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ORIGINAL RESEARCH ARTICLE

Pharmacokinetics and Tolerability of a Single Dose of Semaglutide, a Human Glucagon-Like Peptide-1 Analog, in Subjects With and Without Renal Impairment

Thomas C. Marbury[1] · Anne Flint[2] · Jacob B. Jacobsen[2] · Julie Derving Karsbøl[2] · Kenneth Lasseter[3]

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Abstract

Background The pharmacokinetics and tolerability of semaglutide, a once-weekly human glucagon-like peptide-1 analog in development for the treatment of type 2 diabetes mellitus, were investigated in subjects with/without renal impairment (RI).

Methods Fifty-six subjects, categorized into renal function groups [normal, mild, moderate, severe, and end-stage renal disease (ESRD)], received a single subcutaneous dose of semaglutide 0.5 mg. Semaglutide plasma concentrations were assessed ≤480 h post-dose; the primary endpoint was the area under the plasma concentration–time curve from time zero to infinity.

Results Semaglutide exposure in subjects with mild/moderate RI and ESRD was similar to that in subjects with normal renal function. In subjects with severe RI, the mean exposure of semaglutide was 22% higher than in subjects with normal renal function, and the 95% confidence interval (1.02–1.47) for the ratio exceeded the pre-specified limits (0.70–1.43). When adjusted for differences in sex, age, and body weight between the groups, all comparisons were within the pre-specified clinically relevant limits. Across RI groups there was no relationship between creatinine clearance (CL_{CR}) and semaglutide exposure, or between CL_{CR} and semaglutide maximum plasma drug concentration (C_{max}). Hemodialysis did not appear to affect the pharmacokinetics of semaglutide. No appreciable changes in safety parameters or vital signs and no serious adverse events were noted. One subject with severe RI reported two major hypoglycemic events.

Conclusion When adjusted for differences in sex, age, and body weight, semaglutide exposure was similar between subjects with RI and subjects with normal renal function. Semaglutide (0.5 mg) was well-tolerated. Dose adjustment may not be warranted for subjects with RI.

ClinicalTrials.gov identifier NCT00833716.

Key Points

Semaglutide exposure was similar between subjects with mild/moderate renal impairment (RI) or end-stage renal disease and subjects with normal renal function; equivalence was not demonstrated in subjects with severe RI, in whom mean exposure was 22% higher. However, when exposures were adjusted for differences in age, sex, and body weight, all comparisons were within the pre-specified 'no effect' limits.

A single subcutaneous dose of semaglutide 0.5 mg was well-tolerated across all renal function groups.

Semaglutide appears to be a useful treatment for subjects with diabetes mellitus regardless of renal status, and may not require dose adjustment.

✉ Thomas C. Marbury
tmarbury@ocrc.net

[1] Orlando Clinical Research Center, 5055 South Orange Avenue, Orlando, FL 32809, USA

[2] Novo Nordisk A/S, Søborg, Denmark

[3] Clinical Pharmacology of Miami, Inc., Miami, FL, USA

1 Introduction

Impaired renal function is a common complication of type 2 diabetes mellitus [1–3]. The prevalence of chronic renal disease, characterized by albuminuria or impaired renal function, is reported to be >30% among adults with type 2 diabetes, and duration of diabetes is associated with progression of renal disease [3–8]. Appropriate control of blood glucose is known to slow down the progress of renal impairment (RI) in patients with type 2 diabetes and kidney dysfunction [9, 10].

The metabolism and excretion of antidiabetic drugs required for good glycemic control may, however, be influenced by concomitant RI [10]. Reduced renal clearance, increased elimination half-life ($t_{½}$), and high maximum plasma drug concentration (C_{max}) values of antidiabetic drugs may lead to high and prolonged drug exposure [11–17]. For some antidiabetic drugs, this increases the risk of hypoglycemia, meaning that they are unsuitable for use in patients with RI or that caution is advised [11–17]. Therapeutic options in this particular patient group are therefore limited.

Semaglutide (Novo Nordisk A/S, Denmark) is a human glucagon-like peptide-1 (GLP-1) analog in phase III clinical development for the treatment of type 2 diabetes [18]. Although native human GLP-1 increases insulin secretion and decreases glucagon secretion in a glucose-dependent manner, its short $t_{½}$ makes it unsuitable for clinical use in type 2 diabetes [19, 20]. Furthermore, as GLP-1 is cleared primarily via the kidney, it may be particularly unsuitable for use in patients with RI [19, 20]. While semaglutide has 94% structural homology to native human GLP-1, modifications have been made to extend its $t_{½}$ to approximately 1 week in humans, allowing once-weekly administration [18, 21]. These modifications include acylation of the peptide backbone with a spacer and a C-18 fatty di-acid chain to lysine at position 26, which mediates strong binding to albumin and potentially results in reduced renal clearance, and an amino-acid substitution in position 8, which results in reduced susceptibility to dipeptidyl peptidase-4 (DPP-4) degradation. Studies show limited renal excretion of semaglutide in its intact form [22]. Semaglutide monotherapy has been shown to significantly improve glycemic control and reduce body weight, with a low risk of hypoglycemia in subjects with type 2 diabetes [18, 21, 23].

Several studies have assessed the effect of RI on the pharmacokinetics of GLP-1 receptor agonists [11, 12, 24–28]. Pharmacokinetic, efficacy, and safety data indicate that liraglutide and albiglutide have favorable benefit–risk profiles in patients with type 2 diabetes who also have mild or moderate RI [24, 25, 29]. Both medications have been reported to show little or no change in pharmacokinetics and pharmacodynamics in patients with RI versus those with normal renal function, are well-tolerated, and exhibit a low risk of hypoglycemia, irrespective of renal function [24, 25, 29, 30]. Patients with concomitant type 2 diabetes and RI are expected to be able to use standard treatment regimens without the need for dose adjustments [24, 25, 30].

The aim of this study was to compare the pharmacokinetics of semaglutide in subjects with different degrees of RI versus those with normal renal function, to determine whether semaglutide dose adjustment may be required. The short-term safety and tolerability of semaglutide was also assessed.

2 Methods

2.1 Study Population

Study participants were of both sexes, 18–75 years of age, with a body mass index of ≤40 kg/m^2. At screening, subjects had normal renal function or RI according to predefined creatinine clearance (CL_{CR}) criteria using the Cockcroft–Gault formula [31]. Subjects were classified as one of five groups: normal renal function (CL_{CR} > 80 mL/min); mild RI (CL_{CR} > 50 and ≤80 mL/min), moderate RI (CL_{CR} > 30 and ≤50 mL/min), severe RI (CL_{CR} ≤ 30 mL/min), or subjects with end-stage renal disease (ESRD) requiring hemodialysis. Subjects with type 2 diabetes were allowed to participate in this study.

Renal transplant patients were excluded, as were those with serious cardiac disease [New York Heart Association (NYHA) heart failure functional class III or IV; myocardial infarction within 3 months; unstable angina pectoris], uncontrolled hypertension (diastolic blood pressure ≥100 mmHg or systolic blood pressure ≥180 mmHg), severe hepatic disease within the previous 12 months, and those with elevated liver enzymes (≥2.5 times upper normal range). Medications known to alter tubular secretion of creatinine were not permitted within either 14 days or five half-lives, whichever was longer, prior to dosing.

2.2 Treatment

Semaglutide was administered by subcutaneous injection in the thigh (NordiPen®, Novo Nordisk A/S, Denmark) as a single 0.5 mg dose. In the ESRD group, semaglutide was administered 1–24 h after hemodialysis, with no hemodialysis for 48 h post-dose.

Initially, a single dose of 10 μg/kg (absolute dose range 0.7–1.2 mg) was administered to six subjects (three with

severe RI and three with ESRD) but, based on the frequency and severity of gastrointestinal adverse effects, the 10 μg/kg dose was not considered a tolerable starting dose. Two of these six subjects experienced three serious adverse events (AEs) (angioedema, increased hypertension, and aggravated sciatica pain), three experienced minor or symptoms-only hypoglycemia, and five experienced significant nausea and/or vomiting. To improve tolerability, the study was re-started with a lower, fixed single dose of semaglutide 0.5 mg.

2.3 Study Design and Pharmacokinetic Sampling

This was a multicenter, single-dose, open-label, parallel-group study (ClinicalTrials.gov identifier NCT00833716) conducted in accordance with Good Clinical Practice [32], the Declaration of Helsinki, and relevant guidelines for studies in patients with RI [33, 34]. A sample size of 54 subjects (14 normal renal function and ten in each of the four RI groups) was calculated to be sufficient for the primary objective of the study, with a power of 82% to show equivalence of exposure between subjects with severe RI and subjects with normal renal function. All participants provided written consent prior to initiation of any study-related activities. Participants were informed of the risks and benefits of the study and were permitted to withdraw at any time.

The study period was from Day 1 (dosing) to Day 21 (follow-up visit). Participants remained in-house for a minimum of 72 h after dosing (Fig. 1).

To determine the plasma concentrations of semaglutide, blood samples were taken 15 min prior to administration of semaglutide and 2, 8, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 38, 42, 48, 54, 60, 66, 72, 96, 144, 192, 240, 360, and 480 h after administration of semaglutide. For ESRD subjects on hemodialysis, hourly blood samples (some of which were in addition to those mentioned above) were drawn during each of the first two hemodialysis sessions post-administration (each hemodialysis session lasted for ~2–4 h).

2.4 Assay Methodology

Semaglutide serum concentrations were measured by liquid chromatography with tandem mass spectrometry (Celerion Inc., Fehraltorf, Switzerland), as described elsewhere [21]. The assay measured the total plasma concentration of semaglutide (protein bound and unbound). The lower limit of quantification for semaglutide was 1.94 nmol/L. Blood samples for estimation of protein binding were collected 30 min before dosing. Semaglutide binding was determined using surface plasmon resonance biosensor technology (Biacore T100 Instrument, GE Healthcare Bio-Sciences AB, Umeå, Sweden), in which semaglutide was immobilized at

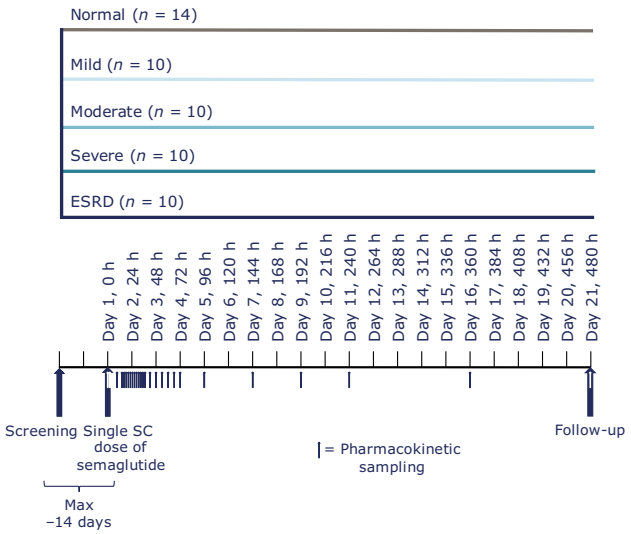

Fig. 1 Study design. In the ESRD group, semaglutide was given 1–24 h after hemodialysis, with no hemodialysis for 48 h post-dose. *ESRD* end-stage renal disease, *Max* maximum, *SC* subcutaneous

the surface and diluted plasma, collected prior to dosing, was passed over the sensor chip. Binding was determined as the resultant change in the resonance angle of polarized light. The affinity (k_d) and fraction unbound were determined using the 1:1 binding model.

2.5 Pharmacokinetic, Safety, and Statistical Analyses

Summary statistics and statistical analyses were based on all subjects exposed to a 0.5 mg dose of semaglutide. The six subjects who received a 10 μg/kg dose were evaluated for safety (reported AEs are described in Sect. 2.2), but were not included in the pharmacokinetics analysis set.

The primary pharmacokinetic endpoint was the area under the semaglutide plasma concentration–time curve (AUC) from time zero to infinity (AUC_∞). Secondary pharmacokinetic endpoints included C_{max}, time to reach C_{max} following drug administration (t_{max}), $t_{½}$, and apparent total clearance of the drug from plasma after subcutaneous administration (CL/F). In addition, for subjects in the ESRD and normal renal function groups, AUC from time zero to 48 h (AUC_{48}) and AUC from 48 to 96 h ($AUC_{48–96}$) were calculated.

The terminal elimination rate constant (λ_z) was approximated by log-linear regression on the log-linear phase of the plasma concentration profile. AUC was calculated using the trapezoidal rule, and AUC_∞ was then extrapolated from the time of last quantifiable observation (t) to infinite time using $AUC_{(t-\infty)} = C(t)/\lambda_z$. The $t_{½}$ was defined as $\ln 2/\lambda_z$ and CL/F was estimated as dose/AUC_∞.

To assess the effect of RI on semaglutide pharmacokinetic parameters, AUC_∞ was log-transformed and analyzed using

an analysis of covariance (ANCOVA) model, with renal group as a fixed effect. In addition, because of differences in baseline characteristics between the groups, the analysis was performed post hoc with age, sex, and log(weight) as explanatory variables. A two-stage procedure was pre-specified: in Stage 1 exposure was considered equivalent between the severe RI group and the normal renal function group if the 95% confidence intervals (CIs) for the ratio of AUC_{∞} (unadjusted) were contained within the pre-specified 'no effect' interval of 0.70–1.43 (both inclusive). The 'no effect' boundaries were selected based on the observation that semaglutide, as a GLP-1 analog, displays a wide therapeutic index. If equivalence was not shown in Stage 1, only then was Stage 2 performed, where equivalence between the mild RI group and the normal renal function group, and between the moderate RI group and the normal renal function group, was tested. Data from the ESRD group were also analyzed regardless of Stage 1 outcome. Correction for multiplicity due to multiple testing was performed by using a CI at the 95% level for each stage instead of 90% and a hierarchical testing scheme for the comparisons in Stage 2 (mild vs. normal followed by moderate vs. normal). As Stage 2 was performed, further analysis of the association between CL_{CR} and AUC_{∞} and CL_{CR} and C_{max} was carried out (as pre-specified) by linear regression of the log-transformed endpoint, with log-transformed CL_{CR} as the independent variable. C_{max} was analyzed in the same model as AUC_{∞}.

Tolerability of semaglutide was assessed through AEs, physical examination, electrocardiogram, vital signs, hypoglycemic events, plasma glucose, and clinical laboratory parameters (biochemistry, hematology, and urinalysis). Treatment-emergent AEs (TEAEs) were defined as events occurring between the dosing day and the follow-up visit +14 days (i.e., up to 5 weeks post-dose, corresponding to five half-lives of semaglutide), or starting before the dosing day with increasing severity during the period.

Hypoglycemic episodes were defined as 'major', 'minor', or 'symptoms only': major if the subject was unable to self-treat, minor if the subject was able to self-treat and plasma glucose was <3.1 mmol/L (56 mg/dL), or symptoms only if the subject was able to self-treat and had either a plasma glucose measurement ≥3.1 mmol/L or no plasma glucose measurement available. Safety endpoints were summarized using descriptive statistics.

3 Results

3.1 Subject Demographics

Following the decision to reduce the semaglutide dose from 10 μg/kg to 0.5 mg, a total of 56 subjects were exposed to a single 0.5 mg dose of semaglutide; 55 subjects completed the study and one subject withdrew due to nausea. Of those entering the study, 14 had normal renal function, 11 had mild RI, 11 had moderate RI, ten had severe RI, and ten had ESRD requiring hemodialysis. The enrollment of subjects with normal renal function was aimed to be balanced with regard to overall age, sex, and body weight distribution of the subjects with RI (Table 1). However, subjects with normal renal function had, on average, a lower body weight and were older than subjects with ESRD, and had a higher body weight and were younger than subjects with mild to severe RI. All groups included male and female subjects but, overall, there were more males than females. Of the subjects with RI, nine had type 2 diabetes as a concomitant illness at baseline.

3.2 Pharmacokinetics

Mean semaglutide plasma concentration over time by renal group is shown in Fig. 2, and all pharmacokinetic endpoints for semaglutide are shown in Table 2. Geometric means [coefficient of variation (CV), %] for AUC_{∞} showed no consistent trend with decreasing renal function, ranging from a lowest exposure of 2567 nmol h/L (18%) in the ESRD group to a highest exposure of 3179 nmol h/L (22%) in the severe RI group. Subjects with severe RI had a 22% higher mean exposure of semaglutide than subjects with normal renal function and the ratio did not demonstrate equivalence according to the predefined criteria for 95% CI (0.70–1.43). The CIs for the ratios of AUC_{∞} for semaglutide in the mild and moderate RI and ESRD groups were within the 'no effect' interval and were considered equivalent to the normal renal function group. When adjusted for differences between groups in age, sex, and log(weight), all of the 95% CIs for the ratio of AUC_{∞} between each RI group and the normal renal function group were contained within the pre-specified interval (0.70–1.43; Table 2).

Mean C_{max} for semaglutide was highest in subjects with normal renal function (10.3 nmol/L) and lowest in subjects with ESRD (7.4 nmol/L), whereas across the other groups mean C_{max} was 9.0–9.8 nmol/L (Table 2). When adjusted for differences between groups in age, sex, and log(weight), C_{max} was 10–20% lower in subjects with RI than in subjects with normal renal function, with no clear trend in severity of RI (Table 2). The t_{max} varied across the groups (range 24–51 h); mean $t_{½}$ was longer in subjects with severe RI (221 h) and those with ESRD (243 h) than in subjects with mild and moderate RI or normal renal function.

Exposure to semaglutide (AUC_{∞}) as a function of CL_{CR} and C_{max} as a function of CL_{CR} in all subjects, following a single dose of 0.5 mg semaglutide, are shown in Fig. 3a, b, respectively. There was no linear relationship between CL_{CR} across groups (normal, mild, moderate, severe, and

Table 1 Baseline demographics

Parameter	Renal function group				
	Normal	Mild	Moderate	Severe	ESRD
Subjects (*n*)	14	11	11	10	10
Sex [M/F (*n*)]	9/5	6/5	6/5	6/4	7/3
Age (years)	54.6 ± 9.1	62.9 ± 8.0	66.5 ± 6.6	62.8 ± 9.1	48.2 ± 7.2
Weight (kg)	84.9 ± 19.1	80.1 ± 13.8	78.7 ± 16.5	78.1 ± 22.7	97.2 ± 15.7
BMI (kg/m^2)	29.2 ± 4.1	28.5 ± 4.3	27.9 ± 5.2	27.8 ± 5.2	31.7 ± 5.1
FPG (mmol/L)	5.6 ± 0.5	5.8 ± 0.6	6.6 ± 1.8	5.8 ± 1.6	5.2 ± 2.4
T2D (*n*)	0	1	2	2	4
Estimated CL_{CR}[a] (mL/min)	119.7 ± 42.6	63.2 ± 9.0	41.5 ± 5.7	21.5 ± 6.2	15.4 ± 6.2

All data are mean ± standard deviation unless stated otherwise

BMI body mass index, *CL_{CR}* creatinine clearance, *ESRD* end-stage renal disease, *F* female, *FPG* fasting plasma glucose, *M* male, *T2D* type 2 diabetes mellitus

[a] CL_{CR} was calculated using the Cockcroft–Gault formula

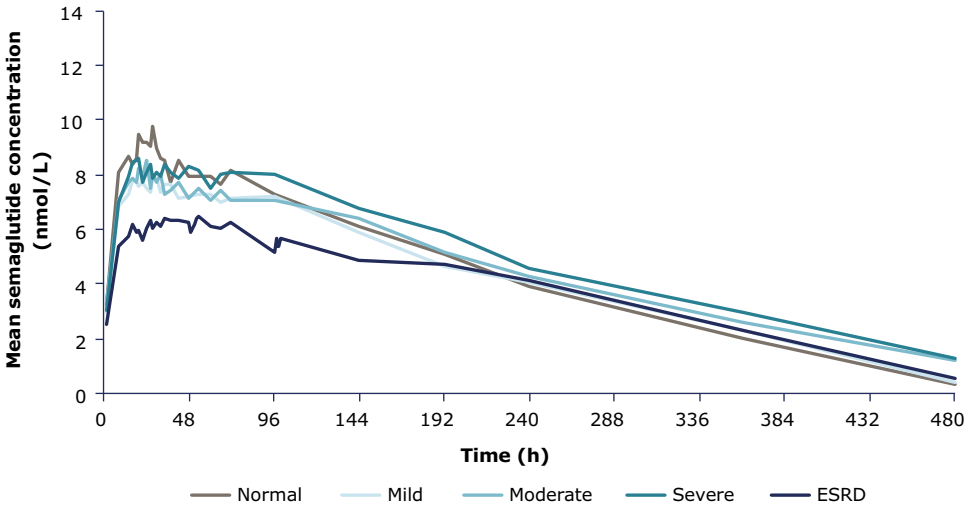

Fig. 2 Mean semaglutide plasma concentration over time by renal function group after a single dose of semaglutide 0.5 mg. The study period was from Day 1, 0 h (dosing) to Day 21, 480 h (follow-up visit). *ESRD* end-stage renal disease

ESRD) and semaglutide exposure ($p = 0.127$), or between CL_{CR} across groups and semaglutide C_{max} ($p = 0.164$). When adjusted for differences in age, sex, and body weight, the small observed slopes for AUC_∞ and C_{max} (approximately −0.06 and 0.08, respectively) were unchanged; however, the association between CL_{CR} and AUC_∞ was statistically significant ($p = 0.041$). A slope of −0.06 corresponds to an increase in exposure of 14% in subjects with a CL_{CR} of 10 mL/min versus subjects with a CL_{CR} of 90 mL/min.

The point estimate of the ratio (ESRD group/normal renal function group) for AUC_{48} (without hemodialysis) was 0.72 (90% CI 0.57–0.91) and for $AUC_{48–96}$ (with hemodialysis) was 0.82 (90% CI 0.67–0.99). The estimated ratios were also comparable when adjusted for differences in age, sex, and body weight [0.81 (90% CI 0.66–1.01) for AUC_{48} and 0.93 (90% CI 0.78–1.10) for $AUC_{48–96}$], indicating that hemodialysis did not appear to affect the pharmacokinetics of semaglutide.

There was no difference in protein binding between the groups; the fraction of unbound semaglutide across renal groups was low (<1%; data not shown). All subjects had normal albumin concentrations at baseline and throughout the study (except for one subject in the normal renal function group at the screening visit).

3.3 Adverse Events and Other Safety Assessments

The safety population comprised all 56 enrolled subjects who received semaglutide 0.5 mg. One subject in the mild RI group withdrew from the study on Day 2 because of nausea.

Overall TEAEs are shown in Table 3. In total, 38 subjects experienced 89 events with semaglutide 0.5 mg; none were serious or severe and the majority were mild. The AE profiles in the normal renal function and mild and moderate RI groups were similar; compared with these three groups, the proportion of subjects experiencing AEs was higher in the severe RI group and lower in the ESRD group. The most frequently

Table 2 Pharmacokinetic endpoints for a single dose of semaglutide 0.5 mg[a]

Parameter	Renal function group				
	Normal	Mild	Moderate	Severe	ESRD
Primary					
AUC_{∞} (nmol h/L)	2600 (27)	2615 (19)[b]	2999 (20)[c]	3179 (22)	2567 (18)[b]
AUC_{∞} estimated ratio (95% CI)[d]		1.01 (0.83–1.21)	1.15 (0.96–1.38)	1.22 (1.02–1.47)	0.99 (0.82–1.19)
Adjusted analysis[e]					
AUC_{∞} estimated ratio (95% CI)[d]		0.99 (0.85–1.16)	1.07 (0.91–1.27)	1.13 (0.97–1.32)	1.10 (0.94–1.28)
Secondary					
C_{max} (nmol/L)	10.3 (35)	9.8 (22)[c]	9.0 (44)	9.8 (37)	7.4 (22)[b]
C_{max} estimated ratio (90% CI)[d]		0.95 (0.76–1.20)	0.88 (0.70–1.10)	0.95 (0.75–1.19)	0.72 (0.57–0.91)
Adjusted analysis[e]					
C_{max} estimated ratio (90% CI)[d]		0.90 (0.73–1.11)	0.79 (0.64–0.99)	0.86 (0.70–1.06)	0.82 (0.66–1.01)
t_{max} (h)	24 (8, 66)	35 (14, 96)[c]	24 (14, 96)	41 (16, 96)	51 (28, 72)[b]
$t_{½}$ (h)	183 (15)	169 (14)[b]	201 (14)[c]	221 (26)	243 (19)[b]
CL/*F* (L/h)	0.047 (27)	0.046 (19)[c]	0.041 (20)	0.038 (22)	0.047 (18)[b]

Values are geometric means [CV (%)] for AUC_{∞}, C_{max}, $t_{½}$, and CL/*F* unless stated otherwise; and median (minimum, maximum) for t_{max}

AUC$_{\infty}$ area under the plasma concentration–time curve from time zero to infinity, *CI* confidence interval, C_{max} maximum plasma drug concentration, *CL/F* apparent total clearance of the drug from plasma after subcutaneous administration, *CV* coefficient of variance, *ESRD* end-stage renal disease, $t_{½}$ elimination half-life, t_{max} time to reach maximum plasma drug concentration following drug administration

[a] The pharmacokinetic population comprised all subjects exposed to subcutaneous semaglutide 0.5 mg with an evaluable drug profile and no relevant protocol violations

[b] The corresponding parameter could only be estimated for $n = 9$

[c] The corresponding parameter could only be estimated for $n = 10$

[d] The corresponding parameter could only be estimated versus the normal renal function group

[e] Adjustment analyses for the primary endpoint and C_{max} were conducted with age, sex, and log(weight) as explanatory variables

reported TEAEs were gastrointestinal (a total of 35 subjects experienced 61 events), with nausea being the most frequent (41% of subjects). A higher proportion of subjects experienced nausea in the severe group than in all other groups. For AEs in the six subjects who received a single dose of semaglutide 10 µg/kg, see Sect. 2.2.

One subject with severe RI (who did not have type 2 diabetes, but had experienced nausea, vomiting, and decreased appetite from the dosing day) had two major hypoglycemic events, one subject with moderate RI and one with ESRD experienced minor hypoglycemia, and two subjects in the moderate RI group experienced symptoms-only hypoglycemia.

No clinically significant values or appreciable changes in vital signs (blood pressure and pulse), electrocardiogram, physical examinations, or clinical laboratory assessments were observed.

4 Discussion

We examined the human GLP-1 analog semaglutide in subjects with normal renal function and those with varying degrees of RI, to investigate whether the pharmacokinetics change across groups and to determine whether dose adjustments are needed. The study population included a broad range of subjects with varying severities of RI: mild, moderate, severe, and a group with ESRD undergoing regular hemodialysis.

The results of this study demonstrate that, for moderate or mild RI, or in subjects with ESRD, the exposure of semaglutide is within the 'no effects' limits, compared with the normal renal function group. The comparison between the group with normal renal function and the group with severe RI did not demonstrate equivalence (the 95% CI exceeded the 'no effect' limits), and the mean semaglutide exposure was 22% higher in the severe RI group. C_{max} for the ESRD group was outside the pre-specified 'no effects' limits and appeared to be lower than in the other RI groups. However, baseline characteristics of subjects with normal renal function were somewhat different from those in the four RI groups. On average, subjects with normal renal function had a higher body weight and were younger (84.9 kg, 54.6 years) than subjects in the mild, moderate, and severe RI groups (78.1–80.1 kg, 62.8–66.5 years) but had a lower body weight and were older than subjects with ESRD (97.2 kg, 48.2 years). When the data were adjusted for differences in age, sex, and body weight among the

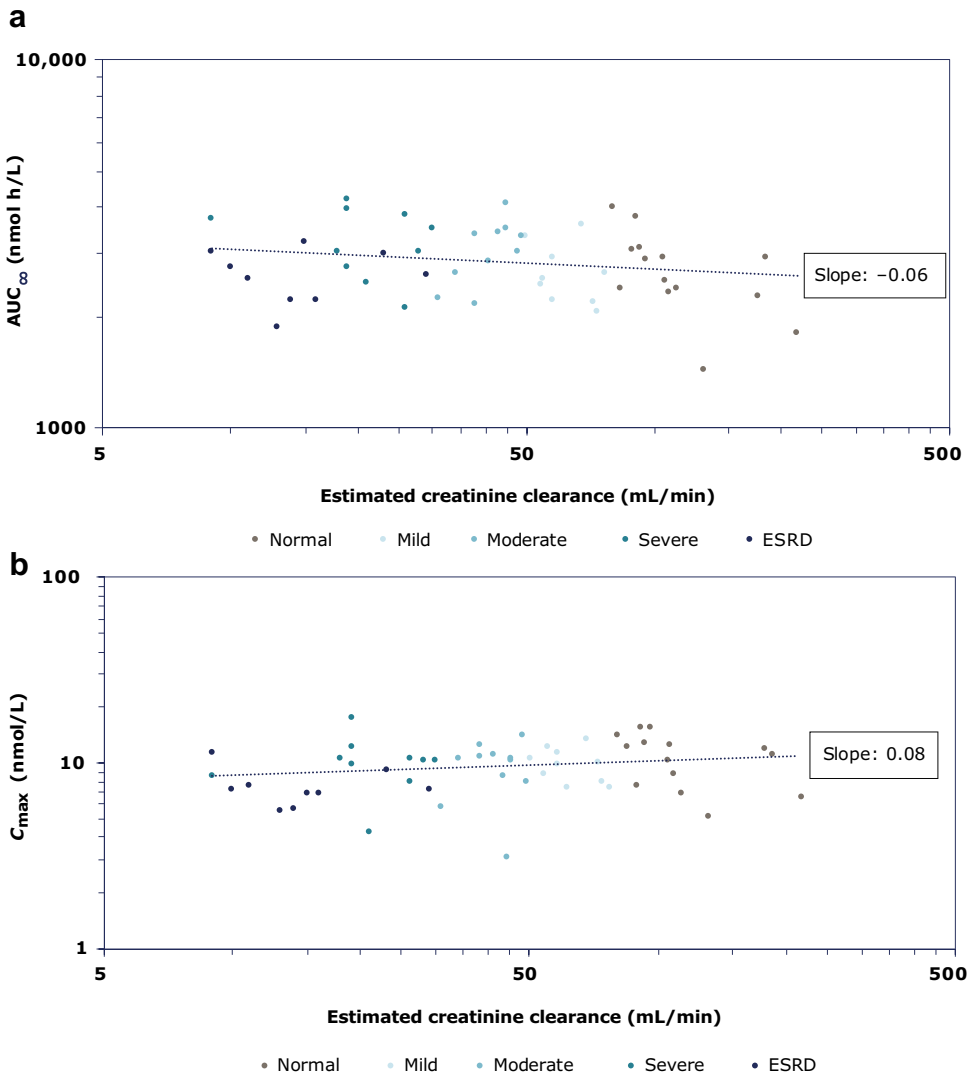

Fig. 3 **a** Exposure of semaglutide and **b** maximum semaglutide plasma concentration versus creatinine clearance following a single dose of semaglutide 0.5 mg by renal function group. AUC_{∞} area under the plasma concentration–time curve from time zero to infinity, C_{max} maximum plasma drug concentration, *ESRD* end-stage renal disease

Table 3 Treatment-emergent adverse events

System organ class and preferred term	Renal function group [*N* (%) *E*]					
	Normal	Mild	Moderate	Severe	ESRD	Total
Subject	14	11	11	10	10	56
Overall						
TEAEs	10 (71) 23	7 (64) 14	8 (73) 17	9 (90) 25	4 (40) 10	38 (68) 89
Withdrawals	0	1 (9) 1	0	0	0	1 (2) 1
Severity						
Mild	9 (64) 17	6 (55) 10	8 (73) 17	9 (90) 18	3 (30) 3	35 (63) 65
Moderate	3 (21) 6	2 (18) 4	0	2 (20) 7	3 (30) 7	10 (18) 24
Severe	0	0	0	0	0	0
Gastrointestinal	7 (50) 10	7 (64) 10	8 (73) 13	9 (90) 21	4 (40) 7	35 (63) 61
Nausea	4 (29) 4	4 (36) 4	4 (36) 4	9 (90) 12	2 (20) 2	23 (41) 26
Vomiting	3 (21) 3	1 (9) 1	3 (27) 3	4 (40) 6	3 (30) 5	14 (25) 18
Dyspepsia	2 (14) 2	3 (27) 4	3 (27) 3	1 (10) 10	0	9 (16) 10

A TEAE is defined as an event occurring between the dosing day and the follow-up visit +14 days (i.e., up to 5 weeks post-dose, corresponding to five half-lives of semaglutide), or starting before the dosing day with increasing severity during the period

E number of adverse events, *ESRD* end-stage renal disease, *N* number of subjects with adverse event, *TEAE* treatment-emergent adverse event, % proportion of subjects in analysis set having adverse event

groups, all comparisons for exposure were within the 'no effect' limits, and C_{max} was similar between RI and ESRD groups, which were all 10–20% lower than the normal renal function group (Table 2). In addition, there was no relationship between CL_{CR} across RI groups (normal, mild, moderate, severe, and ESRD) and semaglutide exposure, or between the CL_{CR} and semaglutide C_{max}. The pharmacokinetics of semaglutide did not appear to be affected by hemodialysis, as the semaglutide exposure ratio of ESRD subjects to healthy subjects during dialysis ($AUC_{48–96}$) was similar to the ratio obtained when subjects were not receiving dialysis (AUC_{48}).

Semaglutide (single dose of 0.5 mg) was well-tolerated, despite not being administered with a dose-escalation regimen. As expected, the AEs were mainly gastrointestinal and, while one subject withdrew from the study because of nausea, the majority of events were mild, and all were mild to moderate, in severity. While this was a single-dose study, the semaglutide dose-escalation regimens used in two other studies—Kapitza et al. [21] (starting dose 0.25 mg for 4 weeks, then 0.5 mg for 4 weeks and 1.0 mg for 5 weeks) and Nauck et al. [18] (0.4 mg for 1 week followed by 0.8 mg for 11 weeks)—reduced the incidence of nausea, indicating tolerance development compared with no or weekly dose escalation. The starting dose and dose-escalation regimen reported by Kapitza et al. [21] has been used in the semaglutide phase III development program, in which semaglutide showed a gastrointestinal AE profile comparable to that of other GLP-1 receptor agonists [23]. As the C_{max} in the RI groups was not higher than in the normal renal function group—indeed, when adjusted for age, sex and body weight, C_{max} was 10–20% lower than in the normal group—no tolerability issues are expected in clinical practice.

In this study, two major episodes of hypoglycemia were reported in a subject with severe RI (who did not have type 2 diabetes). This may be treatment related or could be linked to the presence of RI; in a retrospective cohort analysis of 243,222 patients, Moen et al. [14] showed that chronic renal disease is a significant risk factor for hypoglycemia in patients with or without diabetes. No other safety or tolerability concerns were raised with a single dose of semaglutide 0.5 mg, and none of the TEAEs were classified as serious or severe.

This study was conducted according to regulatory standards comprising four RI groups (mild, moderate and severe RI, and ESRD), with ≥10 subjects in each group and a comparable reference group with normal renal function [33, 34]; the results indicate that the pharmacokinetic properties of semaglutide are not significantly affected by renal function. Therefore, specific dose adjustment may not be warranted in subjects with RI. Our study is supported by a recent trial reporting the absorption, metabolism, and excretion of a single subcutaneous 0.5 mg dose of [^{3}H]-radiolabeled semaglutide in healthy male subjects, showing that semaglutide has very limited renal excretion in its intact form [22].

Other available GLP-1 receptor agonists have been approved for use in mild and moderate RI [35–40]. These drugs are not recommended for patients with severe RI, ESRD, or who are on dialysis because of limited therapeutic experience [30, 35]. Subjects with a broad variety of RI were enrolled in the Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) program (the phase III development program for semaglutide).

Recently, findings from the SUSTAIN 6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes) cardiovascular outcomes study—in which more than two-thirds of patients had some degree of RI (estimated glomerular filtration rate <90 mL/min/1.73 m^2)—showed that treatment with semaglutide (on a background of standard of care) resulted in significant and sustained reductions in glycated hemoglobin (HbA_{1c}) versus placebo (mean HbA_{1c} was 0.7 and 1.0 percentage points lower with semaglutide 0.5 and 1.0 mg, respectively, vs. placebo, both $p < 0.001$). In the SUSTAIN 6 study, gastrointestinal AEs were more frequent with semaglutide than with placebo, but most were mild or moderate in severity [23]. In a subgroup analysis for the primary outcome (first occurrence of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke), no significant treatment interactions were identified for the renal function subgroups analyzed [23]. Therefore, SUSTAIN 6 showed that the effects of semaglutide on the primary composite endpoint were not affected by renal subgroup [23].

5 Conclusion

When adjusted for differences in sex, age, and body weight, semaglutide exposure is not affected by RI. Therefore, semaglutide appears to be a useful treatment option for patients with type 2 diabetes who also have impaired renal function, including those with ESRD undergoing hemodialysis. Dose adjustment may not be warranted for patients with RI.

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Compliance with Ethical Standards

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Conflicts of interest The study was sponsored by Novo Nordisk A/S, the manufacturer of semaglutide. AF, JBJ, and JDK are employees of, and own shares in, Novo Nordisk A/S. TCM is an employee of Orlando Clinical Research Center.

Ethical Approval The study was conducted in accordance with Good Clinical Practice, the Declaration of Helsinki, and current guidelines for studies in patients with RI.

Informed Consent All participants gave their written consent prior to the start of any study-related activities.

Author Contributions TCM conducted the study and collected the data. TCM, AF, JBJ, JDK, and KL performed the data analysis, wrote, and revised the manuscript. All authors gave final approval of the manuscript.

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