timepoints
293 was 12.9 mg/day, 20.0 mg/day, 15.0 mg/day, and 20.0 mg/day, respectively (doses ranged from
294 0 to 60.0 mg/day).

295 For patients who had IGF-I levels above the normal range, 46/112 (41.1%) patients had
296 IGF-I $\geq 2 \times$ ULN at the start of pegvisomant treatment (**Supplementary Fig. 3**), and the number
297 of patients with IGF-I $\geq 2 \times$ ULN decreased from 76/329 (23.1%) at 6 months to 13/133 (9.8%) at

298 year 5. The proportion of patients with modestly elevated IGF-I (between ULN and <1.3x ULN)
299 increased from 23.2% (26/112) at the start of pegvisomant therapy to 56.4% (75/133) at year 5
300 **(Supplementary Fig. 3).**

301

302 **Discussion**

303 ACROSTUDY provided data on the long-term safety and efficacy of pegvisomant-treated pa-
304 tients with acromegaly as part of routine clinical practice over 13 years (2004–2017). In 2021,
305 Fleseriu et al.¹³ reported the findings from the full ACROSTUDY cohort of 2221 patients who
306 received pegvisomant in combination or as monotherapy, with the last analysis that focused
307 specifically on patients who received pegvisomant monotherapy being published in 2015 by
308 Freda et al.¹⁷. As there are currently few published long-term data on pegvisomant monother-
309 apy in patients with acromegaly, we hereby report the final data from the full cohort of 1464 pa-
310 tients from ACROSTUDY who received a mean (SD) of 6.6 (4.58) years of pegvisomant treat-
311 ment and were followed in the study for 7.6 (3.36) years. Compared with the interim analysis of
312 ACROSTUDY reported by Freda et al in 2015, the present report includes twice as many pa-
313 tients and a follow-up period that is twice as long. Based on the findings from ACROSTUDY,
314 pegvisomant monotherapy had a favorable safety profile in real-world clinical practice, with little
315 evidence of increased tumor size or liver enzyme abnormalities during long-term treatment. In
316 terms of efficacy, the mean IGF-I normalization rate at the last observation was 62.3%, with the
317 mean daily dose of pegvisomant utilized being 16.2 mg/day.

318 Given that a substantial proportion of patients treated with SRLs underwent tumor
319 shrinkage²¹, it was of interest to characterize potential changes in tumor size following the ces-
320 sation of SRL treatment and initiation of pegvisomant. Tumor size was monitored during the
321 whole course of pegvisomant treatment, and the percentage of patients who had an increase, or
322 an increase and a decrease, in tumor size reported was 7.2% and 5.1%, respectively. This was

323 very similar to what was observed in the full ACROSTUDY cohort, with the corresponding pro-
324 portions being 7.1% (tumor size increase) and 4.5% (tumor size increase and decrease). The
325 interim analysis of the pegvisomant monotherapy cohort published in 2015 (based on local im-
326 aging results) showed 5.2% of patients had an increase in tumor size and 1.8% of patients had
327 an increase and a decrease in tumor size ¹⁷. A meta-analysis of longitudinal observational stud-
328 ies (considering patients receiving pegvisomant monotherapy) by Leonart et al. ²² reported the
329 rate of increased tumor size as being 7.2% (based on 4 studies). The increase in tumor size ob-
330 served in a small proportion of patients is not unexpected given the discontinuation of SRL treat-
331 ment and the fact that pegvisomant itself does not have any direct antitumor activity. The possi-
332 ble re-expansion of a residual adenoma following cessation of SRLs may partly explain why a
333 proportion of patients received radiotherapy after initiating pegvisomant treatment. Even among
334 patients treated with SRLs, an increase in tumor size has been reported for some patients ^{23,24}.
335 Colao et al. estimated that 1% to 3% of GH-secreting pituitary adenomas continue to grow inde-
336 pendently of the treatment received by the patient ²⁵. A recent review of pegvisomant in the
337 treatment of acromegaly stated that based on current evidence, there is no suggestion that
338 pegvisomant treatment increases the growth rate of tumors beyond what would be observed
339 over the natural course of or during SRL treatment ²⁶. Overall, the findings from our study and
340 previous studies suggest that long-term pegvisomant treatment does not result in a clinically
341 meaningful increase in tumor size in patients with acromegaly. A total of 213 patients who re-
342 ceived pegvisomant monotherapy had a decrease in tumor size. Spontaneous size reduction is
343 not unexpected in pituitary adenomas and may be explained by natural medical history. In a re-
344 view of 14 observational studies comprising 648 patients with reported clinically nonfunctioning
345 pituitary adenomas (no medical, surgical, or radiological intervention received), 419 (65%) pa-
346 tients had macroadenomas and 229 (35%) patients had microadenomas. Of these, 12% of
347 macroadenomas and 7% of microadenomas showed a reduction of tumor size ²⁷.

348 Serum IGF-I normalization rates improved from 15.2% at treatment start to 58.6% after 1
349 year of treatment and remained between 70% and 85% between years 6 and 14. It is important
350 to note that as the length of the observation period increased, there was a substantial reduction
351 in the number of patients for whom data were available, as shown in **Fig. 2A**. The normalization
352 rates reported here are similar to those for the full ACROSTUDY cohort (53.7% within 1 year,
353 remaining above 60% from years 4-14)¹³. Our findings were also consistent with the results
354 from Leonart et al., who reported an IGF-I control rate of 71.7% when considering only patients
355 treated with pegvisomant as monotherapy²². It should also be noted that IGF-I normalization
356 rates observed in the pegvisomant monotherapy cohort were achieved with mean pegvisomant
357 doses <20 mg/day (**Fig. 2A**). This is consistent with the full ACROSTUDY cohort, where the
358 mean daily pegvisomant dose was ≤ 21 mg/day among patients who achieved IGF-I normaliza-
359 tion¹³. As has been reported previously^{17,28-31}, the IGF-I normalization rates observed in real-
360 world studies are substantially lower than those observed in previous clinical studies. Some of
361 the factors that may explain this discrepancy in real-world studies include insufficient upward ti-
362 tration of pegvisomant dose by practicing clinicians, impaired patient adherence, and potential
363 differences in treatment regimens (eg, once daily vs. 2–3 injections per week). Further, variation
364 in IGF-I measurements (which were performed locally) as well as the reference ranges used to
365 calculate the ULN in ACROSTUDY may have influenced the reported normalization rates and
366 the perceived efficacy of pegvisomant.³² Acknowledging this variation in IGF-I measurement
367 and reference ranges, as well as the presence of biological variability, Clemmons and Bidling-
368 maier suggest that for patients with modestly elevated IGF-I levels (1.0× to 1.3× ULN), decisions
369 about whether to intensify treatment should also consider symptoms, comorbidities, and quality
370 of life.³² It is also important to emphasize that the efficacy of pegvisomant should not be com-
371 pared directly with that of other medical therapies in terms of normalization rate because most
372 patients who received pegvisomant were not achieving control using other therapies, which rep-

373 represents a selection bias for the more difficult-to-treat patients. With regards to the 15% of pa-
374 tients who had normal IGF-I levels at the start of ACROSTUDY, this refers to a small proportion
375 of patients who had initiated pegvisomant treatment prior to enrollment in ACROSTUDY. The
376 proportion (15%) is consistent with the proportions that were previously observed in the full
377 ACROSTUDY cohort (11.4%)¹³ and the interim analysis (15%)¹⁷.

378 We observed a reduction in the use of anti-diabetes therapy during the study, with a
379 greater than threefold reduction in patients needing anti-diabetes drugs 6 months after starting
380 pegvisomant treatment. Based on these data, pegvisomant monotherapy appears to have a
381 positive impact on glucose metabolism. A previous 4-year longitudinal analysis of patients in
382 ACROSTUDY showed a moderate reduction in mean fasting glucose values³³ and is consistent
383 with other studies that report an improvement in glucose tolerance and a reduction in HbA1c
384^{17,34}. In a meta-analysis of 13 prospective interventional studies, pegvisomant decreased fasting
385 glucose levels, HbA1c, and fasting insulin levels independently of IGF-I changes¹⁵, and given
386 that SRLs can inhibit insulin secretion¹⁴, pegvisomant monotherapy may be preferred over
387 SRLs for patients with glucose intolerance or diabetes.

388 The data from this study also provide important insights into the timing of treatment for
389 patients with acromegaly in routine clinical practice. The mean time between diagnosis of acro-
390 megaly to the start of pegvisomant treatment is very similar to the mean time between first sur-
391 gery and pegvisomant treatment (7.6 vs. 7.1 years). The mean time between the start of SRL
392 treatment and the first dose of pegvisomant is 4.6 years, which constitutes a substantial delay.
393 This delay may be due to several factors, including the accessibility of pegvisomant. Once first-
394 generation SRLs are no longer effective in patients with acromegaly, other treatments such as
395 pegvisomant could be considered sooner to reduce the duration of active disease. Delays in
396 treatment underscore the need for more stringent and/or personalized treatment protocols in
397 this patient population.

398 Given that acromegaly is a rare disease, a key strength of this study was the fact that it
399 reported real-world data from a large cohort ($n=1464$) of patients with acromegaly who received
400 pegvisomant monotherapy as part of routine clinical practice. ACROSTUDY was carried out in
401 accordance with the EMA guidance on non-interventional post-authorization safety study
402 (PASS) and, in 2013, the EMA confirmed that the PASS commitment of a minimum of 1000 pa-
403 tients followed-up for a period of 5 years was fulfilled, underscoring the robustness of the data
404 collected. ACROSTUDY was then continued via a voluntary extension period for another 4
405 years, providing additional data on long-term, real-world pegvisomant treatment practice across
406 different geographic regions. This study also captured information on tumor volume variations
407 (including the potential effect of radiotherapy) during pegvisomant monotherapy, as well as IGF-
408 I levels >ULN stratified according to IGF-I levels over the duration of treatment. As stated
409 above, one of the main limitations of the data on IGF-I levels is the reduced sample size, partic-
410 ularly in the second half of the study. Therefore, interpretation of IGF-I normalization rates and
411 pegvisomant effectiveness should consider the potential attrition bias in the data, especially in
412 the later years. Another limitation of the study was that several aspects of the study were left to
413 the discretion of the investigators ¹⁷, including AE reporting, scope of data entered, and dose es-
414 calation, which may have resulted in some inconsistencies. Only a small proportion of MRIs
415 were sent for central assessment, and some patients may have had incomplete baseline infor-
416 mation due to initiation of pegvisomant treatment before enrollment in ACROSTUDY ¹³, consti-
417 tuting additional limitations of this study. Lastly, data on glucose homeostasis was only collected
418 from 2014 onwards and compliance was not evaluable in this study.

419

420 **Conclusions**

421 In the largest and longest real-world study of pegvisomant monotherapy in patients with acro-
422 megaly to date, pegvisomant was effective in normalizing IGF-I levels (range: 51.3%-83.3% of

423 patients); at the last observation, 62.3% of patients had normal IGF-I levels, with a median daily
424 dose of 15.0 mg/day. Pegvisomant monotherapy also exerted a favorable safety profile, with a
425 low incidence of tumor growth and liver enzyme abnormalities. These findings confirm that
426 pegvisomant monotherapy constitutes a valuable treatment option for patients with acromegaly.

427 **Statements and Declaration**

428 ***Competing interests***

429 Kevin C. J. Yuen is the principal investigator with research support to the Barrow Neurological
430 Institute from Ascendis, Corcept, Chiesi, and Sparrow, has served as an occasional advisory
431 board member for Novo Nordisk, Ascendis, Chiesi, Recordati, Crinetics, Xeris, and Neurocrine,
432 and has served as an occasional speaker for Recordati, Neurocrine and Novo Nordisk. Greisa
433 Vila has served as a clinical trial investigator (research support to Medical University of Vienna)
434 for Takeda, Pfizer, Ipsen, Recordati, and Corcept, and has received occasional scientific con-
435 sultant and/or speaker fees from Pfizer, Takeda, Ipsen, Merck, Novo Nordisk, Recordati, and
436 Lundbeck. Ignacio Bernabeu has received research grants from Pfizer and consultancy or
437 speaker honoraria from Ipsen, Recordati, and Novo Nordisk. Michael Buchfelder has received a
438 research grant and speaker honoraria from Pfizer. Pamela Freda has been a research investi-
439 gator with and received research grants from Pfizer. Robin Henocque and Daria La Torre are
440 Pfizer employees and stock owners. Pietro Maffei is a principal investigator with research sup-
441 port to Padua University for clinical research studies with Pfizer, Camurus, and Recordati, and
442 serves as an occasional scientific consultant for Pfizer and Recordati. Christian J. Strasburger
443 received occasional consultancy or speaker honoraria from Novo Nordisk, Pfizer, Recordati,
444 Sandoz-Hexal, Crinetics, Amolyth, Debiopharm, and Consilient Health. Sebastian Neggens has
445 received research grants from Pfizer, and is a scientific consultant for Recordati, Novo Nordisk,
446 Crinetics, and Ipsen. Thierry Brue has served as a clinical trial investigator for Xeris, Crinetics,
447 Debiopharm, and Recordati, as an advisory board member for Pfizer, Recordati, and Novo
448 Nordisk, and has received speaker fees from Pfizer, Recordati, and Novo Nordisk, and research
449 grants from Pfizer and AFM (Association Française contre les Myopathies).

450

451 **Author contributions**

452 Conceptualization: KCJY, GV, RH, DLT, PM, CJS, SN, TB; Data curation: PM; Formal Analysis:
453 GV, MB; Funding acquisition: RH, DLT; Investigation: KCJY, GV, IB, MB, PF, PM, CJS, SN, TB;
454 Methodology: GV, MB, PF, RH, DLT, CJS; Resources: IB, PM, CJS, SN, TB; Supervision: GV,
455 RH, DLT, CJS; Validation: GV, RH, DLT; Writing – original draft: all authors participated; Writing
456 – review & editing: all authors participated.

457

458 **Compliance with Ethical Standards**

459 Ethics approval was obtained for all participating centers, and all patients provided written in-
460 formed consent before enrollment into the study.

461

462 **Data Availability Statement**

463 Upon request, and subject to review, the study sponsor, Pfizer, will provide the data that support
464 the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also
465 provide access to the related individual de-identified participant data. Contact Pfizer for more in-
466 formation.

References

- 1 Giustina, A. *et al.* Consensus on criteria for acromegaly diagnosis and remission. *Pituitary* **27**, 7-22, doi:10.1007/s11102-023-01360-1 (2024).
- 2 Melmed, S. *et al.* Clinical Biology of the Pituitary Adenoma. *Endocr Rev* **43**, 1003-1037, doi:10.1210/edrev/bnac010 (2022).
- 3 Holdaway, I. M., Rajasoorya, R. C. & Gamble, G. D. Factors influencing mortality in acromegaly. *J. Clin. Endocrinol. Metab* **89**, 667-674, doi:10.1210/jc.2003-031199 (2004).
- 4 Giustina, A. *et al.* Multidisciplinary management of acromegaly: a consensus. *Rev. Endocr. Metab. Disord* **21**, 667-678, doi:10.1007/s11154-020-09588-z (2020).
- 5 van der Lely, A. J. *et al.* Long-term treatment of acromegaly with pegvisomant, a growth hormone receptor antagonist. *Lancet* **358**, 1754-1759, doi:10.1016/s0140-6736(01)06844-1 (2001).
- 6 Buchfelder, M. *et al.* Long-term treatment with pegvisomant: observations from 2090 acromegaly patients in ACROSTUDY. *Eur. J. Endocrinol* **179**, 419-427, doi:10.1530/EJE-18-0616 (2018).
- 7 Trainer, P. J. ACROSTUDY: the first 5 years. *Eur. J. Endocrinol* **161**, S19-24, doi:10.1530/EJE-09-0322 (2009).
- 8 Bernabeu, I. *et al.* Safety of long-term treatment with pegvisomant: analysis of Spanish patients included in global ACROSTUDY. *Pituitary* **19**, 127-137, doi:10.1007/s11102-015-0691-0 (2016).
- 9 Chanson, P. *et al.* Pegvisomant treatment in patients with acromegaly in clinical practice: the French ACROSTUDY. *Ann. Endocrinol (Paris)* **76**, 664-670, doi:10.1016/j.ando.2015.10.003 (2015).
- 10 Grottoli, S. *et al.* ACROSTUDY: the Italian experience. *Endocrine* **48**, 334-341, doi:10.1007/s12020-014-0393-9 (2015).
- 11 Araujo-Castro, M. *et al.* Pegvisomant and pasireotide in PRL and GH co-secreting vs GH-secreting Pit-NETs. *Endocr. Relat. Cancer* **31**, doi:10.1530/ERC-24-0043 (2024).
- 12 Pirchio, R. *et al.* Control of acromegaly in more than 90% of patients after 10 years of pegvisomant therapy: an European referral centre real-life experience. *J. Endocrinol. Invest.* **46**, 1027-1038, doi:10.1007/s40618-022-01980-7 (2023).
- 13 Fleseriu, M. *et al.* More than a decade of real-world experience of pegvisomant for acromegaly: ACROSTUDY. *Eur. J. Endocrinol* **185**, 525-538, doi:10.1530/EJE-21-0239 (2021).
- 14 Cozzolino, A. *et al.* Somatostatin analogs and glucose metabolism in acromegaly: a meta-analysis of prospective interventional studies. *J. Clin. Endocrinol. Metab* **Mar 23** online ahead of print (2018). <<https://www.ncbi.nlm.nih.gov/pubmed/29590371>>.
- 15 Feola, T. *et al.* Pegvisomant improves glucose metabolism in acromegaly: a meta-analysis of prospective interventional studies. *J. Clin. Endocrinol. Metab* **104**, 2892-2902, doi:10.1210/jc.2018-02281 (2019).
- 16 Tritos, N. A. *et al.* Effectiveness of first-line pegvisomant monotherapy in acromegaly: an ACROSTUDY analysis. *Eur. J. Endocrinol* **176**, 213-220, doi:10.1530/EJE-16-0697 (2017).
- 17 Freda, P. U. *et al.* Long-term treatment with pegvisomant as monotherapy in patients with acromegaly: experience from ACROSTUDY. *Endocr. Pract* **21**, 264-274, doi:10.4158/EP14330.OR (2015).
- 18 Brue, T. *et al.* Which patients with acromegaly are treated with pegvisomant? An overview of methodology and baseline data in ACROSTUDY. *Eur. J. Endocrinol* **161**, S11-S17, doi:10.1530/EJE-09-0333 (2009).

- 19 van der Lely, A. J. *et al.* Long-term safety of pegvisomant in patients with acromegaly: comprehensive review of 1288 subjects in ACROSTUDY. *J. Clin. Endocrinol. Metab* **97**, 1589-1597, doi:10.1210/jc.2011-2508 (2012).
- 20 Buchfelder, M. *et al.* Pituitary tumor size in acromegaly during pegvisomant treatment: experience from MR re-evaluations of the German Pegvisomant Observational Study. *Eur J Endocrinol* **161**, 27-35, doi:10.1530/EJE-08-0910 (2009).
- 21 Gadelha, M. R., Wildemberg, L. E. & Kasuki, L. The future of somatostatin receptor ligands in acromegaly. *J. Clin. Endocrinol. Metab* **107**, 297-308, doi:10.1210/clinem/dgab726 (2022).
- 22 Leonart, L. P., Tonin, F. S., Ferreira, V. L., Fernandez-Llimos, F. & Pontarolo, R. Effectiveness and safety of pegvisomant: a systematic review and meta-analysis of observational longitudinal studies. *Endocrine* **63**, 18-26, doi:10.1007/s12020-018-1729-7 (2019).
- 23 Caron, P. J. *et al.* Tumor shrinkage with lanreotide autogel 120 mg as primary therapy in acromegaly: results of a prospective multicenter clinical trial. *J Clin Endocrinol Metab* **99**, 1282-1290, doi:10.1210/jc.2013-3318 (2014).
- 24 Colao, A. *et al.* Pasireotide versus octreotide in acromegaly: a head-to-head superiority study. *J. Clin. Endocrinol. Metab* **99**, 791-799, doi:10.1210/jc.2013-2480 (2014).
- 25 Colao, A. *et al.* Efficacy of 12-month treatment with the GH receptor antagonist pegvisomant in patients with acromegaly resistant to long-term, high-dose somatostatin analog treatment: effect on IGF-I levels, tumor mass, hypertension and glucose tolerance. *Eur. J. Endocrinol* **154**, 467-477, doi:10.1530/eje.1.02112 (2006).
- 26 Haberbosch, L. & Strasburger, C. J. Efficacy and safety of pegvisomant in the treatment of acromegaly. *Arch. Med. Res* **54**, 102884, doi:10.1016/j.arcmed.2023.102884 (2023).
- 27 Huang, W. & Molitch, M. E. Management of nonfunctioning pituitary adenomas (NFAs): observation. *Pituitary* **21**, 162-167, doi:10.1007/s11102-017-0856-0 (2018).
- 28 Giustina, A. *et al.* Pegvisomant in acromegaly: an update. *J. Endocrinol. Invest* **40**, 577-589, doi:10.1007/s40618-017-0614-1 (2017).
- 29 Marazuela, M. *et al.* Long-term treatment of acromegalic patients resistant to somatostatin analogues with the GH receptor antagonist pegvisomant: its efficacy in relation to gender and previous radiotherapy. *Eur. J. Endocrinol* **160**, 535-542, doi:10.1530/EJE-08-0705 (2009).
- 30 Ramos-Levi, A. M. *et al.* Long-term treatment with pegvisomant for acromegaly: a 10-year experience. *Clin. Endocrinol* **84**, 540-550, doi:10.1111/cen.12993 (2016).
- 31 Tritos, N. A. & Biller, B. M. Pegvisomant: a growth hormone receptor antagonist used in the treatment of acromegaly. *Pituitary* **20**, 129-135, doi:10.1007/s11102-016-0753-y (2017).
- 32 Clemmons, D. R. & Bidlingmaier, M. IGF-I assay methods and biologic variability: evaluation of acromegaly treatment response. *Eur J Endocrinol* **191**, R1-R8, doi:10.1093/ejendo/lvae065 (2024).
- 33 Brue, T. *et al.* Diabetes in patients with acromegaly treated with pegvisomant: observations from acrostudy. *Endocrine* **63**, 563-572, doi:10.1007/s12020-018-1792-0 (2019).
- 34 Vila, G., Jorgensen, J. O. L., Luger, A. & Stalla, G. K. Insulin resistance in patients with acromegaly. *Front. Endocrinol (Lausanne)* **10**, 509, doi:10.3389/fendo.2019.00509 (2019).

Figure Legends

Fig. 1. Therapies received prior to starting pegvisomant treatment.

Fig. 2. Percentage of patients with (a) normal IGF-I levels and (b) IGF-I levels <LLN. IGF-I, insulin-like growth factor-1; LLN, lower limit of normal; M, month; obs, observation; Y, year.

TABLES

Table 1. Pituitary function at the start of pegvisomant therapy.

Pituitary hormone	<i>n</i>	Deficiency <i>n</i> (%)	Normal for age <i>n</i> (%)	Hypersecretion <i>n</i> (%)	Therapy reported <i>n</i> (%)^a
Gonadotropin	429	157 (36.6)	265 (61.8)	7 (1.6)	104 (24.2)
Adrenocorticotrophic hormone	402	115 (28.6)	285 (70.9)	2 (0.5)	112 (27.9)
Thyroid-stimulating hormone	458	133 (29.0)	322 (70.3)	3 (0.7)	160 (34.9)
Prolactin	421	18 (4.3)	357 (84.8)	46 (10.9)	31 (7.4)
Arginine vasopressin	294	5 (1.7)	285 (96.9)	4 (1.4)	10 (3.4)

^aPercentage of patients with pituitary hormone deficiency for which treatment is reported.

Table 2. All-causality treatment-emergent adverse events reported in $\geq 1\%$ of patients.

Adverse event	N=1464 n (%)
IGF-I increased ^a	132 (9)
Vitamin D deficiency	65 (4.4)
Headache	60 (4.1)
Arthralgia	56 (3.8)
Osteoarthritis	54 (3.7)
Hypertension	44 (3.0)
Depression	32 (2.2)
Colonic polyp	31 (2.1)
Asthenia	27 (1.8)
Constipation	24 (1.6)
Atrial fibrillation	23 (1.6)
Transaminases increased	23 (1.6)
Pituitary tumor recurrent	22 (1.5)
Cholelithiasis	21 (1.4)
IGF-I decreased ^a	20 (1.4)
Dyslipidemia	21 (1.4)
Blood thyroid-stimulating hormone decreased	19 (1.3)
Back pain	19 (1.3)
Diabetes mellitus	18 (1.2)
Thyroid neoplasm	17 (1.2)
Sleep apnea syndrome	17 (1.2)

Lipohypertrophy	17 (1.2)
Abdominal pain	16 (1.1)
Disease progression	16 (1.1)
Dyspnea	16 (1.1)
Fatigue	15 (1.0)
ALT increased	15 (1.0)
Paresthesia	15 (1.0)
Nausea	14 (1.0)

Abbreviation:ALT, alanine aminotransferase; IGF-I, Insulin-like growth factor.

^aThese instances of IGF-I increase/decrease were specified as AEs per protocol: laboratory abnormalities were to be reported as AEs if they were associated with symptoms, required additional diagnostic testing or medical intervention, resulted in a dose adjustment (or discontinuation from the study), or were considered an AE based on investigator judgement.

Table 3. Incidence of AEs and SAEs.

Summary of AEs (treatment-related)	Pegvisomant monotherapy with no recorded prior use of SRL or DA or other therapies <i>n</i> (%)		Pegvisomant monotherapy after prior use of SRL or DA or other therapies <i>n</i> (%)		Total ^a <i>N</i> (%)	
	All causality	Treatment-related	All-causality	Treatment-related	All-causality	Treatment-related
Patients evaluable for AEs	249	249	1230	1230	1464	1464
Number of AEs	388	40	2704	283	2994	312
Patients with AEs	94 (37.8)	23 (9.2)	634 (51.5)	179 (14.6)	717 (49.0)	198 (13.5)
Patients with SAEs	36 (14.5)	2 (0.8)	251 (20.4)	23 (1.9)	282 (19.3)	25 (1.7)
Patients with dose reduced due to SAEs	0 (0.0)	0 (0.0)	2 (0.2)	1 (0.1)	2 (0.1)	1 (0.1)
Patients with drug withdrawn (temporarily or permanently or delayed) due to SAEs ^b	10 (4.0)	2 (0.8)	68 (5.5)	8 (0.7)	75 (5.1)	10 (0.7)
Death	4 (1.6)	0 (0.0)	28 (2.3)	0 (0.0)	31 (2.1)	0 (0.0)

Abbreviations: AE, adverse event; DA, dopamine agonist; SAE, serious adverse event; SRL, somatostatin receptor ligand.

^aNot all columns are mutually exclusive because some patients might qualify for pegvisomant only as both with no prior therapies (in the beginning) and with prior therapies, if they remained on pegvisomant only at some later time during the study.

^bDrug withdrawn includes temporary withdrawal, permanent withdrawal, or a delayed dose.

FIGURES

Fig. 1. Therapies received prior to starting pegvisomant treatment.

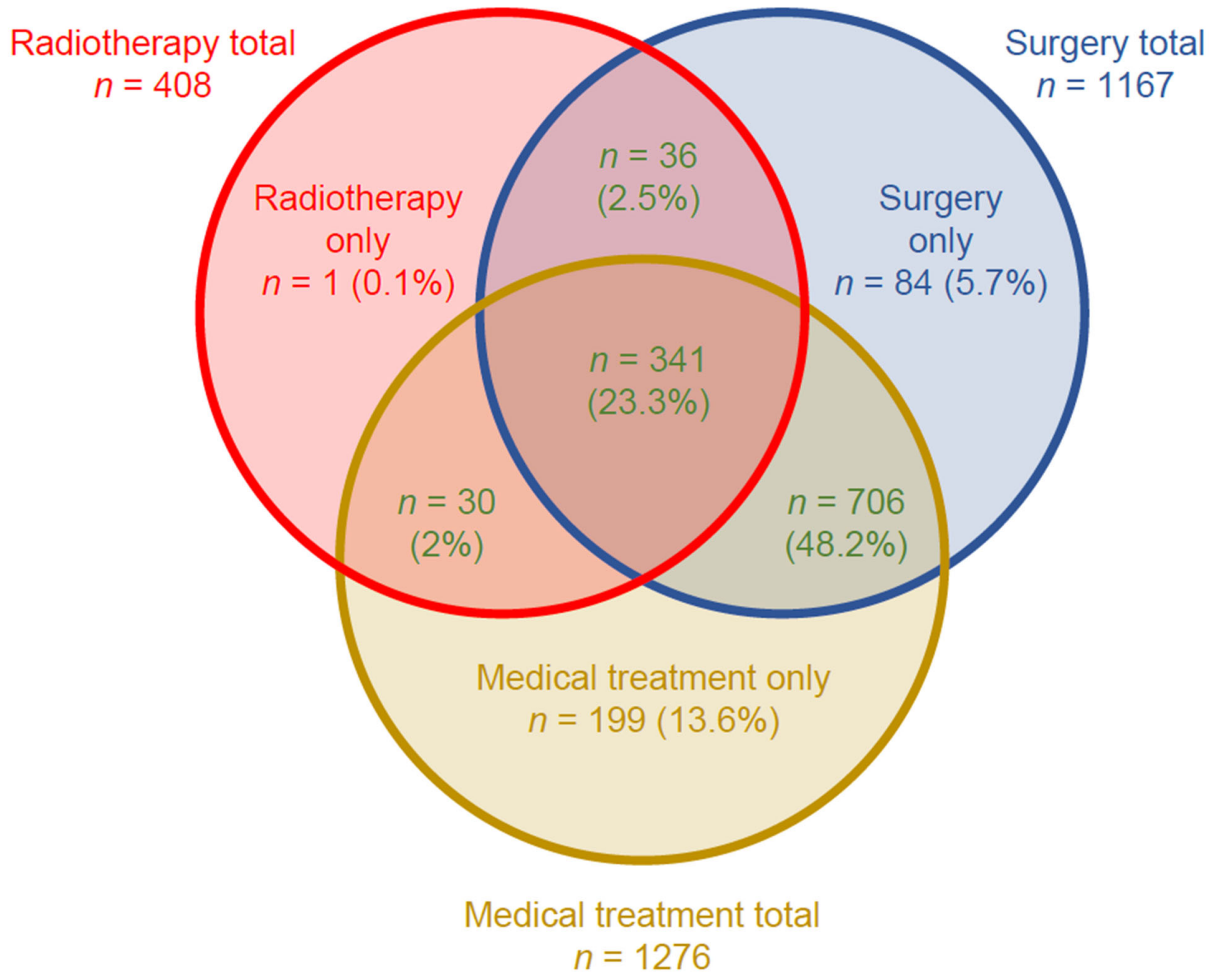
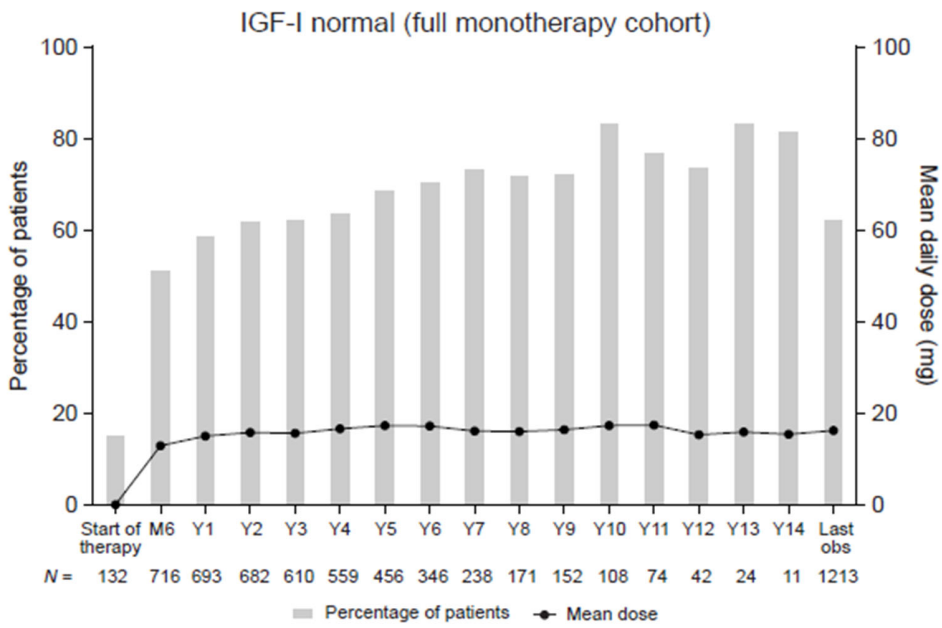
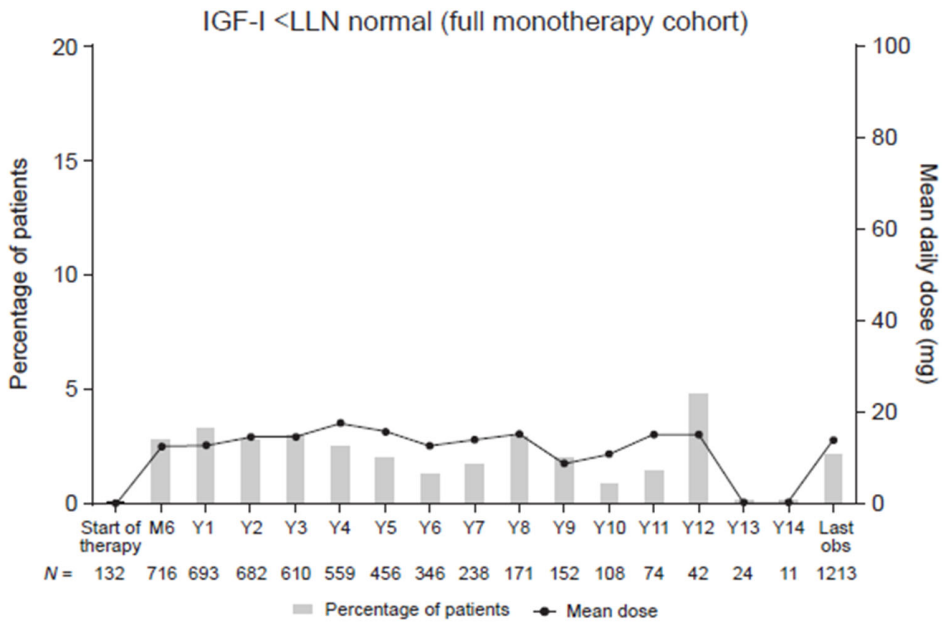


Fig. 2. Percentage of patients with (A) normal IGF-I levels and (B) IGF-I levels <LLN. IGF-I, insulin-like growth factor-1; LLN, lower limit of normal; M, month; n, number of patients with available data; obs, observation; Y, year.

A



B



SUPPLEMENTARY INFORMATION

Supplementary Table 1. Demographic and baseline clinical characteristics.

<i>n</i> (%) ^a	Male (<i>n</i> =725)	Female (<i>n</i> =739)	Total (<i>N</i> =1464)
Country, <i>n</i> (%)			
Austria	1 (0.1)	2 (0.3)	3 (0.2)
Belgium	6 (0.8)	6 (0.8)	12 (0.8)
Germany	198 (27.3)	187 (25.3)	385 (26.3)
Denmark	10 (1.4)	6 (0.8)	16 (1.1)
Spain	74 (10.2)	97 (13.1)	171 (11.7)
France	122 (16.8)	120 (16.2)	242 (16.5)
Great Britain	19 (2.6)	14 (1.9)	33 (2.3)
Greece	9 (1.2)	34 (4.6)	43 (2.9)
Hungary	4 (0.6)	2 (0.3)	6 (0.4)
Italy	147 (20.3)	156 (21.1)	303 (20.7)
The Netherlands	31 (4.3)	23 (3.1)	54 (3.7)
Portugal	3 (0.4)	0 (0.0)	3 (0.2)
Sweden	15 (2.1)	12 (1.6)	27 (1.8)
Slovakia	2 (0.3)	6 (0.8)	8 (0.5)
United States	84 (11.6)	74 (10.0)	158 (10.8)
Age (years) at diagnosis of acromegaly			
0-<18	17 (2.3)	10 (1.4)	27 (1.8)
18-<30	154 (21.2)	115 (15.6)	269 (18.4)
30-<40	206 (28.4)	176 (23.8)	382 (26.1)
40-<50	177 (24.4)	197 (26.7)	374 (25.5)
50-<60	120 (16.6)	141 (19.1)	261 (17.8)
60-<70	35 (4.8)	75 (10.1)	110 (7.5)
≥70	16 (2.2)	22 (3.0)	38 (2.6)
<i>n</i>	725	736	1461
Mean (SD)	40.5 (12.89)	43.9 (13.79)	42.2 (13.46)
Time (years) from diagnosis to start of pegvisomant treatment			
<i>n</i>	725	736	1461
Mean (SD)	7.9 (8.24)	7.3 (7.90)	7.6 (8.08)

Time (years) between first dose of SRL and first dose of pegvisomant			
<i>n</i>	647	655	1302
Mean (SD)	4.9 (4.61)	4.3 (4.58)	4.6 (4.60)
Time (years) between first pituitary surgery and first dose of pegvisomant			
<i>n</i>	598	601	1199
Mean (SD)	7.3 (7.62)	7.0 (7.50)	7.1 (7.56)
Actual years of pegvisomant-only treatment			
<1	102 (14.1)	96 (13.0)	198 (13.5)
1–<3	113 (15.6)	113 (15.3)	226 (15.4)
3–<5	90 (12.4)	112 (15.2)	202 (13.8)
5–10	212 (29.2)	218 (29.5)	430 (29.4)
>10	208 (28.7)	200 (27.1)	408 (27.9)
<i>n</i>	725	739	1464
Mean (SD)	6.7 (4.65)	6.5 (4.51)	6.6 (4.58)
Age (years) at pegvisomant start			
0–<18	6 (0.8)	3 (0.4)	9 (0.6)
18–<30	61 (8.4)	53 (7.2)	114 (7.8)
30–<40	137 (18.9)	107 (14.5)	244 (16.7)
40–<50	191 (26.3)	168 (22.7)	359 (24.5)
50–<60	183 (25.2)	190 (25.7)	373 (25.5)
60–<70	105 (14.5)	144 (19.5)	249 (17.0)
≥70	42 (5.8)	74 (10.0)	116 (7.9)
<i>n</i>	725	739	1464
Mean (SD)	48.4 (13.49)	51.3 (14.12)	49.9 (13.88)
BMI (kg/m ²) at pegvisomant start			
<i>n</i>	493	505	998
Mean (SD), <i>n</i> (%)	30.0 (4.71)	28.7 (5.81)	29.3 (5.33)

Abbreviations: BMI, body mass index; SRL, somatostatin receptor ligand.

^aExcept where otherwise indicated.

Supplementary Table 2. Reported comorbidities.

	Before pegviso- mant start (N=1464) n (%)	Between pegviso- mant start and ACROSTUDY start (N=1125) n (%)	After ACROSTUDY start (N=1464) n (%)
Number of patients with missing report	87 (5.9)	626 (42.8)	N/A ^b
Number of patients without reported comorbidities	74 (5.1)	135 (9.2)	N/A ^b
Number of patients with reported comorbidities ^a	1303 (89.0)	364 (24.9)	118 (8.1)
Metabolic	410 (31.5)	38 (10.4)	16 (13.6)
Diabetes mellitus	410 (31.5)	38 (10.4)	16 (13.6)
Cardiovascular	722 (55.4)	85 (23.4)	20 (16.9)
Coronary heart disease	57 (4.4)	4 (1.1)	0 (0.0)
Hypertension	678 (52.0)	43 (11.8)	16 (13.6)
Coronary artery bypass surgery	15 (1.2)	1 (0.3)	0 (0.0)
Coronary angioplasty with or without stent	25 (1.9)	3 (0.8)	0 (0.0)
Arrhythmia	83 (6.4)	23 (6.3)	3 (2.5)
Cardiomyopathy	93 (7.1)	18 (4.9)	1 (0.8)
Myocardial infarction	30 (2.3)	4 (1.1)	1 (0.8)
Cerebrovascular	31 (2.4)	5 (1.4)	2 (1.7)
Transient ischemic attack	18 (1.4)	3 (0.8)	1 (0.8)
Infarction	10 (0.8)	2 (0.5)	1 (0.8)
Hemorrhage	3 (0.2)	0 (0.0)	0 (0.0)
Respiratory	358 (27.5)	35 (9.6)	13 (11.0)
COPD	45 (3.5)	3 (0.8)	2 (1.7)
Sleep apnea	286 (21.9)	22 (6.0)	4 (3.4)
Other respiratory disease	83 (6.4)	10 (2.7)	7 (5.9)
Musculoskeletal	460 (35.3)	57 (15.7)	15 (12.7)
Osteoarthritis	313 (24.0)	37 (10.2)	11 (9.3)
Osteoporosis	43 (3.3)	13 (3.6)	2 (1.7)
Surgery for carpal tunnel syndrome	160 (12.3)	3 (0.8)	1 (0.8)
Other surgery for musculoskeletal disease	71 (5.4)	7 (1.9)	1 (0.8)
Tumors	545 (41.8)	108 (29.7)	24 (20.3)

Breast	45 (3.5)	6 (1.6)	1 (0.8)
Lung	6 (0.5)	3 (0.8)	2 (1.7)
Prostate	30 (2.3)	8 (2.2)	2 (1.7)
Colon	218 (16.7)	37 (10.2)	8 (6.8)
Skin	27 (2.1)	9 (2.5)	3 (2.5)
Thyroid	246 (18.9)	31 (8.5)	7 (5.9)
Other	173 (13.3)	30 (8.2)	4 (3.4)
Liver/Gallbladder	295 (22.6)	64 (17.6)	4 (3.4)
Hepatic disease	91 (7.0)	44 (12.1)	2 (1.7)
Surgery for gallstones	229 (17.6)	26 (7.1)	2 (1.7)
Other comorbidity	771 (59.2)	108 (29.7)	38 (32.2)
Other clinically significant comorbidity	672 (51.6)	95 (26.1)	38 (32.2)
Goitre	68 (5.2)	2 (0.5)	0 (0.0)
Headache	31 (2.4)	11 (3.0)	0 (0.0)

Abbreviations: AE, adverse event; COPD, chronic obstructive pulmonary disease; N/A, not available.

^aPatients can have >1 comorbidity. Percentages for comorbidities use this number as denominator.

^bAccording to protocol, disorders with onset after ACROSTUDY start should be reported as AEs.

Supplementary Table 3. Deaths in the study.

Adverse event resulting in death	<i>n</i>
Death	8
Cardiac failure	4
Sudden cardiac death	2
Adenocarcinoma	1
Cardiac aneurysm	1
Cerebrovascular accident	1
Disease progression	1
Drug hypersensitivity	1
General physical health deterioration	1
Hypertensive crisis	1
Hypophagia	1
Metastases to liver	1
Metastasis	1
Myocardial infarction	1
Oedema due to cardiac disease	1
Oesophageal carcinoma	1
Respiratory failure	1
Sepsis	1
Venous thrombosis	1
Ventricular fibrillation	1

Supplementary Table 4. Shift table of liver function tests (AST or ALT) measured during pegvisomant treatment.

Baseline Measurement	n (%)¹	Missing^a n (%)²	Normal^b n (%)²	1 × ULN to 3 × ULN^c n (%)²	>3 × ULN to 5 × ULN^d n (%)²	>5 × ULN^e n (%)²	Total n (%)²
Missing ^a	525 (36)	53 (10)	336 (64)	123 (23)	8 (2)	5 (1)	525 (100)
Normal ^b	864 (59)	58 (7)	567 (66)	209 (24)	13 (2)	17 (2)	864 (100)
1 × ULN to 3 × ULN ^c	68 (5)	3 (4)	22 (32)	34 (50)	7 (10)	2 (3)	68 (100)
>3 × ULN to 5 × ULN ^d	6 (0)	0 (0)	2 (33)	2 (33)	1 (17)	1 (17)	6 (100)
>5 × ULN ^e	1 (0)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	1 (100)
Total	1464 (100)	114 (8)	927 (63)	369 (25)	29 (2)	25 (2)	1464 (100)

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; ULN, upper limit of normal.

Not all columns are mutually exclusive as some patients might qualify for pegvisomant as both with no prior therapies (in the beginning) and also with prior therapies, if they remained on pegvisomant only at some later time during the study.

^aPatients had missing AST and ALT.

^bPatients had normal AST and normal ALT.

^cPatients had AST or ALT in the range of 1 × ULN - 3 × ULN.

^dPatients had AST or ALT in the range of >3 × ULN - 5 × ULN.

^ePatients had AST or ALT in the range of >5 × ULN.

¹Percentages are calculated using the Total count in this column as the denominator.

²Percentages are calculated using the Total count in their respective row as the denominator.

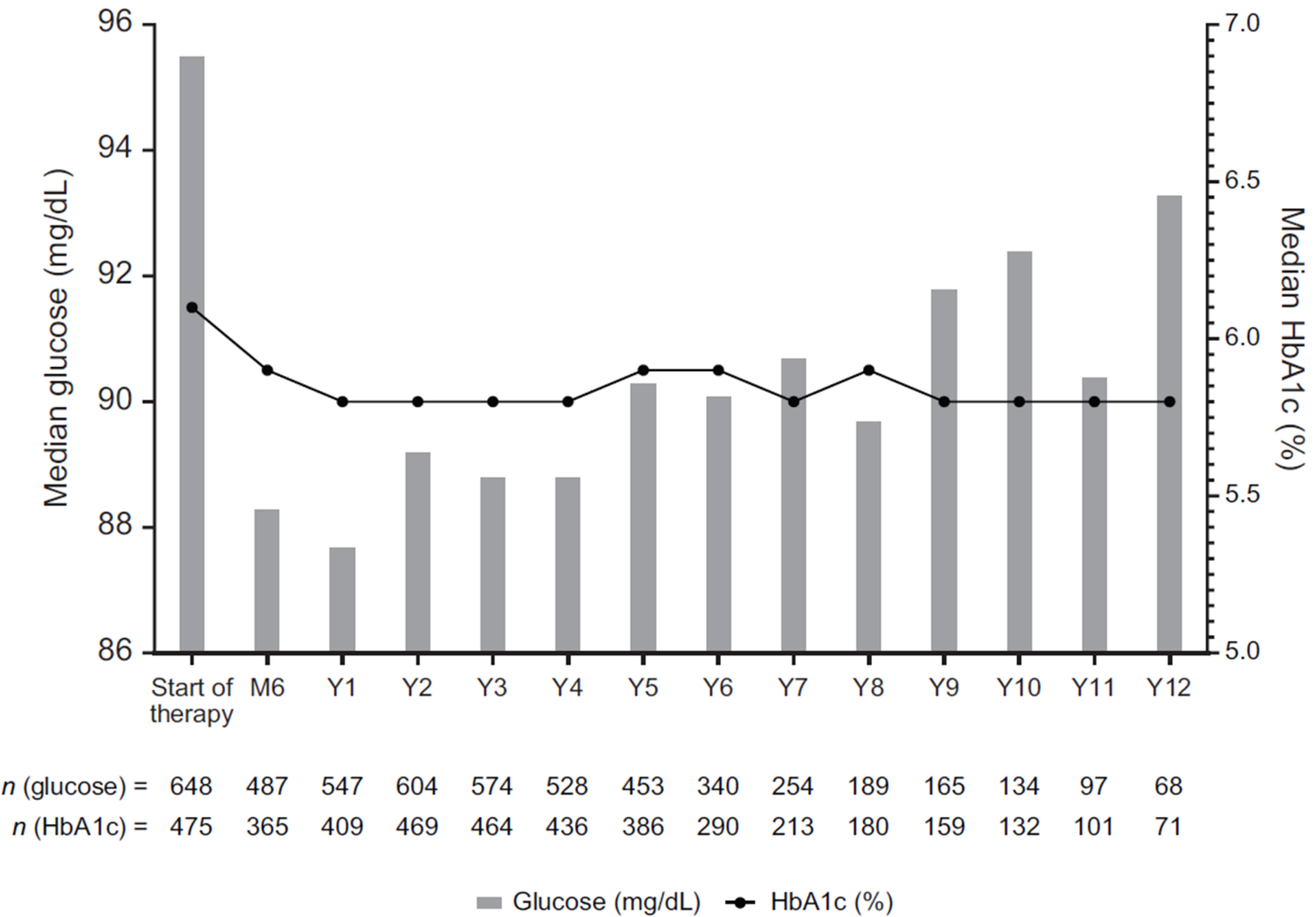
SupplementaryTable 5. Pituitary tumor imaging results.

	Pituitary imaging (N=1464)			Pituitary imaging (stratified according to radiotherapy treatment) (N=1352)		
	Pituitary imaging (N=1248) n (%)	Surgery before tumor change ^a (N=112) n (%)	Radiotherapy before tumor change ^b (N=570) n (%)	No radiotherapy (N=716) n (%)	Received radiotherapy before start of pegvisomant (N=427) n (%)	Received radiotherapy after start of pegvisomant (N=209) n (%)
Relative to last examination or to start of pegvisomant therapy						
Increase or decrease, at least once	367 (29.4)	65 (58.0)	181 (31.8)	310 (43.3)	188 (44.0)	145 (69.4)
Increase only, at least once	90 (7.2)	1 (0.9)	21 (3.7)	65 (9.1)	11 (2.6)	16 (7.7)
Decrease only, at least once	213 (17.1)	39 (34.8)	127 (22.3)	193 (27.0)	146 (34.2)	91 (43.5)
Both increase and decrease	64 (5.1)	5 (4.5)	33 (5.8)	52 (7.3)	31 (7.3)	38 (18.2)
No change	881 (70.6)	47 (42.0)	387 (67.9)	406 (56.7)	239 (56.0)	64 (30.6)

^aAt least 1 surgery has been performed up to 1 year before the tumor examination date.

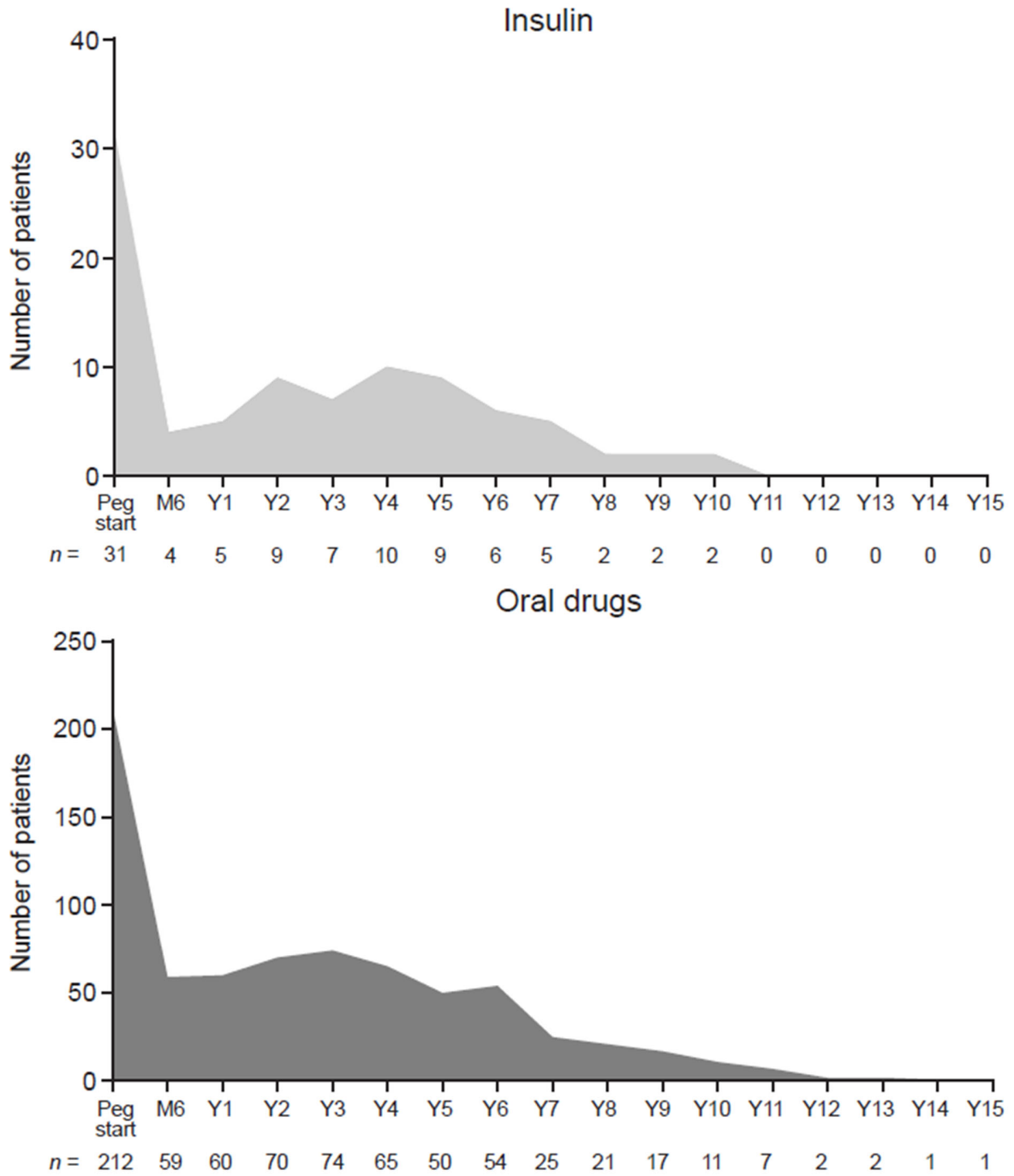
^bAt least 1 radiotherapy treatment has started before the tumor examination date.

Supplementary Fig. 1. Median glucose and HbA1c levels. M, month; Y, year.

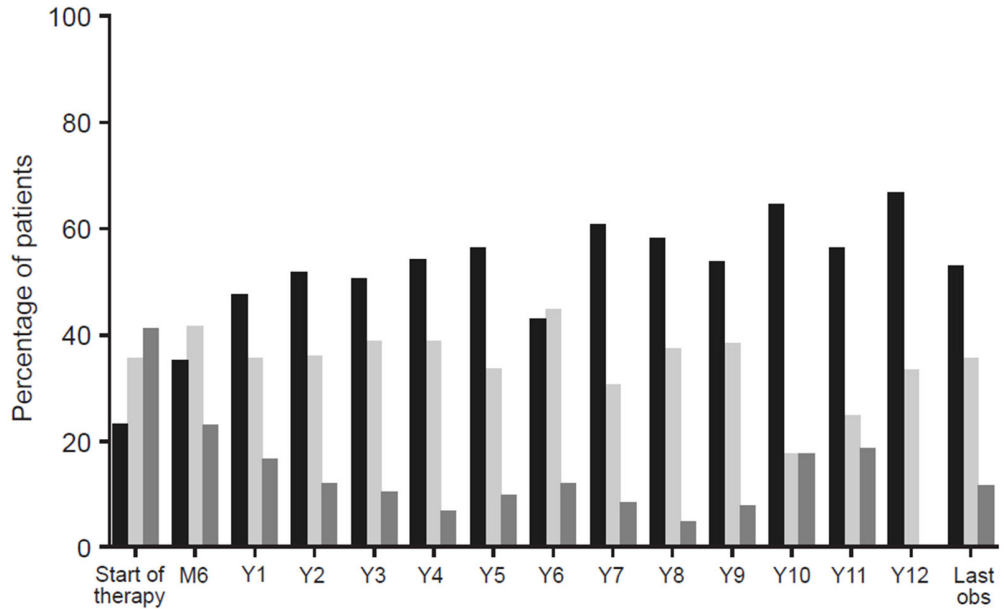


<i>n</i> (glucose) =	648	487	547	604	574	528	453	340	254	189	165	134	97	68
<i>n</i> (HbA1c) =	475	365	409	469	464	436	386	290	213	180	159	132	101	71

Supplementary Fig. 2. Diabetes therapy utilization over the course of pegvisomant monotherapy. M, month; Peg, pegvisomant; Y, year.



Supplementary Fig. 3. Patients with IGF-I levels >ULN stratified according to IGF-I levels over the duration of pegvisomant treatment. IGF-I, insulin-like growth factor-1; M, month; n, number of patients with available data; obs, observation; ULN, upper limit of normal; Y, year.



ULN and <1.3 × ULN; n =	26	116	126	125	107	102	75	42	36	25	21	11	9	6	431
≥1.3 × ULN and <2 × ULN; n =	40	137	94	87	82	73	45	44	18	16	15	3	4	3	287
≥2 × ULN; n =	46	76	44	29	22	22	13	12	5	2	3	3	3	0	94

ULN and <1.3 × ULN
 ≥1.3 × ULN and <2 × ULN
 ≥2 × ULN