

Supplemental Material

**Supplemental Table 1. Nasal and Non-Nasal Score Questionnaire**

Please select the number that corresponds best to the effects/symptoms you are experiencing at this time, or have experienced since last questioning.

0=Not experiencing this (no symptoms at all).

1=Only experiencing a mild case of this and it is easily tolerated.

2=Experiencing a moderate level of this symptom. It is bothersome but tolerable.

3=Experiencing a severe level of this symptom. It is hard to tolerate and interferes with your activities.

| Symptoms                                  | Scale     |           |               |             |
|---|-----------|-----------|---------------|-------------|
|   | 0         | 1         | 2             | 3           |
|   | None      | Mild      | Moderate      | Severe      |
| 1. Runny nose                             | 0<br>None | 1<br>Mild | 2<br>Moderate | 3<br>Severe |
| 2. Nasal congestion<br>(nostrils plugged) | 0<br>None | 1<br>Mild | 2<br>Moderate | 3<br>Severe |
| 3. Nasal itching                          | 0<br>None | 1<br>Mild | 2<br>Moderate | 3<br>Severe |
| 4. Sneezing                               | 0<br>None | 1<br>Mild | 2<br>Moderate | 3<br>Severe |
| 5. Watery eyes                            | 0<br>None | 1<br>Mild | 2<br>Moderate | 3<br>Severe |
| 6. Itchy eyes                             | 0<br>None | 1<br>Mild | 2<br>Moderate | 3<br>Severe |
| 7. Redness of eyes                        | 0<br>None | 1<br>Mild | 2<br>Moderate | 3<br>Severe |
| 8. Itching of ears                        | 0<br>None | 1<br>Mild | 2<br>Moderate | 3<br>Severe |
| 9. Itching of throat                      | 0<br>None | 1<br>Mild | 2<br>Moderate | 3<br>Severe |

**Supplemental Table 2. Pharmacokinetic parameters of the plasma glucagon  
change from baseline**

| Parameter                                  | Geometric Mean (Geometric CV%) |                          |
|--|--------------------------------|--------------------------|
|  | 3 mg Nasal Glucagon<br>(N=63)  | 1 mg GlucaGen®<br>(N=66) |
| CFB AUC(0-t <sub>last</sub> ) (pg•hour/mL) | 2740 (68%)                     | 3320 (40%) <sup>†</sup>  |
| CFB C <sub>max</sub> (pg/mL)               | 6130 (74%)                     | 3750 (44%)               |
| CFB t <sub>max</sub> <sup>‡</sup> (hour)   | 0.25 (0.17 – 0.50)             | 0.25 (0.08 – 0.50)       |
| CFB t <sub>last</sub> <sup>‡</sup> (hour)  | 4.00 (1.50 – 4.00)             | 4.00 (2.00 – 4.00)       |

Abbreviations: AUC(0-t<sub>last</sub>), area under the concentration versus time curve from time zero to time t<sub>last</sub>, where t<sub>last</sub> is the last time point with a measurable concentration; CFB, change from baseline; C<sub>max</sub>, maximum observed drug concentration; CV, coefficient of variation; N, number of patients studied; t<sub>last</sub>, time of last observed drug concentration; t<sub>max</sub>, time of maximum observed drug concentration.

<sup>†</sup> N = 65

<sup>‡</sup> Data are median (minimum – maximum)

**Supplemental Table 3. Statistical analysis of plasma glucose pharmacodynamic parameters**

| Parameter                                   | Treatment           | N  | Geometric Least Squares Mean (p-value) | Ratio <sup>†</sup> of Geometric LS Means (90% CI) | p-value |
|---|---------------------|----|--|---|---------|
| AUEC <sub>(0-1.5)</sub><br>(mg•hour/dL)     | 1 mg GlucaGen®      | 69 | 242.91                                 | 0.91 (0.88, 0.94)                                 | <0.0001 |
|   | 3 mg Nasal Glucagon | 68 | 221.57                                 |   |         |
| CFB AUEC <sub>(0-1.5)</sub><br>(mg•hour/dL) | 1 mg GlucaGen®      | 69 | 154.90 (<0.0001)                       | 0.86 (0.81, 0.91)                                 | 0.0001  |
|   | 3 mg Nasal Glucagon | 68 | 132.83 (<0.0001)                       |   |         |
| BG <sub>max</sub><br>(mg/dL)                | 1 mg GlucaGen®      | 69 | 219.47                                 | 0.87 (0.83, 0.91)                                 | <0.0001 |
|   | 3 mg Nasal Glucagon | 68 | 190.80                                 |   |         |
| CFB BG <sub>max</sub><br>(mg/dL)            | 1 mg GlucaGen®      | 69 | 160.30 (<0.0001)                       | 0.82 (0.77, 0.87)                                 | <0.0001 |
|   | 3 mg Nasal Glucagon | 68 | 131.20 (<0.0001)                       |   |         |

Abbreviations: AUEC<sub>(0-1.5)</sub>, area under the effect concentration-time curve from time zero (predose) up to 1.5 hours; BG<sub>max</sub>, maximal blood glucose; CFB, change from baseline; CI, confidence interval; CV, coefficient of variation; LS, least squares; N, number of participants studied; PD, pharmacodynamics; t<sub>max</sub>, time of maximum observed drug concentration.

<sup>†</sup> Ratio is calculated as 3 mg nasal glucagon : 1 mg GlucaGen®

Model: Log(PD) = Patient + Sequence+ Treatment + Period +Random Error, where Patient is fitted as a random effect.

Geometric least squares mean p-values are calculated based on the null hypothesis: LS mean = 0

t<sub>max</sub> is analysed using the procedure PROC UNIVARIATE and p-values reported from the Wilcoxon signed rank test.

**Supplemental Table 4. Summary of treatment-emergent adverse events (all causalities and related to study treatment)**

| Treatment           | Number of Patients | TEAEs of All Causalities          |  |                |   | TEAEs Related to Study Treatment  |  |                |   |   |   |
|---------------------|--------------------|-----------------------------------|--|----------------|---|-----------------------------------|--|----------------|---|---|---|
|                     |                    | Number of Patients (%) with TEAEs | Number of TEAEs and Severity <sup>†‡</sup> | Number of SAEs | Number of Patients Discontinued due to a TEAE | Number of Patients (%) with TEAEs | Number of TEAEs and Severity <sup>†‡</sup> | Number of SAEs | Number of Patients Discontinued due to a TEAE |   |   |
| 3 mg Nasal Glucagon | 70                 | 31<br>(44.3%)                     | Mild                                       | 31             | 0   | 0                                 | 31<br>(44.3%)                              | Mild           | 30  | 0 | 0 |
|                     |                    |                                   | Moderate                                   | 19             | 0   | 1                                 |  | Moderate       | 18  | 0 | 1 |
|                     |                    |                                   | Severe                                     | 0              | 0   | 0                                 |  | Severe         | 0   | 0 | 0 |
|                     |                    |                                   | Total                                      | 50             | 0   | 1                                 |  | Total          | 48  | 0 | 1 |
| 1 mg IM GlucaGen®   | 69                 | 32<br>(46.4%)                     | Mild                                       | 36             | 0   | 0                                 | 32<br>(46.4%)                              | Mild           | 36  | 0 | 0 |
|                     |                    |                                   | Moderate                                   | 15             | 0   | 0                                 |  | Moderate       | 15  | 0 | 0 |
|                     |                    |                                   | Severe                                     | 0              | 0   | 0                                 |  | Severe         | 0   | 0 | 0 |
|                     |                    |                                   | Total                                      | 51             | 0   | 0                                 |  | Total          | 51  | 0 | 0 |
| Total               | 70                 | 46<br>(65.7%)                     | Mild                                       | 67             | 0   | 0                                 | 46<br>(65.7%)                              | Mild           | 66  | 0 | 0 |
|                     |                    |                                   | Moderate                                   | 34             | 0   | 1                                 |  | Moderate       | 33  | 0 | 1 |
|                     |                    |                                   | Severe                                     | 0              | 0   | 0                                 |  | Severe         | 0   | 0 | 0 |
|                     |                    |                                   | Total                                      | 101            | 0   | 1                                 |  | Total          | 99  | 0 | 1 |

Abbreviations: SAE, serious adverse event; TEAE, treatment-emergent adverse event.

<sup>†</sup> Possibly or probably related as determined by investigator

<sup>‡</sup> Only the maximum severity of each adverse event is report.