

Diabetes & its Complications

Effects of BTI320 on Glycemic Control in Patients with Type 2 Diabetes

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ABSTRACT

Background/Purpose: Treatment of Type 2 diabetes (T2D) remains an unmet need, particularly a medication with low toxicity. BTI320 (SugarDown[®]) is fractionated galactomannan with inhibitory activity on carbohydrate-hydrolyzing enzymes. The primary objective of this study was to investigate the efficacy and safety of BTI320 on glycemic control in T2D.

Subjects/Methods: This was a double-blind, placebo-controlled, multi-center study in 60 T2D adults. Subjects ingested 4 g BTI320 or placebo 10 minutes before meals 3 times daily for 12 weeks. The primary endpoint was the change from Baseline to Week 12 in 2-hr post-prandial glucose (PPG) AUC between groups.

Results/Conclusion: A consistent trend was observed in favor of BTI320 vs. placebo in change from Baseline at Week 12 in 2-hr PPG AUC (-795.00 vs. -228.75 mg/dL*min), HbA_{1c} (-0.7% vs. +1.1%), lipids, weight/BMI, and blood pressure. At Week 12, BTI320 had more subjects with stable glucose levels (84.6% vs. 79.2%). According to CGM, the BTI320 group had more subjects with stable glucose levels (84.6 vs. 79.2%) and BTI320 subjects experienced relative hypoglycemia for shorter duration than placebo consistently across all visits. No differences were observed in AE profiles between groups. BTI320 was proven to be efficacious and safe in T2D.

This study is registered at ClinicalTrials.gov (NCT03655535).

Keywords

BTI320, SugarDown[®], Type 2 diabetes, NIDDM, galactomannans.

Introduction

Type 2 diabetes is a multi-factorial disease and identification of various pathological mechanisms that contribute to the progression of the disease is ongoing [1-4]. There is also a socioeconomic link between obesity and diabetes mellitus [5,6]. The incidence of diabetes is increasing, and new drugs for the treatment of diabetes have been targets in the pharmaceutical pipeline for many years [7-9]. One of the pharmaceutical targets for glycemic control in the diabetic population is hemoglobin A_{1c} (HbA_{1c}) and is often

monitored to guide medication adjustments. HbA_{1c} reflects the fasting and postprandial glucose (PPG) levels typically over a 3-month period. Decreasing and maintaining a lower HbA_{1c} leads to a significant, sustained reduction in micro- and macrovascular diabetes-related complications [10-12].

Type 2 diabetics are often prescribed metformin as the initial oral agent to treat diabetes, in addition to lifestyle management through healthy eating, weight control, and increased physical activity [13]. Metformin targets the liver and inhibits hepatic gluconeogenesis, resulting in lower fasting plasma glucose levels [14]. If blood glucose is still not at goal, metformin will

often be used in combination with other anti-diabetic agents in different drug classes, such as sulfonylureas, thiazolidinediones (TZDs), dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) agonists, and/or insulin [15,16]. Higher doses and extended-release dosage forms of metformin as well as these other classes of anti-diabetic agents have been complicated with safety issues [17].

BTI320 (SugarDown® or PAZ320) has been shown to be safe and well-tolerated in several clinical studies involving obese, otherwise healthy volunteers, and pre-diabetics [18,19]. BTI320 reduces the amount of available glucose from digested foods to be absorbed. In one study of BTI320, 24 subjects with Type 2 diabetes were studied after receiving a single low dose (8 g) and then a single high dose (16 g) of BTI320 [20,21]. A total of 20 subjects completed the study. Fifteen subjects (75%) responded to low-dose (8 g), high-dose (16 g), or both single-dose medication regimens. Three mild hypoglycemic episodes requiring treatment with glucose tablets were recorded. Flatulence was the most common adverse reaction, observed in 26% of subjects with low dose and 18% of subjects with high dose. There were no significant differences in adverse events (AEs) between responders and non-responders.

In a Phase 2, double-blind, randomized, placebo-controlled, proof-of-concept study in Chinese subjects with pre-diabetes (N=60), no spikes in fructosamine levels but rather a trend to lower fructosamine levels following meals were associated with 4 g or 8 g BTI320, compared with placebo [22]. Subjects receiving BTI320 had greater body weight reduction compared with placebo. Continuous Glucose Monitoring (CGM) data indices suggest that BTI320 may be effective in reducing glycemic variability. Management of PPG spikes is critical for the prevention of diabetes and diabetic-related complications, and treatment with 4 g BTI320 significantly reduced PPG area under the curve (AUC) in 1-hour ($p<0.01$), 2 hours ($p=0.01$), and 3 hours ($p=0.02$) and post-meal maximum glucose (MAGE, $p=0.01$). Reductions were also observed in the high dose group, albeit not reaching statistical significance. The most common adverse events possibly associated with BTI320 were gastrointestinal in nature (abdominal distension, flatulence, and diarrhea) occurring in approximately 20-30% of treated patients. Most of these AEs were mild to moderate in severity. No deaths or serious adverse events have occurred in prior studies with BTI320.

The objective of the current study was to confirm the safety and efficacy of BTI320 compared with placebo over a 12-week period in T2D patients.

Methods

Study subjects

This was a randomized, double-blind, placebo-controlled, multi-center study to evaluate the safety and immediate effects of BTI320 in addition to current treatment with metformin and/or sulfonylureas on glycemic control in T2D subjects. Subjects were instructed to not take the study drug with concomitant medications

at the same time (within 1 hour). Subjects who were non-compliant for 2 consecutive visits were discontinued and replaced to meet the goal of 60 evaluable subjects. Additional mealtime medication was taken after consumption of the meal. The study was approved by the associated Institutional Review Boards and conducted in accordance with the Declaration of Helsinki.

Eligibility criteria included: males or females between 18-75 years of age, maintained on a stable dose of metformin and/or sulfonylureas for at least 3 months prior to study participation, body mass index (BMI) >23 kg/m², and type 2 diabetes as assessed by an HbA_{1c} $>7\%$, a fasting serum glucose ≥ 126 mg/dL, or 2-hour post-prandial glucose (PPG) >200 mg/dL. Amongst the exclusion criteria included the need for insulin therapy and/or Type 1 diabetes mellitus, known uncontrolled cardiovascular diseases or uncontrolled cardiovascular risk factors, participation in a previous BTI320 study, other diseases that will influence glycemic levels (e.g., need for chronic steroids), and an active disease that would affect absorption, distribution, metabolism, and/or excretion of BTI320.

Written informed consent was obtained from all participants prior to any trial-related activities.

The primary objective was to investigate the change from Baseline to Week 12 in the area under the glucose concentration-time curve (AUC) 2-hr PPG excursions in subjects receiving BTI320 compared with those subjects receiving placebo (PBO); all subjects continued with their current metformin and/or sulfonylurea therapy for glycemic control and encouraged to not change the dosage throughout the study unless determined by the Principal Investigator. Secondary objectives were the change from baseline of the biomarkers: HbA_{1c}, 1-hr and 3-hr PPG excursions, BMI, fasting serum lipid levels, systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial blood pressure (MAP), highly sensitive C-reactive protein (hsCRP), C-peptide, and insulin levels, fasting blood glucose, CGM AUC, and oral hypoglycemic medication dosage at Weeks 3, 6, and 12.

Safety assessments, including adverse events and changes in clinical laboratory safety test results, vital signs, physical examinations, hypoglycemia events and withdrawals or drop-out rates were collected. A symptomatic hypoglycemia episode was defined as an event with symptoms consistent with hypoglycemia and confirmed by blood glucose readings <70 mg/dL. Symptoms included but were not limited to: sweating, dizziness, tremors, lightheadedness, nervousness, hunger, headaches, weakness, and/or tiredness.

Randomization and treatments

Enrolled subjects were randomized at a 1:1 ratio to two treatment arms: intervention group (current treatment + BTI320) or placebo control group (current treatment + placebo) by the centralized distribution source (Fisher Clinical Services). The subjects and investigators were blinded to the randomization. No change in

current therapy was allowed except for lowering the metformin and/or sulfonylurea dose if hypoglycemia was determined. All subjects were instructed to take 4 g of BTI320 or placebo, 10-15 minutes prior to breakfast, lunch, and dinner daily. The oral hypoglycemics were taken after meals.

The commercially available CGMS used during the study was the Abbott Freestyle Libre Pro system, which consists of a glucose sensor and data reader that assesses systemic glucose readings every 15 minutes. The Abbott Freestyle Libre Pro system was blinded to the subject, but the investigator was unblinded for safety monitoring of hypoglycemia. Data from the device were downloaded at each visit and recorded for statistical analyses.

On average, no large differences in the number of tablets consumed at each visit were observed between the two treatment groups at any visit, with the compliance rate at approximately 85%. There was a slight increase to 89% in placebo treatment group at Week 12.

Statistical analyses

Due to the exploratory nature of the study, appropriate statistical comparisons were performed. Three populations were identified in the statistical analysis plan (SAP) for analyses:

- Intent-to-Treat (ITT): Subjects who were randomized, received any study drug, and had any efficacy data recorded after taking study drug.
- Per Protocol (PP): All ITT subjects who did not have a major protocol deviation
- Safety: Subjects who received at least one dose of study drug.

All study results were summarized by descriptive statistics per treatment arm at each study visit. For continuous variables, data were presented by non-missing sample size (n), mean, standard deviation, median, and range (minimum, maximum). For categorical variables, data were presented by frequency count and percentage.

Analysis was performed using SPSS version 26. For the statistical comparisons, the two-sided significance level was set at 0.05. Analysis was performed using Statistical Analysis System (SAS) version 9.2 or later. The statistical significance of the change from Baseline of continuous variables was examined by paired t-tests.

In addition to the SAP standard analysis identifying the difference of the means between BTI320 and placebo groups, a statistical re-analysis was performed using each subject as his/her own control, minimizing intrasubject variability, and the comparison of percent changes minimizes inter-subject variability. Further, since the original statistical analysis substituted a value of 0 or interpolation for missing data, a statistical re-analysis was performed, avoiding patient data where these datasets were incomplete. This dataset included re-visiting the 72-hour CGM data which were missing more than 50% of the time due to the lack of adherence of the CGM glucose sensor patches to the subject's skin. Patient-specific, non-interpretable data for efficacy determinations were defined

as subjects with insufficient sampling during the 180-minute postprandial test or missing the Baseline (pre-prandial) level; these data were not analyzed in the efficacy assessments but included in the safety population. Both datasets (statistical analysis and statistical re-analysis) are presented in this paper.

Results

A total of 102 subjects were screened at five study sites within the US; 36 subjects were screen failures (29 not meeting the inclusion criteria, 5 declined to participate, and 2 with other reasons) and excluded from the study. Sixty-six (66) subjects were randomized into the study, of which 33 each received BTI320 treatment or placebo were included in the safety population. Thirty subjects (30) subjects in each treatment group completed the study and were included in the ITT population, and 51 subjects who did not have a major protocol deviation were included in the PP population (data not shown).

Demographics

Demographic characteristics between the two treatment arms appeared reasonably balanced, except for gender where more males were in the placebo treatment group (n=18 of 30) than in the BTI320 treatment group (n=15 of 30). As such, subjects in the placebo treatment group had slightly greater average body weight (102.6 ± 18.6 vs. 96.1 ± 22.3 kg) and body mass index (34.9 ± 4.8 vs. 33.5 ± 6.3 kg/m²) than those in the BTI320 treatment group. In contrast, baseline HbA_{1c} values (mean \pm SD) were greater in the BTI320 treatment group compared with the placebo group ($8.1 \pm 1.3\%$ vs. $7.5 \pm 1.1\%$). The other baseline biomarkers including C-reactive protein, glucose, insulin, cholesterol, HDL, and LDL (direct) levels were also greater in the BTI320 treatment group compared with the placebo group; all other characteristics and biomarkers including age, blood pressures (systolic, diastolic, mean arterial), C-peptide, LDL (calculated), and triglycerides were effectively equivalent between the two treatment groups (Table 1).

Efficacy analysis

PPG AUC

For the ITT population, both treatment groups showed a reduction in 2-hr PPG AUC from Baseline at Week 12, whereas BTI320 (-795.0 mg/dL*min) demonstrated a greater reduction in mean 2-hr PPG AUC than placebo (-228.75 mg/dL*min) (Table 2). Median 2-hr PPG AUC values were -401.25 vs. $+101.25$ mg/dL*min in BTI320 and placebo groups, respectively. BTI320 treatment group also showed a greater mean reduction at Week 12 than the placebo group in the secondary efficacy parameters: 1-hr (-108.21 vs. $+99.91$ mg/dL*min) and 3-hr (-1543.39 vs. -480.54 mg/dL*min) PPG AUC. All PPG AUC measurements in the BTI320 treatment group showed a decreasing trend from Baseline at Weeks 6 and 12 compared with placebo which demonstrated an increasing trend at Week 6 and a slight decrease at Week 12 (Figure 1).

Utilizing the 72-hour CGM readings, parallel increases in CGM glucose AUC were observed from Baseline to Week 3 in both treatment groups and then separation occurred (Figure 2). CGM

Table 1: Mean \pm SD baseline demographics of the mITT patient population.

	BTI320	Placebo
Gender (F=female, M=male)	15F/15M	12F/18M
Age (yr)	60.3 \pm 9.4	60.8 \pm 10.8
Actual body weight (kg)	96.1 \pm 22.3	102.6 \pm 18.6
Body mass index (kg/m ²)	33.5 \pm 6.3	34.9 \pm 4.8
Blood pressure – systolic (mmHg)	125 \pm 17	126 \pm 11
Blood pressure – diastolic (mmHg)	78 \pm 9	79 \pm 8
Blood pressure – MAP (mmHg)	94 \pm 11	94 \pm 7
C-reactive protein (mg/dL)	4.5 \pm 5.9	2.6 \pm 2.7
C-peptide (ng/mL)	2.84 \pm 1.36	3.14 \pm 1.48
Glucose (mg/dL)	156 \pm 43	141 \pm 44
Insulin (ng/mL)	25.9 \pm 36.8	22.9 \pm 18.1
Hemoglobin A _{1c} (%)	8.1 \pm 1.3	7.5 \pm 1.1
Cholesterol – total (mg/dL)	172.1 \pm 37.2	148.2 \pm 36.4
High-density lipoproteins (mg/dL)	44.0 \pm 9.0	38.4 \pm 6.9
Low-density lipoprotein (calc.) (mg/dL)	60.7 \pm 38.1	60.2 \pm 41.0
Low-density lipoprotein (direct) (mg/dL)	134.9 \pm 38.4	94.4 \pm 38.0
Triglycerides (mg/dL)	178.7 \pm 65.5	181.9 \pm 94.8

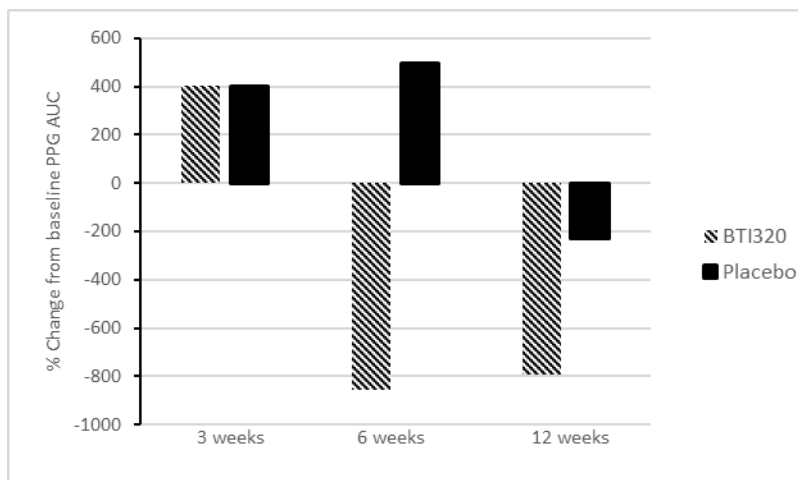


Figure 1: Changes from Baseline in 2-hr PPG AUC (mg/dL*min) at Weeks 3, 6 and 12 (mITT Population). BTI320 treatment group showed a greater reduction in 2-hr PPG AUC from Baseline at Weeks 6 and 12 than placebo.

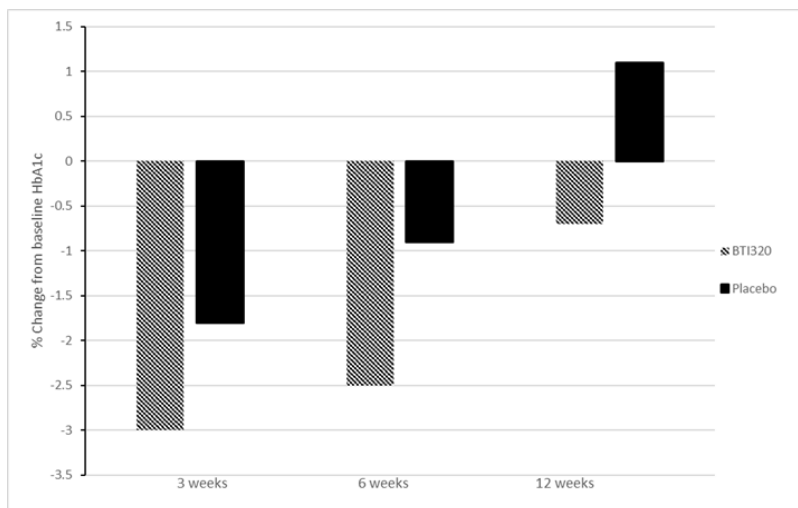


Figure 2: Mean percent change from Baseline HbA_{1c} AUC at Weeks 3, 6, and 12 (mITT Population). BTI320 treatment group showed a greater mean percent decrease of HbA_{1c} AUC from Baseline at Weeks 3, 6 and 12. At Week 3 and 6 weeks, placebo showed a mean percent increase from Baseline.

Table 2: Summary of Changes in 1-hr, 2-hr and 3-hr PPG AUC (mg/dL*min) from Daily Baseline at Weeks 3, 6 and 12 (ITT population).

Treatment	Parameter	Changes between Baseline & Week 3			Changes between Baseline & Week 6			Changes between Baseline & Week 12		
		Changes in 1-hr	Changes in 2-hr	Changes in 3-hr	Changes in 1-hr	Changes in 2-hr	Changes in 3-hr	Changes in 1-hr	Changes in 2-hr	Changes in 3-hr
BTI320	Mean	186.43	402.86	440.89	-310.45	-858.48	-1037.95	-108.21	-795.00	-1543.39
	SD	1248.996	3948.508	6281.455	1697.182	4797.962	7968.577	1484.472	3414.564	5694.758
	Median	502.50	873.75	540.00	-75.00	-322.50	525.00	-11.25	-401.25	-1117.50
	Min	-2242.50	-10117.50	-17962.50	-5257.50	-16012.50	-25147.50	-4050.00	-11625.00	-19065.00
	Max	2400.00	7605.00	10215.00	3007.50	8580.00	19455.00	3187.50	3825.00	5745.00
	N	28	28	28	28	28	28	28	28	28
PBO	Mean	268.66	399.91	569.73	195.54	495.00	621.96	99.91	-228.75	-480.54
	SD	1198.412	3447.247	5960.628	936.783	2663.650	4474.998	1114.415	3501.430	5803.968
	Median	348.75	352.50	652.50	120.00	652.50	-176.25	18.75	101.25	-558.75
	Min	-2227.50	-5257.50	-8880.00	-1507.50	-3547.50	-5257.50	-2145.00	-6952.50	-11115.00
	Max	3000.00	10035.00	19770.00	2025.00	6900.00	14235.00	2685.00	8475.00	16005.00
	N	28	28	28	28	28	28	28	28	28

The reported AUC is adjusted for the Baseline glucose value of the day at the individual subject level, and overall changes compare the difference between Visits 2 and 4, 6 and 9.

Values in **bold** represent the primary efficacy endpoint.

glucose AUC of the PBO group continued to rise, suggesting that placebo had no effect on glucose excursions. In contrast, CGM glucose AUC of the BTI320 group leveled off at Weeks 6 and 12. It is important to note that many CGM readings were not evaluated due to errors in collection of glucose levels by the CGM; thus, these data should be used cautiously.

Fasting (pre-meal) blood glucose

Within the ITT population, the fasting (pre-meal) PPG results showed that all the minimum fasting (pre-meal) PPG levels were >70 mg/dL at Baseline, Weeks 3, 6 and 12, suggesting that no subject had experienced hypoglycemia during the pre-meal time period. However, the maximum fasting (pre-meal) PPG levels were all >180 mg/dL at Baseline, Weeks 3, 6, and 12, suggesting that many subjects had experienced hyperglycemia pre-meal. There were more subjects (24.2%) in the BTI320 treatment group that experienced hyperglycemia under fasting conditions at their Baseline level than the placebo group (16.1%), yet the number of subjects who experienced hyperglycemia was similar between treatment groups at Week 12 (BTI320, 25.0%; PBO, 24.1%). At Week 12, the net difference in fasting glucose between treatment groups BTI320 and placebo was 7.79 mg/dL. The results are not statistically significant, and the 95% CI fails to demonstrate the potential changes between treatment groups (95% CI: -21.14, 36.71), likely due to the small numbers of subjects and the wide variability amongst groups.

HbA_{1c}

For the ITT population, BTI320 treatment group showed a greater mean reduction in HbA_{1c} from Baseline at Week 3 (BTI320, -0.19%; PBO, -0.16%) and Week 6 (BTI320, -0.16%; PBO, -0.11%) compared to placebo. At Week 12, BTI320 treatment group showed a modest reduction in HbA_{1c} from Baseline (-0.03%) while the placebo treatment group had an increase from Baseline (0.04%), with a net difference of 0.08%. The results are not statistically significant, and the 95% CI shows the potential changes between treatment groups (Figure 3).

For the Statistical Re-Analysis mITT population, the mean (±SD) HbA_{1c} at Baseline in BTI320 treated subjects was 8.2 ± 1.2% (range: 6.4 – 10.6%), and 8.1 ± 1.5% at Week 12, with a mean percent decrease of -0.7±12.7%. The mean HbA_{1c} at Baseline in placebo treated subjects was 7.5 ± 1.1% (range: 5.3 – 10.0%), and 7.5 ± 1.3% at Week 12, with a mean percent of Baseline increase of +1.1 ± 13.0%. The absolute mean change of HbA_{1c} in BTI320 treated subjects was -0.1% from Baseline and in placebo treated subjects was 0.0% from Baseline at Week 12 (Table 3). Further, the mean slope of HbA_{1c} was -0.003 ± 0.088 for all subjects taking BTI320 compared with +0.008 ± 0.080 in the placebo group.

To understand the interplay between the mean 2-hr PPG AUC and mean Hb_{A1c} values, a bubble plot was utilized (Figure 4). The location of the bubble represents the mean of the 2-hr PPG AUC i.e., the higher the bubble, the higher the 2-hr PPG AUC. Note that baseline PPG AUC for BTI320 was higher than those receiving PBO (7567.50 vs. 6552.59 mg/dL*min). The size of the bubble reflects the HbA_{1c} (%) level at any given Week, where the bubble size is proportional to the level of HbA_{1c}. The bubble was much larger and greater in those subjects administered BTI320 than those treated with PBO, suggesting that the group administered BTI320 was less compliant compared to the PBO group, including at baseline prior to the addition of study drug.

Postprandial Insulin (PPI) AUC

PPI levels were measured at each visit and measurements were collected at pre-meal (fasting), and then 15, 30, 60, 90, 120, 150, and 180 mins post-meal after taking the treatment. There was a sequential increase from pre-meal up to 120 or 150 min and then decrease or plateau until 180 min regardless of the treatment groups. There was no obvious pattern of increased or decreased PPI across visits at any given time point in both treatments. This finding may be related to the first and second phase of insulin release after a meal.

For the Statistical Re-Analysis mITT population, BTI320 treatment group had a mean percent baseline difference of 57.6 ±

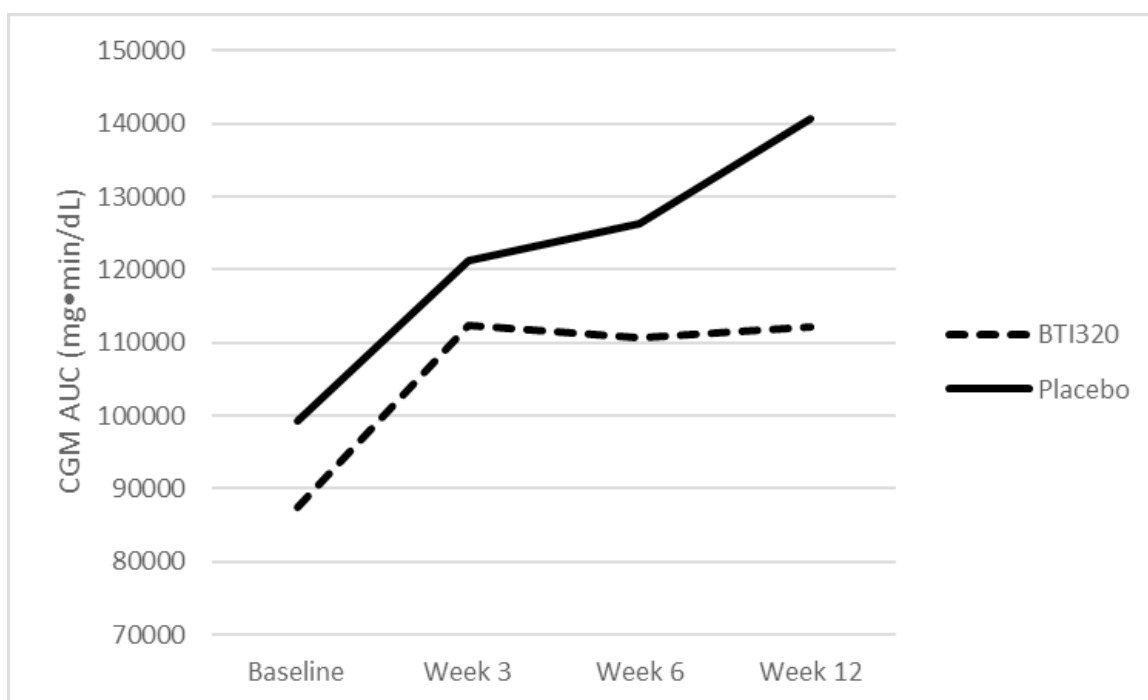


Figure 3: 72-hr CGM AUC at Baseline, Week 3, Week 6 and Week 12 (ITT Population). The BTI320 treatment group showed a gradual mean decrease in 72-hr CGM AUC from Baseline at Weeks 3, 6 and 12. The placebo treatment group showed a gradual mean increase in 72-hr CGM AUC from Baseline.

Table 3: Summary of Efficacy.

Parameter	Statistical report (Change from Baseline at Week 12 per SAP)		Statistical Re-analysis report (% Change from Baseline at Week 12 per subject)	
	BTI320	PBO	BTI320	PBO
2-hr PPG AUC	-795.00 g/dL*min	-228.75 g/dL*min		
1-hr PPG AUC	-108.21 g/dL*min	+99.91 mg/dL*min		
3-hr PPG AUC	-1543.39 g/dL*min	-480.54 mg/dL*min		
HbA _{1c}	-0.03%	+0.04%	-0.7% (absolute -0.1%)	+1.1% (absolute 0.0%)
Body Weight	-0.93 kg	-0.53 kg	-1.13%	-0.96%
BMI	-0.32 kg/m ²	-0.20 kg/m ²	-1.11%	-0.75%
Total cholesterol	-0.31 mg/dL	+5.17 mg/dL	+0.1%	+3.9%
Triglycerides	-16.66 mg/dL	+7.07 mg/dL	-5.4%	+2.0%
LDL calculated	-0.31 mg/dL	+7.82 mg/dL	+2.3%	+22.5%
LDL direct	-6.92 mg/dL	+0.08 mg/dL	-2.1%	+6.6%
HDL	+0.62 mg/dL	-0.24 mg/dL	+1.0%	-0.5%
SBP	-1.97 mmHg	+1.23 mmHg	-0.70%	+1.3%
DBP	-0.07 mmHg	+1.00 mmHg	+1.25%	+1.66%
MAP	-0.70 mmHg	+1.08 mmHg	+0.1%	+1.3%
hsCRP	-0.48 mg/dL	+0.22 mg/dL	+9.5%	+75.3%
C-peptide AUC			+31.28%	+0.53%
PPI AUC			+220.1%	+221.3%

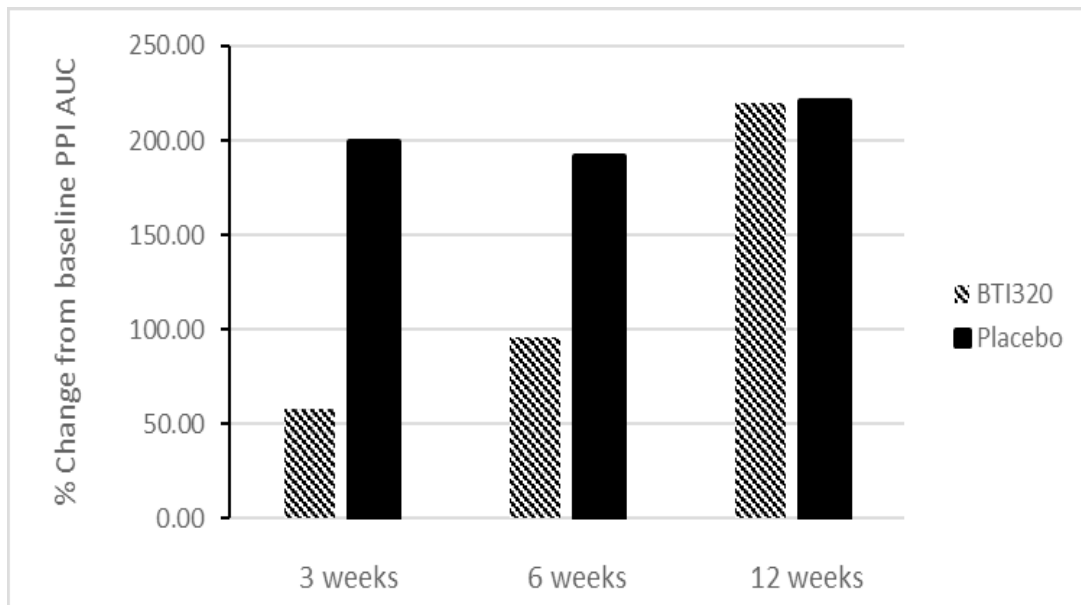


Figure 4: Mean percent change from Baseline insulin AUC at Weeks 3, 6, and 12 (mITT Population). BTI320 treatment group suppressed insulin levels at Weeks 3 and 6 but equivalent to levels found in subjects treated with placebo.

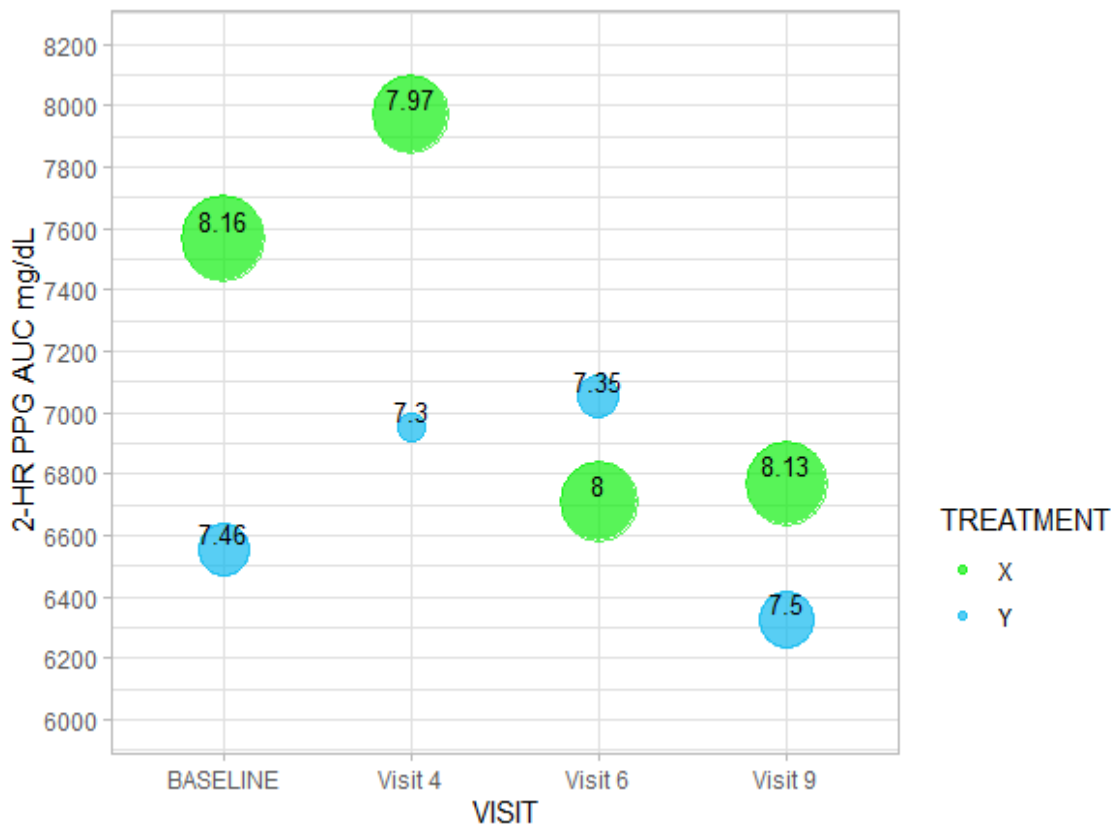


Figure 5: The primary end point (2-hr PPG) AUC at Baseline and week 12. The size of the dot represents the HbA_{1c} (%) at the given time point (Baseline and week 12). The bigger the dot, the greater the HbA_{1c} (%). The location of the dot represents the average 2-hr PPG AUC by treatment group. (Figure 14.3-1 of the Statistical Analysis Report).

227, 96.0 ± 299.8 , and $220.1 \pm 463.2\%$ in PPI AUC at Weeks 3, 6, and 12, respectively, and placebo with a mean percent difference of 199.3 ± 583.6 , 192.0 ± 659.7 , and $221.3 \pm 572.4\%$ at Weeks 3, 6, and 12, respectively. Low PPI AUC values were observed at Weeks 3 and 6 in the BTI320 treatment group, which would be expected per the mechanism of action of BTI320, however, there were no differences in insulin levels at Week 12 between groups. Interestingly, insulin levels were high and consistent at Weeks 3, 6, and 12 in the placebo group (Figure 5).

Body weights

For the Statistical Re-Analysis mITT population, there was a mean net difference from Screening in body weight (BTI320, $-1.13 \pm 2.26\%$, n=30; PBO, $-0.96 \pm 3.54\%$, n=28) and BMI (BTI320, $-1.11 \pm 2.28\%$, n=30; PBO, $-0.75 \pm 3.65\%$; n=30) at Week 12. In the

study, weight loss was reported in 20 subjects (67%) on BTI320 and 16 (59%) on placebo; and loss in baseline BMI in 18 subjects (60%) on BTI320 and 17 (57%) on placebo.

Fasting serum lipid levels

For the Statistical Re-Analysis mITT population, at Week 12, the lipid panel test results showed a mean percent difference from Baseline favoring BTI320 treatment group compared to placebo treatment group (n=31 in each group except where denoted) in total cholesterol (BTI320, $0.1 \pm 12.6\%$; PBO, $3.9 \pm 20.5\%$, triglycerides (BTI320, $-5.4 \pm 26.4\%$; PBO, $2.0 \pm 39.0\%$, n=31), LDL calculated (BTI320, $2.3 \pm 27.6\%$, n=18; PBO, $22.5 \pm 72.8\%$, n=17), LDL direct (BTI320, $-2.1 \pm 16.5\%$, n=13; PBO, $6.6 \pm 28.6\%$, n=12), and HDL (BTI320, $1.0 \pm 11.5\%$, n=31; PBO, $-0.5 \pm 9.1\%$, n=31) (Figure 6).

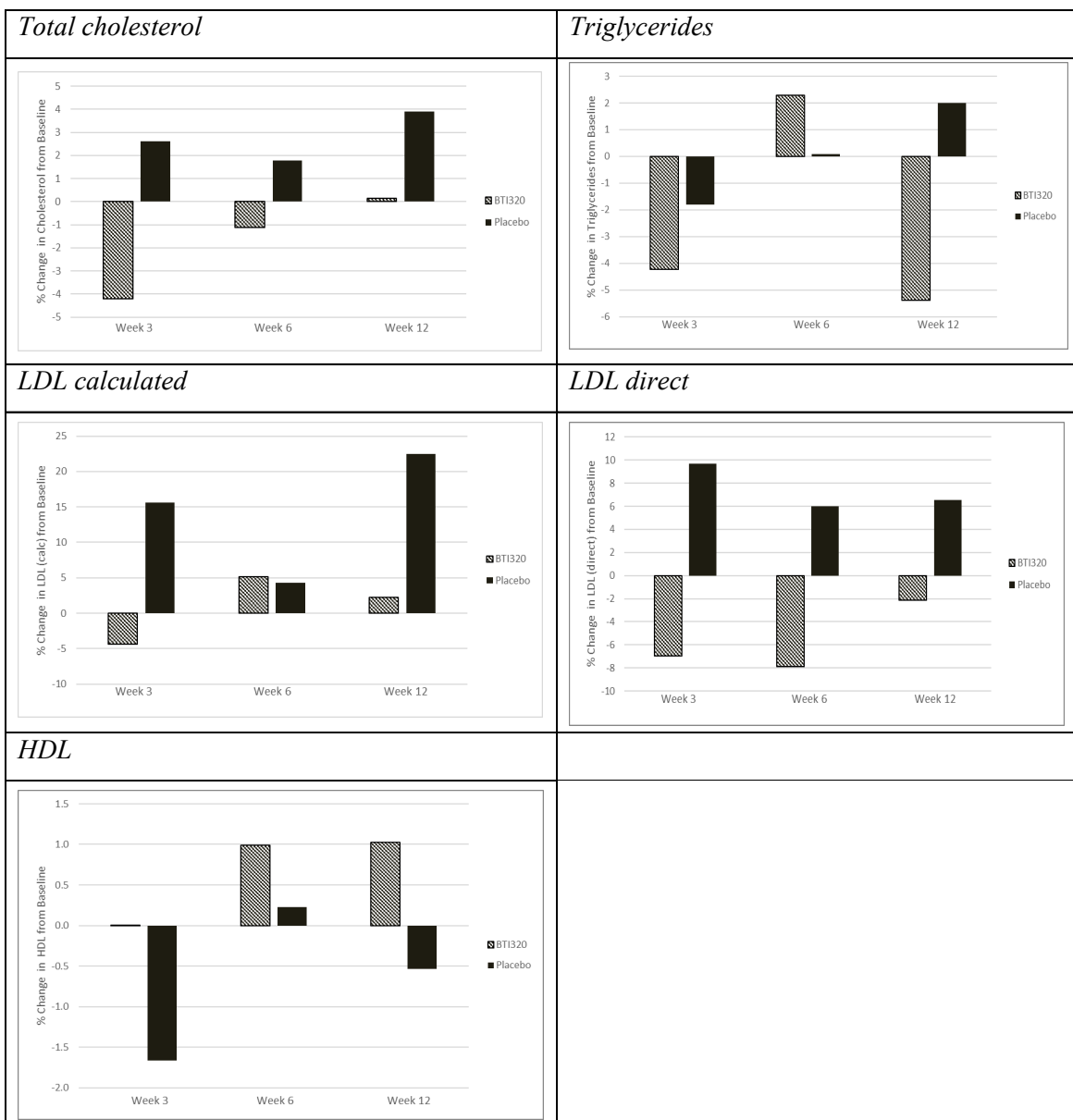


Figure 6: Lipids (mITT Population). The lipid panel test results showed a mean percent difference from Baseline favoring BTI320 treatment group compared to the placebo treatment group at Weeks 3, 6 and 12.

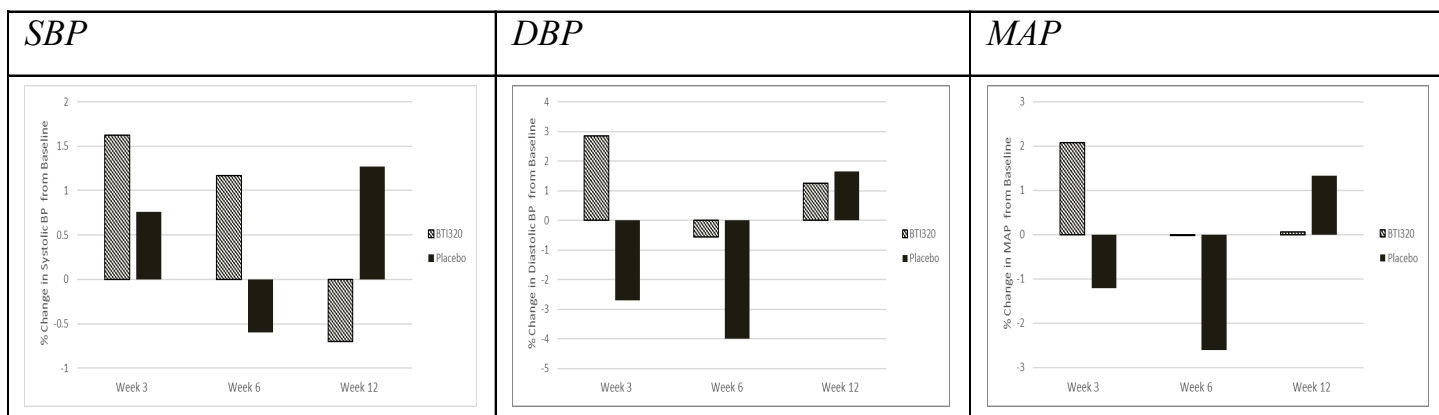


Figure 7: Blood Pressure (mITT Population). At Week 12, BTI320 treatment group had a mean reduction from Baseline compared to a mean increase with the placebo treatment group in systolic blood pressure (SBP), and a modest mean increase in diastolic blood pressure (DBP) and mean arterial pressure (MAP) compared with placebo.

SBP, DBP, and MAP

For the Statistical Re-Analysis mITT population, at Week 12, BTI320 treatment group had a mean reduction from Baseline in SBP ($-0.70 \pm 13.3\%$, $n=30$) compared to a mean increase with the placebo treatment group ($+1.3 \pm 9.7\%$, $n=30$), and a mean increase in DBP (BTI320, $+1.25 \pm 17.2\%$, $n=30$; PBO, $+1.66 \pm 9.11\%$, $n=30$) and MAP (BTI320, $+0.1 \pm 12.5\%$, $n=30$; PBO, $+1.3 \pm 8.2\%$, $n=30$) (Figure 7).

hsCRP levels

For the ITT population, the BTI320 treatment group had a mean reduction in hsCRP from Baseline at Week 12 (-0.48 mg/dL, $n=30$), while the placebo treatment group had a mean increase ($+0.22$ mg/dL, $n=27$). Ten (33%) BTI320 and 11 (41%) placebo treated subjects had hsCRP levels above the reference range at Week 12.

For the Statistical Re-Analysis mITT population, both treatment groups had a mean percent (%) increase in hsCRP from Baseline at Week 12 with wide variability despite comparing to their own controls (BTI320, $9.5 \pm 75.1\%$, $n=31$; PBO, $75.3 \pm 228.9\%$, $n=31$). This is most likely due to the variability of the hsCRP laboratory assay rather than individual differences in hsCRP.

Postprandial C-peptide (PPC)

PPC levels were measured at each visit and measurements were collected at pre-meal (fasting), and then 15, 30, 60, 90, 120, 150 and 180 mins post-meal after taking the treatment. There was a sequential increase from pre-meal up to 150 min and then mostly decreasing slightly at 180 min regardless of the treatment groups. There was no obvious pattern of increased or decreased PPC levels across visits at any given time point in both treatments.

For the Statistical Re-Analysis mITT population, BTI320 treatment group had a mean net difference of 15.81 ± 60.23 , 13.66 ± 34.65 , and $31.28 \pm 80.32\%$ in C-peptide AUC at Weeks 3, 6, and 12, respectively, and placebo with a mean net difference of 6.1 ± 25.77 , 2.71 ± 21.84 , and $0.53 \pm 27.86\%$ at Weeks 3, 6, and 12, respectively; note the large standards of deviation found in these data.

All concomitant and oral hypoglycemic medication discontinuations and/or changes in regimen

A total of 13 subjects (4 in the BTI320 group, 9 in the placebo group) involving 18 concomitant drugs were discontinued during the 12-week period. Of these drugs, 8 were antibiotics/cough and cold medications, 2 gastrointestinal drugs, 1 lipid-lowering drug, 1 antihypertensive, 1 antidepressant, and 5 oral hypoglycemics. There were no oral hypoglycemics discontinued in the BTI320 group.

Five (5) subjects in the placebo treatment group experienced change in medications within the 12-week period, with one subject having his medication changed from glipizide 5 mg to insulin 10 IU, two subjects had their Type 2 diabetes medication dosage reduced (metformin 500 mg from BID to QD, glimepiride 4mg was reduced to 2mg), and two subjects stopped their Type 2 diabetes medication (glipizide).

The CGM results showed that subjects in the BTI320 treatment group experienced hypoglycemia in a slightly shorter time (1-2 hours) than those in the placebo treatment group (2-3 hours) and this is consistent across all visits. However, there is no obvious pattern regarding hyperglycemia between groups and across visits during the 72-hour observation period, and the average hyperglycemia time periods were 20-29 hours for the BTI320 treatment group and 20-23 hours for the placebo group.

Glycemic variability

Both %CV and SD were used to explore glucose stability and variability based on the available CGM data for each visit or any glucose measurement at frequent and regular basis. At Week 12, BTI320 treatment group had a slightly higher number of subjects (84.6%) compared to placebo (79.2%) in stable glucose condition. However, the CGM data consisted of a substantial amount of missing data, hence these results may be biased due to insufficient data.

Safety analysis

Overall, five BTI320 treated subjects experienced 8 treatment-related AEs that included diarrhea (3), dyspepsia, flatulence, frequent bowel movements, nausea, and gastroenteritis (Table 4).

Three placebo treated subjects experienced 5 treatment-related AEs that included hypoglycemia (3 subjects), abdominal pain and diarrhea. There were no serious adverse events or severe adverse events. All events were either mild or moderate in severity.

Table 4: Frequency of Treatment-Emergent AE (Related / Possibly Related to Study Drug).

System Organ Class Preferred Term	BTI320 (N = 33)	PBO (N = 33)
Overall Total	5 (15.2) [8]	3 (9.1) [5]
Gastrointestinal Disorders		
Abdominal Pain	0 (0) [0]	1 (3.0) [1]
Diarrhea	2 (6.1) [3]	1 (3.0) [1]
Dyspepsia	1 (3.0) [1]	0 (0) [0]
Flatulence	1 (3.0) [1]	0 (0) [0]
Frequent Bowel Movements	1 (3.0) [1]	0 (0) [0]
Nausea	1 (3.0) [1]	0 (0) [0]
Infections and Infestations		
Gastroenteritis	1 (3.0) [1]	0 (0) [0]
Metabolism and Nutrition Disorders		
Hypoglycemia	0 (0) [0]	3 (9.1) [3]

N: Number of subjects studied

(): Percentage of subjects with adverse events

[]: Number of adverse events

The five most common concomitant medications used were Biguanides (metformin) in >90% of subjects, followed by HMG CoA reductase inhibitors, Sulfonylureas, ACE inhibitors (pain), and Platelet aggregation inhibitors excluding heparin in >30% of subjects in both treatment groups. There were no safety concerns observed in the laboratory safety tests.

Discussion

The primary objective of this study was to determine the effectiveness of BTI320 on glycemic control at 12 weeks compared to placebo as an add-on therapy to standard of care for patients with Type 2 diabetes. The data show that there was a reduction in the PPG AUC as early as 6 weeks and at 12 weeks post-Baseline in subjects treated with BTI320 compared with placebo. In addition, there was a trend of greater improvement in BTI320 treated subjects compared to placebo in HbA_{1c} levels, lipids, and blood pressure parameters (secondary objective outcome). Overall, these similarities and differences remained true in the ITT, PP (data not shown), and the Statistical Re-Analysis mITT populations.

There were no differences in the number, severity, and treatment relationship of adverse events between the two treatment groups.

This study was designed to establish sample size calculations for a larger, adaptive Phase 3 program and affirmation of efficacy in patients with Type 2 diabetes mellitus. Clearly these two objectives were met. Of significant importance is the findings of the difference in the mean HbA_{1c} levels at Baseline between those administered BTI320 and placebo ($8.2 \pm 1.2\%$ vs. $7.5 \pm 1.1\%$) and changes in HbA_{1c} levels over time between the two treatment groups. There was a mean absolute difference of -0.1% (consistent with a mean

net difference of -1.8%) in those treated with BTI320. The within group control and trends are able to demonstrate a significant effect with BTI320 despite the relative differences at Baseline. While the difference appears small, this is a clinically significant difference in a relatively short period of treatment duration [23,24], although others have stated that 16 weeks or more should be evaluated for meaningful change in HbA_{1c} changes [25]. Nonetheless, there were positive changes observed in this study.

The difference in mean HbA_{1c} between groups also highlights an inherent bias against the BTI320 group. The greater the percentage of glycosylated hemoglobin suggests a greater preponderance of non-compliant diabetic patients [26-28]. Other factors such as elevated CRP, glucose, insulin, cholesterol, and LDL (direct) were substantially higher than the placebo group at Baseline, and only Baseline HDL levels were lower in the placebo group, suggesting that the totality of medical evidence showed that those subjects randomized to the BTI320 group were less well-controlled than those randomized to placebo [29,30]. Further, there were more patients in the BTI320 group with hyperglycemia after fasting prior to dosing in the PPG studies compared with those randomized into the placebo group. Despite these negative Baseline clinical and laboratory parameters, those administered BTI320 had better outcomes.

To overcome the limitations learned from this study and the importance of moving forward with the use of CGMS, the electronic records need improvement at the site level. A more educational aspect of the technology should be added to the study to help study personnel and subjects better understand the application of the technology and how to make suitable lifestyle changes to improve compliance, thereby maximizing the benefit learned from the CGM. It is believed that effective use of technology may reduce the growing burden of diabetes by improving the accessibility, sustainability, and affordability of diabetic care.

The use of CGM is becoming more useful for people with Type 2 diabetes (even those not on intensive insulin therapy) as many of them experienced more stable glucose levels with CGM use. A reliable CGM program with adequate training and vigilant monitoring would allow identification of critically important prognostic glycemic metrics: time-in-range (TIR) which has been linked with good outcomes, and two metrics that predict poorer outcomes: time-above-range (TAR) and time-below-range (TBR). This is of great importance as glycemic metrics allow an individual to obtain immediate feedback on glucose levels, as well as direction and rate of change in glucose levels in real-time. By understanding the dynamic and dramatic effect of postprandial glucose excursions (“the spike”), diabetic patients can make informed decisions regarding therapeutic regimens, allowing them to react immediately and appropriately to reduce or prevent acute glycemic events such as hypoglycemia.

Unfortunately, the CGM component of this study failed to deliver as expected, such as data consisting of substantial gaps in the data

stream per individual, most often due to lack of adherence of the sensor patch on the skin of the subject. In a few cases, surgical tape was used to keep the sensor in place, but these were very rare. Due to the specific format and volume of missing data plus insufficient detail on the reasons behind these errors in data collection, it was not possible to salvage the use of the CGM data nor apply any imputations. Further, the monitoring period of 72 hours (very few lasted even the 72 hours) may have been too short of a period to accurately measure the usefulness of the CGM in determining the TIR, TAR, and TBR. These are valuable lessons learned in planning subsequent confirmatory studies.

In previous studies as well as in this study, BTI320 attenuates the rapid rise in postprandial glucose by reducing both the rate and the amount of glucose absorbed in the small intestine. The reduced glucose absorption and reduction in glycemic variability, as confirmed by CGM indices, are thought to contribute to the modest weight loss seen in BTI320 treated subjects. Furthermore, improvements in blood pressure and lipid profiles may have an effect on diabetic comorbidities including cardiovascular disease (CVD) with long-term use, as reductions in blood pressure (by 10mm Hg) or LDL cholesterol concentration (by 1 mmol/L or 39 mg/dL) have been observed to independently reduce the risk of CVD, all-cause death, or both, by 10-20% in Type 2 diabetics [31].

Conclusion

This trial was underpowered to draw a definitive conclusion on the efficacy of BTI320 to reduce HbA_{1c} as an add-on treatment to standard of care in patients with T2D. Nonetheless, the totality of evidence of these data from this exploratory study support the efficacy of BTI320 in patients with T2D, provide support for a phase 3 registration study, and can provide a road map for the control and variation adjustments on an expedited timeline, thus achieving better long-term patient outcomes and controls. Although these findings were not statistically significant, the results show the potential of BTI320 treatment effect. A larger sample size is warranted for confirming the safety and immediate and long-term effects of BTI320, demonstrating a significant benefit in this population.

References

1. Paneni F, Lüscher TF. Cardiovascular protection in the treatment of type 2 diabetes: A review of clinical trial results across drug classes. *Am J Cardiol.* 2017; 120: S17-S27.
2. Reutrakul S, Mokhlesi B. Obstructive sleep apnea and diabetes: A state-of-the-art review. *Chest.* 2017; 152: 1070-1086.
3. Sharma M, Nazareth I, Petersen I. Trends in incidence, prevalence and prescribing in type 2 diabetes mellitus between 2000 and 2013 in primary care: a retrospective cohort study. *BMJ Open.* 2016; 6: e010210.
4. Luk AOY, Ma RCW, Lau ESH, et al. Risk association of HbA_{1c} variability with chronic kidney disease and cardiovascular disease in type 2 diabetes: prospective analysis of the Hong Kong Diabetes Registry. *Diab/Metab Res Rev.* 2013; 29: 384-390.

5. Agardh EE, Ahlbom A, Andersson T, et al. Explanations of socioeconomic differences in excess risk of Type 2 diabetes in Swedish men and women. *Diabetes Care.* 2004; 27: 716-721.
6. Volaco A, Cavalcanti AM, Filho RP, et al. Socioeconomic status: The missing link between obesity and diabetes mellitus? *Curr Diabetes Rev.* 2018; 14: 321-326.
7. Baribault H. Mouse models of type 2 diabetes mellitus in drug discovery. *Methods Mol Biol.* 2016; 1438: 153-115.
8. Bolen S, Feldman L, Vassy J, et al. Systematic review: Comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. *Ann Intern Med.* 2007; 147: 386-399.
9. Stein SA, Lamos EM, Davis SN. A review of the efficacy and safety of oral antidiabetic drugs. *Exp Opin Drug Safety.* 2013; 12: 153-175.
10. Chan JCN, So W, Ma RCW, et al. The complexity of vascular and non-vascular complications of diabetes: The Hong Kong Diabetes Registry. *Curr Cardiovasc Risk Rep.* 2011; 5: 230-239.
11. Chan JCN, Malik V, Jia W, et al. Diabetes in Asia: Epidemiology, risk factors, and pathophysiology. *JAMA.* 2009; 301: 2129-2140.
12. Cade WT. Diabetes-related microvascular and macrovascular diseases in the physical therapy setting. *Phys Ther.* 2008; 88: 1322-1335.
13. Stowers JM. Modern approach to diabetes mellitus 1. *Brit Med J.* 1976; 1: 509-511.
14. Rena G, Pearson ER, Sakamoto K. Molecular mechanism of action of metformin: old or new insights. *Diabetologia.* 2013; 56: 1898-1906.
15. Nauck MA, Wefers J, Meier JJ. Treatment of type 2 diabetes: challenges, hopes, and anticipated successes. *Lancet Diabetes Endocrinol.* 2021; 9: 525-544.
16. Liu Z, Zhao X, Sun W, et al. Metformin combined with acarbose vs. single medicine in the treatment of type 2 diabetes: A meta-analysis. *Exp Therap Med.* 2017; 13: 3137-3145.
17. FDA 2020. FDA Alerts Patients and Health Care Professionals to Nitrosamine Impurity Findings in Certain Metformin Extended-Release Products. 28-May-2020. Accessed 22-Sept-2021.
18. Luke DR, Cheng EMY, Stokes E, et al. Dose-ranging study of BTI320 in type 2 diabetic patients. *Trend Diabet Metabol.* 2020; 1-9.
19. Luke DR, Lee KYL, Rausch CW, et al. Phase 1 study of the pharmacology of BTI320 before high-glycemic meals. *Clin Pharmacol Drug Dev.* 2019; 8: 395-403.
20. Trask LE, Chaidarun SS, Platt D, et al. Treatment with novel galactomannan derivative reduces 2-hour postprandial glucose excursions in individuals with type 2 diabetes treated with oral medications and/or insulin. *J Diab Sci Technol.* 2014; 8: 1018-1022.

21. Trask LE, Kasid N, Homa K, et al. Safety and efficacy of the nonsystemic chewable complex carbohydrate dietary supplement PAZ320 on post prandial glycemia when added to oral agents or insulin in patients with type 2 diabetes mellitus. *Endocr Pract.* 2013; 19: 627-632.
22. Luk AOY, Zee BCY, Chong M, et al. A proof-of-concept study to evaluate the efficacy and safety of BTI320 on post-prandial hyperglycemia in Chinese subjects with pre-diabetes. *BMC Endocrine Dis.* 2018; 59: 1-10.
23. Hirst JE, Mackillop L, Loerup L, et al. Acceptability and user satisfaction of a smartphone-based, interactive blood glucose management system in women with gestational diabetes mellitus. *J Diabetes Sci Technol.* 2014; 9: 111-115.
24. Kennedy L, Herman WH, Strange P, et al. Impact of active versus usual algorithmic titration of basal insulin and point-of-care versus laboratory measurement of HbA 1c on glycemic control in patients with type 2 diabetes: the Glycemic Optimization with Algorithms and Labs at Point of Care (GOAL A1C) trial. *Diabetes Care.* 2006; 29: 1-8.
25. Munk J, Lind B, Jørgensen. Change in HbA 1c concentration as decision parameter for frequency of HbA 1c measurement. *Scand J Clin Lab Invest.* 2019; 79: 320-324.
26. Viana LV, Gomes MB, Zajdenverg L, et al. Interventions to improve patients' compliance with therapies aimed at lowering glycated hemoglobin (HbA 1c) in type 1 diabetes: systematic review and meta-analyses of randomized controlled clinical trials of psychological, telecare, and educational interventions. *Trials.* 2016; 17: 94.
27. Lyon AW, Higgins T, Wesenberg JC, et al. Variation in the frequency of hemoglobin A1c (HbA 1c) testing: population studies used to assess compliance with clinical practice guidelines and use of HbA 1c to screen for diabetes. *J Diabetes Sci Technol.* 2009; 3: 411-417.
28. Krapek K, King K, Warren SS, et al. Medication adherence and associated hemoglobin A1c in type 2 diabetes. *Ann Pharmacother.* 2004; 38: 1357-1362.
29. Mamo Y, Bekele F, Nigussie T, et al. Determinants of poor glycemic control among adult patients with type 2 diabetes mellitus in Jimma University Medical Center, Jimma zone, south west Ethiopia: a case control study. *BMC Endocrine Disorders.* 2019; 19: 91.
30. Sacks DB, Arnold M, Bakris GL, et al. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. *Diabetes Care.* 2011; 34: e61-99.
31. WHO. Constitution of the World Health Organization. Basic documents, 45 th ed. Geneva: World Health Organization. 2005.