Comparison of Insulin Degludec/Insulin Aspart and Biphasic Insulin Aspart 30 in Uncontrolled, Insulin-Treated Type 2 Diabetes: A Phase 3a, Randomized, Treat-to-Target Trial

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OBJECTIVE
Insulin degludec/insulin aspart (IDegAsp) is the first combination of a basal insulin with an ultralong duration of action, and a rapid-acting insulin in a single injection. This trial compared IDegAsp with biphasic insulin aspart 30 (BIAsp 30) in adults with type 2 diabetes inadequately controlled with once- or twice-daily (OD or BID) pre- or self-mixed insulin with or without oral antidiabetic drugs.

RESEARCH DESIGN AND METHODS
In this 26-week, randomized, open-label, multinational, treat-to-target trial, participants (mean age 58.7 years, duration of diabetes 13 years, BMI 29.3 kg/m², and HbA₁c 8.4% [68 mmol/mol]) were exposed (1:1) to BID injections of IDegAsp (n = 224) or BIAsp 30 (n = 222), administered with breakfast and the main evening meal and dose titrated to a self-measured premeal plasma glucose (PG) target of 4.0–5.0 mmol/L.

RESULTS
After 26 weeks, mean HbA₁c was 7.1% (54 mmol/mol) for both groups, with IDegAsp achieving the prespecified noninferiority margin for mean change in HbA₁c (estimated treatment difference [ETD] –0.03% points [95% CI –0.18 to 0.13]). Treatment with IDegAsp was superior in lowering FPG (ETD –1.14 mmol/L [95% CI –1.53 to –0.76], P < 0.001) and had a significantly lower final mean daily insulin dose (estimated rate ratio 0.89 [95% CI 0.83–0.96], P = 0.002). Fewer confirmed, nocturnal confirmed, and severe hypoglycemia episodes were reported for IDegAsp compared with BIAsp 30.

CONCLUSIONS
IDegAsp BID effectively improves HbA₁c and fasting PG levels with fewer hypoglycemia episodes versus BIAsp 30 in patients with uncontrolled type 2 diabetes previously treated with once- or twice-daily pre- or self-mixed insulin.

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Insulin is the most effective therapy for achieving glycemic control in patients with type 2 diabetes (1). Owing to the progressive nature of type 2 diabetes, many patients will become candidates for prescription of insulin—frequently basal insulin initially on a variable background of anti-diabetic therapy. However, as type 2 diabetes progresses, further treatment intensification in the form of prandial insulin is commonly required to achieve HbA1c targets and potentially to avoid the long-term consequences of hyperglycemia (2). Currently, this approach is achieved through the addition of one or more separate prandial insulin injections to an existing basal insulin regimen or by switching to premixed insulin containing a fixed ratio of rapid- and intermediate-acting insulin (1). However, several barriers remain to insulin intensification. While separate basal and bolus injections offer the most precise and adaptable mealtime glycemic control (1), they can be perceived as complex (1,3–5). In some patients, this may result in an increased burden of treatments and decreased adherence to injections (6). Currently, available premix insulins offer a more convenient alternative, with fewer injections and the potential use of a single insulin pen device (7), but are associated with an increased rate of postmeal hypoglycemia, including nocturnal hypoglycemia (8). The fear of hypoglycemia represents a significant barrier to treatment (9,10). As a result, patients with type 2 diabetes may continue to have poor glucose control and an increased risk of developing diabetes-related complications (1).

Comprising 70% insulin degludec (IDeg) and 30% insulin aspart (IAsp), IDegAsp (Ryzodeg; Novo Nordisk A/S, Bagsværd, Denmark) is the first soluble combination product of a basal insulin with an ultralong duration of action and a rapid-acting insulin in a single injection. As a soluble coformulation, IDegAsp does not require resuspension, which eases administration (11) and, more importantly, eliminates the risk of incomplete mixing and therefore increased hypoglycemia (12). In solution, the individual components of IDegAsp exist separately as di- hexamers (IDeg) and hexamers (IAsp) (13). Upon injection, the IDeg di-hexamers assemble to form soluble and stable multihexamers in the subcutaneous tissue that slowly dissociate to provide continuous IDeg absorption to meet basal needs. At the same time, IAsp hexamers immediately dissociate into monomers that are rapidly absorbed into the circulation, providing mealtime coverage (13,14). Pharmacodynamic studies have demonstrated that the glucose-lowering effect of IDegAsp is characterized by a distinct peak action (from IAsp) and a separate basal action (from IDeg). This is a closer approximation of physiological action than seen with current biphasic formulations. The long-acting basal component of IDegAsp allows for a pharmacodynamic profile that is flat and stable throughout the day, mimicking that of IDeg alone (14). The IDeg component in IDegAsp has been demonstrated to have a predictable glucose-lowering effect and up to four times lower day-to-day variability compared with insulin glargine at steady-state conditions (15). Clinical trials have demonstrated a lower risk of IDeg causing hypoglycemia compared with insulin glargine (16) and the possibility of flexibility in the timing of injections (17).

An earlier proof-of-concept study demonstrated favorable efficacy and safety profiles of IDegAsp as an add-on to metformin in insulin-naïve patients with type 2 diabetes inadequately controlled on oral antidiabetic drugs (OADs) (18). IDegAsp twice daily (BID) plus metformin provided overall glycemic control at lower insulin doses and significantly lower rates of hypoglycemia compared with the widely used premixed insulin, biphasic IAsp 30 (BIAsp 30) (NovoMix 30, NovoLog Mix 70/30; Novo Nordisk A/S) in combination with metformin in insulin-naïve patients with type 2 diabetes with an HbA1c of 7–11% (18). These phase 2 results, while promising, were limited by a relatively small sample size (n = 61 in the IDegAsp arm; n = 60 in BIAsp 30 arm) and short study duration (16 weeks).

In this phase 3a randomized, multinational clinical trial, the efficacy and safety of IDegAsp were compared with those of BIAsp 30 in adults with type 2 diabetes inadequately controlled on once-daily (OD) or twice-daily (BID) premixed or self-mixed insulin regimens with or without concomitant OADs.

### RESEARCH DESIGN AND METHODS

#### Trial Design

A total of 50 sites in 10 countries (Australia, Denmark, Finland, India, Malaysia, Poland, Sweden, Taiwan, Thailand, and Turkey) participated in this multinational 26-week, phase 3a, open-label, randomized, treat-to-target trial.

The protocol, protocol amendments, consent form, and subject information sheet were reviewed and approved by health authorities according to local regulations and by the local independent ethics committees prior to trial initiation. This trial was performed in accordance with the Declaration of Helsinki and Good Clinical Practice (19). All study participants gave written consent prior to any trial-related activities, and the investigator retained the consent forms.

#### Trial Population

Adults with a clinical diagnosis of type 2 diabetes for ≥6 months were enrolled if they had an HbA1c of 7–10% (53–86 mmol/mol), had a BMI of ≤40 kg/m², and were ≥18 years of age. Patients were on premixed human or analog insulin or self-mixed insulin regimens containing 20–40% fast-/rapid-acting component, administered OD or BID with or without OADs (metformin, sulfonylureas, glinides, α-glucosidase inhibitors, DPP-4 inhibitors, or pioglitazone) for ≥3 months prior to trial initiation.

Patients were excluded if they had received treatment in the 3 months prior to trial initiation with other insulin regimens, rosiglitazone, or a glucagon-like peptide 1 receptor agonist or a history of recurrent severe hypoglycemia (more than one severe hypoglycemic episode during the past 12 months) or hypoglycemic unawareness. Patients were also excluded if they had cardiovascular disease (heart failure: New York Heart Association class III or IV, unstable angina pectoris, or a myocardial infarction) within 6 months preceding trial and uncon trollled severe hypertension (systolic blood pressure ≥180 mmHg or sitting diastolic blood pressure ≥100 mmHg).

#### Randomization

After randomization, eligible patients discontinued their diabetes treatment except for metformin, DPP-4 inhibitors, and pioglitazone and were switched from their prior insulin to IDegAsp or
BIAsp 30. Patients were randomized (1:1) to BID injections of IDegAsp (100 units/mL Ryzodeg) or BIAsp 30 (100 units/mL NovoMix 30, NovoLog 70/30) either with or without OADs (metformin with or without dipeptidyl peptidase [DPP]-4 inhibitors with or without pioglitazone) for 26 weeks. Randomization was stratified based on the number of daily insulin injections at screening to ensure equal distribution of insulin regimens in the two treatment groups. As BIAsp 30 requires resuspension prior to injection, whereas IDegAsp does not, the trial design could not be blinded and was therefore open-label.

Treatment and Titration
Patients on premixed insulin BID were to transfer their prebreakfast and pre–main evening meal dose 1:1 to trial insulin. Patients on a self-mixed regimen were to transfer to trial insulin at doses corresponding to their respective self-mixed premeal dose. Patients previously receiving premixed or self-mixed insulin OD were to divide their dose into two equal doses of IDegAsp or BIAsp 30 for prebreakfast and pre–main evening meal administration. During the treatment period, insulin dose was titrated based on the mean prebreakfast and pre–main evening meal plasma glucose (PG) level from the preceding 3 days. Titration of pre–main evening meal insulin doses was based on the individual subject’s mean prebreakfast glucose values. Treatment of prebreakfast insulin doses were based on the subject’s mean pre–main evening meal glucose values. In both cases, titration was to a self-measured PG target of 4.0–5.0 mmol/L.

Insulins were administered subcutaneously (abdomen, deltoid, or thigh for IDegAsp; thigh or abdominal wall for BIAsp 30) with breakfast and main evening meals. The injection region was kept the same for the duration of the trial, and all insulin products were administered by the FlexPen insulin delivery device (Novo Nordisk A/S). Pretrial OAD dose levels remained unchanged during the treatment period.

Trial End Points
The primary efficacy end point was change from baseline in HbA1c after 26 weeks of treatment. Secondary efficacy end points included the change from baseline in fasting PG (FPG) and the changes in nine-point self-measured PG (SMPG) profiles. Other secondary end points included the proportion of patients achieving HbA1c <7.0% (53 mmol/mol) at the end of the trial, the number of responders without hypoglycemic episodes (defined as HbA1c <7.0% at end of trial with no severe or minor hypoglycemic episodes during the last 12 weeks of treatment and including only patients exposed for ≥12 weeks), and the change from baseline in body weight.

Safety variables included hypoglycemic episodes, insulin dose, adverse events, and standard laboratory-measured safety measures. Hypoglycemia was classified as severe (requiring assistance from another person) or confirmed (PG measurement of <3.1 mmol/L [56 mg/dL] or classification as severe hypoglycemia). Nocturnal confirmed hypoglycemia included episodes with time of onset from 0001 h to 0559 h.

Statistical Analyses
The primary objective of this trial was to demonstrate noninferiority of IDegAsp to BIAsp 30 (noninferiority limit of 0.4%), as assessed by change in HbA1c from baseline after 26 weeks. If noninferiority was confirmed for the primary end point, a number of confirmatory secondary end points were to be tested to assess for superiority of IDegAsp over BIAsp 30. The primary efficacy end point of change from baseline in HbA1c after 26 weeks of treatment was analyzed using an ANOVA with treatment, antidiabetic therapy at screening, sex and age as fixed factors; age as a covariate; and exclusion of insulin dose, adverse events, and standard laboratory-measured safety measures. Hypoglycemia was classified as severe (requiring assistance from another person) or confirmed (PG measurement of <3.1 mmol/L [56 mg/dL] or classification as severe hypoglycemia). Nocturnal confirmed hypoglycemia included episodes with time of onset from 0001 h to 0559 h.

RESULTS
Patient Characteristics
Of the 661 patients enrolled into the study, 447 were randomized to receive either IDegAsp or BIAsp 30; one patient in the BIAsp 30 group was withdrawn prior to receiving insulin treatment, as they did not fulfill the inclusion criteria (Fig. 1). Baseline characteristics were comparable between the two treatment groups including level of glycemic control, duration of diabetes, BMI, and previous therapies (Table 1 and Supplementary Table 1).

Figure 1—Trial flow diagram. *One participant randomized to BIAsp 30 was excluded from the trial before receiving insulin treatment, as the participant did not fulfill the inclusion criteria. †Noncompliance with protocol-specified dosing of drug. ‡Other, violation of inclusion/exclusion criteria, withdrawal on informed consent, lost to follow-up, and other reasons.
Table 1—Characteristics of randomized population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IDegAsp</th>
<th>BIAsp 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>224</td>
<td>222</td>
</tr>
<tr>
<td>Male/female, %</td>
<td>58/42</td>
<td>54/46</td>
</tr>
<tr>
<td>Age, years</td>
<td>58.7 (9.9)</td>
<td>58.8 (9.8)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>81.5 (18.1)</td>
<td>78.9 (17.6)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.6 (4.6)</td>
<td>29.0 (4.9)</td>
</tr>
<tr>
<td>Duration of diabetes, years</td>
<td>12.8 (6.8)</td>
<td>13.1 (7.4)</td>
</tr>
<tr>
<td>HbA₁c, %</td>
<td>8.3 (0.8)</td>
<td>8.4 (0.9)</td>
</tr>
<tr>
<td>FPG, mmol/L</td>
<td>8.9 (2.9)</td>
<td>8.6 (2.6)</td>
</tr>
</tbody>
</table>

Pretreatment insulin regimen (n (%) of patients):
- Premixed or self-mixed OD ± OADs: IDegAsp 16 (7.1), BIAsp 30 12 (5.4)
- Premixed or self-mixed BID ± OADs: IDegAsp 203 (90.6), BIAsp 30 206 (92.8)
- Only OADs: IDegAsp 4 (1.8), BIAsp 30 3 (1.4)
- Premixed or self-mixed three times daily: IDegAsp 1 (0.4), BIAsp 30 —
- OAD (1 only): IDegAsp 125 (55.8), BIAsp 30 138 (62.2)
- α-Glucosidase inhibitor: IDegAsp 2 (0.9), BIAsp 30 3 (1.4)
- Biguanide: IDegAsp 117 (52.2), BIAsp 30 125 (56.3)
- Sulfonylurea: IDegAsp 4 (1.8), BIAsp 30 10 (4.5)
- Thiazolidinedione: IDegAsp 2 (0.9), BIAsp 30 —
- 2 OADs: IDegAsp 40 (17.9), BIAsp 30 33 (14.9)
- >2 OADs: IDegAsp 8 (3.6), BIAsp 30 3 (1.4)

Data are means (SD) unless otherwise indicated. *This individual was randomized in error and was later withdrawn from the trial without being exposed to the trial drug.

**Glycemic Control**

After 26 weeks of treatment, the observed mean ± SD HbA₁c decreased from 8.3 ± 0.8% to baseline to 7.1 ± 0.9% with IDegAsp and from 8.4 ± 0.9% to baseline to 7.1 ± 0.9% with BIAsp 30 (Fig. 2A). For the primary endpoint of mean change from baseline in HbA₁c, IDegAsp was noninferior to BIAsp 30 (estimated treatment difference [ETD] −0.03% points [95% CI −0.18 to 0.13]). The proportion of patients achieving HbA₁c targets of <7.0% (53 mmol/mol) was comparable between IDegAsp (50.4%) and BIAsp 30 (48.6%). The odds of achieving this target without hypoglycemic episodes during the last 12 weeks were 60% higher for IDegAsp (21% of patients) than for BIAsp 30 (14% of patients); odds ratio 1.60 (95% CI 0.94–2.72) (Supplementary Fig. 1).

Observed mean (SD) FPG decreased from 8.9 ± 2.9 mmol/L to baseline to 5.8 ± 1.9 mmol/L for IDegAsp and from 8.6 ± 2.6 mmol/L to 6.8 ± 2.4 mmol/L for BIAsp 30 (Fig. 2B). IDegAsp was superior to BIAsp 30 in lowering FPG (ETD −1.14 mmol/L [95% CI −1.53 to −0.76], P < 0.001).

After 26 weeks, mean SMPG levels before breakfast (ETD −0.98 mmol/L [95% CI −1.58 to −0.39]), and before breakfast the following day (ETD −0.85 mmol/L [95% CI −1.21 to −0.48]) were significantly lower with IDegAsp compared with BIAsp 30. Similarly, the overall mean glucose level at 26 weeks (as evaluated by SMPG levels) was significantly lower with IDegAsp compared with BIAsp 30. In a post hoc analysis of the maintenance period of treatment (from 16 weeks to end of trial after stable glycemic control and insulin dose had been achieved), statistically significant and more pronounced reductions were seen in all hypoglycemia categories. More specifically, a 39% reduction in overall confirmed hypoglycemia (RR 0.61 [95% CI 0.45–0.83], P = 0.0015), 77% reduction in nocturnal confirmed hypoglycemia (RR 0.23 [95% CI 0.13–0.41], P < 0.0001), and an 89% reduction in severe hypoglycemic episodes (RR 0.11 [95% CI 0.01–0.91], P = 0.04) were observed for IDegAsp compared with BIAsp 30.

**Body Weight**

The observed body weight change from baseline to week 26 with IDegAsp (increase of 1.7 kg) was statistically significantly lower than with BIAsp 30 (increase of 2.2 kg) (ETD −0.62 kg [95% CI −1.15 to −0.10]).

**Insulin Dose**

Mean daily insulin dose after 26 weeks was 1.08 units/kg for IDegAsp and 1.20 units/kg for BIAsp 30 (estimated rate ratio [RR] 0.89 [95% CI 0.83–0.96], P = 0.002). Mean morning and evening doses after 26 weeks were 38 units and 52 units for IDegAsp (a 42% and 58% dose split) and 44 units and 54 units for BIAsp 30 (45% and 55% dose split), respectively.

**Hypoglycemic Episodes**

Confirmed hypoglycemia (severe or PG <3.1 mmol/L) was reported for 66.1% and 68.9% of patients in the IDegAsp and BIAsp 30 groups, respectively (Table 2). Superiority of IDegAsp versus BIAsp 30 was demonstrated with a 32% reduction in confirmed hypoglycemic episodes: 9.7 vs. 14.0 episodes per patient-year for IDegAsp and BIAsp 30 groups, respectively (estimated RR 0.68 [95% CI 0.52–0.89], P = 0.0049) (Fig. 2C). A significant 73% reduction in nocturnal confirmed hypoglycemia was observed for IDegAsp versus BIAsp 30: 0.7 vs. 2.5 episodes per year, respectively (RR 0.27 [95% CI 0.18–0.41], P < 0.0001) (Fig. 2D).

Adverse Events

The incidence of adverse events was similar between IDegAsp and BIAsp 30 (65.6% vs. 63.1%), with the majority being mild to moderate in severity. Serious adverse events were reported in 19 and 36 patients in the IDegAsp and BIAsp 30 treatment groups, respectively, the majority of whom recovered completely. Two deaths...
were reported in this trial (interstitial lung disease in the IDegAsp group and head injury in the BIAsp 30 group).

The most frequent adverse events in both treatment groups were nasopharyngitis, upper respiratory tract infection, and headache. Injection site reactions were low in both treatment groups (IDegAsp, 0.4%; BIAsp 30, 0.9%; two events in each group). No clinically relevant differences were observed between the two treatment groups with respect to physical examination findings, vital signs, standard laboratory analyses (hematology and biochemistry), fundoscopy, or electrocardiogram.

CONCLUSIONS

This confirmatory, randomized, controlled, 26-week, phase 3a trial demonstrated the efficacy and safety of IDegAsp BID, with or without concomitant OADs, in the treatment of patients with type 2 diabetes inadequately controlled on premixed or self-mixed insulin regimens OD or BID. IDegAsp provided effective overall glycemic control that was noninferior and comparable with that of BIAsp 30, with both treatments achieving clinically meaningful improvements in HbA1c of $\leq 1.3\%$ points. Moreover, IDegAsp demonstrated superior reductions in FPG for IDegAsp, in combination with an 11% lower mean end of trial dose compared with BIAsp 30.

The efficacy of IDegAsp is further supported by the results from the nine-point SMPG profile reported in the current trial, with significantly lower mean PG levels at end of trial and significantly lower PG levels at three out of the nine time points: before breakfast, 90 min after breakfast, and before breakfast the following day. The treatment differences in FPG and prebreakfast SMPG indicate that IDegAsp provides full 24-h basal coverage compared with BIAsp 30.

Importantly, the greater reduction in FPG was accompanied by reductions in confirmed (32%), nocturnal confirmed (73%), and severe (50%) hypoglycemia, verifying previous findings of a lower risk of IDegAsp to cause hypoglycemia compared with premixed insulin (18). The percentage of patients achieving HbA1c $\leq 7\%$ without hypoglycemia in the previous 12 weeks was greater for IDegAsp versus BIAsp 30 (Supplementary Fig. 1). Furthermore, the differences in hypoglycemia rates in favor of IDegAsp (39%, 77%, and 89% reduction in overall confirmed, nocturnal confirmed, and severe hypoglycemic episodes, respectively, compared with...
IDegAsp in Insulin-Treated Type 2 Diabetes

Diabetes Care

The glucose infusion profile of IDegAsp 30, which is a formulation containing soluble (30%) and protaminated (70%) IAsp. Protaminated IAsp in IDegAsp 30 exhibits an initial peak followed by a gradual decline, falling below detectable levels ~20 h postdose (14). The basal component of IDegAsp has been demonstrated in pharmacodynamic studies to have an ultralong duration of action, exceeding 42 h (14). Therefore, IDegAsp provides full 24-h coverage of basal insulin requirements as shown by a distinct peak action due to prandial IAsp and separate and stable basal action from IDeg (20). The low variability of the IDeg component reported at steady state over a 24 h period (12,21) could further contribute to the low rates of hypoglycemia observed with IDegAsp.

Basal insulin and premixed insulin are the most common treatment regimens used when initiating insulin treatment in patients with type 2 diabetes (22). Currently, when insulin intensification is required (to provide sufficient prandial coverage) this is often achieved through use of premixed insulin. However, pharmacodynamic studies have shown that premixed insulin does not provide 24 h glycemic control in all patients and, moreover, is associated with higher variability and a lack of sustained and stable glucose infusion rate profile (23). On the other hand, basal-bolus insulin therapy requires multiple daily injections and frequent blood glucose measurements and, hence, is a more complex treatment regimen. Use of a “basal plus” regimen (involving basal insulin and addition of a single bolus insulin injection) has recently demonstrated similar HbA1c control with improved FPG, less weight gain, lower rates of hypoglycemia, and lower total daily insulin use compared with twice-daily premixed insulin in insulin-naive patients (24). Similar benefits are demonstrated for IDegAsp versus BIAsp 30 in the current publication and highlight, in insulin-experienced patients, the advantage of full 24-h basal coverage and distinct rapid-acting mealtime coverage with the additional simplicity of being combined in a single injection. This may help to address the commonly cited issues of complexity and inconvenience as barriers to timely insulin intensification (22) without the need to compromise prandial or basal insulin coverage in patients with type 2 diabetes.

Table 2—Hypoglycemic episodes in the IDegAsp and BIAsp 30 groups

<table>
<thead>
<tr>
<th></th>
<th>IDegAsp BID</th>
<th></th>
<th>BIAsp 30 BID</th>
<th></th>
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<tbody>
<tr>
<td>Participants</td>
<td>n</td>
<td>%</td>
<td>Episodes</td>
<td>Rate: PYE</td>
</tr>
<tr>
<td>Safety analysis set: entire trial period</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>7</td>
<td>3.1</td>
<td>9</td>
<td>0.09</td>
</tr>
<tr>
<td>Overall confirmed</td>
<td>148</td>
<td>66.1</td>
<td>993</td>
<td>9.72</td>
</tr>
<tr>
<td>Nocturnal confirmed</td>
<td>52</td>
<td>23.2</td>
<td>76</td>
<td>0.74</td>
</tr>
<tr>
<td>Patients in safety analysis set with at least 16 weeks of exposure: maintenance period (16 weeks to end of treatment)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>1</td>
<td>0.5</td>
<td>1</td>
<td>0.03</td>
</tr>
<tr>
<td>Overall confirmed</td>
<td>104</td>
<td>51.7</td>
<td>362</td>
<td>9.51</td>
</tr>
<tr>
<td>Nocturnal confirmed</td>
<td>21</td>
<td>10.4</td>
<td>27</td>
<td>0.71</td>
</tr>
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</table>

NS, not significant; PYE, patient year of exposure.

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Author Contributions. G.R.F. designed the study, performed the research, and edited the manuscript. J.S.C. designed the study and contributed to the manuscript. G.B. performed the research. M.P.-M. contributed to the manuscript. H.M. designed the study, analyzed data, and edited the manuscript. T.H.A. contributed to the manuscript and analyzed data. L.K.N. performed the research and contributed to the manuscript. G.R.F. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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