CLINICAL STUDY

Coadministration of lanreotide Autogel and pegvisomant normalizes IGF1 levels and is well tolerated in patients with acromegaly partially controlled by somatostatin analogs alone

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Abstract

Objective: To evaluate the efficacy and safety of coadministered lanreotide Autogel (LA; 120 mg/month) and pegvisomant (40–120 mg/week) in acromegaly.

Design: This is a 28-week, multicenter, open-label, single-arm sequential study.

Methods: Patients (n=92) biochemically uncontrolled, on somatostatin analogs (SSAs) or using pegvisomant monotherapy entered a 4-month run-in taking LA (120 mg/month). Patients uncontrolled after the run-in period (n=57) entered a 28-week coadministration period, receiving LA 120 mg/month plus pegvisomant (60 mg once weekly, adapted every 8 weeks based on IGF1 levels to 40–80 mg once weekly or 40 or 60 mg twice weekly).

Results: In total, 33 (57.9%) patients had normalized IGF1 following coadministration (P<0.0001 versus 30% minimum clinically relevant); median pegvisomant dose in normalized patients was 60 mg/week. IGF1 normalized at any time during coadministration in 45 (78.9%) patients (P<0.0001) with median pegvisomant dose at 60 mg/week. Being nondiabetic (odds ratio (OR): 4.65) and older (OR, upper versus lower quartile: 3.40) showed increased likelihood of normalization. Symptom reduction was greatest for arthralgia (−0.6 ± 1.6) and soft tissue swelling (−0.6 ± 1.8). Five patients reported treatment-emergent adverse events causing treatment withdrawal: three serious (treatment related – thrombocytopenia, urticaria; not treatment related – abdominal pain/vomiting) and two nonserious (hepatotoxicity and cytolytic hepatitis, both elevating alanine aminotransferase to > 5× upper limit of normal with normalization after withdrawal).

Conclusions: In patients partially controlled by SSAs, LA (120 mg/month) plus pegvisomant normalized IGF1 in 57.9% of patients after 7 months, at a median effective pegvisomant dose of 60 mg/week, and 78.9% at any time. In these patients, results suggest a pegvisomant-sparing effect versus daily pegvisomant monotherapy.

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Introduction

Acromegaly is a chronic disorder caused by excess GH secretion, usually due to a benign GH-secreting pituitary somatotroph adenoma. Pharmaceutical management of acromegaly includes somatostatin analogs (SSAs), the GH receptor antagonist (GHRA) pegvisomant, or, less commonly, the dopamine agonist cabergoline. There are currently two commercially available long-acting SSAs, octreotide LAR (Novartis International AG) and lanreotide Autogel (LA, Beaufour-Ipsen Industrie, Dreux, France), both of which normalize insulin-like growth factor 1 (IGF1) levels in 30–60% of unselected patients and reduce symptom burden (1, 2). Long-acting SSAs, administered by monthly injection, are generally well tolerated; the most notable adverse effect, increased incidence of small gallstones and gallbladder sludge, rarely causes clinically significant symptoms (1, 3).

Pegvisomant, a recombinant human GH analog and highly selective GHRA (4, 5), is the only approved agent in its class, and it is indicated in Europe in patients who have responded incompletely, or are intolerant, to maximal dose SSA therapy. Although typically injected daily, emerging data now support once-weekly dosing of pegvisomant (6). Pegvisomant monotherapy has been shown to normalize IGF1 levels in ~90–100% of patients at doses of 20–40 mg/day (7, 8), but long-term...
data from the observational, registry-based ACROS-TUDY, representing 2625 patient-years of treatment, indicated IGF1 normalization in only ~60% of patients at mean weekly doses exceeding 120 mg (9). The relatively high cost and traditional daily injection frequency of pegvisomant remain key limitations to its wider use, as does concern that pegvisomant may not inhibit tumor growth. The potential for hepatitis is also acknowledged in the product’s ‘Summary of Product Characteristics’, along with a recommendation that hepatic transaminases be monitored at 4–6-week intervals for the first 6 months of treatment, and in all cases with symptoms consistent with hepatitis (10). There is therefore increasing interest in combination therapy as a means of sparing pegvisomant.

Patients with only a partial response to full-dose SSA therapy can achieve further reductions in IGF1 levels by combining weekly pegvisomant with monthly SSA injections (11–13). This strategy capitalizes on the complementary modes of action of the two drug classes and mitigates concerns about tumor growth by incorporating SSAs, agents that can induce pituitary tumor shrinkage (14–16). Weekly, rather than daily, pegvisomant dosing offers the advantage of reduced injection frequency, which patients may prefer, even in the absence of further reduction in IGF1 levels (6, 17).

Based on the findings from two small (26–32 patients) published trials of combination SSA/pegvisomant therapy (12, 18), this study is the first to examine LA in combination with pegvisomant in a rigorously selected larger population of patients partially controlled by SSAs.

**Patients and methods**

**Study objective**

This is a multicenter, open-label, single-arm, sequential study in which patients served as their own controls; study design is presented in Fig. 1a. The primary study objective is to evaluate the efficacy of coadministered LA (120 mg/month) and pegvisomant (40–120 mg/week), as determined by the change in IGF1 levels over 28 weeks, in patients with acromegaly. Secondary objectives are to assess the effects of combined therapy on acromegaly symptoms and quality of life (QoL) and to assess treatment safety.

**Patient selection**

Patients were eligible for inclusion if aged 18–75 years and with a documented diagnosis of acromegaly. They were also either responders to daily pegvisomant monotherapy (and thus given the approved indication for pegvisomant, previously uncontrolled on SSA therapy) or partial responders to the highest marketed doses of either pegvisomant or a long-acting SSA.

As such, they had either IGF1 levels that were greater than the upper limit of normal (ULN) following pegvisomant 30 mg/day for at least 3 months or IGF1 levels >ULN 28 days after the last SSA injection, following at least 6 months of treatment with LA or octreotide LAR, including 3 months at the highest marketed dose. Unlike similar studies conducted previously (12, 18), this study employed a two-step process to confirm that patients entering the coadministration period were incomplete responders to full-dose SSA therapy. Eligible subjects (n=92) entered a 4-month run-in period, during which they received LA at the highest available dose (120 mg/month). Patients with serum IGF1 >1.2× ULN (n=54) or between ULN and 1.2× ULN with serum GH nadir ≥1 μ/l on oral glucose tolerance testing (n=3) 28 days after the third injection of LA were considered to have remained uncontrolled and entered the coadministration period (n=57 total). Exclusion criteria were pituitary surgery or radiotherapy within the previous 6 months or planned during the study; dopamine agonists within 6 weeks of study entry; previous SSA/GHRA therapy; and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2× ULN. None of the patients in this study had participated in any previous coadministration studies. All patients provided written informed consent prior to entering the study.

**Treatments**

LA (120 mg) was administered by a single s.c. injection in the buttock at the same time each day, every 28 days. Pegvisomant was administered by a single s.c. injection once or twice weekly in the abdomen, buttock, thigh, or upper arm. The starting dose of pegvisomant in the coadministration period, 60 mg/week, was the median dose that normalized IGF1 levels in the Feenstra et al. (12) study. The pegvisomant dose was evaluated every 8 weeks based on IGF1 levels taken 4 weeks after the previous dose adaptation, and according to the rules presented in Fig. 1b. If dosing was twice weekly, the second injection was given 4 days after the first. Pegvisomant doses exceeding 40 mg were delivered as two separate injections at the same time.

**Efficacy and safety analyses**

The primary efficacy end point was the number and percentage of patients with normalized age- and sex-adjusted IGF1 levels at the end of coadministration; this was compared with the estimated minimum clinically relevant percentage of 30%, using a one-sided exact test based on the binomial distribution. Sensitivity analyses were performed to investigate the potential impact on the primary end point of patients achieving a normalized IGF1 level during the coadministration phase that was not maintained until study end because of a subsequent reduction in pegvisomant dose.
The analyses determined i) the number and percentage of patients with a normal IGF1 level at any time during the coadministration period while taking the dose used prior to the last study assessment and ii) the number and percentage of patients with a normal IGF1 level at any time during coadministration. IGF1 z-score was a secondary efficacy end point and was calculated using the following formula: \( z = \frac{\ln(\text{IGF1 value}) - \text{mean}}{\text{s.d.}} \), with mean and s.d. being age- and sex-specific and were determined on the logarithmic scale. Additional secondary end points included acromegaly symptoms, rated on a 0–8 scale of increasing severity, and ACROQoL questionnaire scores. Only summary statistics were prepared for secondary end points. To investigate whether various predisposing factors were associated with the primary efficacy variable, logistic regression methods were applied in an exploratory analysis with normalization at the end of the coadministration period as the response variable. The predisposing factors included IGF1 z-score at the end of the run-in period, previous treatment, diabetic status, age, sex, pituitary tumor size, whether the patient had received previous radiotherapy or surgery (as two separate factors), and time since diagnosis. These variables were tested using backward elimination (with a significance level of \( P = 0.15 \) for keeping a term in the final model). All efficacy analyses were performed on the intention-to-treat (ITT) population, defined as all coadministered subjects with \( R \geq 1 \) baseline and \( R \geq 1 \) postbaseline IGF1 assessment where values were missing at the end of coadministration and last observation carried forward was used.

Safety end points were adverse events (AEs), defined as serious if they were life threatening or fatal or resulted in significant disability. In this study, the safety endpoints chosen were glucose tolerance (in subjects without diabetes only), gallbladder ultrasound, electrocardiograms (ECGs), hepatic function tests (including ALT and AST), and standard hematological and biochemical laboratory tests. The duration of the study was inadequate for the assessment of the full impact of treatment on pituitary size, and thus this parameter was included as a safety end point only. The safety population comprised all patients who received at least one dose of both trial products during coadministration.

Figure 1 (a) Study design and (b) pegvisomant dose adaptation schedule. If pegvisomant dosing was twice weekly, the second injection was given 4 days after the first. Pegvisomant doses exceeding 40 mg were delivered as two separate injections at the same time.
The planned sample size of 60 subjects was based on having at least 95% power to detect the difference between the null hypothesis of 30% (estimated as the minimum clinically relevant percentage of responders) and the expected response rate (80%) at the 5% significance level.

**Results**

**Patients and conduct of study**

All 57 subjects received at least one dose of both study medications and had at least one baseline and at least one postbaseline IGF1 assessment; the ITT and safety populations were therefore identical.

Baseline demographics and clinical characteristics for the ITT population are presented in Table 1. The most frequent comorbid conditions in study patients were other endocrine disorders (n = 36; 63%), previous interventional procedures (n = 33; 58%), and metabolic/nutritional disorders (n = 31; 54%). Acromegaly treatments taken prior to run-in by patients who entered into the coadministration period were lanreotide (n = 24; 42%), octreotide (n = 20; 35%), and pegvisomant (n = 13; 23%).

**Efficacy**

A total of 33 patients (57.9%; 90% confidence interval (CI): 46.1, 69.0) achieved normal serum IGF1 levels by the end of coadministration (P < 0.0001 versus theoretical 30% estimated as minimum clinically relevant; Fig. 2), with a median effective weekly pegvisomant dose of 60 mg for all (normalized) subjects and for nondiabetics, and 80 mg for those with diabetes.

The proportion of subjects with normalized IGF1 at the end of coadministration (or for a small number of patients at early withdrawal) were similar across final pegvisomant dose groups of 40, 60, and 80 mg/week (Fig. 3), and were statistically significant in nondiabetic (24/38; 63.2%, 90% CI: 48.5, 76.2; P < 0.0001) but not in diabetic patients (9/19; 47.4%, 90% CI: 27.4, 68.0; P = 0.008); this finding was consistent with higher median reductions in z-scores in nondiabetics. Similarly, in an exploratory multivariate logistic regression analysis, being nondiabetic (OR: 4.65) and being older (OR for upper versus lower quartile: 3.40) were both associated with increased odds of normalization. None of the other potential predisposing factors tested, including tumor size, baseline IGF1 SDS, and previous radiotherapy, were significant predictors of a response. The biochemical response rate at study end was 76.9% in patients taking a final pegvisomant dose of 40 mg once weekly, 61.5% in those taking 60 mg once weekly, 75% with 80 mg once weekly, and 60% with 40 mg twice weekly (Fig. 3), leaving ~30% of patients across these groups suboptimally controlled on their final pegvisomant dose. A notable lack of efficacy was apparent for pegvisomant 60 mg twice weekly, suggesting that these subjects may need more pegvisomant and/or a different dose regimen to normalize IGF1. Biochemical response was significant in patients previously treated with octreotide LAR (n = 14 (70.0%); P = 0.0003) and LA (n = 13 (54.2%); P = 0.01), but not pegvisomant (n = 6 (46.2%); P = 0.17). Of the 13 patients previously treated with pegvisomant, 10 (76.9%) had normal IGF1 levels at baseline; none of these patients remained biochemically controlled at the end of run-in. However, only one patient failed to normalize during coadministration. Of the three
patients previously treated with pegvisomant, who had abnormal IGF1 levels at baseline, none of whom were biochemically controlled at the end of the run-in period, two (66.7%) remained uncontrolled at the end of coadministration. A post hoc analysis involving eight patients whose mean IGF1 levels were similar while on pegvisomant monotherapy and on at least one occasion during the coadministration period (202.4 ± 51.6 and 193.3 ± 53.0 ng/ml respectively) showed that these patients were able to reduce their weekly pegvisomant dose by an average of 51% (P = 0.008) from 131.3 ± 36.2 to 62.5 ± 16.7 mg.

Serum IGF1 normalized at least once in 38 (66.7%; 90% CI: 55.0, 77.0) patients at their final doses (median final pegvisomant dose of 60 mg/week: Fig. 4). At any time during coadministration, serum IGF1 normalized at least once in 45 patients (78.9%; 90% CI: 68.1, 87.4) (both P < 0.0001; Fig. 4).

There was a positive correlation between IGF1 z-score at the end of the run-in period and final weekly pegvisomant dose at normalization (Fig. 5): patients with lower IGF1 z-scores on entering the coadministration period required less pegvisomant to achieve normal IGF1 levels than those with higher entry scores.

Coadministration of LA and pegvisomant decreased mean acromegaly symptom scores (± S.D.) with greatest reductions for arthralgia (−0.6 ± 1.6) and soft tissue swelling (−0.6 ± 1.8); small mean improvements in global QoL score (mean increase = 2.2 ± 8.8) and multiple subcores were also apparent, although there was considerable data variability. There was no correlation between change in IGF1 z-score and change in QoL score.

Safety
Mean study duration was 47.6 weeks; durations of lanreotide and pegvisomant therapy during coadministration were 26.8 and 25.8 weeks respectively. Treatment-emergent AEs (TEAEs) related to treatment occurred in more subjects during coadministration (n = 24; 42%), when predominant complaints were gastrointestinal, hepatobiliary, and injection-site disorders (n = 6; 11% for all), than during run-in (n = 13; 23%), when the most frequent symptoms were gastrointestinal and hepatobiliary (n = 5; 9% for both) and metabolic/nutritional disorders (n = 4; 7%). The most common gastrointestinal complaint during coadministration was diarrhea (n = 3; 5%), which occurred with similar frequency during run-in with lanreotide alone (n = 4; 7%).

Of the serious AEs reported during coadministration (n = 8 patients; 14%), two (thrombocytopenia and urticaria) were considered treatment-related and led to withdrawal from the study, according to protocol; a third, severe abdominal pain and vomiting in one patient, was not considered treatment-related, but led to treatment discontinuation nonetheless. The patient with thrombocytopenia had a known history of idiopathic thrombocytopenia purpura; her lowest recorded platelet count, 87 G/l, occurred 6 weeks after the final pegvisomant dose and the thrombocytopenia resolved 6 weeks later. A further two patients reported nonserious treatment-related AEs that led to treatment withdrawal: transient hepatotoxicity and cytolytic hepatitis, both leading to transient elevations in transaminases (ALT > 5 × ULN), which returned

Figure 3 Serum IGF1 normalization by final pegvisomant dose. ‘Final dose’ was the dose taken by patients at the end of the study or at the time of withdrawal.

Figure 4 Serum IGF1 normalization occurring at least once, by diabetic status and time of normalization.
to normal after treatment discontinuation. Gallbladder ultrasound was normal in both cases.

A transient increase in AST and/or ALT to >2×ULN occurred in 6 (11%) patients, including the two patients in whom the increase exceeded 5×ULN and led to withdrawal. In the four patients who continued in the study, increases occurred during coadministration and were either normalized within the coadministration period (three patients) or shortly after (one patient; 3 months later while continuing to receive LA). Gallbladder echography was unchanged in all four patients. There was no relationship between diabetic status and elevated transaminases. No clinically significant changes were observed during coadministration in mean values for hematological or biochemical parameters, nor for liver function tests; individual abnormalities were consistent with TEAEs. A clinically significant decrease in mean fasting insulin (−12.7 ±41.5 pmol/l) was observed in nondiabetic patients after coadministration; mean blood glucose parameters remained otherwise normal. Gallbladder sludge and/or lithiasis developed in four (7%) patients during coadministration, and preexisting sludge and/or lithiasis appeared to resolve in five (9%). The majority of these changes were seen in patients previously treated with SSAs.

Magnetic resonance imaging revealed considerable interindividual variability in tumor size. During the run-in period, tumor size decreased by >20% in 3/54 patients (5.6%) and increased by >20% in 9/54 patients (16.7%). Corresponding values for the coadministration period were 7/53 patients (13.2%) and 13/53 patients (24.5%) respectively. There was no statistically significant correlation between change in tumor size and IGF1 z-score. There were no clinically significant changes in mean ECG parameters during the coadministration period and there were no clinical significant individual treatment-emergent changes.

Discussion

This study investigated the efficacy and safety of coadministration of LA (120 mg/month) and pegvisomant (40–120 mg/week), administered once or twice weekly. Combination therapy in 57 patients with acromegaly and partial response to SSA normalized IGF1 levels in 58% of patients at a median pegvisomant dose of 60 mg once weekly. In all, 79% of patients had normalized IGF1 levels at least once during coadministration. Patients with lower IGF1 levels at the end of run-in, including nondiabetic patients who had lower baseline IGF1 z-scores than their noninsulin-dependent diabetic counterparts, were more likely to achieve normal IGF1 levels during coadministration, with a lower pegvisomant dose. The higher pegvisomant dose required in hyperinsulinemic diabetic compared with nondiabetic patients may reflect the higher number of hepatic GH receptors in individuals with diabetes (19), necessitating higher concentrations of pegvisomant for full receptor blockade (19, 20). The lower response rate in patients previously treated with pegvisomant may be confounded by the higher frequency of previous radiotherapy and longer time since diagnosis in this patient subset, both indicators of more severe baseline disease. In the, albeit small, subset of patients whose disease was similarly controlled on pegvisomant monotherapy and coadministration with LA, there was a significant fall in the required weekly dose of pegvisomant.

The rates of IGF1 normalization observed in this study are somewhat lower than those in similar studies of combination therapy, which typically report biochemical response in ≥95% of patients. In a study by Neggers et al. (18), 100% of patients achieved normal IGF1 after 138 weeks, with a median pegvisomant dose of 60 mg/week. In a similar study by Feenstra et al. (12), normalization was reported in 95% of patients after 42 weeks with the same median pegvisomant dose. There are several possible explanations for the lower response rates in this study. First, this study had a much shorter duration, with a coadministration period of ~26 weeks. Second, our two-step recruitment process excluded SSA responders, whose inclusion cannot be entirely ruled out in studies that employ a single-step selection process. Third, our titration schedule aimed to determine the lowest effective pegvisomant dose, whereas the aforementioned studies used an escalating titration schedule to achieve maximum efficacy. Consequently, of the 31 patients in this study who responded at a dose of 60 mg/week, 13 no longer responded when the dose was reduced to 40 mg/week, and only 8 responded again when the 60 mg dose was reinstated.
IGF1 normalization rates in this study were, however, similar to those in the Trainer et al.’s (21) randomized controlled trial, which compared 5–30 mg/day (35–210 mg/week) pegvisomant monotherapy (56% response rate) with the same dose combined with octreotide LAR combination (62% response rate). Two points should be noted with respect to Trainer et al.’s study: first, it employed a single-step selection process and may have included some SSA responders; second, the RIA for IGF1 was discontinued by the manufacturer midway through the study, requiring a switch to a chemiluminescent assay, which was used to reanalyze the previous IGF1 levels, and could have accounted for lower than expected IGF1 normalization rates.

Key, short- (8) and long-term (7), studies of pegvisomant monotherapy document IGF1 normalization rates of up to 90% using doses ≤20 mg/day (≤140 mg/week) and ≥97% at doses up to 40 mg/day (≤280 mg/week), although the highest normalization rates were reported when the definition included normalization at any time, not specifically at study end point (7). Interestingly, the combination of pegvisomant with SSAs in this study appears to have similar efficacy to pegvisomant monotherapy 15 mg/day (105 mg/week; ~75% IGF1 normalization after 12 weeks) and more effective than 10 mg/day (70 mg/week; ~38% response) (8), a dose that exceeds the median weekly dose in this study. Further to this, although direct comparisons between our data and those from uncontrolled studies should be made with caution, coadministration of LA and pegvisomant in this study achieved similar efficacy to pegvisomant monotherapy in the uncontrolled registry-based ACROSTUDY (9). ACROSTUDY, in which 80% of patients were taking pegvisomant ≤20 mg/day (≤140 mg/week) reported a 60–70% response rate during 5 years of follow-up, while the median dose required to achieve a similar level of efficacy in this study was considerably lower. Although the ACROSTUDY results offer a perspective on outcomes that may be expected in the ‘real-life’ setting, the value of such comparisons is limited by important differences in study design and patient selection.

In this study, combination therapy was well tolerated with only three serious adverse events leading to treatment withdrawal, of which two were related to treatment. Furthermore, the increase in transaminase levels to ≥2×ULN was observed in six patients, of whom only two had levels ≥5×ULN; as such, these rates were lower than those in other combination therapy studies (11, 12, 18), and closer to the rates observed during pegvisomant monotherapy (7, 8, 22) and were described in the ‘Summary of Product Characteristics’ for pegvisomant (10). It should also be noted that the incidence of raised transaminases in this study was no higher in diabetic than nondiabetic patients, a finding that differs from certain other study data (11). Although SSA/pegvisomant combination therapy appears to be well tolerated in long-term therapy of up to 5 years (11), and some studies have shown reversal of elevated transaminases during continued pegvisomant treatment (11, 18), it was not possible in this study to evaluate the outcomes in patients with transaminases ≥5×ULN as the protocol mandated withdrawal under these circumstances; we remain cautious about continuing treatment in the face of raised transaminases.

Compared with monotherapy, coadministration with an SSA requires a lower dose of pegvisomant per week to achieve a similar degree of efficacy (7, 23, 24), through a variety of mechanisms. These may include elevation of serum pegvisomant levels (13), reduced insulin concentration in the portal vein, which decreases the number of available hepatocyte GH receptors (25), and reduction in endogenous GH levels. Pegvisomant is also a more expensive treatment than high-dose, long-acting SSA treatment (LA and long-acting octreotide) (26). It can therefore be presumed that combination therapy will result in a cost benefit.

Limitations of this study include the open-label design and almost exclusively Caucasian study population. The final sample size of 57 coadministered patients, while lower than the planned cohort of 60, retained a power close to 95% to detect the difference between the null hypothesis of 30% minimum clinically relevant percentage of responders and the expected percentage of responders of 80%; this difference was not anticipated to affect the validity of statistical testing. The study was not designed to determine the pegvisomant dose that would maximize efficacy, but rather the lowest dose necessary to normalize IGF1 levels; it is possible that higher pegvisomant doses and/or a different therapeutic regimen might have achieved greater efficacy. There is also a margin of error relating to intra-individual variability in the IGF1 assay. Finally, the study was not designed to examine changes in tumor size; indeed, most patients either had microadenomas or had undergone tumor debulking surgery, and SSA-induced tumor shrinkage was likely to be maximal during prior SSA treatment rather than with SSA–pegvisomant combination therapy.

In conclusion, combination therapy using pegvisomant (40–120 mg/week) and LA (120 mg/month) in partial SSA responders normalized IGF1 levels at the end of coadministration in 57.9% of patients at a median effective pegvisomant dose of 60 mg/week, and in 79% at any time during coadministration, at the same median weekly dose. Treatment was generally well tolerated. Compared with pegvisomant monotherapy, combination therapy with lanreotide offers the benefit of reduced pegvisomant injection frequency.

Declaration of interest

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Novartis. Prof. Caron had been a consultant for and received lecture fees from Ipsen, Pfizer, and Novartis. Prof. Colao is the recipient of research grants from Ipsen, Pfizer, and Novartis and is a member of scientific advisory boards for Ipsen and Novartis. Prof. Marek has received travel grants from Ipsen, Pfizer, and Novartis. Prof. Neggers has no conflicts to declare. Dr Birman is an employee of Ipsen.

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