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**Author:** Meer, L. van  
**Title:** Anti sense and sensibility: renal and skin effects of (antisense) oligonucleotides  
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Table 3  Plasma pharmacokinetics Single Ascending Dose study. N=number

<table>
<thead>
<tr>
<th>Dose</th>
<th>N</th>
<th>AUC 0-48hr (ug*hr/mL)</th>
<th>Cmax (ug/mL)</th>
<th>Tmax (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg</td>
<td>3</td>
<td>5.82 ± 2.18</td>
<td>1.31 ± 0.59</td>
<td>1.17 ± 0.58</td>
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<td>100 mg</td>
<td>3</td>
<td>13.0 ± 0.78</td>
<td>1.72 ± 0.35</td>
<td>1.17 ± 0.76</td>
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<tr>
<td>200 mg</td>
<td>3</td>
<td>22.2 ± 0.88</td>
<td>2.88 ± 0.52</td>
<td>0.83 ± 0.29</td>
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<td>400 mg</td>
<td>3</td>
<td>42.8 ± 4.47</td>
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<td>1.5 ± 1.31</td>
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</table>

Table 4  Plasma pharmacokinetics Multiple Ascending Dose study. N=number

<table>
<thead>
<tr>
<th>Dose</th>
<th>Study Day</th>
<th>N</th>
<th>AUC 0-48hr (ug*hr/mL)</th>
<th>Cmax (ug/mL)</th>
<th>Tmax (hr)</th>
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<tbody>
<tr>
<td>50 mg</td>
<td>1 36</td>
<td>6</td>
<td>9.58 ± 1.39</td>
<td>1.65 ± 0.37</td>
<td>1.25 ± 0.27</td>
</tr>
<tr>
<td>100 mg</td>
<td>1 12</td>
<td>6</td>
<td>9.78 ± 1.53</td>
<td>1.67 ± 0.26</td>
<td>1.33 ± 0.61</td>
</tr>
</tbody>
</table>

Novel antisense SGLT2 inhibitor causes serum creatinine increases without affecting renal blood flow or glomerular filtration

Leonie van Meer, Marloes van Dongen, Matthijs Moerland, Marieke de Kam, Erica Klaassen, Adam Cohen, Jacobus Burggraaf
Abstract

ISIS 388626 is an antisense oligonucleotide designed to inhibit the renal SGLT2 receptor to treat Type 2 Diabetes Mellitus by inducing glucosuria. The first-in-human trial with this drug candidate was halted early due to unexpected effects on renal function. Additional and more extensive preclinical testing of ISIS 388626 with different dose regimens provided more insight into the renal effects. An adapted study design without loading dose was proposed to avoid these untoward effects and the study was restarted with a multiple ascending dose design with weekly 50, 100, and 200 mg for 13 weeks. Despite changing the dose regimen, treatment with 50 mg ISIS 388626 induced serum creatinine increases and increases in urinary renal markers. These changes prohibited dose escalation to the 100 mg dose. Instead, a new cohort of volunteers was treated at the 50 mg dose level to explore if the observed transient increases in renal damage markers coincided with functional renal changes. This was assessed with renal clearance tests to evaluate the impact of ISIS 388626 on GFR and renal plasma flow. Weekly ISIS 388626 treatment at a dose level of 50 mg for 13 weeks increased average serum creatinine (with 0.15 mg/dl) and renal damage markers. The changes were relatively mild and fully reversible upon cessation of dosing. The renal clearance test revealed no indications for impairment of glomerular filtration or renal perfusion. No increase in renal glucose excretion was observed at the 50 mg dose level, as was expected based on preclinical data. To elicit pharmacological activity exposure is to be increased. Exploration of higher ISIS 388626 dose levels in healthy volunteers is possible as long as a careful approach is applied with close monitoring of renal function and damage markers.

Introduction

The strategy of SGLT2 Inhibition in the treatment of Diabetes Mellitus Type 2 has proven its efficacy and has led to the registration and approval of several small molecule SGLT2 inhibitors [1-3]. An alternative to SGLT2 inhibition by small molecules, which result in a moderate 30-50 % inhibition only, could be antisense-mediated SGLT2 knock-down. ISIS 388626 is such an antisense oligonucleotide which in animal models causes ≥ 80% reduction of renal SGLT2 mRNA expression at doses of 1-3 mg/kg/week (rodents) to 30 mg/kg/week (monkeys), resulting in effective glucosuria [4,5].

As ISIS 388626 appeared to be effective and safe in animal studies ranging from 6 weeks to 6 months in duration the compound was tested in humans. These first clinical studies with 50-100 mg SC weekly after a loading dose regimen of three doses during the first week showed, contrary to expectations, possibly untoward renal effects (chapter 2 of this thesis, L. van Meer et al.). In summary, 3-4 week treatment with ISIS 388626 resulted in dose-dependent, transient, fully reversible, and variable (range: 0 - 73 % at 100 mg ISIS 388626) increases in serum creatinine that was accompanied by increased urinary excretion of renal markers such as beta-2-microglobulin (B2M) and Kidney Injury Molecule 1 (KIM1). This was unexpected as in animals assessments at 6 and 13 weeks had not shown such results. The pertaining clinical study was halted early and further pre-clinical data were collected. First, bio-banked samples collected earlier than 6 weeks in previously performed pre-clinical experiments were analyzed. This showed that also in animals, relatively early during weekly treatment with ISIS 388626 after using loading doses resulted in transient increases in serum creatinine and urinary excretion of B2M and protein. The changes were reversible even upon continuation of dosing (unpublished data, on file). Thus, the apparent discrepancy of renal effects of ISIS 388626 treatment in rodents and monkeys and humans could be explained by the timing of the assessments [4-6]. In a further dedicated experiment in monkeys it was explored if the renal effects by ISIS 388626 could be explained by the loading dose. Animals were dosed for 13 weeks with either 30 mg/kg every other day or a single dose in the first week, followed by weekly dosing for another 12 weeks. This experiment showed that changes in renal markers occurred only with the loading dose regimen. Importantly, this study also showed that abandoning the loading dose ISIS 388626 still resulted in glucosuria, while changes in serum creatinine did not occur.

Based on these findings, the clinical study was restarted with the aim to investigate the effects of 13 weekly 50, 100, and 200 mg ISIS 388626. However, omitting the loading dose did not prevent increases in renal markers, as described here. Dose escalation after 50 mg was stopped and further explorations were done to investigate whether the transient increases in renal markers in humans could be explained by functional changes in renal blood flow and/or glomerular filtration rate.
Materials and Methods

**Subjects**

Adult subjects (18-65 yrs), male or female (post-menopausal or surgically sterile) with a BMI < 30 kg/m2 and a fasting plasma glucose and a normal HbA1c could participate in this study. Subjects with significant abnormalities in medical history, physical examination, 12-lead electrocardiogram, and clinical laboratory evaluations (including positive protein in urine dipstick analysis and calculated eGFR below 60 ml/min by MDRD equation[7]) were excluded. The study was conducted in accordance with good clinical practice guidelines, after approval by the national ethics committee.

**Study Design**

This was a double-blind, randomized, placebo-controlled multiple ascending dose study of 12 weeks duration and 5 weeks follow-up, with weekly administration of ISIS 388626 to establish the safety profile and pharmacodynamics of the compound, performed at the Centre for Human Drug Research in the Netherlands. Per cohort, 16 randomly assigned subjects received multiple doses of either ISIS 388626 or placebo (in a 3:1 ratio), administered as subcutaneous injection. An oral glucose tolerance test (OGTT) was performed before the first administration of ISIS 388626 (or matching placebo) and at week 9 and 13. The OGTT consisted of ingestion of a 75 mg glucose solution, given after an overnight fast. Subsequently blood was drawn regularly during 4 hours for determination of glucose, insulin and C-peptide concentrations. It was anticipated to investigate the effects of 50, 100 and 200 mg ISIS 388626, but due to unexpected findings in the 50 mg cohort, execution of the 100 and 200 mg cohort was cancelled. To explore the nature of the observed safety signals in more detail, renal clearance tests (using PAH and sinistrin infusions) were performed regularly in an additional cohort treated with the same dose regimen (weekly administration of 50 mg ISIS 388626 or placebo).

**Dose Rationale**

It was anticipated to explore 50, 100 and 200 mg of ISIS 388626. The doses were based on a MABEL approach, taking into account a No Adverse Effect Level estimated to be 10 mg/kg/week (including a loading dose regimen) in monkeys. In preclinical studies across multiple species, the pharmacologically active dose range of ISIS 388626 was 1-3 mg/kg/week. At this exposure, a significant reduction in SGLT2 mRNA occurred (74 to 97% in mice and approximately 30 to 90% in monkeys over the dose range 1-30 mg/kg/week), accompanied by a 25-200 fold increase in urinary glucose excretion [5;6;8]. Based on this, estimation of the equivalent human effective dose falls in the range of 1-3 mg/kg/week. Experience with other 2′-MOE-modified antisense oligonucleotides, safely administered (intravenously and subcutaneously) in multiple clinical studies at doses up to weekly 750 mg (which translates into 10.7 mg/kg/week assuming an average weight of 70 kg), with treatment durations exceeding one year [9], further supports the safety of this dose range.

The dose regimen was chosen because the loading dose (3 doses in the first week) resulted in creatinine increases in prior human studies (chapter 2 of this thesis, L. van Meer et al.) and dedicated experiments in monkeys showed that changes in renal markers occurred only with the loading dose regimen. The treatment duration of 12 weeks (13 doses) was selected, which was expected to be safe and resulting in sufficient steady state tissue concentrations, based on animal studies.

**Clinical Measurements**

Safety assessments, performed throughout the study period, included vital signs, electrocardiograms, physical examinations, and clinical laboratory tests (including clinical chemistry, hematology, coagulation, cytokines, complement tests and urinalysis (including B2m and protein)) as well as registration of adverse events. Adverse events were defined as any new medical occurrence or worsening of a pre-existing condition after administration of the study drug or placebo. Predefined stopping rules regarding renal parameters were defined as changes in serum creatinine change from baseline of more than 0.3 mg/dL or more than 40% on two consecutive weeks, or proteinuria of more than 0.5 g/24hr occurring on two consecutive weeks.

**Renal Markers**

The biomarkers B2M, AGST and NAG were chosen based on their performance on detecting injury to the proximal tubule where SGLT2 is located [10]. Analysis of renal damage markers AGST and NAG was performed batch-wise upon study completion by quantitative enzyme immunoassays.
RENAL PERFUSION AND GLOMERULAR FILTRATION

Renal clearance tests to assess RPF and GFR were performed using established and validated techniques [11-13]. Sinistrin infusion allows calculation of glomerular filtration rate (GFR) as it is not secreted or reabsorbed in any appreciable amount by the kidney. PAH infusion allows calculation of renal plasma flow (RPF) as it is completely secreted and not reabsorbed by the tubules. The intravenous infusion of sinistrin and PAH started 90 minutes after administration of ISIS 388626 or placebo. Infusion rates were calculated with the aim to obtain a steady state concentration that was comparable between subjects and within the measurable range. PAH and sinistrin doses, corrected for lean body mass, serum creatinine and age were administered via a continuous infusion of 120 minutes (infusion rates ranging from 400 to 750 mg/hr and from 380 to 740 mg/hr for sinistrin and PAH, respectively), preceded by a 10-minute priming dose that was corrected for body surface area (ranging from 825 to 1200 mg and from 840 to 1200 mg for sinistrin and PAH respectively). Plasma samples for PAH, sinistrin and hematocrit measurement and urine samples for PAH and sinistrin measurement were collected at 30 minute intervals. During the infusion period, hydration was maintained by subjects drinking amounts of water matching urinary output, with a maximum of 4 L, to ensure sufficient urine production. Serum and urinary sinistrin levels were analyzed according to the method described by Looye ([14]) PAH levels were measured according to the method described by Waugh et al. [15].

No formal power calculation was performed, however group size (12 treated subjects) was considered to be sufficient as expected effect size of change in GFR (in case present) was around 17% and as previously shown, differences of 10% GFR can be detected with a group size of 9 healthy volunteers [12].

PHARMACOKINETICS

ISIS 388626 plasma levels were measured in using a validated hybridization enzyme-linked immunosorbent assay (PDD laboratories, Richmond, USA) frequently for a 24 hour profile after the first and 13th ISIS 388626 dose, and predose on weeks 3, 8, 10 during treatment and on 5 weekly follow-up visits. In addition, ISIS 388626 urine levels were measured using a validated Capillary Gel Electrophoresis method (PDD Laboratories, Richmond, USA), in 24 hour collections after the first and 13th dose (up to 24 and 48 hours post-dose).

DATA ANALYSIS AND STATISTICAL METHODS

Safety and tolerability evaluation was based on descriptive statistics. ISIS 388626 plasma concentrations were subjected to non-compartmental pharmacokinetic evaluation in order to determine the maximum observed plasma concentration (Cmax), the time to maximum plasma concentration (Tmax), the area under the plasma concentration-time curve from dosing to 24 hours after dosing (AUCO-24h) using WINNONLIN (version 5.3, Pharsight Corporation, USA).

Results

SUBJECTS

Sixteen subjects were enrolled and thirteen subjects completed the first study part (50mg/placebo). One subject withdrew consent for personal reasons after receiving 12 doses, and in two subjects dosing was stopped due to safety findings; in one subject after 5 doses due to increases in serum creatinine, in the other subject after 7 doses due to increased liver biochemistry parameters (see safety results for details). Another sixteen subjects were enrolled in the second study part study which included renal clearance tests (RCT); demographics are presented in table 1. Subjects were randomized to 13 weekly SC injections of 50 mg ISIS 388626 (n=12) or placebo (n=4).

SAFETY

All reported adverse events (AEs) were of mild intensity and transient (table 2). The most common AEs were headache, gastrointestinal complaints (diarrhea, nausea or abdominal discomfort) and mild upper respiratory complaints (nasopharyngitis and flu-like symptoms). Since the incidence of AEs was comparable between active treatment...
and placebo, it is considered unlikely that these AES are related to ISIS 388626 administration. Injection site reactions (ISRs) were observed in 2 out of 12 ISIS 388626-treated subjects (17%) in the first study part. No ISRs were observed in the second study part (table 2). In one subject hyperpigmentation was reported. The ISRs were not progressive and not accompanied by local lymphadenopathy. ISRs were considered to be related to administration of study drug and all resolved completely and spontaneously during the study period.

ISIS 388626 treatment did not result in any clinically relevant changes in vital signs, ECG-derived parameters, body temperature, hematology, coagulation, complement or cytokines. Also chemistry parameters, including hepatic enzymes and glucose levels, were generally unchanged with the exception of elevated serum creatinine levels in multiple subjects. It was also observed that in one participant after 7 doses of ISIS 388626 transiently increased liver biochemistry parameters occurred (maximal change from baseline AST 3.6-fold ULN, ALT 4-fold ULN, confirmed by repeated measurement). This laboratory finding was suspect for a viral infection as it coincided with mild joint pain and tonsillitis. Study drug administration was discontinued and hepatic chemistry normalized in 5 weeks after treatment cessation. Average excretion of urinary protein was larger in the ISIS 388626 -treated group, but variability was substantial in both treatment groups (figure 1C).

RENAL PERFUSION AND GLOMERULAR FILTRATION

To explore the nature of the observed renal findings in more detail, an additional cohort was treated with the same dose regimen e.g. weekly administration of 50 mg ISIS 388626 or placebo. Renal clearance tests (with PAH and sinistrin) were performed to assess kidney function. Comparable ISIS 388626-induced effects were observed as in the first study part, with transient increases in serum creatinine and urinary B2M and mildly elevated urinary protein levels (figure 2A,B,C). AGST was slightly elevated in the ISIS 388626-treated group, but variability was substantial (data not shown). RPF and GFR were in the expected range, as was the filtration fraction (GFR/RPF100) of approximately 20%. Neither RPF nor GFR changed during the entire 13-weeks ISIS 388626 treatment period (figure 3).

PHARMACOKINETICS

After the first dose average maximal plasma concentrations of 1240±274.4 ng/mL were reached at 1.25±0.32 hours, and the AUC 0-24hr was 7627±1202 ng·hr/mL. Following the 15th dose comparable values were found (Tmax 1.4±0.56 hours, Cmax 1275±470.6 ng/mL, AUC0-24hr 8626±1037 ng·hr/mL), suggesting little or no accumulation of the study drug. Mean urinary excretion after the first dose was low (1.9±0.72%) during the first 24 hours after dosing and also during the subsequent 24 hours (1.6±0.60%).

PHARMACODYNAMICS

To explore the pharmacological activity of ISIS 388626, oral glucose tolerance tests were performed before the first administration of ISIS 388626 or placebo and at week 9 and 13. The observed time-concentration curves for serum glucose, insulin and c-peptide after OGTT were not different

B2M (figure 1B) with a maximal average change from baseline of 1250± 1361 µg/24hr (15-fold increase) at week 12. Although the inter-individual variability in urinary B2M was substantial, in 9 out of 12 ISIS 388626-treated subjects an increase was observed, returning to baseline levels within 5 weeks after treatment cessation. Average excretion of urinary protein was larger in the ISIS 388626 -treated group, but variability was substantial in both treatment groups (figure 1C).
between the treatment groups (data not shown). During the first four hours after glucose intake of the OGTT urinal glucose excretion was increased in the ISIS 388626 treated groups (figure 4A). At week 13 the observed difference in change from baseline values was 1.41 g/4hr compared to 0.04 g/4hr in the placebo group. The average 24 hr urinary glucose excretion and the fractional glucose excretion over time during the treatment period did not differ between the treatment groups (Figure 4B).

Discussion

This clinical study was performed to investigate the effects of multiple ISIS 388626 doses, administered weekly for a period of 13 weeks, without using a loading dose regimen. It was anticipated to explore dose levels of 50, 100 and 200 mg. Changes in renal parameters at the 50 mg dose precluded dose escalation to the 100 mg dose. Instead, a new cohort of volunteers was treated with the same dose to explore if the observed transient increases in renal markers coincided with functional renal changes.

In the first 50 mg cohort commonly observed adverse events such as headache, mild upper respiratory complaints and mild gastrointestinal complaints occurred in the placebo group at a similar incidence, and were not considered to be ISIS 388626-related. In several ISIS 388626-treated subjects injection site reactions were observed. The observed ISRs were of mild severity and regressed spontaneously. The frequency and severity of the observed skin reactions appears to be lower than described for other molecules targeting oligonucleotides at similar doses [16,17]. Furthermore, in one ISIS 388626-treated subject transiently increased liver biochemistry parameters were observed, resulting in discontinuation of study drug. Although no explanation was found, it is unclear if the event was related to ISIS 388626 treatment.

Repeated administration of 50 mg ISIS 388626 resulted in gradually increasing serum creatinine concentrations that were maximal (+20%) after the final dose, concomitant with an increase in urinary B2M. B2M is generally considered to be a marker of glomerular injury, although certain types of tubular dysfunction also result in increases [18-20]. The urinary excretion of NAG and AGST did not change upon ISIS 388626 treatment. Generally, phosphorothioate antisense compounds are known to induce renal changes including degeneration and regeneration effects in proximal tubules, but these are generally observed at least 10- to 100-fold higher dose levels (exceeding 50 mg/kg) [21-23]. Moreover, the observed creatinine increases were unexpected, since dedicated animal experiments had previously demonstrated that ISIS 388626-induced creatinine changes were dependent on the application of a loading dose regimen, which was avoided in this clinical study.

To explore whether the observed transient increases in renal markers coincided with functional changes, a new cohort of volunteers exposed to the same ISIS 388626 dose level and regimen, and Pah and sinistrine clearance was assessed to estimate RPF and GFR. The effects on serum creatinine and urinary markers were reproduced in this second cohort, but we found no indications that the changes can be explained by ISIS 388626-induced changes in GFR and RPF. This may suggest that the observed increase in serum creatinine and other renal markers are more likely related to changes in tubular function.

No effect of ISIS 388626 treatment on glucose handling was observed which was not surprising given the relatively limited exposure, and the fact the study was not designed to demonstrate pharmacodynamic effects. In general, pharmacologically effective dose levels for second generation oligonucleotides exceed 100 mg/week [16;24;25]. Small molecules targeting SGlt2 induced glucose excretion in the range of 10 to 80 grams per 24 hrs, even in healthy subjects [26]. The glucose excretion observed in our study ranged from 0.03 to 9.84 grams, which indicates that the maximal ISIS 388626 dose level tested may be far below dose levels anticipated to have intended pharmacological activity.

In summary, weekly ISIS 388626 treatment at a dose level of 50 mg for 13 weeks increased serum creatinine and renal damage markers in a relatively mild, fully reversible manner and was not associated with impairment of glomerular filtration or renal blood flow. This dose level and regimen did not significantly alter renal glucose handling. Exploration of higher ISIS 388626 dose levels in healthy volunteers is possible as long as a careful approach is applied with close monitoring of renal function.
REFERENCES

Figure 1  First study part with 50 mg. A. Average serum creatinine (mg/dl), change from baseline values with ± error bars. B. Average urinary b2m excretion (ug), change from baseline values with ± error bars. C. Average urinary protein excretion (g), absolute values with ± error bars.

Figure 2  Repeat study with 50 mg. A. Average serum creatinine (mg/dl), change from baseline values with ± error bars. B. Average urinary b2m excretion (ug), change from baseline values with ± error bars. C. Average urinary protein excretion (g), absolute values with ± error bars.

Figure 3  A. GFR calculated by sinistrin clearance. B. RPF calculated by pah clearance.

Novel antisense SGLT2 inhibitor causes serum creatinine increases without affecting renal blood flow or glomerular filtration – Chapter 3
Anti sense and sensibility – renal and skin effects of (antisense) oligonucleotides

Journal of Experimental Therapeutics, 2016 116.233809

Leonie van Meer, Matthijs Moerland, Bas Goulouze, Erica Klaassen, Adam Cohen, Jacobus Burggraaf

Table 1 Summary of subject baseline characteristics.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Age (yrs, Std)</th>
<th>BMI (Kg/m2, Std)</th>
<th>% Male</th>
<th>Early termination of subjects</th>
<th>Serum Creatinine (mg/dl, Std)</th>
<th>Whaic (%, Std)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg</td>
<td>12</td>
<td>33.9 +/- 14.23</td>
<td>23.3 +/- 3.13</td>
<td>100</td>
<td>2</td>
<td>0.88 +/- 0.068</td>
<td>5.2 +/- 0.21</td>
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<tr>
<td>Placebo</td>
<td>4</td>
<td>40.7 +/- 16.78</td>
<td>22.7 +/- 4.12</td>
<td>75</td>
<td>1</td>
<td>0.91 +/- 0.169</td>
<td>5.4 +/- 0.29</td>
</tr>
<tr>
<td>50 mg with rct</td>
<td>12</td>
<td>35.2 +/- 14.68</td>
<td>23.1 +/- 2.62</td>
<td>92</td>
<td>None</td>
<td>0.91 +/- 0.125</td>
<td>5.0 +/- 0.27</td>
</tr>
<tr>
<td>Placebo with rct</td>
<td>4</td>
<td>31.3 +/- 8.06</td>
<td>24.1 +/- 2.32</td>
<td>100</td>
<td>None</td>
<td>0.87 +/- 0.104</td>
<td>5.0 +/- 0.29</td>
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</table>

* In one subject dosing was stopped due to increases in serum creatinine after five doses and another subject was stopped due to increased liver biochemistry parameters after seven doses (see safety results) and one subject stopped after 12 doses due to personal reasons.

Table 2 Frequency overview of adverse events reported in more than one subject (%).

<table>
<thead>
<tr>
<th>Event</th>
<th>50 mg (n=12)</th>
<th>Placebo (n=4)</th>
<th>50 mg with rct (n=12)</th>
<th>Placebo with rct (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>33% (n=4)</td>
<td>50% (n=2)</td>
<td>50% (n=6)</td>
<td>25% (n=3)</td>
</tr>
<tr>
<td>Mild upper respiratory complaints</td>
<td>28% (n=2)</td>
<td>75% (n=3)</td>
<td>75% (n=9)</td>
<td>75% (n=3)</td>
</tr>
<tr>
<td>Mild gastrointestinal complaints</td>
<td>28% (n=2)</td>
<td>75% (n=3)</td>
<td>33% (n=4)</td>
<td>25% (n=1)</td>
</tr>
<tr>
<td>URE</td>
<td>17% (n=2)</td>
<td>0% (n=0)</td>
<td>0% (n=0)</td>
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</tr>
</tbody>
</table>

IV

RENAL EFFECTS OF SGLT2 INHIBITION WITH A NOVEL ANTISENSE OLIGONUCLEOTIDE

Anti sense and sensibility – renal and skin effects of (antisense) oligonucleotides

Figure 4 A. urinary glucose excretion during the first 4 hour interval of the OGGT (4hr). The grey bar indicates the treatment phase. B. Urinary 24 hr glucose excretion. The grey bar indicates the treatment phase. The black bar indicates the 5 weeks of follow-up.

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