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A *Post Hoc* Analysis of the Phase IV B2219 Study to Determine Predictive Factors for Hyperglycemia During Treatment With Pasireotide

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*Potential conflict of interest may exist. Refer to the Meeting App; †AMP was an employee of Recordati at time of abstract/poster development

Plain language summary

Why was this research carried out?

- Pasireotide has been shown in many clinical trials to benefit people with acromegaly or Cushing's disease
- People can sometimes experience high blood sugar, known as hyperglycemia, especially at the start of treatment
- We wanted to explore why some people are more likely to experience this side effect than others

How was this research carried out?

- A clinical trial (named B2219) was carried out between 2014 and 2018 to look at how best to treat people who developed hyperglycemia during pasireotide treatment
- Using these data, we were able to look for reasons why some people required medication to manage hyperglycemia while others did not

What were the overall results?

- Older people, as well as those with increased blood sugar levels or with diabetes at the start of treatment, were more likely to require antihyperglycemic medication while receiving pasireotide

What do the results mean?

- Knowing these risk factors will help identify people who may benefit from careful monitoring of blood sugar levels during pasireotide treatment
- Antihyperglycemic therapies, as well as lifestyle changes, can be prescribed so that people can continue receiving pasireotide

Conclusions

- Age, HbA_{1c}, FPG, and having pre-diabetes or diabetes conditions at baseline were associated with an increased risk of requiring antihyperglycemic medication during pasireotide treatment
  - Data are consistent with previous clinical studies of pasireotide[7,8]
- Hyperglycemia-related AEs were manageable with concomitant antihyperglycemic medication (metformin as initial treatment, followed by incretin-based therapy if needed),[6] and most participants were able to continue treatment with pasireotide; dietary modification, exercise and education are also important[9]
- Potential risk factors for pasireotide-associated hyperglycemia may identify those who require more vigilant monitoring to ensure optimal outcomes during pasireotide treatment

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Disclosures

This study was funded by Novartis Pharma AG; however, as of July 12, 2019, pasireotide is an asset of Recordati.

Abbreviations

AE, adverse event; bid, twice daily; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; NGT, normal glucose tolerance; OAD, oral antidiabetic drug; SMBG, self-monitored blood glucose

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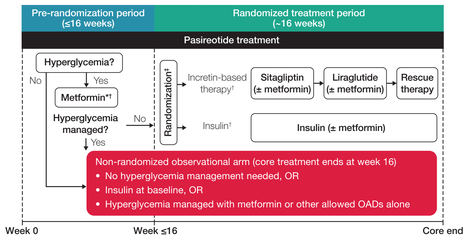
Introduction

- Pasireotide, a second-generation somatostatin receptor ligand, is an effective long-term medical treatment for people with acromegaly[1,2] or Cushing's disease[3,4]
- Pasireotide-associated hyperglycemia is an expected side effect owing to the specific targeting of somatostatin receptors, but with appropriate management, it rarely requires treatment discontinuation, allowing clinical benefit to be achieved and sustained[1–5]
- The Phase IV B2219 (NCT02060383) trial was a prospective, randomized, open-label study designed to specifically assess the optimal management of pasireotide-associated hyperglycemia[6]
  - Metformin was shown to be an effective initial treatment, followed by incretin-based therapy over insulin, if needed
- This *post hoc* analysis evaluated patients according to whether antihyperglycemic medication was needed during pasireotide treatment
- We also retrospectively investigated changes in insulin dose needed to manage hyperglycemia during pasireotide treatment

Methods

- Adult participants with confirmed acromegaly (including *de novo* if not surgical candidates) or Cushing's disease (persistent, recurrent or *de novo*) were enrolled
- If receiving pasireotide at screening, a washout of ≥3 months (long acting) or 1 week (twice-daily formulation) was required
- Upon entering the pre-randomization period, participants initiated long-acting pasireotide 40 mg/28 days intramuscularly (acromegaly) or pasireotide 600 µg subcutaneously bid (Cushing's disease)
- Medication for hyperglycemia was initiated if SMBG levels were ≥126 mg/dL on three consecutive days
- Participants who did not require antihyperglycemic medication, who were successfully managed with metformin alone, or who were receiving insulin from study baseline entered a non-randomized observational arm
- Participants who developed hyperglycemia not manageable with metformin (SMBG ≥126 mg/dL on three consecutive days) were randomized to incretin-based therapy or insulin, administered in accordance with local prescribing information
- This *post hoc* analysis evaluated participants according to whether they required any antihyperglycemic medication during pasireotide treatment in the pre-randomization period
  - Logistic-regression analyses evaluated quantitative and qualitative predictive factors present at baseline
  - Predictors with $P \leq 0.2$ remained in the logistic-regression model; data from the reduced model are shown
- Diabetic status at baseline was defined as follows:
  - Diabetic: HbA_{1c} ≥6.5% and/or FPG ≥126 mg/dL at two visits, prior history of diabetes mellitus, or treatment with antihyperglycemic medication
  - Pre-diabetic: Not qualifying as diabetic and FPG ≥100 mg/dL and/or HbA_{1c} 5.7–<6.5%
  - NGT: Not qualifying as diabetic or pre-diabetic and with FPG <100 mg/dL and/or HbA_{1c} <5.7%

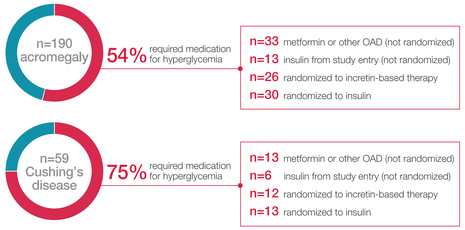
B2219 core study design



*Participants who could not tolerate, or who had a contraindication to, metformin were randomized immediately if SMBG was ≥126 mg/dL on three consecutive days; †Participants could continue other permitted OADs at the investigator's discretion; ‡Randomization was stratified by disease (Cushing's disease or acromegaly) and baseline HbA_{1c} (<7% or ≥7%)

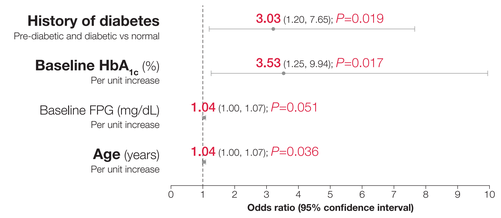
Results

1. Not all participants who received pasireotide required antihyperglycemic medication

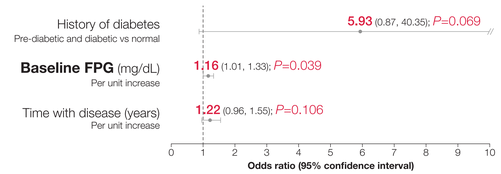


- Average median dose (min–max) at week 16 was **40** (20–60) **mg/28 days** and **1200** (600–1200) **µg bid** in participants with acromegaly and Cushing's disease, respectively
- In all participants, median (min–max) duration of exposure to pasireotide during the core study period was **3.7** (0.0–8.0) **months**

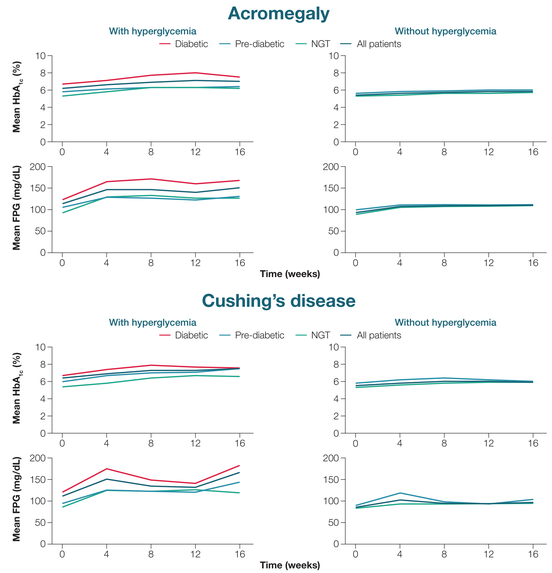
2. Age, baseline HbA_{1c} and history of diabetes/pre-diabetes were identified as risk factors for requiring antihyperglycemic medication during pasireotide treatment in participants with acromegaly



3. Baseline FPG was identified as a risk factor for requiring antihyperglycemic medication during pasireotide treatment in participants with Cushing's disease



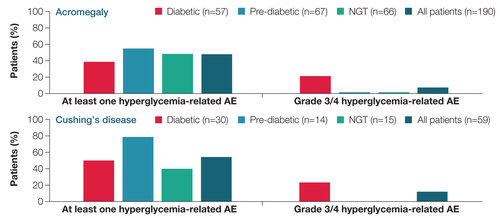
4. During the 16-week pre-randomization period, mean HbA_{1c} and FPG levels increased during pasireotide treatment in participants who required antihyperglycemic medication, particularly in those with diabetes/pre-diabetes at baseline (with acromegaly or Cushing's disease)



5. Participants who required antihyperglycemic medication were generally older, had higher baseline FPG and HbA_{1c} levels, and were diagnosed with diabetes

Patient characteristics	Acromegaly (n=190)		Cushing's disease (n=59)	
	Hyperglycemia, n=102	No hyperglycemia, n=88	Hyperglycemia, n=44	No hyperglycemia, n=15
Mean **age**, years (min–max)	46.1 (21–79)	38.5 (22–66)	44.5 (18–72)	33.9 (21–70)
Mean **HbA_{1c}**, % (min–max)	6.2 (4.6–10.6)	5.4 (4.5–6.0)	6.4 (5.0–8.2)	5.5 (4.4–6.0)
Mean **FPG**, mg/dL (min–max)	113.9 (60.0–295.4)	93.4 (70.3–120.7)	111.2 (79.3–262.0)	85.5 (70.3–97.3)
Diabetic, n (%)	57 (55.9)	0	30 (68.2)	0

6. Grade 3/4 hyperglycemia-related AEs were infrequent overall and more common in participants diagnosed with diabetes at baseline



Hyperglycemia-related AEs included diabetes mellitus, glycosuria, hyperglycemia, impaired fasting glucose, impaired glucose tolerance, inadequately controlled diabetes mellitus, increased blood glucose, increased HbA_{1c} and type 2 diabetes mellitus

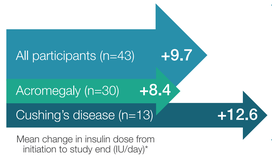
- As reported by the investigator, the most common AEs (>10%) of special interest related to hyperglycemia were:
  - Hyperglycemia (21.1%), diabetes mellitus (14.2%) and impaired fasting glucose (12.1%) in participants with acromegaly
  - Hyperglycemia (28.8%) and diabetes mellitus (11.9%) in participants with Cushing's disease

7. Few participants interrupted or discontinued treatment because of hyperglycemia-related AEs; participants receiving antihyperglycemic medication mostly had diabetes or pre-diabetes at baseline

	Management of participants with a hyperglycemia-related AE	
	Acromegaly (n=190)	Cushing's disease (n=59)
Dose reduction or interruption	3.7% (n=7)	10.2% (n=6)
Concomitant antihyperglycemic medication	26.3% (n=50)	30.5% (n=18)
Permanently discontinued	1.1% (n=2)	0%

NGT at baseline; Diabetic or pre-diabetic at baseline

8. Participants who were randomized to receive insulin required increased doses during the randomized treatment period to manage hyperglycemia



- Mean dose at initiation: **9.0 IU/day**
- Median (min–max) duration of exposure to insulin: **3.7 (1.4–4.3) months**

*Insulin was administered according to local prescribing information. The suggested starting dose was 10 IU/day administered at bedtime, with weekly titration to achieve SMBG levels ≤126 mg/dL on three consecutive days