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 None                            | 1 Mild  |
| 1 Mild                            | 2 Moderate |
| 2 Moderate                        | 3 Severe |
| 1. Runny nose                     |         |
| 0 None                            | 1 Mild  |
| 1 Mild                            | 2 Moderate |
| 2 Moderate                        | 3 Severe |
| 2. Nasal congestion (nostrils plugged) |       |
| 0 None                            | 1 Mild  |
| 1 Mild                            | 2 Moderate |
| 2 Moderate                        | 3 Severe |
| 3. Nasal itching                  |         |
| 0 None                            | 1 Mild  |
| 1 Mild                            | 2 Moderate |
| 2 Moderate                        | 3 Severe |
| 4. Sneezing                       |         |
| 0 None                            | 1 Mild  |
| 1 Mild                            | 2 Moderate |
| 2 Moderate                        | 3 Severe |
| 5. Watery eyes                    |         |
| 0 None                            | 1 Mild  |
| 1 Mild                            | 2 Moderate |
| 2 Moderate                        | 3 Severe |
| 6. Itchy eyes                     |         |
| 0 None                            | 1 Mild  |
| 1 Mild                            | 2 Moderate |
| 2 Moderate                        | 3 Severe |
| 7. Redness of eyes                |         |
| 0 None                            | 1 Mild  |
| 1 Mild                            | 2 Moderate |
| 2 Moderate                        | 3 Severe |
| 8. Itching of ears                |         |
| 0 None                            | 1 Mild  |
| 1 Mild                            | 2 Moderate |
| 2 Moderate                        | 3 Severe |
| 9. Itching of throat              |         |
| 0 None                            | 1 Mild  |
| 1 Mild                            | 2 Moderate |
| 2 Moderate                        | 3 Severe |
Supplemental Table 2. Pharmacokinetic parameters of the plasma glucagon change from baseline

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

Abbreviations: AUC(0-t_last), area under the concentration versus time curve from time zero to time t_{last}, where t_{last} is the last time point with a measurable concentration; CFB, change from baseline; C_{max}, maximum observed drug concentration; CV, coefficient of variation; N, number of patients studied; t_{last}, time of last observed drug concentration; t_{max}, time of maximum observed drug concentration.

† N = 65
‡ 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† of Geometric LS Means (90% CI) | p-value |
|--------------------|---------------------|----|---------------------------------------|---------------------------------------|---------|
| AUEC(0-1.5)        | 1 mg GlucaGen®      | 69 | 242.91                                | 0.91 (0.88, 0.94)                      | <0.0001 |
|                    | 3 mg Nasal Glucagon | 68 | 221.57                                |                                       |         |
| CFB AUEC(0-1.5)    | 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)                      |                                       |         |
| BGmax              | 1 mg GlucaGen®      | 69 | 219.47                                | 0.87 (0.83, 0.91)                      | <0.0001 |
|                    | 3 mg Nasal Glucagon | 68 | 190.80                                |                                       |         |
| CFB BGmax          | 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(0-1.5), area under the effect concentration-time curve from time zero (predose) up to 1.5 hours; BGmax, maximal blood glucose; CFB, change from baseline; CI, confidence interval; CV, coefficient of variation; LS, least squares; N, number of participants studied; PD, pharmacodynamics; tmax, time of maximum observed drug concentration.

† 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

Tmax 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 | Number of Patients (%) with TEAEs | Number of TEAEs and Severity$^\ddagger$ | Number of SAEs | Number of Patients Discontinued due to a TEAE | TEAEs of All Causalities | Number of Patients (%) with TEAEs | Number of TEAEs and Severity$^\ddagger$ | Number of SAEs | Number of Patients Discontinued due to a TEAE | TEAEs Related to Study Treatment |
|----------------------------|--------------------|-----------------------------------|------------------------------------------|----------------|---------------------------------------------|--------------------------|-----------------------------------|------------------------------------------|----------------|---------------------------------------------|-------------------------------|
| 3 mg Nasal Glucagon        | 70                 | 31 (44.3%)                        | Mild                                      | 31             | 0                                           | 0                         | 31 (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                                      | 50             | 1                                           |                                  |
| 1 mg IM GlucaGen®          | 69                 | 32 (46.4%)                        | Mild                                      | 36             | 0                                           | 0                         | 32 (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 (65.7%)                        | Mild                                      | 67             | 0                                           | 0                         | 46 (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.

$^\ddagger$ Possibly or probably related as determined by investigator

$^\ddagger$ Only the maximum severity of each adverse event is report.