# Long-term follow up of carbohydrate metabolism and adverse events after termination of Omnitrope® treatment in children born small for gestational age

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***Abstract***

**Background:** Recombinant human growth hormone (rhGH) therapy can affect carbohydrate metabolism and lead to impaired glucose tolerance during treatment. In addition, short children born small for gestational age (SGA) are predisposed to metabolic abnormalities. This study assessed the long-term safety of rhGH (Omnitrope®) use in short children born SGA.

**Methods:** This was a follow-up observational study of patients from a phase IV study. The baseline visit was the final visit of the phase IV study. Further visits were planned after 6 months (F1), 1 year (F2), 5 years (F3), and 10 years (F4). The primary objective was to evaluate the long-term effect of rhGH treatment on the development of diabetes mellitus; secondary objectives included incidence/severity of adverse events (AEs).

**Results:** In total, 130 subjects were enrolled in the follow-up study; 99 completed F1, 88 completed F2, and 13 completed F3 (no subject reached F4). The full analysis set for evaluation comprised 118 patients (64 female). Mean (standard deviation) duration of follow up was 39.6 (24.4) months. No subject was newly diagnosed with diabetes. The results for carbohydrate metabolism parameters were consistent with this finding. A total of 144 AEs were reported in 54 subjects; these were mostly of mild-to-moderate intensity (96.5%) and not suspected to be related to previous rhGH treatment (94.4%). Serious AEs ($n = 18$) were reported in eight patients; three (in one patient) were suspected as possibly related to previous rhGH treatment (anemia, menorrhagia, oligomenorrhoea). One fatal event occurred (sepsis), which was judged as not related to previous rhGH treatment.

**Conclusions:** None of the participating subjects, who had all been previously treated with Omnitrope® in a phase IV study, developed diabetes during this follow-up study. In addition, no other unexpected or concerning safety signals were observed.

***Keywords:*** growth hormone, paediatrics, recombinant human growth hormone, small for gestational age

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## Introduction

Approximately 10% of children are born small for gestational age (SGA), making this a relatively common condition.[1] The etiology of SGA is heterogeneous, and may include environmental, maternal, placental, and endogenous factors, including defined gene variants.[2,3] This is one factor in the variable outcomes seen between individuals. Early catch-up growth occurs in most infants born SGA; however, short stature persists (defined as length SDS $<-2$) into childhood and often in to adulthood in around 1 in 10 of patients.[4,5]



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There is some evidence that SGA patients are predisposed to metabolic abnormalities, and may be more likely to develop insulin resistance, type 2 diabetes mellitus and cardiovascular disease in later life.[6–9] The biological association between intrauterine growth disturbance and metabolic abnormalities is still not fully understood, although multiple hypotheses exist.[10,11]

Growth hormone (GH) replacement therapy is approved to treat short stature in children born SGA who show no evidence of catch-up growth by 4 years of age in Europe,[12] and by 2 years of age in the United States[13] (US). The efficacy of recombinant human GH (rhGH) treatment in improving height in SGA patients has been widely documented,[14–16] and its use in this indication is recommended by consensus guidelines.[17]

Omnitrope® is an rhGH. Licensed by the European Medicines Agency (EMA) in 2006, Omnitrope® was the first medicine to be approved *via* the European biosimilar regulatory pathway.[12] Omnitrope® is approved to treat growth disorders in the following pediatric indications: GH deficiency, Turner syndrome, chronic renal insufficiency, Prader–Willi syndrome, and short children born SGA.[12]

Despite the widespread use of rhGH for a range of pediatric growth disorders, extended follow up is required, as some concerns have previously been raised about its long-term safety, including development of diabetes mellitus.[18–20] The largest prospective study of rhGH treatment in SGA patients (study EP00-401) previously reported no significant adverse impact on carbohydrate metabolism, and no confirmed cases of new-onset diabetes, after a minimum of 2 years of treatment.[15,21]

Here, we present data from the follow-up study (EP00-402), which assessed the long-term safety of Omnitrope® after discontinuation of treatment in short children born SGA.

## Methods

### *Study design*

EP00-402 was an international, observational follow-up study of SGA patients who participated in the phase IV EP00-401 study.[15] This study was performed as part of the post-marketing pharmacovigilance plan for Omnitrope®, and was conducted between June 2009 and October 2018, at which point the study was prematurely terminated, following agreement with the EMA.

The study was conducted at 24 centers in 6 countries (Germany, Poland, Czech Republic, Hungary, Romania, and Georgia). Patients born SGA who participated in the phase IV study and received at least one dose of study medication (Omnitrope®) were invited to enter this safety follow-up period, after termination of study medication.

The baseline visit of this study (F0) was the final visit of the phase IV study. Further visits were scheduled for 6 months (F1), 1 year (F2), 5 years (F3), and 10 years (F4) following the end of Omnitrope® treatment. Subjects were not treated with study drug during this safety follow-up study. Following early study closure, active patients completed an end of study (EOS) visit; assessments were carried out as planned for visit F4. Therefore, one group of EOS data will comprise data from patients following a range of durations of follow up.

The primary objective of this study was to evaluate the long-term effect of rhGH treatment on the development of diabetes mellitus type 2, according to the World Health Organization definition[22] and assessed by carbohydrate metabolism [fasting plasma glucose (FPG) and oral glucose tolerance test (OGTT)]. Long-term effect of Omnitrope® treatment on carbohydrate metabolism was also assessed by changes in FPG, baseline and 2 h plasma glucose (by OGTT), homeostasis model assessment (HOMA), quantitative insulin sensitivity check index (QUICKI), fasting insulin and glycosylated hemoglobin ($HbA_{1C}$).

Secondary objectives included evaluation of serum levels of insulin-like growth factor (IGF)-1 and IGF binding protein (IGFBP)-3, and of the incidence and severity of adverse events (AEs) that started or worsened during the follow-up period. AEs were considered adverse drug reactions if a causal relationship to the study drug was suspected by the investigator. Eligible patients (and/or their parents/guardians where the patient was aged <18 years) provided written informed consent to participate in the study. The study protocol and all amendments were reviewed by the independent ethics committee or institutional review board for each study center. The study was conducted according to the ethical principles

of the 1964 Declaration of Helsinki and its later amendments.

### *Data collection and statistical analysis*

Patient data were entered into a case report form (CRF) at each visit. On-site monitoring of the CRFs was performed by a contract research organization, and the CRFs were also reviewed by data managers for missing information or data discrepancies. The full analysis set (FAS) population included all patients who (a) received at least one dose of Omnitrope® in the phase IV EP00-401 study and who entered the follow-up study, and (b) in this follow-up study, had at least one visit date additional to visit F0, or an AE starting or worsening on or after baseline. All endpoints were summarized descriptively. Continuous data were presented as the mean ± standard deviation (SD) and categorical data were presented as the frequency and percentage, respectively. Statistical analyses for this study were performed using the software SAS 9.4.

Height SD score (SDS) was calculated as $SDS = (X1 - X2)/SD$, where X1 means the measured value, X2, the mean value for the relevant chronological age and sex, and SD, the SD for the relevant chronological age and sex. If respective national references did not provide mean and SD values, height SDS was calculated as $SDS = (X1 - X3)/[0.5 \times (X3 - X4)]$, where X1 means the measured value, X3, the median value for the relevant chronological age and sex, and X4, the third percentile for the relevant chronological age and sex. Body mass index (BMI) SDS was calculated by the LMS method.[23]

Standardization of IGF-1 and IGFBP-3 was performed according to the method of Elmlinger *et al.*[24] SDS values were assessed according to the following formulas: $SDS = (X1 - X2)/[(X2 - X3)/2]$ if $X1 < X2$ and $SDS = (X1 - X2)/[(X4 - X2)/2]$ if $X1 \geqslant X2$, where X1 means the measured value, X2 is the mean value for the relevant chronological age and sex, X3 is the −2 SD value for the relevant chronological age and sex, and X4 is the +2 SD value for the relevant chronological age and sex. Published mean, −2 SD, and +2 SD values for age intervals[24] were used as references for patients with an age equal to the mid of this age interval. For patients with an age between two mids of age intervals, mean, −2 SD, and +2 SD values were interpolated.

HOMA and QUICKI were determined using previously published equations and methods.[25,26]

## Results

### *Patient characteristics*

In total, 130 patients were enrolled in the follow-up study: 99 completed F1; 88 completed F2; and 13 completed F3. No patient reached F4 (10 years' follow up), due to the early termination of the study, which was agreed with the EMA in June 2018, based on published evidence,[27,28] and lack of clinical concern about risk of diabetes development more than 12 years after initial EMA registration. The maximum duration of follow up is therefore 5 years (visit F3). Of the 130 enrolled patients, 11 had no post-baseline visit documented in the CRF, leading to exclusion from the FAS. Another subject received treatment with commercially available Omnitrope® during this follow-up study, which was not consistent with the protocol. The FAS therefore comprised 118 patients; baseline characteristics for this group are shown in Table 1. Median (range) duration of rhGH treatment in the EP00-401 study was 72.0 (3–121) months; median duration of follow up was 36.2 months (range 3–105 months).

### *Diabetes mellitus and carbohydrate metabolism*

No patient was newly diagnosed with diabetes mellitus type 1 or 2 during this follow-up study. Carbohydrate metabolism parameters were consistent with this finding (Table 2). The mean (SD) HOMA score was 2.08 (1.03) at baseline and stable during the follow-up period [mean (SD) change from baseline of −0.333 (1.14) points at the EOS visit]. The mean (SD) QUICKI score was 0.354 (0.05) at baseline, and also remained stable throughout the follow-up period; at the EOS visit the mean (SD) change from baseline was 0.008 (0.03) points.

### *Additional metabolic parameters of interest*

Table 3 shows data for weight, BMI SDS, blood pressure and total cholesterol. As observed for carbohydrate metabolism parameters, values for these additional metabolic parameters of interest were stable over the follow-up period.

**Table 1.** Baseline characteristics (full analysis set, $n = 118$).

| | | |
|---|---|---|
| Gender | | |
| Female | *n* (%) | 64 (54.2) |
| Male | *n* (%) | 54 (45.8) |
| Ethnic origin | | |
| White | *n* (%) | 118 (100.0) |
| Age, years | Mean (SD) | 14.79 (2.85) |
| | Median (IQR) | 15.36 (13.86, 16.58) |
| Height SDS[a] | Mean (SD) | −1.89 (1.12) |
| | Median (IQR) | −1.87 (−2.64, −1.09) |
| Height,[a] cm | Mean (SD) | 152.63 (13.36) |
| | Median (IQR) | 155.30 (147.40, 163.30 |
| Weight,[a] kg | Mean (SD) | 44.97 (13.34) |
| | Median (IQR) | 45.20 (38.00; 53.70) |
| BMI,[a] kg/m$^2$ | Mean (SD) | 18.75 (3.24) |
| | Median (IQR) | 18.53 (16.59, 20.64) |
| BMI SDS[a] | Mean (SD) | −0.84 (1.37) |
| | Median (IQR) | −0.92 (−2.01, 0.22) |

[a]$n = 115$.
BMI, body mass index; IQR, interquartile range; SD, standard deviation; SDS, standard deviation score.

### *IGF-1 and IGFBP-3*

Mean (SD) IGF-1 SDS was 0.38 (1.25) at baseline ($n = 108$), −0.36 (1.03) at F1 ($n = 95$), −0.38 (1.04) at F2 ($n = 80$), and 0.05 (1.21) at the EOS visit ($n = 84$). Mean (SD) IGFBP-3 SDS was 0.35 (0.80) at baseline ($n = 110$), 0.01 (0.76) at F1 ($n = 95$), 0.05 (0.88) at F2 ($n = 82$), and 0.29 (0.66) at the EOS visit ($n = 84$).

### *Adverse events*

A total of 144 AEs were reported in 54 patients; these were mostly of mild-to-moderate intensity (96.5%) and not suspected to be related to previous rhGH treatment (94.4%). Tables 4 and 5 provide a summary of AEs. Treatment-related AEs were reported in four patients (3.4%, $n = 7$ events), including impaired glucose tolerance ($n = 2$ events, $n =$ two patients), liver disorder ($n = 1$ event, $n = 1$ patient) and impaired fasting glucose ($n = 1$ event, $n = 1$ patient).

Of the subjects with impaired glucose tolerance, in one patient this was determined to be a mild, non-serious, clinically meaningful, treatment-related AE, lasting from day 1 to day 205, and resolved completely without any action taken. In the other patient, the AE was determined to be mild, treatment related, and occurred from day 1 of the follow up without any action taken. The event was ongoing at database closure. This patient's laboratory values for $HbA_{1C}$ were 5.04% (31.6 mmol/mol) at baseline and 5.18% (33.1 mmol/mol) at the EOS (termination visit); FPG levels were 4.56 mmol/l at baseline and 4.22 mmol/l at EOS. At baseline the patient's FPG was 4.6 mmol/l and 8.6 mmol/l after 2 h, and at EOS (termination visit), FPG was 4.2 mmol/l and 7.8 mmol/l after 2 h. In two further subjects, mild impaired fasting glucose was recorded: in one patient the event was determined to be treatment-related, recorded on day 1–167 and resolved completely without action taken; in the other subject the event was judged to have no relationship to previous treatment with study drug, started on day 10 and was ongoing at database closure, with no treatment given for the event. The case of liver disorder involved clinically significant increases in liver enzymes (gamma-glutamyl transferase and alanine aminotransferase), which resolved completely without any action taken.

There was a total of 18 serious AEs, reported in 8 patients. Of these, three events (in one patient) were suspected to be related to previous rhGH treatment (anemia, menorrhagia, oligomenorrhoea, which were all considered mild in severity). The patient received concomitant medication and the serious AEs resolved completely. One fatal event occurred (sepsis), which was judged as not related to previous rhGH treatment. One event was reported in the MedDRA system order class of 'Neoplasms benign, malignant and unspecified'; this was kidney angiomyolipoma of mild severity, which was not suspected to be related to previous rhGH treatment.

## Discussion

This observational follow-up study assessed the long-term safety (in particular, the risk of diabetes mellitus) after discontinuation of Omnitrope®

**Table 2.** Summary of carbohydrate metabolism parameters.

| | Baseline (*n* = 115) | Absolute change from baseline | | | |
|---|---|---|---|---|---|
| | | F1 (6 months, *n* = 99) | F2 (1 year, *n* = 88) | F3 (5 years, *n* = 13) | EOS (*n* = 86) |
| FPG (mmol/l) | | | | | |
| *n* | 109 | 90 | 79 | 11 | 80 |
| Mean (SD) | 4.69 (0.49) | −0.13 (0.57) | −0.14 (0.46) | −0.37 (0.86) | 0.00 (0.48) |
| Median (range) | 4.67 (3.2–6.9) | −0.09 (−2.8 to 1.1) | −0.17 (−1.5 to 0.8) | −0.33 (−2.2 to 1.1) | −0.02 (−2.0 to 1.6) |
| 2 h plasma glucose during OGTT (mmol/l) | | | | | |
| *n* | 106 | 87 | 77 | 11 | 73 |
| Mean (SD) | 5.33 (1.30) | −0.19 (1.58) | −0.28 (1.27) | −0.49 (1.11) | −0.06 (1.47) |
| Median (range) | 5.35 (2.8–8.6) | −0.28 (−4.0 to 5.1) | −0.22 (−3.4 to 2.8) | −0.50 (−2.4 to 1.0) | −0.33 (−4.7 to 5.1) |
| $HbA_{1C}$ (%) | | | | | |
| *n* | 107 | 87 | 78 | 12 | 79 |
| Mean (SD) | 5.28 (0.36) | −0.06 (0.36) | −0.11 (0.29) | −0.31 (0.60) | −0.16 (0.33) |
| Median (range) | 5.30 (3.80–6.20) | −0.09 (−1.30 to 1.20) | −0.10 (−1.10 to 0.60) | −0.10 (−1.97 to 0.15) | −0.18 (−1.30 to 0.90) |
| Fasting insulin (pmol/l) | | | | | |
| *n* | 109 | 88 | 75 | 12 | 80 |
| Mean (SD) | 70.87 (38.48) | −2.34 (38.27) | −7.48 (34.68) | 3.40 (52.53) | −12.47 (37.80) |
| Median (range) | 66.46 (2.1–251.4) | −0.73 (−90.3 to 188.9) | −1.11 (−120.8 to 77.1) | −3.02 (−84.3 to 126.2) | −12.54 (−138.9 to 84.7) |
| HOMA score | | | | | |
| *n* | 107 | 86 | 73 | 11 | 78 |
| Mean (SD) | 2.08 (1.03) | −0.07 (1.14) | −0.21 (1.02) | 0.09 (1.88) | −0.33 (1.14) |
| Median (range) | 2.00 (1.20–3.01) | −0.06 (−2.35 to 5.10) | −0.05 (−2.96 to 2.84) | −0.26 (−2.42 to 4.58) | −0.35 (−4.05 to 2.59) |
| QUICKI score | | | | | |
| *n* | 107 | 86 | 73 | 11 | 78 |
| Mean (SD) | 0.35 (0.05) | 0.004 (0.04) | 0.012 (0.041) | 0.02 (0.07) | 0.008 (0.03) |
| Median (range) | 0.34 (0.30–0.72) | 0.001 (−0.09 to 0.16) | 0.002 (−0.05 to 0.23) | 0.02 (−0.08 to 0.16) | 0.01 (−0.09 to 0.11) |

EOS, end of study; FPG, fasting plasma glucose; $HbA_{1C}$, glycated hemoglobin; HOMA, homeostasis model assessment; OGTT, oral glucose tolerance test; QUICKI, quantitative insulin sensitivity check index; SD, standard deviation.

treatment in short children born SGA. Children born SGA are at higher risk of developing metabolic abnormalities regardless of therapeutic intervention with rhGH; it is therefore important to maintain surveillance of SGA patients treated with rhGH therapy during treatment and in the years following.[28,29] Changes in insulin sensitivity in SGA patients are well documented, and although multiple hypotheses have been proposed, the precise mechanism for this is not yet known.[8]

A number of studies have demonstrated that long-term rhGH treatment in children born SGA is not a significant risk factor for developing type 2 diabetes mellitus or metabolic syndrome in later

**Table 3.** Summary of additional metabolomic parameters of interest.

| | Baseline (*n* = 115) | Absolute values | | | |
|---|---|---|---|---|---|
| | | F1 (6 months, *n* = 99) | F2 (1 year, *n* = 88) | F3 (5 years, *n* = 13) | EOS (*n* = 86) |
| Weight (kg) | | | | | |
| *n* | 115 | 99 | 88 | 13 | 86 |
| Mean (SD) | 44.97 (13.34) | 45.30 (14.18) | 44.38 (14.24) | 42.91 (15.55) | 50.63 (11.02) |
| Median (range) | 45.20 (10.0–76.2) | 47.00 (12.0–80.0) | 45.25 (11.0–82.0) | 42.00 (25.0–84.0) | 48.00 (29.0–95.0) |
| BMI SDS | | | | | |
| *n* | 115 | 99 | 88 | 13 | 86 |
| Mean (SD) | −0.84 (1.37) | −0.89 (1.52) | −1.18 (1.55) | −0.72 (1.38) | −0.63 (1.58) |
| Median (range) | −0.92 (−3.4 to 2.2) | −0.90 (−4.1 to 2.5) | −1.31 (−4.2 to 2.3) | −0.40 (−3.7 to 1.3) | −0.75 (−4.5 to 3.0) |
| Systolic blood pressure (mmHg) | | | | | |
| *n* | 115 | 99 | 88 | 13 | 86 |
| Mean (SD) | 108.0 (12.85) | 107.3 (11.44) | 108.0 (11.56) | 106.4 (14.07) | 108.8 (10.79) |
| Median (range) | 110.0 (80–145) | 110.0 (80–136) | 110.0 (80–135) | 100.0 (80–125) | 110.0 (90–137) |
| Diastolic blood pressure (mmHg) | | | | | |
| *n* | 115 | 99 | 88 | 13 | 86 |
| Mean (SD) | 67.0 (9.96) | 67.4 (8.74) | 67.5 (8.36) | 64.5 (12.83) | 69.2 (8.55) |
| Median (range) | 65.0 (40–100) | 70.0 (40–90) | 69.5 (50–88) | 60.0 (40–92) | 70.0 (54–91) |
| Total cholesterol (mmol/l) | | | | | |
| *n* | 112 | 98 | 88 | 13 | 85 |
| Mean (SD) | 4.07 (0.86) | 4.05 (0.85) | 4.06 (0.90) | 4.03 (0.90) | 4.20 (1.00) |
| Median (range) | 4.00 (2.5–7.0) | 4.07 (1.9–7.2) | 4.07 (1.9–7.2) | 3.80 (2.7–6.0) | 4.18 (2.6–7.1) |

BMI, body mass index; EOS, end of study; SD, standard deviation; SDS, standard deviation score.

life.[27,28,30,31] Furthermore, changes in insulin sensitivity during rhGH treatment have been found to be reversible after cessation of treatment.[30–32] This sentiment was reflected in the 2015 GH Safety Workshop Position Paper (a convening of the European Society of Paediatric Endocrinology, the GH Research Society, and the Pediatric Endocrine Society), which concluded that rhGH treatment does not increase the incidence of type 2 diabetes mellitus in SGA patients in the short term.[29]

The findings from this study are in line with previously published research; no cases of new-onset diabetes mellitus were diagnosed during the course of the study, and the laboratory parameters analyzed indicated no significant long-term effect on carbohydrate metabolism following rhGH therapy. Two cases of mild treatment-related impaired glucose tolerance were reported in this follow-up study; one had resolved during the study and one was ongoing at database closure. One case of mild impaired fasting glucose (IFG) was deemed to be treatment related and resolved during the study. Most AEs reported in this follow-up study were considered unrelated to rhGH therapy and were mild or moderate in intensity. No new safety concerns were raised from this analysis.

The safety of rhGH therapy in children born SGA has been well documented in the last few decades; our findings are consistent with reports from other observational studies of long-term rhGH therapy.[28,33–36] These findings are also in line with the safety profile of Omnitrope® reported to date; in the phase IV clinical study EP00-401[15] and in a long-term, post-marketing surveillance study [study EP00-501; PAtients TReated with Omnitrope® (PATRO) children].[37,38]

The prior phase IV study (EPOO-401) reported an increase in IGF-1 levels during rhGH treatment. In the present study, numeric IGF-1 levels decreased gradually over the follow-up period, resulting in a mean IGF-1 SDS of 0.05 at EOS. The largest IGF-1 numeric reduction occurred in the first 6 months following rhGH treatment cessation (baseline to visit F1).

There were some limitations of this study. Observational research has several associated limitations *versus* placebo-controlled randomized trials, including the lack of comparison populations.[29] However, the exclusion of a placebo group was necessitated by the proven treatment benefit derived from rhGH therapy. There was potential for selection bias, due to enrolment of patients from selected centers who were motivated to participate in the study. As the study was terminated early (due to lack of clinical concern about risk of diabetes development), the mean follow-up period of 39.6 months after discontinuation of Omnitrope® therapy was relatively short. In addition, due to the number of patients lost to follow up, the most reliable data are for the 2 years after rhGH treatment was stopped.

## Conclusions

The data from this study provide reassurance that the long-term risk of developing insulin resistance and diabetes mellitus is not increased in children born SGA who have received Omnitrope® treatment. No other unexpected or concerning safety signals were observed. Safety results were consistent with those from previous studies of rhGH in SGA patients.

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**Table 4.** Summary of adverse events.

| | Number of patients | | Number of AEs | |
|---|---|---|---|---|
| | *n* | % | *n* | % |
| Any AE | 54 | 45.8 | 144 | 100 |
| Relationship to study drug | | | | |
| Not applicable[a] | 1 | 0.8 | 1 | 0.7 |
| Not suspected | 53 | 44.9 | 136 | 94.4 |
| Suspected | 4 | 3.4 | 7 | 4.9 |
| Intensity | | | | |
| Not applicable[a] | 1 | 0.8 | 1 | 0.7 |
| Mild | 53 | 44.9 | 121 | 84.0 |
| Moderate | 9 | 7.6 | 18 | 12.5 |
| Severe | 1 | 0.8 | 4 | 2.8 |
| SAE | | | | |
| Not applicable[a] | 1 | 0.8 | 1 | 0.7 |
| No | 51 | 43.2 | 125 | 86.6 |
| Yes | 8 | 6.8 | 18 | 12.5 |
| Outcome | | | | |
| Resolved completely | 39 | 33.1 | 93 | 64.6 |
| Resolved with sequelae | 3 | 2.5 | 3 | 2.1 |
| Ongoing | 21 | 17.8 | 31 | 21.5 |
| Fatal | 1 | 0.8 | 1 | 0.7 |
| Unknown | 7 | 5.9 | 15 | 10.4 |
| Missing | 1 | 0.8 | 1 | 0.7 |
| Action taken[b] | | | | |
| None | 32 | 27.1 | 56 | 38.9 |
| Concomitant medication given | 33 | 28.0 | 68 | 47.2 |
| Non-drug therapy | 9 | 7.6 | 14 | 9.7 |
| Hospitalization | 8 | 6.8 | 18 | 12.5 |
| Missing | 1 | 0.8 | 1 | 0.7 |

[a]Pregnancy.
[b]More than one option possible.
AE, adverse event; SAE, serious adverse event.

**Table 5.** Incidence by intensity of adverse events by MedDRA system organ class occurring in >2% of patients.

| System organ class | Number of subjects ($n$ = 118) | | | Number of AEs | |
|---|---|---|---|---|---|
| | Intensity ($n$, %) | | | | |
| | Mild | Moderate | Severe | Total | AEs/subject-years |
| Blood and lymphatic system disorders | 6 (5.1) | 0 | 0 | 6 | 0.016 |
| Endocrine disorders | 5 (4.2) | 2 (1.7) | 0 | 7 | 0.019 |
| Gastrointestinal disorders | 4 (3.4) | 0 | 1 (0.8) | 7 | 0.019 |
| General/administration site conditions | 4 (3.4) | 0 | 0 | 5 | 0.013 |
| Infections and infestations | 27 (22.9) | 4 (3.4) | 1 (0.8) | 50 | 0.133 |
| Injury, poisoning and procedural complications | 4 (3.4) | 1 (0.8) | 0 | 6 | 0.016 |
| Investigations | 5 (4.2) | 1 (0.8) | 0 | 7 | 0.019 |
| Metabolism and nutrition disorders | 8 (6.8) | 0 | 0 | 10 | 0.027 |
| Musculoskeletal and connective tissue disorders | 8 (6.8) | 1 (0.8) | 0 | 7 | 0.019 |
| Nervous system disorders | 5 (4.2) | 2 (1.7) | 0 | 10 | 0.027 |
| Psychiatric disorders | 3 (2.5) | 0 | 0 | 3 | 0.008 |
| Renal and urinary disorders | 3 (2.5) | 0 | 0 | 3 | 0.008 |
| Reproductive system and breast disorders | 3 (2.5) | 1 (0.8) | 0 | 5 | 0.013 |
| Respiratory, thoracic, and mediastinal disorders | 3 (2.5) | 2 (1.7) | 0 | 5 | 0.013 |
| Skin and subcutaneous tissue disorders | 5 (4.2) | 1 (0.8) | 0 | 7 | 0.019 |

AEs, adverse events.

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## Author contributions

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## Conflict of interest statement

MS has been involved in clinical trials for, and received consultancy and speaker's fees from, Novo Nordisk, Pfizer, AstraZeneca, and Sandoz.

MW has received fees from Sandoz as the country coordinating investigator for the study in Poland.

JL has been involved in clinical trials for, and received consultancy and speaker's fees from, Pfizer, Novo Nordisk, Merck, and Sandoz.

FM, MN, GH and BKF have no relevant financial or non-financial interests to disclose.

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