Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Griffin KJ, Thompson PA, Gottschalk M, Kyllo JH, Rabinovitch A. Combination therapy with sitagliptin and lansoprazole in patients with recent-onset type 1 diabetes (REPAIR-T1D): 12-month results of a multicentre, randomised, placebo-controlled, phase 2 trial. Lancet Diabetes Endocrinol 2014; published online July 3. http://dx.doi.org/10.1016/S2213-8587(14)70115-9.
Supplemental Materials for Griffin, et al., “Combination Therapy With Sitagliptin and Lansoprazole in Patients with Recent-onset Type 1 Diabetes (REPAIR-T1D): 12 Month Results of a Multi-centre Randomized, Placebo-controlled, Phase 2 Trial.”

Methods

Additional Primary Analyses

For all longitudinal analyses, several alternative approaches are available for analysis. In randomized controlled trials, the standard analyses are the mixed-effects repeated measures (MERM) analysis and the covariate adjusted (COVA) analysis. The difference lies in the use of the baseline values. In the MERM analysis, the baseline value is considered another time-point, and the analysis is performed by testing differences and interactions (differences of differences) between time points. In the COVA analysis, the baseline value is used as a covariate. Both of these analyses were performed with this data. While minor differences exist in the results, no appreciable differences were seen.

Subgroup Analyses

Prespecified subgroup analyses included age, sex, C-peptide, HbA1c, and insulin use. After the primary results were found to be negative, we preformed additional post-hoc analyses to determine whether the agents produced the expected increases in GLP-1 and gastrin. We defined a subgroup of treated subjects as “Responsive,” whose fasting GLP-1 and gastrin levels while on treatment were both above the maximum placebo arm values. Similarly, a “Non-responsive” subgroup was defined by those subjects for whom fasting GLP-1 and gastrin levels were both less than the maximum placebo value. Since these hormones are stimulated by food, samples collected at visits when all subjects were fasting were used (V2, V4, and V6). “Per hypothesized effect” (Responsive, Non-Responsive, placebo) subgroup analyses were performed in parallel with the primary analyses. and interactions for both treatment and "per hypothesized effect" conditions were assessed.

Results

Subgroup Analyses

Prespecified subgroup analyses were performed to assess possible effects of baseline parameters: age, sex, C-peptide, HbA1c, and insulin use. None of these baseline parameters had a significant effect on the primary endpoint (Supplemental Figure 1). Prior T1D intervention studies have identified subgroups of “responders” who maintained C-peptide production above one of several defined thresholds.2,3 When these various criteria were applied to the results from this study, there were no differences in the number of responders maintaining C-peptide production between treatment and placebo groups (p=0.55–0.68).

Our hypothesis stated that the effects of the treatment on the progression of T1D will be mediated through elevated levels of gastrin and GLP-1. As an exploratory analysis, this “per hypothesized effect” was used to define “Responsive” and “Non-Responsive” participants within the active treatment group as described above. While the treatment group as a whole demonstrated elevations of these intermediary hormones, 8 subjects (20%) in the active treatment arm were “Non-responsive,” failing to increase both fasting GLP-1 and gastrin above levels seen in the placebo group (lines in Supplemental Figure 2). Eighteen subjects (45%) were in the “Responsive” subgroup with fasting GLP-1 and gastrin levels both above the maximum placebo arm values. There were no significant differences in baseline characteristics of subjects among these groups (Supplemental Table 1); these Responsive subjects had baseline GLP-1 and gastrin levels indistinguishable from the placebo and Non-Responsive groups. GLP-1 and gastrin levels were also increased at Visits 3 and 5 (3, 9 months) in the Responsive subjects, however subjects were not required to be fasting for these visits and it is not possible to determine relative effects of the treatment and food intake.

When the Responsive group was compared to the Non-Responsive and placebo groups, there was a nonsignificant trend towards improved preservation of C-peptide in the Responsive group with a suggestion of decreased rate of fall through 12 months (Supplemental Figure 3A): the Responsive group had a mean change of −166 pmol/l (95% CI: −361 to +29, p=0.4114 vs. placebo), the Non-Responsive group changed by −364 pmol/l (95% CI: −578 to −150; p=0.4808 vs. placebo), and the placebo group changed by −253 pmol/l (95% CI: −435 to −71). C-peptide responses to the MMTT are presented for each subject in Supplemental Figure 4. Analyses were similar for groups defined alternatively by the change in hormone levels compared to baseline, and for peak C-peptide vs. AUC. Glucose AUC increased in all groups, with a trend towards lower values in the Responsive subgroup (Supplemental Figure 3B).

Similarly, HbA1c (Supplemental Figure 3C) was maintained at baseline levels in the Responsive group, with trends towards increasing levels in the Non-Responsive and placebo groups. After 12 months of therapy, HbA1c decreased by 0.04% (95%
CI: −0.59 to +0.52, p=0.3241 vs. placebo) in the Responsive group while it increased by 0.94% (95% CI: −0.5 to +2.38) in the Non-Responsive group and by 0.48% (95% CI: −0.35 to +1.31) in the placebo group. Over the course of treatment, insulin use (Supplemental Figure 3D) increased by 0.03 Units·kg⁻¹·d⁻¹ (95% CI: −0.10 to +0.16) in the Responsive group, by 0.28 Units·kg⁻¹·d⁻¹ (95% CI: +0.10 to +0.46) in the Non-Responsive group, and by 0.08 Units·kg⁻¹·d⁻¹ (95% CI: +0.01 to +0.16) in the placebo group; the difference between Non-Responsive and placebo reached significance (p=0.0328). IDA-A1c (Supplemental Figure 3E) was essentially unchanged in the Responsive subgroup (+0.08%; 95% CI: −0.67 to +0.82; p=0.222 vs. placebo), but increased in the Non-Responsive group (+2.06%; 95% CI: +0.2 to +3.92; p=0.1199 vs. placebo) and in the placebo group (+0.82%; 95% CI: −0.15 to 1.79).

Discussion

When faced with the primary outcome under an intent to treat approach, we sought to understand what factors may have contributed to the negative results. The preclinical data in mice suggested that increases in GLP-1 and gastrin protect β cell from autoimmune damage, and it was through this mechanism that we expected benefits from the agents in this study. However, not all the subjects experienced increases in these intermediary hormones. This prompted analysis of the GLP-1 + gastrin Responsive subgroup, which showed a non-significant trend towards preservation of C-peptide and the possibility of a benefit in some subjects. This study is the first to define a subgroup of “Responsive” subjects based not on C-peptide preservation, but instead, on whether the expected elevations GLP-1 and gastrin were achieved by the intervention. Although DPP-4i do not delay gastric emptying to the same extent as GLP-1 receptor agonists, this may be contributing to the trend towards decreased glucose AUC during the MMTT. Any such effect might decrease β cell stimulation during the test and C-peptide measurements might underestimate β cell function. We attempted to minimize this by asking the subjects to withhold study medication for 24 hours prior to each MMTT.

Several factors may be contributing to the lack of induction of GLP-1 and gastrin. DPP-4 inhibitors and PPI are known to produce widely variable blood levels in different individuals, at least part of which has been attributed to polymorphisms in cytochrome P450 enzymes that catalyze metabolism of these drugs.4,7 We considered whether giving a smaller dose to subjects who were < 18 years old but nearly adult size might have contributed to poor induction of GLP-1 and gastrin. We were surprised to find that neither age nor dose per weight (mg/kg) had any correlation with the extent of elevation in GLP-1 or gastrin levels (data not shown). Similarly, the dose had no effect on C-peptide responses to the mixed meal separate from the underlying effect of age. Future studies with these agents should include further investigation of factors that determine the extent of elevation of GLP-1 and gastrin.

As we look towards designing future trials, there are several things that should be considered with these agents. It may be necessary to titrate dosing in individual subjects or to limit this intervention to those subjects who produce a robust elevation in GLP-1 and gastrin in response to an initial challenge. As has been done for other studies, it will also be important to limit enrollment to subjects who are still making significant C-peptide. Another consideration would be to use a GLP-1 receptor agonist instead of a DPP-4i. Although these two classes of agents ostensibly target the same pathway, there are key differences. The GLP-1 receptor agonist are stronger, have more side effects and must be given as injections. The DPP-4i are not only less potent, but also less specific:  at least 62 peptides are cleaved by this enzyme resulting in either cytochrome P450 enzymes that catalyze metabolism of these drugs.

In considering T1D studies with agents that may increase insulin production, we must consider the possible interactions of effects among metabolism, autoimmunity, and β cell survival. GLP-1 acts, in part by improving glucose-stimulated insulin secretion, potentially exacerbating ER stress and autoimmunity. Rodent models suggest that β cell rest is protective and increased stress (ER or oxidative) hastens β cell destruction. The extent to which these phenomena occur in humans is not clear. Diazoxide has had variable results results on β cell preservation.6,10 A recent closed-loop insulin pump study failed to show any benefit.10 In human studies with incretins, including the current one, it is difficult to ascertain extent of β cell rest or stimulation.
Supplemental Figure 1: Ratio of Treatment Effects on 2h C-peptide AUC at 12 months. Ratios (Active:Placebo) and associated 95% CI bounds are calculated using generalized linear model methods (using SAS PROC GLIMMIX) of the C-peptide AUC value, log-transformed. The actual calculation was performed by a contrast calculation of the difference between active and placebo groups of the log-transformed C-peptide AUC values, which is effectively a ratio of values in the original scale. The terms incorporated into each calculation include log-transformed baseline C-peptide AUC, age (continuous), treatment group, group factor being examined, and interaction between group factor and treatment.
Supplemental Figure 2: Distribution of Fasting GLP-1 and Gastrin Values. Grey lines represent the upper limit of values measured in the placebo group.
Supplemental Figure 3: Population Means of Change in Outcome Measurements for Subgroups Based on Fasting GLP-1 and Gastrin Levels: (A) C-peptide AUC during 2h MMTT. \( p = 0.4114 \) for Treatment Responsive vs. placebo, \( p = 0.4808 \) for treatment Non-Responsive vs. placebo. Within groups over time, \( p = 0.0137 \) for treatment Responsive, \( p = 0.0017 \) for treatment Non-Responsive, and \( 0.0004 \) for placebo. (B) Blood Glucose AUC. \( p = 0.2786 \) for treatment Responsive vs. placebo, \( p = 0.9355 \) for treatment Non-Responsive vs. placebo. Error bars represent 95% CI.
Supplemental Figure 3 (Continued): (C) $Hb_{A1C}$, $p=0.3241$ for treatment Responsive vs. placebo, $p =0.4953$ for treatment Non-Responsive vs. placebo. (D) exogenous insulin use, $p=0.3823$ for treatment Responsive vs. placebo, $p =0.0328$ for treatment Non-Responsive vs. placebo. Error bars represent 95% CI.
Supplemental Figure 3 (Continued):  (E) Insulin Dose-Adjusted HbA1c, p=0.222 for Responsive and p=0.1199 for Responsive vs. placebo. Over time, p=0.8075 for Responsive, p=0.0024 for Non-Responsive, and p=0.0487 for placebo. Error bars represent 95% CI.

Supplemental Figure 4: C-peptide responses to MMTT for all subjects. C-peptide AUC (baseline, V4, V6) is plotted against the age of the subject at that visit. Subgroups are labeled according to which hormones were elevated above placebo values. The “responsive” subgroup discussed in the text include subject with both GLP-1 and gastrin elevations. The “non-responsive” group had elevations in neither of these hormones. For completeness, subjects who increased only GLP-1 or gastrin, but not both, are so labeled.
Supplemental Table 1: Baseline Characteristics of REPAIR-T1D Participants. p values are for the difference between all cases of sitagliptin + lansoprazole vs. placebo, from *ANOVA or ^χ^2 test; entries are *mean (StDev) or ^n (%)*.

|                        | DPP-4i + PPI All Cases N=46 | DPP-4i + PPI Non-Responsive N=8 | DPP-4i + PPI Responsive N=18 | Placebo All Cases N=22 | p Value All DPP-4i + PPI vs. Placebo |
|------------------------|-------------------------------|---------------------------------|-------------------------------|-------------------------|-------------------------------------|
| Age (y)                | 15.5 (5.1)                    | 15.3 (4.9)                      | 16.0 (4.2)                    | 17.6 (6.9)              | 0.1728^a                           |
| Age                   | 11–18                         | 35 (76.1)                      | 6 (75)                        | 12 (66.7)               | 17 (73.9)                          | 0.7731^b                           |
|                         | 18+                           | 11 (23.9)                      | 2 (25.0)                      | 6 (33.3)                | 6 (26.1)                           |
| Gender                 | Male                          | 27 (58.7)                      | 6 (75.0)                      | 11 (61.1)               | 12 (52.2)                          | 0.6064^a                           |
| Ethnicity              | Hispanic                      | 3 (6.5)                        | 1 (12.5)                      | 2 (11.1)                | 0 (0.0)                            | 0.2105^a                           |
| Height (cm)            | 166.4 (13.3)                  | 167.8 (9.5)                    | 170.1 (13.0)                  | 167.4 (13.3)            | 0.7599^a                           |
| Weight (kg)            | 60.0 (17.5)                   | 64.9 (16.0)                    | 66.0 (19.0)                   | 63.5 (21.1)             | 0.4668^a                           |
| BMI (kg/m^2)           | 21.25 (3.69)                  | 22.83 (3.91)                   | 22.30 (3.92)                  | 22.05 (4.49)            | 0.4307^a                           |
| Days post diagnosis    | 102.8 (51.8)                  | 105.9 (51.4)                   | 104.2 (49.6)                  | 104.7 (52.8)            | 0.8913^a                           |
| GAD Antibody Positive  | 42 (91.3)                     | 6 (75.0)                       | 17 (94.4)                     | 22 (100)                | 0.1540^a                           |
| ICA-512 Antibody Positive | 36 (80.0)                    | 7 (87.5)                       | 12 (66.7)                     | 18 (81.8)               | 0.5751^a                           |
| HLA DR Allele          | Neither DR3 nor DR4           | 2 (4.3)                        | 0 (0.0)                       | 1 (5.6)                 | 3 (13.6)                           | p=0.4002^a                         |
| DR3 only               | 11 (23.9)                     | 1 (12.5)                       | 2 (11.1)                      | 7 (31.8)                |                                     |
| DR4 only               | 19 (41.3)                     | 4 (50.0)                       | 10 (55.6)                     | 6 (27.3)                |                                     |
| Both DR3 and DR4       | 14 (30.4)                     | 3 (37.5)                       | 5 (27.8)                      | 6 (27.3)                |                                     |
| Insulin use (Units/kg/d) | 0.43 (0.22)                  | 0.37 (0.27)                    | 0.46 (0.22)                   | 0.38 (0.17)             | 0.4078^a                           |
| C-Peptide AUC (pmol/L) | 656 (385)                     | 659 (354)                      | 740 (450)                     | 747 (468)               | 0.3910^a                           |
| Glucose AUC (mmol/L)   | 10.61 (3.35)                  | 10.79 (2.05)                   | 9.52 (2.88)                   | 10.47 (3.43)            | 0.8670^a                           |
| HbA1c                  | 7.19 (1.09)                   | 7.46 (0.94)                    | 6.92 (1.14)                   | 7.15 (1.13)             | 0.8777^a                           |
| IDA-HbA1c              | 8.9 (1.53)                    | 8.96 (1.65)                    | 8.77 (1.6)                    | 8.68 (1.43)             | 0.5718^a                           |
**Supplemental Table 2: Detailed Adverse Event Listing.** All events were classified according to the Common Terminology Criteria for Adverse Events (CTAE), version 4.03 (NCI).

| CATEGORY and ADVERSE EVENT                   | DPP-4i + PPI n = 46 | Placebo n = 22 | All Subjects n = 68 |
|---------------------------------------------|---------------------|----------------|---------------------|
| Blood and lymphatic system disorders        |                     |                |                     |
| Anemia                                      | 1 1                 | 0 0            | 1 1                 |
| Cardiac disorders                           |                     |                |                     |
| Palpitations                                | 2 2                 | 0 0            | 2 2                 |
| Ear and labyrinth disorders                 |                     |                |                     |
| Vertigo                                     | 0 0                 | 1 1            | 1 1                 |
| Eye disorders                               |                     |                |                     |
| Blurred vision                              | 0 0                 | 1 1            | 1 1                 |
| Conjunctivitis                              | 1 1                 | 0 0            | 1 1                 |
| Eye disorders - Other, specify               | 0 0                 | 1 1            | 1 1                 |
| Eye pain                                    | 0 0                 | 1 1            | 1 1                 |
| Gastrointestinal disorders                  |                     |                |                     |
| Abdominal pain                              | 11 15               | 3 6            | 14 21               |
| Constipation                                | 2 2                 | 0 0            | 2 2                 |
| Diarrhea                                    | 3 3                 | 6 7            | 9 10                |
| Dyspepsia                                   | 1 2                 | 0 0            | 1 2                 |
| Flatulence                                  | 1 1                 | 0 0            | 1 1                 |
| Gastroesophageal reflux disease             | 3 3                 | 0 0            | 3 3                 |
| Nausea                                      | 8 8                 | 2 5            | 10 13               |
| Stomach pain                                | 1 1                 | 1 1            | 2 2                 |
| Vomiting                                    | 10 10               | 5 5            | 15 15               |
| General disorders and administration site conditions |             |                |                     |
| Chills                                      | 1 1                 | 0 0            | 1 1                 |
| Fever                                       | 4 4                 | 2 4            | 6 8                 |
| Flu like symptoms                           | 0 0                 | 1 1            | 1 1                 |
| Injection site reaction                     | 1 1                 | 0 0            | 1 1                 |
| Localized edema                             | 0 0                 | 1 1            | 1 1                 |
| Pain                                        | 0 0                 | 1 2            | 1 2                 |
| Immune system disorders                     | Autoimmune disorder | 0 0            | 1 1                 |
| Infections and infestations                 | 8 14                | 2 2            | 10 16               |
| Lung infection                              | 1 1                 | 0 0            | 1 1                 |
| Lymph gland infection                       | 1 1                 | 0 0            | 1 1                 |
| Otitis media                                | 3 3                 | 2 2            | 5 5                 |
| Papulopustular rash                         | 2 2                 | 0 0            | 2 2                 |
| Pharyngitis                                 | 7 7                 | 2 2            | 9 9                 |
| Sinusitis                                   | 7 8                 | 2 3            | 9 11                |
| Skin infection                              | 1 2                 | 1 1            | 2 3                 |
| Soft tissue infection                       | 1 1                 | 0 0            | 1 1                 |
| Upper respiratory infection                 | 20 33               | 9 13           | 29 46               |
| Urinary tract infection                     | 1 1                 | 0 0            | 1 1                 |
| Vaginal infection                           | 3 3                 | 0 0            | 3 3                 |
| Injury, poisoning and procedural complications | Fall  1 1            | 0 0            | 1 1                 |
| Fracture                                    | 1 1                 | 1 2            | 2 3                 |
| Other                                       | 3 4                 | 0 0            | 3 4                 |
| Investigations                                                                 | DPP-4i + PPI n = 46 | Placebo n = 22 | All Subjects n = 68 |
|-------------------------------------------------------------------------------|---------------------|----------------|-------------------|
| Cholesterol high                                                              | 1 1                 | 1 1            | 2 2               |
| Investigations - Other, specify                                                | 1 1                 | 0 0            | 1 1               |
| Neutrophil count decreased                                                    | 2 2                 | 3 5            | 5 7               |
| White blood cell decreased                                                    | 0 0                 | 2 2            | 2 2               |
| **Metabolism and nutrition disorders**                                        |                     |                |                   |
| Anorexia                                                                      | 1 1                 | 1 1            | 2 2               |
| Hypocalcemia                                                                  | 0 0                 | 1 1            | 1 1               |
| Obesity                                                                       | 1 1                 | 0 0            | 1 1               |
| **Musculoskeletal and connective tissue disorders**                           |                     |                |                   |
| Back pain                                                                     | 2 2                 | 0 0            | 2 2               |
| Joint range of motion decreased                                               | 1 1                 | 0 0            | 1 1               |
| Other, specify                                                                | 1 1                 | 1 1            | 2 2               |
| Myalgia                                                                       | 1 1                 | 1 2            | 2 3               |
| Neck pain                                                                     | 1 1                 | 1 1            | 2 2               |
| Pain in extremity                                                             | 1 1                 | 1 1            | 2 2               |
| **Neoplasms benign, malignant and unspecified**                               |                     |                |                   |
| Other – papillary thyroid cancer                                              | 1 1                 | 0 0            | 1 1               |
| **Nervous system disorders**                                                  |                     |                |                   |
| Dizziness                                                                     | 1 1                 | 0 0            | 1 1               |
| Headache                                                                      | 15 16               | 6 9            | 21 25             |
| Presyncope                                                                    | 0 0                 | 1 1            | 1 1               |
| Syncope                                                                       | 2 2                 | 1 1            | 3 3               |
| **Psychiatric disorders**                                                     |                     |                |                   |
| Anxiety                                                                       | 1 1                 | 2 2            | 3 3               |
| Depression                                                                    | 1 1                 | 1 2            | 2 3               |
| **Renal and urinary disorders**                                               |                     |                |                   |
| Urinary tract pain                                                            | 1 1                 | 0 0            | 1 1               |
| **Reproductive system and breast disorders**                                  |                     |                |                   |
| Irregular menstruation                                                        | 0 0                 | 1 1            | 1 1               |
| **Respiratory, thoracic and mediastinal disorders**                           |                     |                |                   |
| Allergic rhinitis                                                             | 4 6                 | 0 0            | 4 6               |
| Aspiration                                                                    | 1 1                 | 0 0            | 1 1               |
| Cough                                                                         | 6 7                 | 2 2            | 8 9               |
| Epistaxis                                                                     | 1 1                 | 0 0            | 1 1               |
| Nasal congestion                                                              | 7 7                 | 1 2            | 8 9               |
| Other, specify                                                                | 0 0                 | 1 1            | 1 1               |
| Sore throat                                                                   | 3 3                 | 1 1            | 4 4               |
| **Skin and subcutaneous tissue disorders**                                    |                     |                |                   |
| Bullous dermatitis                                                            | 1 1                 | 0 0            | 1 1               |
| Dry skin                                                                      | 1 1                 | 0 0            | 1 1               |
| Lipohypertrophy                                                               | 3 3                 | 1 1            | 4 4               |
| Palmar-plantar erythrodynesthesia syndrome                                     | 0 0                 | 1 1            | 1 1               |
| Pruritus                                                                      | 1 1                 | 0 0            | 1 1               |
| Rash acniform                                                                 | 4 4                 | 1 1            | 5 5               |
| Rash maculo-papular                                                           | 3 3                 | 0 0            | 3 3               |
| Other, specify                                                                | 5 6                 | 1 1            | 6 7               |
| **Vascular disorders**                                                        |                     |                |                   |
| Hypertension                                                                  | 2 2                 | 0 0            | 2 2               |
References

1. Orban T, Bundy B, Becker DJ, DiMeglio LA, Gitelman SE, Goland R, et al. Co-stimulation modulation with abatacept in patients with recent-onset type 1 diabetes: a randomised, double-blind, placebo-controlled trial. Lancet 2011;378(9789):412-9.

2. Herold KC, Gitelman SE, Ehlers MR, Gottlieb PA, Greenbaum CJ, Hagopian W, et al. Teplizumab (anti-CD3 mAb) treatment preserves C-peptide responses in patients with new-onset type 1 diabetes in a randomized controlled trial: metabolic and immunologic features at baseline identify a subgroup of responders. Diabetes 2013;62(11):3766-74.

3. Greenbaum CJ, Beam CA, Boulware D, Gitelman SE, Gottlieb PA, Herold KC, et al. Fall in C-peptide during first 2 years from diagnosis: evidence of at least two distinct phases from composite Type 1 Diabetes TrialNet data. Diabetes 2012;61(8):2066-73.

4. Gumus E, Karaca O, Babaoglu MO, Baysoy G, Balamtekin N, Demir H, et al. Evaluation of lansoprazole as a probe for assessing cytochrome P450 2C19 activity and genotype-phenotype correlation in childhood. Eur J Clin Pharmacol 2012;68(5):629-36.

5. Ward MB, Foster DJ. CYP2C19-guided design of a proton pump inhibitor dose regimen to avoid the need for pharmacogenetic individualization in H. pylori eradication. Eur J Clin Pharmacol 2011;67(3):261-6.

6. Hu YM, Mei Q, Xu XH, Hu XP, Hu NZ, Xu JM. Pharmacodynamic and kinetic effect of rabeprazole on serum gastrin level in relation to CYP2C19 polymorphism in Chinese Hans. World J Gastroenterol 2006;12(29):4750-3.

7. Ligumsky M, Lysy J, Siguencia G, Friedlander Y. Effect of long-term, continuous versus alternate-day omeprazole therapy on serum gastrin in patients treated for reflux esophagitis. J Clin Gastroenterol 2001;33(1):32-5.

8. Ortvqvist E, Bjork E, Wallensteen M, Ludvigsson J, Aman J, Johansson C, et al. Temporary preservation of beta-cell function by diazoxide treatment in childhood type 1 diabetes. Diabetes Care 2004;27(9):2191-7.

9. Radtke MA, Nermoen I, Kollind M, Skeie S, Sorheim JI, Svartberg J, et al. Six months of diazoxide treatment at bedtime in newly diagnosed subjects with type 1 diabetes does not influence parameters of {beta}-cell function and autoimmunity but improves glycemic control. Diabetes Care 2010;33(3):589-94.

10. Buckingham B, Beck RW, Ruedy KJ, Cheng P, Kollman C, Weinzimer SA, et al. Effectiveness of early intensive therapy on beta-cell preservation in type 1 diabetes. Diabetes Care 2013;36(12):4030-5.