U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW

CLINICAL STUDIES

NDA / Sequence Number:	210134
Drug Name:	BAQSIMI (Glucagon Nasal Powder)
Proposed Indications:	Treatment of severe hypoglycemia
Applicant:	Eli Lilly and Company
Date(s):	Submission Date: 6/28/2018 PDUFA Date: 4/28/2019
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
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Keywords:	NDA review, Clinical Studies, Hypoglycemia

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1 Executive Summary

Glucagon is used for the treatment of severe hypoglycemia outside of a hospital setting and is currently only available as a powder which must be administered by injection. On June 28th 2018, Eli Lilly submitted a new application under NDA 210134 for BAQSIMI (Glucagon Nasal Powder) for the treatment of severe hypoglycemia.

1.1 Brief Overview of Clinical Studies

This submission included the results from the following studies:

- Two adult, randomized, open-label, 2-treatment, 2-period, cross-over studies IGBC and IGBI
- One pediatric, randomized, quasi-blinded, quasi-cross-over study IGBB

The two adult studies were randomized, open-label, 2-treatment, 2-period, cross-over studies, where the primary objective was to assess the efficacy and safety of intranasal (IN) glucagon (BAQSIMI) compared to intramuscular glucagon (IMG) in reversing insulin-induced hypoglycemia. The studies were non-inferiority designs with a pre-specified margin of -10%.

The primary endpoint for the two adult studies was the percentage of patients who achieve treatment success, which was defined as an increase in glucose to ≥ 70 mg/dL or an increase of ≥ 20 mg/dL from nadir within 30 minutes after administration of glucagon. A 2-sided 95% confidence interval (CI) was obtained from the 1-sample paired differences across the 2 treatment visits. Noninferiority of nasal glucagon was to be declared if the lower limit of the 2-sided 95% CI of the difference in proportion of success (BAQSIMI – IMG) was greater than the noninferiority margin of -10%.

The pediatric study results were descriptive and exploratory. No primary endpoint was pre-specified, however, mean time to reach glucose increase ≥ 20 mg/dL was proposed for labelling.

1.2 Collective Evidence

The difference in treatment success for patients with type 1 diabetes (T1DM) only in study IGBC was -0.013 with a 95% C.I of (-0.049, 0.023). Results for patients with T1DM and T2DM are -0.013 with a 95% C.I of (-0.046, 0.022). The difference in treatment success in study IGBI, where only patients with T1DM were studied was 0.00 with a 95% C.I of (-0.029, 0.029). See Section 3.2.4 for a table that includes individual success proportions. Based on the results, each study met their primary objective and demonstrated that intranasal glucagon is non-inferior to intramuscular glucagon in increasing glucose to ≥70 mg/dL or increasing to ≥20 mg/dL from nadir within 30 minutes after administration of glucagon.

1.3 Statistical Issues

Regarding the adult studies, there were two sources of missing data that could potentially affect the evaluation of the treatment effect: 1) Patients who were excluded from the primary analysis and 2) Missing measurements during patient visits. The impact of these sources of missing data was explored and it was determined that they had no impact on the estimated treatment effect. See Section 3.2.5 for more details.

1.4 Conclusions and recommendation

The results of the adult studies demonstrate that BAQSIMI is non-inferior to IMG for the treatment of severe hypoglycemia, therefore, I recommend approval from a statistical perspective. See Section 5.1 for details.

2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Nasal glucagon is a needle-free drug and device combination product that delivers a single dose of a (b) (4) powder containing synthetic glucagon as the active pharmaceutical ingredient and β-cyclodextrin and dodecylphosphocholine (DPC) as excipients. The glucagon component is a synthetic single-chain, 29 amino acid polypeptide identical in amino acid sequence to human glucagon.

The proposed indication is for the treatment of severe hypoglycemia.

2.1.2 Specific Studies Reviewed

Two randomized adult studies (IGBC and IGBI) and one randomized pediatric study (IGBB) were reviewed. This statistical review summarizes the analysis of the primary endpoint and impact of missing data.

Study IGBC was a phase 3 study initiated and conducted by AMG Medical Incorporation and later by Locemia Solutions. A Special Protocol Assessment (SPA) was agreed upon in 2013 with FDA. The study was initiated in December 2013 and completed in January 2015. In May 2015, FDA confirmed that the study was conducted in accordance with the SPA. Eli Lilly acquired the product in October 2015 from Locemia Solutions. However, study IGBC used a drug product that was not produced using the commercial manufacturing process. Therefore, FDA recommended that Eli Lilly conduct a new clinical study (IGBI) highly similar to study IGBC in design to bridge the commercial nasal glucagon product to the product used in study IGBC. Study IGBI was initiated in November 2017 and completed in December 2017.

Study IGBB was a pediatric study conducted by AMG Medical Incorporation and Locemia Solutions in accordance with an agreed upon initial pediatric study plan (iPSP) in December 2013. The study was initiated in December 2013 and completed in January 2015.

2.2 Data Sources

The data and final study report were submitted electronically as an eCTD submission. The submission can be accessed at the following link: \\CDSESUB1\evsprod\NDA210134\0000.

The following documents were used to support this review.

Document
Clinical Study Report for Study IGBC
Clinical Pharmacology Study Report for Study IGBI
Clinical Study Report for Study IGBB
Protocol for Study IGBC
Protocol for Study IGBI
Protocol for Study IGBB
Statistical Analysis Plan for Study IGBC
Statistical Analysis Plan for Study IGBI
Statistical Analysis Plan for Study IGBB

All results presented in this review were based on data derived from the submitted datasets.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

There were no issues concerning the quality of the submitted data sets and files.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

- **Study AMG106 / IGBC:**

Study IGBC was a randomized, open-label, 2-treatment, 2-period, cross-over study. The primary objective was to assess the efficacy and safety of 3 mg intranasal glucagon (BAQSIMI) in comparison with commercially available 1 mg IMG in reversing insulin-induced hypoglycemia in patients with T1DM and T2DM. Furthermore, pharmacokinetic (PK) and pharmacodynamic (PD) parameters of BAQSIMI and IMG were evaluated.

As part of the inclusion criteria, patients needed to be within the age of 18 and 65 and have had a clinical diagnosis of either T1DM and have been receiving daily insulin since the time of diagnosis for at least 2 years, or T2DM and receiving multiple daily insulin doses for at least 2 years. Further,

patients were required to be in good general health with no conditions that could influence the outcome of the trial.

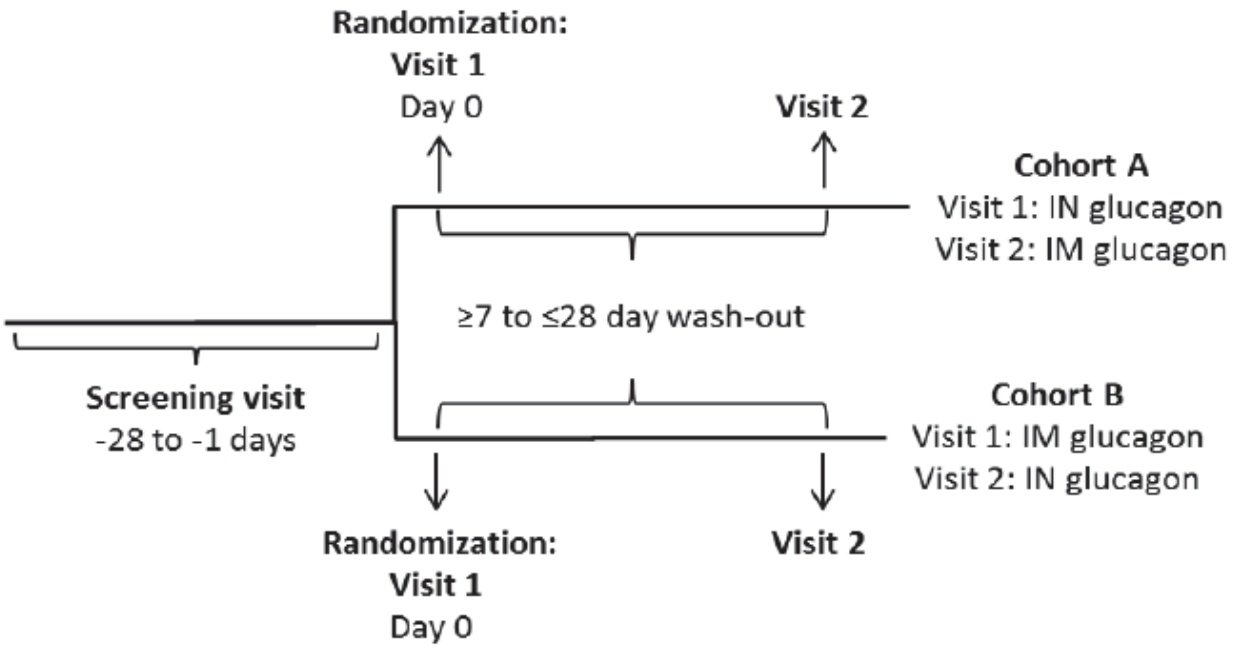
At each visit, plasma glucose levels must have been ≥ 90 mg/dL prior to the start of the procedure. Hypoglycemia was induced by an IV infusion of regular insulin diluted in normal saline at a rate of 2 mU/kg/min and adjusted up to a rate of 3 mU/kg/min to reach a target nadir plasma glucose level of < 50 mg/dL. Once plasma glucose levels reached < 90 mg/dL, the infusion rate may have been decreased at the investigator's discretion to 1.5 or 1.0 mU/kg/min. After plasma glucose levels were < 60 mg/dL, insulin infusion was stopped. Blood glucose levels were measured at 5, 10, 15, 20, 25, 30, 40, 50, 60, and 90 minutes following administration of glucagon.

A total of 83 patients (77 with T1DM and 6 with T2DM) were randomized in a 1:1 fashion to one of the following two sequences:

1. BAQSIMI at visit 1 and IMG at visit 2
2. IMG at visit 1 and BAQSIMI at visit 2

There was a 7 to 28-day wash-out period between visits. Figure 1 below displays the study design:

Figure 1: Trial design for study IGBC



[Source: Study AMG106 / IGBC CSR Page 19 (29 September 2015)]

- **Study IGBI:**

Study IGBI was a randomized, open-label, 2-treatment, 2-period, cross-over study. The primary objective was to compare 3 mg nasal glucagon (BAQSIMI) versus 1 mg IMG in the percentage of adult patients with T1DM who achieve treatment success during controlled insulin-induced hypoglycemia. As part of the inclusion criteria, patients needed to be in the age of 18 to 64 and who were diagnosed with T1DM for at least 2 years and have been receiving daily insulin since the time of diagnoses and had a HbA1c value of ≤ 10%.

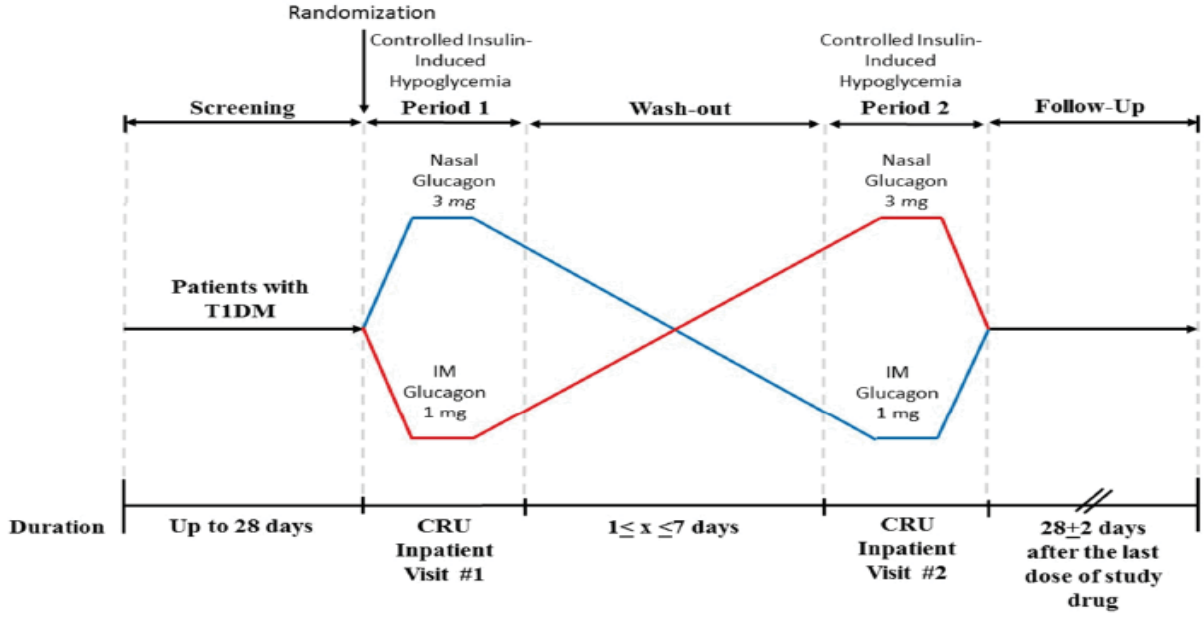
At each visit, plasma glucose levels must have been ≥ 90 mg/dL prior to the start of the procedure. To induce hypoglycemia, 15 units of Humalog was diluted in saline to 0.3 U/mL and infused at a variable rate to lower PG to < 60 mg/dL in a controlled manner. Once plasma glucose levels were < 60 mg/dL, insulin infusion was stopped and glucagon was administered approximately 5 minutes later. Plasma glucose levels were measured at 5, 10, 15, 20, 25, 30, 40, 50, 60, and 90 minutes following administration of glucagon.

A total of 70 patients were randomized in a 1:1 fashion to one of the following two sequences:

1. BAQSIMI at visit 1 and IMG at visit 2
2. IMG at visit 1 and BAQSIMI at visit 2

There was a 1 to 7-day wash-out period between visits. Figure 2 below displays the study design:

Figure 2: Trial design for study IGBI



Abbreviations: CRU = clinical research unit; IM = intra-muscular; T1DM = type 1 diabetes mellitus.

[Source: Study IGBI Pharmacology CSR Page 11 (26 March 2018)]

- **Study AMG103 / IGBB:**

Study IGBB was a randomized, quasi-blinded, quasi-crossover, multi-center, trial in pediatric patients. The primary objective was to assess the PK and PD of BAQSIMI in comparison with commercially available IMG in a pediatric population with T1DM.

As part of the inclusion criteria, patients needed to be at least 4 years of age and less than 17 with a history of T1DM and have been receiving daily insulin therapy from the time of diagnosis for at least 12 months. Further, patients were required to be in good general health with no conditions that could influence the outcome of the trial.

At each visit, insulin was infused until plasma glucose levels reached < 80 mg/dL. Basal rate was then returned to normal for participants using an insulin pump, and insulin infusion was stopped for participants using insulin injections. Five minutes later, glucagon was administered. If a patient's starting plasma glucose was < 80 mg/dL, no additional insulin was given and glucagon was administered.

A total of 48 T1DM patients were randomized according the following:

- 36 patients from 4 to < 12 years old were randomized in a 2:1 fashion to either:
    - A second randomization in a 1:1 fashion to one of the following two sequences:
        - 2 mg BAQSIMI at visit 1 and 3 mg BAQSIMI at visit 2
        - 3 mg BAQSIMI at visit 1 and 2 mg BAQSIMI at visit 2

OR

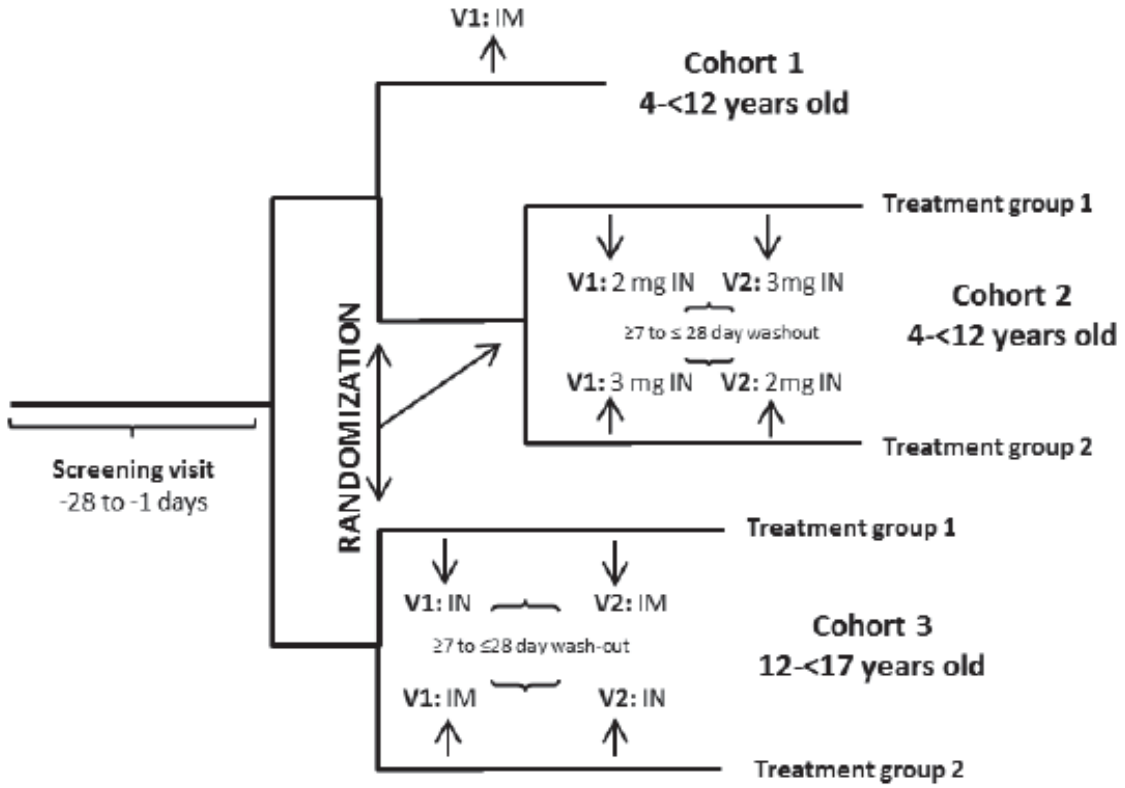
    - Only one visit in which they receive only 1 mg IMG

Reviewer's comment: The sponsor stratified by 4 to < 8 years old and 8 to < 12 years old, though the diagram (Figure 3) below does not reflect this.

- 12 patients from 12 to < 17 years old were randomized in a 1:1 fashion to one of the following two sequences:
    - 3 mg BAQSIMI at visit 1 and 1 mg IMG at visit 2
    - 1 mg IMG at visit 1 and 3 mg BAQSIMI at visit 2

Blood glucose levels were measured at 5, 10, 15, 20, 30, 40, 60, and 90 minutes following administration of glucagon. Figure 3 below displays the study design:

Figure 3: Trial design for study IGBB



[Source: AMG103 / IGBB CSR Page 22 (29 September 2015)]

Primary Efficacy Endpoint

The primary endpoint for the adult studies was the percentage of patients who achieve treatment success, which was defined as an increase in glucose to ≥ 70 mg/dL or an increase of ≥ 20 mg/dL from nadir within 30 minutes after administration of glucagon, without receiving additional actions to increase glucose levels. Nadir was defined as the minimum glucose measurement at the time of, or within 10 minutes following administration of glucagon.

The pediatric study did not pre-specify any primary efficacy endpoint.

Secondary Efficacy Endpoints

There were no secondary efficacy endpoints proposed for labelling.

3.2.2 Statistical Methodologies

- **Study IGBC/IGBI:**

Primary analysis set: All T1DM patients who received both doses of study drug with eligible glucose and glucagon concentrations.

Combined primary analysis set (Study IGBC): All T1DM and T2DM patients who received both doses of study drug with eligible glucose and glucagon concentrations.

Sponsor's Primary Analysis Model: The point estimate and 2-sided 95% confidence interval (CI) was obtained from the 1-sample paired differences using the student t-distribution, with n-1 degrees of freedom, where n is the number of matched pairs. Noninferiority of nasal glucagon was to be declared when the lower limit of the 2-sided 95% CI of the difference in proportion of success (BAQSIMI – IMG) was greater than the noninferiority margin of -10%.

Statistical Reviewer's Primary Analysis Model: To ensure proper coverage (i.e., the correct probability that the CI contains the underlying true difference in proportion of success), Wald's confidence interval for 1-sample paired differences was improved by using the correction proposed by Agresti and Min, whereby 0.5 was added to each cell count. For example, consider study IGBC in the analysis for T1DM and T2DM, the observed data are:

		IMG		
		Success	**Failure**	
BAQSIMI	**Success**	79	0	**79**
	Failure	1	0	**1**
		80	**0**	**80**

To construct a 95% CI, using the correction proposed by Agresti and Min, we obtain the following table:

		IMG		
		Success	**Failure**	
BAQSIMI	**Success**	79 + 0.5	0 + 0.5	**80**
	Failure	1 + 0.5	0 + 0.5	**2**
		81	**1**	**82**

Reviewer's comment: It should be understood that this table does not alter the observed data and should not be used to derive a new point estimate but is solely used for the construction of the 95% CI.

- **Study IGBB**

Results from Study IGBB were summarized using descriptive statistics.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

- **Study IGBC:**

Table 1 below describes the analysis population(s). We see that a total of 83 patients received at least 1 dose of study drug, 77 of which had T1DM and 6 had T2DM. There were 3 patients who were excluded from the analysis population, 2 of whom had T1DM and 1 who had T2DM.

Table 1: Analysis populations - Study IGBC

	N=83	T1DM (N=77)		T2DM (N=6)	
	Overall n (%)	BAQSIMI n (%)	IMG n (%)	BAQSIMI n (%)	IMG n (%)
Safety Cohort: Randomized and Received at least 1 Dose of Study Drug	83 (100)	77 (100)	76 (98.7)	6 (100)	6 (100)
Primary Analysis population (T1DM only)	75 (90.4)	75 (97.4)	75 (97.4)		
Combined Primary Analysis population (T1DM and T2DM)	80 (96.4)	75 (97.4)	75 (97.4)	5 (83.3)	5 (83.3)

[Source: Study AMG106 / IGBC CSR Page 52 (29 September 2015) and statistical reviewer's analysis]

Table 2 below describes the demographics and patient characteristics of the randomized population. We see that majority of patients were women and most patients were under the age of 35. Whites made up the majority of the study, in particular those with T1DM.

Table 2: Demographics and patient characteristics – Study IGBC: Safety Cohort

	T1DM (N=77)	T2DM (N=6)
Age (years)		
Mean (SD)	32.9 (12.3)	47.8 (14.7)
Age group [n(%)]		
18 to < 25	28 (36.4)	1 (16.7)
25 to < 35	23 (29.9)	0
35 to < 45	10 (13.0)	1 (16.7)
45 to < 55	11 (14.3)	3 (50.0)
≥ 55	5 (6.5)	1 (16.7)
Sex [n(%)]		
Male	32 (41.6)	2 (33.3)
Female	45 (58.4)	4 (66.7)
Race [n(%)]		
White	74 (96.1)	1 (16.7)
Black	1 (1.3)	2 (33.3)
Hispanic or Latino	1 (1.3)	1 (16.7)
Other	1 (1.3)	2 (33.3)
Duration of diabetes (years)		
Mean (SD)	18.1 (11.2)	18.8 (7.8)
Duration of diabetes (years) [n(%)]		
< 10	27 (35.1)	0
10 to < 20	16 (20.8)	4 (66.7)
20 to < 30	20 (26.0)	1 (16.7)
≥ 30	14 (18.2)	1 (16.7)

[Source: Study AMG106 / IGBC CSR Page 53-54 (29 September 2015) and statistical reviewer's analysis]

- **Study IGBI:**

Table 3 below describes the analysis population. We see that a total of 70 patients received at least 1 dose of study drug, however 4 patients who were excluded from the analysis population.

Table 3: Analysis populations - Study IGBI

	N=70	T1DM (N=70)	
	Overall n (%)	BAQSIMI n (%)	IMG n (%)
Enrolled (Randomized)	70 (100)		
Received at least 1 Dose of Treatment	70 (100)	70 (100)	69 (98.6)
Primary Analysis population	66 (94.3)	66 (94.3)	66 (94.3)

[Source: Study IGBI Pharmacology CSR Page 25, 27 (26 March 2018) and statistical reviewer's analysis]

Table 4 below describes the demographics and patient characteristics of the randomized population. In contrast to study IGBC, most patients were male and the distribution across age categories were roughly uniform for patients more than 25 years of age. Whites made up 100% of the randomized population.

Table 4: Demographics and patient characteristics – Study IGBI: Enrolled (Randomized) population

	T1DM (N=70)
Age (years)	
Mean (SD)	41.7 (12.7)
Age group [n(%)]	
18 to < 25	6 (8.6)
25 to < 35	18 (25.7)
35 to < 45	16 (22.9)
45 to < 55	16 (22.9)
≥ 55	14 (20.0)
Sex [n(%)]	
Male	43 (61.4)
Female	27 (38.6)
Race [n(%)]	
White	70 (100)
Non-White	0 (0)
Duration of diabetes (years)	
Mean (SD)	20.1 (10.7)
Duration of diabetes (years) [n(%)]	
< 10	14 (20.0)
10 to < 20	21 (30.0)
20 to < 30	21 (30.0)
≥ 30	14 (20.0)

[Source: Study IGBI Pharmacology CSR Page 24 (26 March 2018) and statistical reviewer's analysis]

- **Study IGBB:**

Table 5 below describes the analysis population. A total of 48 patients were randomized and by design, a total of 84 visits were possible, however data for 81 visits were included in the analysis.

Table 5: Analysis Populations – Study IGBB

	4 to <8			8 to <12			12 to <17		Total
	2mg BAQSIMI	3mg BAQSIMI	IM	2mg BAQSIMI	3mg BAQSIMI	IM	3mg BAQSIMI	IM	
Randomized	12		6	12		6	12		**48**
Population with Visits Included in the analysis	10	12	6	11	12	6	12	12	**81**

[Source: AMG103 / IGBB CSR Page 58 (29 September 2015) and statistical reviewer's analysis]

Table 6 describes the demographics and patient characteristics. Most patients were male, especially in the 4 to < 8 group and whites made up most of the study.

Table 6: Demographics and patient characteristics – Study IGBB Randomized Population

	4 to < 8 (N=18)	8 to < 12 (N=18)	12 to < 17 (N=12)
Age group [n(%)]			
4 to < 6	6 (33.3)		
6 to < 8	12 (66.7)		
8 to < 10		1 (5.6)	
10 to < 12		17 (94.4)	
12 to < 14			4 (33.3)
14 to < 17			8 (66.7)
Sex [n(%)]			
Male	15 (83.3)	10 (55.6)	7 (58.3)
Female	3 (16.7)	8 (44.4)	5 (41.7)
Race [n(%)]			
White	18 (100)	16 (88.9)	10 (83.3)
Black	0	1 (5.6)	1 (8.3)
Hispanic or Latino	0	0	1 (8.3)
Other	0	1 (5.6)	0 (0)
Duration of diabetes (years)			
Mean (SD)	2.8 (1.3)	4.9 (1.8)	6.6 (3.9)
Duration of diabetes (years) [n(%)]			
1 to < 2	4 (22.2)	0	0
2 to < 4	11 (61.1)	6 (33.3)	4 (33.3)
4 to < 6	3 (16.7)	6 (33.3)	2 (16.7)
6 to < 8	0	5 (27.8)	3 (25.0)
8 to < 10		1 (5.6)	1 (8.3)
≥ 10		0	2 (16.7)

[Source: AMG103 / IGBB CSR Page 59-60 (29 September 2015) and statistical reviewer's analysis]

3.2.4 Results and Conclusions

Primary Endpoint

- **Study IGBC:**

Table 7 below displays the efficacy results for the primary endpoint. There were 75 patients included in the analysis among the T1DM population. For BAQSIMI, there were 74 patients who achieved success (98.7%). Looking at each individual success criteria, there were 72 patients (96%) who achieved ≥ 70 mg/dL and 74 patients (98.7%) who achieved an increase of ≥ 20 mg/dL from nadir. For IMG, there were 75 patients achieved success (100%). Looking at each individual success criteria, there were 74 patients (98.7%) who achieved ≥ 70 mg/dL and 75 patients (100%) who achieved an increase of ≥ 20 mg/dL from nadir.

According to the sponsor's pre-specified analysis, the difference in proportion of success was -0.013 with a 95% of (-0.040, 0.013). From the statistical reviewer's analysis, the difference in proportion of success remains -0.013, however, using the Agresti and Min correction the 95% CI is (-0.049, 0.023). The lower bound is greater than -0.10 (the pre-specified non-inferiority margin), which supports that BAQSIMI is non-inferior to IMG.

Table 7: Difference in Proportion of success (T1DM Only) - Study IGBC

	BAQSIMI (N=75[c])	**IMG (N=75[c])**
# of successes (%)	74 (98.7%)	75 (100%)
Success criterion met n, (%):		
≥ 70 mg/dL	72 (96.0%)	74 (98.7%)
Increase by ≥ 20 mg/dL from nadir	74[a] (98.7%)	75[b] (100%)
Difference in Proportion of success (95% C.I.) (Sponsor's analysis)	-0.013 (-0.040, 0.013)	
Difference in Proportion of success (95% C.I.) (Statistical reviewer's analysis)	-0.013 (-0.049, 0.023)	

a There were 2 patients on BAQSIMI who achieved ≥ 20 mg/dL from nadir but did not achieve ≥ 70 mg/dL
b There was 1 patient on IMG who achieved ≥ 20 mg/dL from nadir but did not achieve ≥ 70 mg/dL
c There were 2 randomized patients excluded from the analysis. See Section 3.5.2 below for details
[Source: Study AMG106 / IGBC CSR Page 56 (29 September 2015) and statistical reviewer's analysis]

There were 5 patients with T2DM, each of whom achieved both success criteria for BAQSIMI and IMG (Table 8 below). Thus, the success rate among T1DM and T2DM for BAQSIMI is 98.8% and remains 100% for IMG. The difference in proportion of success from the sponsor's pre-specified analysis was -0.013 with a 95% of (-0.037, 0.012). From the statistical reviewer's analysis, the difference in proportion of success remains -0.013, however, using the Agresti and Min correction, the 95% is (-0.046, 0.022). We see that the conclusion for non-inferiority remains unchanged.

Table 8: Difference in Proportion of success (T1DM and T2DM) – Study IGBC

	BAQSIMI (N=80)	IMG (N=80)
# of successes (%)	79 (98.8%)	80 (100%)
Success criterion met n, (%):		
≥ 70 mg/dL	77 (96.3%)	79 (98.8%)
Increase by ≥ 20 mg/dL from nadir	79[a] (98.8%)	80[b] (100%)
Difference in Proportion of success (95% C.I.) (Sponsor's analysis)	-0.013 (-0.037, 0.012)	
Difference in Proportion of success (95% C.I.) (Statistical reviewer's analysis)	-0.013 (-0.046, 0.022)	

a There were 2 patients on BAQSIMI who achieved ≥ 20 mg/dL from nadir but did not achieve ≥ 70 mg/dL
b There was 1 patient on IMG who achieved ≥ 20 mg/dL from nadir but did not achieve ≥ 70 mg/dL
c There were 3 randomized patients excluded from the analysis. See Section 3.2.5 below for details
[Source: Study AMG106 / IGBC CSR Page 60 (29 September 2015) and statistical reviewer's analysis]

- **Study IGBI:**

Table 9 below displays the efficacy results for the primary endpoint. There were 66 patients included in the analysis. We see that there was a 100% success rate on both arms and further, each patient achieved both criteria for BAQSIMI and IMG.

According to the pre-specified analysis, the difference in proportion of success was 0.00 with a 95% of (0.00, 0.00). From the statistical reviewer's analysis, the difference in proportion of success remains 0.00 and using the Agresti and Min correction, the 95% CI is (-0.029, 0.029). Since the lower bound is greater than -0.10 (the pre-specified non-inferiority margin), which supports that BAQSIMI is non-inferior to IMG.

Table 9: Difference in Proportion of success – Study IGBI

	BAQSIMI (N=66)	IMG (N=66)
# of success (%)	66	66
Success criterion met n, (%):		
≥ 70 mg/dL	66 (100%)	66 (100%)
Increase by ≥ 20 mg/dL from nadir	66 (100%)	66 (100%)
Difference in Proportion of success (95% C.I.) (Sponsor's analysis)	0.00 (0.00, 0.00)	
Difference in Proportion of success (95% C.I.) (Statistical reviewer's analysis)	0.00 (-0.029, 0.029)	

a There were 4 randomized patients excluded from the analysis. See Section 3.2.5 below for details
[Source: Study IGBI Pharmacology CSR Page 27 (26 March 2018) and statistical reviewer's analysis]

- **Study IGBB:**

Table 10 below displays the results for mean time (in minutes) to reach blood glucose increase ≥ 20 mg/dL by age group. These results are descriptive and not part of any pre-specified plan.

Table 10: Mean time (in minutes) to reach blood glucose increase ≥ 20 mg/dL - Study IGBB

Increase from Nadir	Mean Time (mins) to Reach Glucose Increase ≥ 20 mg/dL					
	4 to < 8 yrs old		8 to < 12 yrs old		12 to < 17 yrs old	
	IMG (N=6)	BAQSIMI (N=12)	IMG (N=6)	BAQSIMI (N=12)	IMG (N=12)	BAQSIMI (N=12)
≥ 20 mg/dL	10.0	10.8	12.5	11.3	12.5	14.2

(b) (4)]

3.2.5 Addressing Missing Data

There were two forms of missing data that may impact the evaluation of treatment effect:

1. Patients who were excluded from the analysis
2. Missing glucose measurements at time points during patient visits

- **Patients excluded from the analysis**

First, we'll address patients who were excluded from the analysis. Since there were 7 patients in total who were excluded between the two adult studies, we'll look at the profile for each patient and evaluate if there is concern of excluding them (Tables 11 and 13). The glucose measurements of the patients who were excluded from Time 0 to Time 30 are listed in Tables 12 and 14, respectively. The nadir measurement is denoted by "N".

Table 11: Patients excluded from the primary analysis – Study IGBC

Patient	Reason for Exclusion	Comment
(b) (6)	Study withdrawal and only took BAQSIMI	Achieved success on BAQSIMI
	Premature administration of carbohydrates	Achieved success on both arms
	Failure to reach < 70 mg/dL while on IMG	Achieved success on BAQSIMI and achieved ≥ 20 mg/dL from "Nadir" on IMG

[Source: Statistical reviewer's analysis]

Table 12: Measurements from visits of patients excluded from the primary analysis -Study IGBC

Patient	Drug	Time 0	Time 5	Time 10	Time 15	Time 20	Time 25	Time 30
(b) (6)	BAQSIMI	58	55 (N)	67	80	87	92	99
	IMG	--	--	--	--	--	--	--
	BAQSIMI	43	39 (N)	65	90	112	112	123
	IMG	51 (N)	66	87	110	136	154	180
	BAQSIMI	73	66 (N)	70	78	93	103	112
	IMG	75	74 (N)	84	107	109	123	126

[Source: Statistical reviewer's analysis]

Table 13: Patients excluded from the primary analysis -Study IGBI

Patient	Reason for Exclusion	Comment
(b) (6)	Study withdrawal and only took BAQSIMI	Achieved success on BAQSIMI
	Failure to reach < 70 mg/dL while on IMG	Achieved success on BAQSIMI and achieved ≥ 20 mg/dL from "Nadir" on IMG
	Failure to reach < 70 mg/dL while on BAQSIMI	Achieved success on IMG and achieved ≥ 20 mg/dL from "Nadir" on BAQSIMI
	Failure to reach < 70 mg/dL while on BAQSIMI	Achieved success on IMG and achieved ≥ 20 mg/dL from "Nadir" on BAQSIMI

[Source: Statistical reviewer's analysis]

Table 14: Measurements from visits of patients excluded from the primary analysis – Study IGBI

Patient	Drug	Time 0	Time 5	Time 10	Time 15	Time 20	Time 25	Time 30
(b) (6)	BAQSIMI	61 (N)	61	76	94	106	113	126
	IMG	--	--	--	--	--	--	--
	BAQSIMI	59 (N)	63	88	101	113	124	133
	IMG	72 (N)	72	95	113	117	130	151
	BAQSIMI	76	74 (N)	83	88	113	119	164
	IMG	58	54 (N)	74	97	121	139	166
	BAQSIMI	77	74	72 (N)	95	112	128	141
	IMG	59 (N)	65	74	92	130	137	151

[Source: Statistical reviewer's analysis]

In the cases where the goal of < 70 mg/dL was not reached, if we are willing to consider the minimum glucose value as "nadir", then we see that for both studies, each patient who took BAQSIMI had achieved success. For example, in study IGBI, the lowest value that patient (b) (6) reached, while on BAQSIMI, was 74. However, we see by Time 20 that the patient reached 113, thus a ≥20 increase was achieved. Therefore, we remain confident that the exclusion of these patients has no impact on the result of the primary endpoint.

- **Missing glucose measurements at time points during patient visits**

During patient visits, after being induced to a hypoglycemic state, glucose measurements were taken every 5 minutes. If central laboratory measurements were missing, then bedside measurements were used in the analysis. However, if bedside measurements were also missing then measurements were imputed. The number of imputed measurements are summarized as follows:

Study	Number of Imputed Glucose Measurements
IGBC	2
IGBI	6

We now consider the impact of missing values on the treatment effect. Since 7 patients had measurements that were imputed, we'll look at the profile of measurements for each patient. The imputed measurement is denoted by "I". From Tables 15 and 16 below, we see that imputed values have no impact on whether success was achieved, even among cases where the nadir measurement was imputed since each patient achieved an increase in glucose to ≥ 70 mg/dL or an increase of ≥ 20 mg/dL from nadir within 30 minutes after administration of glucagon based on observed values.

Table 15: Measurements of patients who had an imputed measurement – Study IGBC

Patient	Drug	Time 0	Time 5	Time 10	Time 15	Time 20	Time 25	Time 30
(b) (6)	IMG	44	42 (N)	53	59	87.3[a] (I) 89.1[b] (I)	74	144
	IMG	51 (N)	51	84	105	128	145.0[a] (I) 144.9[b] (I)	154

a Calculated based off only T1DM patients
b Calculated based off T1DM and T2DM patients
[Source: Statistical reviewer's analysis]

Table 16: Measurements of patients who had an imputed measurement - Study IGBI

Patient	Drug	Time 0	Time 5	Time 10	Time 15	Time 20	Time 25	Time 30
(b) (6)	BAQSIMI	41 (I, N)	52	65	81	92	97	115
	BAQSIMI	47	40 (I, N)	52	65	76	97	106
	BAQSIMI	50 (I, N)	56	65	77	90	94	106
	IMG	50	43 (I, N)	49	52	61	68	70
	BAQSIMI	50 (N)	54 (I)	76	86	119	137	166
	BAQSIMI	54 (N)	58	74	97	108	104 (I)	128

[Source: Statistical reviewer's analysis]

3.3 **Safety Analysis**

Table 17 below displays the common adverse events that are being proposed for labelling for studies IGBC and IGBI, with the exception of nasal congestion and nasal discomfort / itching. We see that more subjects had nausea with IMG in both studies while more subjects had headaches with BAQSIMI in both studies. As expected, more subjects had nasal congestion and nasal discomfort / itching on BAQSIMI, where we see even larger differences in study IGBI.

Table 17: Adverse Events – Study IGBC and IGBI

	Study IGBC		Study IGBI	
Adverse Reaction	**BAQSIMI (n=83) %**	**IMG (n=82) %**	**BAQSIMI (n=70) %**	**IMG (n=69) %**
Nausea	21.7	26.8	31.4	42
Headache	20.5	8.5	15.7	10.1
Upper Respiratory Tract Irritation	19.3	1.2	4.3	1.4
Vomiting	15.7	11	14.3	17.4
Lacrimation increased	8.4	1.2	0	0
Pruritus	3.6	1.2	0	0
Eye Pruritus	2.4	1.2	0	0
Nasal Congestion	8.4	1.2	38.6	4.3
Nasal Discomfort / Itching[a]	9.6	0	48.6	0

a Nasal discomfort was described for Study IGBC and nasal itching was described for Study IGBI

(b) (4)

Table 18 below displays the common adverse events (b) (4) for study IGBB. We see that vomiting is slightly higher for IMG. There appears to be an increase in headaches for BAQSIMI and an increase in nausea for IMG.

Table 18: Adverse Events – Study IGBB

	Study IGBB	
Adverse Reaction	**BAQSIMI 3 mg (n=36) %**	**IMG (n=24) %**
Vomiting	30.6	37.5
Headache	25	12.5
Nausea	16.7	33.3
Upper Respiratory Tract Irritation	16.7	0

(b) (4)

In discussion with the medical reviewer, the increase in headaches and nasal symptoms will not preclude approval, therefore, no benefit-risk assessment was performed.

4 Findings in Special/Subgroup Populations

4.1 Subgroup Analyses of Efficacy

Due to the high success rate on both arms for both studies IGBC and IGBI, there was almost no difference in treatment effect across subgroups. The tables below summarize the counts and percentage of success for sex, race, and age for each study.

- **Study IGBC**

  - **T1DM:**

	BAQSIMI # of successes (%)	**IMG # of successes (%)**
Sex		
Males (N=32)	32 (100%)	32 (100%)
Females (N=43)	42 (97.7%)	43 (100%)
Race		
White (N=73)	72 (98.6%)	73 (100%)
Non-White (N=2)	2 (100%)	2 (100%)
Age		
< 35 (N=49)	48 (98.0%)	49 (100%)
≥ 35 (N=26)	26 (100%)	26 (100%)

  - **T1DM and T2DM**

	BAQSIMI # of successes (%)	**IMG # of successes (%)**
Sex		
Males (N=33)	33 (100%)	33 (100%)
Females (N=47)	46 (97.9%)	47 (100%)
Race		
White (N=75)	74 (98.7%)	75 (100%)
Non-White (N=5)	5 (100%)	5 (100%)
Age		
< 35 (N=50)	49 (98.0%)	50 (100%)
≥ 35 (N=30)	30 (100%)	30 (100%)

- **Study IGBI**

	BAQSIMI # of successes (%)	**IMG # of successes (%)**
Sex		
Males (N=40)	40 (100%)	40 (100%)
Females (N=26)	26 (100%)	26 (100%)
Race		
White (N=66)	66 (100%)	66 (100%)
Non-White (N=0)	--	--
Age		
< 35 (N=21)	21 (100%)	21 (100%)
≥ 35 (N=45)	35 (100%)	35 (100%)

5 Summary and Conclusions

5.1 Statistical Issues

There were two statistical issues that arose in this review. The first issue was that due to the presence of small to zero frequency counts, the CIs from the sponsor's primary analysis method does not provide proper coverage for the difference in proportions of success. The statistical reviewer used a method proposed by Agresti and Min which improves on the coverage probability.

The second issue is in regard to missing data. There were two forms of missing data in the two adult clinical studies. The first form were patients who were excluded from the primary analysis. There were three reasons why patients were excluded: 1) Study withdrawal which resulted in the patient participating in only 1 visit 2) Pre-mature administration of carbohydrates and 3) Did not reach induced hypoglycemia state (PG < 70) at one of the visits. Investigation in these patients' profile revealed no concern for the exclusion of these patients in the primary analysis.

The second form of missing data came during visits where measurements were not captured and therefore were imputed. The number of these measurements were small and investigation into these imputed values revealed that there was no impact on whether a patient achieved success (Section 3.2.5)

5.2 Collective Evidence

Two clinical studies in adults were conducted where there was a 100% and 98.8% success rate in the control and treatment arms (among T1DM and T2DM; (100% and 98.7% among T1DM only)), respectively in one study and a 100% success rate in both the treatment and control arms in the second study. With a pre-specified non-inferiority margin of -10%, there is strong evidence that intranasal glucagon (BAQSIMI) is non-inferior to intramuscular glucagon (the commercial drug) in increasing glucose to ≥70 mg/dL or increasing to ≥20 mg/dL from nadir within 30 minutes after administration of glucagon. An assessment of missing data revealed that there was no impact on the results of the primary analysis.

A study was conducted in pediatrics in the age range of 4 to 17 years old. While there was no pre-specified endpoint, the percentage and mean time to achieve ≥ 20 mg/dL from nadir are proposed for labelling.

5.3 Conclusions and Recommendations

The statistical reviewer's primary analysis results demonstrate that intranasal glucagon (BAQSIMI) is non-inferior to intramuscular glucagon (the commercial drug) for the treatment of severe hypoglycemia. Investigation of missing data revealed no concern in study results and interpretation. The initiation of the second study (IGBI) was to bridge the test product to the commercial product and from a statistical perspective this objective was achieved. Therefore, based on the collective efficacy evidence, I recommend approval of the product for the treatment of severe hypoglycemia in adults. However, regarding the pediatric study, since there was no pre-specified endpoint, whether the product should be approved for use in pediatric patients will require further discussion with the clinical team.

5.4 Labeling Recommendations

The CIs derived from the sponsor's pre-specified primary analysis does not provide proper coverage for the underlying true difference in proportions of success. We sent an information request (IR) to the sponsor and recommended they use the Agresti and Min correction or another appropriate method. The sponsor responded to our IR on March 20, 2019: \\cdsesub1\evsprod\nda210134\0037\m1\us\response.pdf. The sponsor derived the same CIs as those from the reviewer's analyses in Table 7, 8, and 9. The statistical reviewer recommends the corrected CIs be presented in the product label.

Mean Time to (b) (4). The statistical reviewer evaluated the impact of missing values (i.e., the impact of including imputed measurements in these calculations). Tables 19 and 20 below display the mean time to recovery calculated by the sponsor using imputed values and the statistical reviewer using only observed values. We see that the mean time to (b) (4) are almost the same using either approach.

Table 19: Mean Time to [redacted] – Study IGBC

	Mean Time to [redacted] (N=75)
Sponsor:	
BAQSIMI	[redacted]
IMG	
Reviewer's:	
BAQSIMI	16.2
IMG	12.333

[Source: Study AMG106 / IGBC CSR Page 60 (29 September 2015) and statistical reviewer's analysis]

Table 20: Mean Time to [redacted] – Study IGBI

	Mean Time to [redacted] (N=75)
Sponsor:	
BAQSIMI	11.44
IMG	9.85
Reviewer's:	
BAQSIMI	11.59
IMG	9.92

[Source: Study IGBI Pharmacology CSR Page 29 (26 March 2018) and statistical reviewer's analysis]

Mean Nadir: On the proposed product label, mean nadir glucose values are described. Here, we consider the impact of including imputed measurements in these calculations. Upon confirmation of the sponsor's results, it was found that for study IGBC, a different algorithm was used to calculate mean nadir than from study IGBI.

Study IGBC: There were no nadir values that were a result of an imputation, however, the sponsor (Locemia) calculated mean nadir by [redacted]

[redacted]

For my calculation, I took the average of all nadir glucose measurements to be consistent with study IGBI. Table 21 below shows the results.

Table 21: Mean Nadir glucose – Study IGBC

	Mean Nadir blood glucose (N=75)
Sponsor:	
BAQSIMI	(b) (4)
IMG	
Reviewer's:	
BAQSIMI	43.53
IMG	46.88

(b) (4)

Study IGBI: The sponsor (Eli Lilly) calculated mean nadir by averaging across nadir values, however, 4 measurements were imputed values, while my calculation used only observed values. Table 22 below displays the results.

Table 22: Mean Nadir glucose – Study IGBI

	Mean Nadir blood glucose (N=75)
Sponsor:	
BAQSIMI	(b) (4)
IMG	
Reviewer's:	
BAQSIMI	54.52
IMG	55.79

[Source: Proposed product label and statistical reviewer's analysis]

For Study IGBC, we see a slight difference between the two algorithms. However, for Study IGBI, we see almost no difference.

Study IGBB: On the proposed product label, the percentage achieving and mean time to ≥ 20 mg/dL from nadir are described. There was one measurement used by the sponsor in the calculation of mean time to ≥ 20 mg/dL from nadir that was an imputed value (Table 23 below). Table 24 display the results of the statistical reviewer using only observed measurements. The only change is in the IMG arm in the 4 to < 8 year old group.

Table 23: Percentage achieving and Mean Time to ≥ 20 mg/dL from Nadir (Sponsor's analysis)

	4 to < 8 yrs old		8 to < 12 yrs old		12 to < 17 yrs old	
	IMG	**NG 3mg**	**IMG**	**NG 3mg**	**IMG**	**NG 3mg**
N	6	12	6	12	12	12
% increase 20 mg/dl from Nadir	100	100	100	100	100	100
Mean Time to achieve increase 20 mg/dl from Nadir	(b) (4)	10.8	12.5	11.3	12.5	14.2

[Source: Proposed product label and statistical reviewer's analysis]

Table 24: Percentage achieving and Mean Time to ≥ 20 mg/dL from Nadir (Statistical Reviewer's analysis)

	4 to < 8 yrs old		8 to < 12 yrs old		12 to < 17 yrs old	
	IMG	**NG 3mg**	**IMG**	**NG 3mg**	**IMG**	**NG 3mg**
N	6	12	6	12	12	12
% increase 20 mg/dl from Nadir	100	100	100	100	100	100
Mean Time to achieve increase 20 mg/dl from Nadir	10.8	10.8	12.5	11.3	12.5	14.2

[Source: Statistical reviewer's analysis]

Reference:

Agresti, A and Min, Y (2005). Simple improved confidence intervals for comparing matched proportions, Statistics in Medicine, 24:729-740.

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