### Supplemental Material

### Supplemental tables

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Supplemental Table S1.** Various clinical outcomes at baseline and after 10 weeks of treatment. | | | | | | | | | | | |
| **Parameter [unit]** | **Treatment with lixisenatide** | | | | **Treatment with  liraglutide** | | | | | **Difference between the groups** | |
| Baseline | After 10 weeks of treatment | Difference vs. baseline | p-value | | Baseline | After 10 weeks of treatment | Difference vs. baseline | p-value | Difference between treatments\* | p-value |
| Weight [kg] | 91.9 | 90.0 | -1.9 | **<0.0001** | | 95.5 | 91.9 | -3.6 | **<0.0001** | 1.7 | **0.0078** |
| (± 16.4) | (± 15.8) | (-2.7, -1.2) | (± 14.4) | (± 14.8) | (-4.6, -2.6) | (0.5, 2.9) |
| BMI [kg/m²] | 32.0 | 31.3 | -0.7 | **<0.0001** | | 31.4 | 30.2 | -1.2 | **<0.0001** | 0.5 | **0.020** |
| (± 4.9) | (± 4.6) | (-1.0, -0.4) | (± 3.7) | (± 3.8) | (-1.5, -0.9) | (0.1, 0.9) |
| Waist circumference [cm] | 109.7 | 108.1 | -1.5 | **0.0081** | | 109.9 | 108.1 | -1.8 | **0.021** | 0.3 | 0.74 |
| (± 10.6) | (± 9.8) | (-2.6, -0.4) | (± 9.5) | (± 11.0) | (-3.4, -0.3) | (-1.6, 2.2) |
| Pulse [beats/min] | 68.7 | 66.4 | -2.3 | 0.12 | | 63.5 | 64.0 | 0.5 | 0.73 | -2.8 | 0.18 |
| (± 8.6) | (± 8.1) | (-5.2, 0.7) | (± 8.1) | (± 9.7) | (-2.4, 3.4) | (-6.8, 1.3) |
| Systolic Blood Pressure [mmHg] | 141.4 | 137.2 | -4.2 | **0.049** | | 144.3 | 139.0 | -5.3 | 0.065 | 1.1 | 0.76 |
| (± 12.8) | (± 14.0) | (-8.4, -0.0) | (± 11.6) | (± 13.7) | (-10.9, 0.4) | (-5.8, 7.9) |
| Diastolic Blood Pressure [mmHg] | 85.0 | 82.8 | -2.2 | 0.13 | | 83.9 | 85.4 | 1.5 | 0.34 | -3.7 | 0.082 |
| (± 7.5) | (± 6.1) | (-5.1, 0.7) | (± 7.0) | (± 7.9) | (-1.7, 4.7) | (-7.9, 0.5) |

Parameters were measured once in the morning at presentation on the trial site. Data are expressed as means (± SD). Delta and difference of delta is presented as mean delta (95-% confidence interval). P-values were calculated from student’s t-test for paired samples or student’s t-test with Welch’s correction. BMI = Body Mass Index, SD = Standard deviation. \*Difference between the treatments is displayed for changes from baseline.

|  |  |  |  |
| --- | --- | --- | --- |
| **Supplemental table S2.** Concomitant antidiabetic medication used by patients during the study period. | | | |
| **Class** | **Treatment with lixisenatide** | **Treatment with  liraglutide** | **p-value** |
| Biguanides (Metformin) [yes/no (% yes)] | 17 / 7 (70.8 %) | 19 / 7 (73.1 %) | >0.99 |
| *Dose / day* [mg] | 1727 (± 607) | 1726 (± 619) | 0.99 |
| Glimepiride [yes/no (% yes)] | 1 / 23 (4.2 %) | 0 / 26 (0 %) | n/a |
| *Dose / day* [mg] | 4 | 0 | n/a |
| Rapid- acting insulins [yes/no (% yes)] | 9 / 15 (37.5 %) | 12 / 14 (46.2 %) | 0.58 |
| *Dose / day* [I.U.] | 34.4 (± 22.9) | 43.6 (± 19.1) | 0.35 |
| Intermediate- acting insulins [yes/no (% yes)] | 3 / 21 (12.5 %) | 3 / 23 (11.5 %) | >0.99 |
| *Dose / day* [I.U.] | 28.0 (± 32.1) | 46.7 (± 15.3) | 0.43 |
| Long- acting insulins [yes/no (% yes)] | 7 / 17 (29.2 %) | 12 / 14 (46.2 %) | 0.25 |
| *Dose / day* [I.U.] | 21.9 (± 8.9) | 34.3 (± 22.9) | 0.11 |
| Combination of long- and rapid-acting insulins [yes/no (% yes)] | 1 / 23 (4.2 %) | 1 / 25 (3.9 %) | >0.99 |
| *Dose / day* [I.U.] | 90 | 37 | n/a |
| DPP-IV inhibitors [yes/no (% yes)] | 3 / 21 (12.5 %) \* | 2 / 24 (7.7 %) † | 0.66 |
| *Dose / day* [mg] | 100 (± 0.0) | 100 (± 0.0) | n/a |

Data are expressed as number of patients receiving drug / number of patients not receiving drug (% of patients receiving drug per group) or mean dose of drug (± SD). P-values were calculated by student’s t-test with Welch’s correction for unpaired samples or Fisher’s exact test.; DPP-IV = Dipeptidyl peptidase-4, SD = Standard deviation, \*Sitagliptin in all patients, †Sitagliptin in one patient and Vildagliptin in the other.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Supplemental Table S3.** Numbers and causes regarding failed procedures (that could not be analyzed and reported). | | | | |
| **Procedure** | **Treatment with  lixisenatide** | | **Treatment with  liraglutide** | |
| Failures [n] | Cause for failure | Failures [n] | Cause for failure |
| 24-hour ambulatory esophageal pH-measurement | 1 (4.2 %) | Injection of study drug by patient too early | 3 (11.5 %) | Injection of study drug by patient too early |
| 4 (16.7 %) | Technical issues | 2 (7.7 %) | Technical issues |
| High-resolution esophageal manometry | 1 (4.2 %) | Injection of study drug by patient too early | 2 (7.7 %) | Injection of study drug by patient too early |
| 2 (8.3 %) | Disturbed interpretability (e.g. due to coughing) | 1 (3.8 %) | Technical issues |
| 2 (8.3 %) | Technical issues |  |  |
| 13C-Sodium octanoate breath test | 2 (8.3 %) | Calculation with Wagner Nelson equation not possible |  |  |
| 1 (4.2 %) | Technical issues |  |  |

Data are expressed as number of patients (% of group).

|  |  |  |  |
| --- | --- | --- | --- |
| Supplemental Table S4. Hypoglycemic and gastrointestinal adverse events. | | | |
|  | **Treatment with lixisenatide** | **Treatment with  liraglutide** | **p-value** |
| **Hypoglycemic event** |  | | |
| Number of participants [n (%)] | 7 (29.2 %) | 5 (19.2 %) | 0.51 |
| Total number of events [n] | 14 | 21 | 0.30 |
| Severe hypoglycemia [n] | 0 | 0 | n/a |
| Mean lowest blood glucose documented [mmol/l] | 3.2 (± 0.4) | 3.0 (± 0.2) | 0.42 |
| Therapy with insulin [n (%)] | 6 (85.7 %) | 5 (100 %) | >0.99 |
| Therapy with Glimepiride [n (%)] | 1 (14.3 %) | 0 | >0.99 |
| **Gastrointestinal adverse event** |  | | |
| Heartburn [n (%)] | 2 (8.3 %) | 3 (11.5 %) | >0.99 |
| Nausea [n (%)] | 9 (37.5 %) | 4 (15.4 %) | 0.11 |
| Vomiting [n (%)] | 1 (4.2 %) | 4 (15.4 %) | 0.35 |
| Diarrhea or loose stool [n (%)] | 4 (16.7 %) | 6 (23.1 %) | 0.73 |

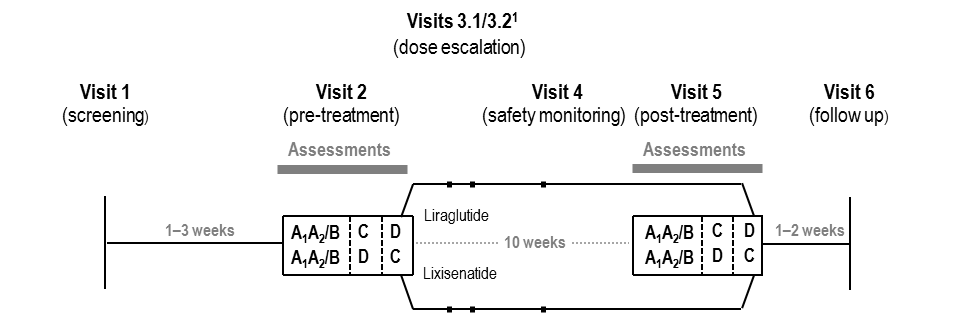
Data are expressed as means (± SD) or number of patients (% of group). P-values were calculated from student’s t-test for unpaired samples with Welch’s correction or Fisher’s exact test. SD = Standard deviation.

### Randomization process

Randomization was performed regarding both treatment allocation and order of the main gastrointestinal assessments (days dedicated to high-resolution esophageal manometry and 24-h pH registration, respectively) C and D. The randomization list was generated using the program RANCODE Professional 3.6 (idv Datenanalyse & Versuchsplanung, Gauting, Germany) which is validated for the use in clinical studies. The investigators responsible for the endpoint assessments remained blinded regarding treatment allocation. Each subject was randomly allocated to administrations of either liraglutide (up to 1.8 mg q.d.) or lixisenatide (up to 20 μg q.d.) in an open manner (e.g., using the standard injection devices). All trial participants were trained on the use of the pen device by unblinded study staff during the first assessment visit (Visit 2) on the last assessment day at the trial and provided with an instruction leaflet. Unblinded staff was not involved in the assessment or analysis of data.

Further information on the randomization process is depicted in supplemental figure SF1.

**Supplemental figure SF1: Schematic overview of the trial design**



Schematic overview of the trial design. Visit 1 only took place in case informed consent has been obtained (Visit 0; not shown). The pre-treatment and post-treatment visits for assessment of end point parameters (Visits 2 and 5) were performed ambulatory. First dosing took place prior to the final discharge from the trial site on the last assessment day of Visit 2. Liraglutide and lixisenatide were provided to trial subjects in pen-type injectors for self-administration.

### Blinding process

The trial was performed in an investigator-blinded manner. Treatment with the study drugs was open label but investigators and staff members who assessed endpoints remained blinded regarding treatment allocation. Three sets of sealed codes containing treatment information were prepared for each subject. The sets were kept by the trial sites (throughout the entire trial period) and by the sponsor. The code for a particular subject could be broken in a medical emergency, if knowing the identity of the treatment allocation would influence the treatment of the subject. No codes were broken in this trial. All hard copy codes were kept throughout the trial period until accountability of the codes had been performed after end of trial.