SUGARDOWN®

[Also known as BTI320]

PROTOCOL SG01

Protocol Title: A Study to Evaluate the Effect of BTI320 (SUGARDOWN®) on Post-Prandial Hyperglycemia in High Risk Chinese Subjects with Pre-Diabetes

Indication studied:	Post-Prandial Hyperglycemia in Pre-diabetes
Developmental phase of study:	Phase 2
First patient enrolled:	30Mar2015
Last patient completed:	19Feb2016
Release date of full report:	08Jun2017
Company/Sponsor signatory:	Boston Therapeutics Inc. SugarDown Company Limited G/F GMP Centre, 12 Dai Fu Street, Tai Po Industrial Estate, New Territories, Hong Kong SAR

This trial was conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonized Tripartite Guideline.

2. SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
Boston Therapeutics Inc.
SugarDown Company Limited
G/F GMP Centre, 12 Dai Fu Street, Tai Po,
Industrial Estate, New Territories,
Hong Kong SAR of China</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier

Volume:

Page:</td><td rowspan="3">(For National Authority Use only)</td></tr>
<tr><td>Name of Finished Product: BTI320</td></tr>
<tr><td>Name of Active Ingredient:
Galactomannan</td></tr>
<tr><td colspan="3">Title of Study: Protocol SG01 Title: A Study to Evaluate the Effect of BTI320 (SUGARDOWN®) on Post-Prandial Hyperglycemia in High Risk Chinese Subjects with Pre-Diabetes</td></tr>
<tr><td colspan="3">Investigators: Prof. Andrea Luk, Prince of Wales Hospital, Department of Medicine & Therapeutics, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong, China</td></tr>
<tr><td colspan="3">Study center(s): One study center from Hong Kong, SAR of China</td></tr>
<tr><td colspan="2">Studied period (years):
Date of first enrolment: 30Mar2015
Date of last completed: 19Feb2016</td><td>Phase of development: Phase 2</td></tr>
<tr><td colspan="3">Objectives: The primary objective of study SG01 was to compare the effect of high dose BTI320 (HDB, 8 g) and low dose BTI320 (LDB, 4 g) with placebo on serum fructosamine in subjects at high risk for diabetes (pre-diabetic).

The secondary objectives of study SG01 were to compare the effect of HDB and LDB with placebo on CGMS parameters in subjects at high risk for diabetes and compare the effect of HDB and LDB with placebo on HbA_{1c} in subjects at high risk for diabetes.</td></tr>
<tr><td colspan="3">Methodology: BTI-320 is a non-systemic, non-toxic, chewable drug.

Randomization was performed after the investigator confirmed that the subject met all inclusion criteria. Upon randomization, each eligible subject was assigned a subject randomization number (01, 02, 03 …) in consecutive order which corresponded to one of the three study intervention arms (HDB, LDB, placebo). The allocation of study intervention to each subject was by pre-determined randomization number using computation procedures.

Study drug was taken prior to each meal ingestion.

The subjects, investigators, and site personnel involved in the study were blinded to the assignment of the investigational drug. The coding of the investigational drug remained blinded throughout the study period and could not be broken by the investigator unless information concerning the investigational drug was necessary for the medical treatment of the subject.

All subjects were maintained on the same medications throughout the entire study period, as medically feasible, with no introduction of new chronic therapies. All medications were allowed except for medications noted in the exclusion criteria as described above, including anti-diabetic agents and dietary supplements known to affect glucose or galactose metabolism.

Subjects were required to bring study medication containers to each clinic visit regardless of whether the study medication container was empty. Compliance with the study drug was calculated based on doses of study drugs taken as determined by counts of returned tablets and the number of main meals consumed. Thus, the subject who only consumed two main meals per day was expected to take 4 study drug tablets (two before each meal) for the day. The subject was asked to record the number of main meals (breakfast, lunch, dinner) consumed between Visits 3 and 4, Visits 4 and 5, Visits 5 and 6, and Visits 6 and 7.</td></tr>
</table>

Study drug was returned to the Sponsor or its designee for destruction according to local law after completion of drug accountability and reconciliation at study closure.

Number of patients (planned and analyzed): Assuming the screen failure is 67%, i.e., screen 3 subjects to have 1 subject randomized, at least 180 Chinese subjects were to be screened to achieve the target number of 60 subjects randomized.

A total of 7 visits was scheduled for this 16-week study. Subjects were followed closely for 30 ± 7 days after study.

A total of 77 subjects were screened and 60 subjects were eligible for enrollment (Data Listing 2.1, Appendix 16.2). Of the 60 subjects, 12, 24, and 24 subjects were randomly assigned to placebo, LDB, and HDB, respectively. Of the 24 subjects who received LDB, 2 (8%) discontinued from the study due to an adverse event. Of the 24 subjects who received HDB, 1 (4%) withdrew consent. Fifty-seven (57) subjects completed the study.

Diagnosis and main criteria for inclusion: Subjects who met all of the following criteria were eligible for enrollment:

1. Adult subjects ≥ 18–70 years of age
2. Chinese ethnicity
3. High risk subject with pre-diabetes as defined by meeting at least 2 of the following criteria:
    - FPG ≥ 5.6-6.9 mmol/L and/or 2-hour PG ≥ 7.8-11.0 mmol/L during 75 g OGTT
    - HbA_{1c} ≥ 5.7-6.4%
    - At least one of the following risk factors:
    - History of gestational diabetes
    - Family history of diabetes in first degree relative
    - Two or more components of the metabolic syndrome:
    - Triglyceride ≥ 1.7 mmol/L
    - Blood pressure (BP) ≥130/80 mmHg
    - High-density lipoprotein cholesterol (HDL-cholesterol) <1.3 mmol/L in women or <1.1 mmol/L in men
    - Waist circumference ≥80 cm in women or ≥ 90 cm in men.
    - Subjects on anti-hypertensive agent for treatment of hypertension or a lipid-lowering drug for the treatment of hyperlipidemia were respectively considered to have one component of the metabolic syndrome.
4. A female subject of childbearing potential who is sexually active with a non-sterilized male partner agrees to use routinely adequate and effective contraception to avoid pregnancy during the study period and up to 30 days after the final visit.
5. Able and willing to consistently record food diary to facilitate CGMS evaluation
6. Signed informed consent prior to the initiation of any study-related procedures.

Test product, dose and mode of administration: Study drug was supplied by SugarDown Company Limited as a chewable tablet containing 4 g BTI320. Control product was a placebo tablet of same appearance and taste to the study drug. All subjects were instructed to take 2 chewable tablets prior to meal ingestion:

- HDB: consists of 2 active chewable tablets
- LDB: consists of 1 active chewable tablet and 1 placebo chewable tablet
- Placebo: consists of 2 placebo chewable tablets

Subjects were recruited and randomized into High-Dose BTI320 (HDB) three times daily, Low-Dose BTI320 (LDB) three times daily, or placebo in a 2:2:1 ratio:

- HDB 8 g three times daily (n=24)
- LDB 4 g three times daily (n=24)

- Placebo three times daily (n=12)

Duration of treatment: A total of 7 visits was scheduled for this 16-week study. Subjects were followed closely for 30 ± 7 days after study.

Criteria for evaluation:

Efficacy Endpoints:

The primary efficacy endpoint was the change in serum fructosamine in subjects treated with HDB and LDB compared with placebo from baseline to Week 4.

The secondary efficacy endpoints were:

- Changes in subjects treated with HDB and LDB compared with placebo from baseline to Week 4 and Week 16 in continuous glucose monitoring system (CGMS) parameters as follows:
  - AUC post-prandial glucose at 1 hour, 2 hours, and 3 hours
  - Mean post-meal maximum glucose (MPMG)
  - Mean amplitude of glucose excursion (MAGE)
  - Mean blood glucose (MBG)
  - AUC_180
- Changes in HbA_{1c} in subjects treated with HDB and LDB compared with placebo from baseline to Week 16.
- Changes in fructosamine in subjects treated with HDB and LDB compared with placebo from baseline to Week 8, Week 12, and Week 16.
- Changes in subjects treated with HDB and LDB compared with placebo from baseline to Week 4 and Week 16 during standard meal tolerance test (MTT) in AUC of glucose, insulin, and C-peptide from 0 minute to 15, 30, 60, 90, and 120 minutes, as well as changes in glucagon-like peptide-1 (GLP-1).
- Proportion of subjects with impaired fasting glucose or impaired glucose tolerance at 30-day post-treatment compared to baseline in HDB, LDB and placebo groups.

The other secondary endpoint was between-group and within-group comparisons with repeated measures from baseline to Week 4 and Week 16:

- Blood pressure, waist circumference, body weight, BMI.
- Serum lipids, highly-sensitive C-reactive protein (hs-CRP) and urate.
- Quality of life (QOL), food satiety, nutritional intake and exercise.

Safety:

- Adverse events
- Concomitant medications
- Laboratory test results
  - Complete blood count (hemoglobin, hematocrit, platelet count and white blood cell count)
  - Renal (serum sodium, potassium, urea, creatinine) and liver function (bilirubin, alkaline phosphatase, alanine aminotransferase)
- Oral Glucose Tolerance Test (OGTT)
- Standard Meal Tolerance Test (MTT)
- Continuous Glucose Monitoring System (CGMS)

Statistical methods:
All data were expressed as mean ± standard deviation (SD) or mean (inter-quartile range [IQR]) as appropriate.

Two subject populations were analyzed:

- Intention-to-treat (ITT): All subjects who received at least one dose of BTI320 were included in the safety analysis.
- Per protocol (PP): subjects who have taken ≥ 70% of the assigned treatment were included in the

efficacy analysis.

Efficacy Results: The primary efficacy analysis results showed that the three treatment groups had a minor mean decrease in fructosamine level after 4 weeks of treatment; none of the change was statistically significant. Similar results of a minor mean decrease in serum fructosamine level from baseline were also observed in the secondary efficacy comparison of the LDB and HDB treatment groups to the placebo group after 8, 12 and 16 weeks of treatment. No hypoglycemic effect was observed.

There were no significant differences with the LDB and HDB treatment groups compared to the placebo group in the mean change from baseline in all CGMS parameters evaluated at Visit 4 (Week 4) and Visit 7 (Week 16): AUCs at 1-hour, 2-hour, and 3-hour; AUC at 24 and 72 hr; MPMG, MBG, and MAGE.

In a linear mixed model analysis adjusting for repeated measures within visits, the LDB treatment group demonstrated statistically significant differences in lowering mean post-prandial glucose levels and post-meal glucose over meals within visits compared to placebo at 1, 2, and 3-hour post meal and overall post-meal glucose with p-values ranging from <0.01 to 0.02.

The mean HbA_{1c} levels were similar among the three treatment groups at Visit 1 (-7 to -14 days) and Visit 7 (Week 16). All values remained within the defined HbA_{1c} range of 5.7-6.4%. The LDB and HDB treatment groups showed no statistically significant differences in mean changes of HbA_{1c} levels from baseline at Week 16 compared to the placebo group.

The standard meal tolerance test (MTT) results showed subjects treated with HDB and LDB showed less decrease in AUCs of 120-min glucose and C-Peptide from baseline compared to placebo at Week 16. None of the differences were statistically significant, except for the LDB treatment group at Week 4 which showed a significant mean increase in AUC 120 min C-Peptide from baseline compared with the placebo group (p=0.04). Dose dependent results were observed at Week 16 (Visit 7) in AUC 120-min plasma glucose, C-Peptide, and GLP1.

Results of the oral glucose tolerance test showed a greater number of subjects in the HDB treatment group (21, 91.3%) with no change in IFG, IGT, or worsened to normal glucose levels at 30 days post Week 16 than either the LDB (17, 77.3%) or placebo (8, 66.7%) treatment groups.

The majority of systolic and diastolic BP values measured were within the normal reference range. Overall, the highest mean SBP was <130 mmHg and the highest mean DBP was <82 mmHg; the mean changes in SBP and DBP were minor throughout all visits.

The LDB treatment group showed a statistically significant decrease in mean weight at Visit 7 (p=0.03), which also approached significance at the follow-up visit (p=0.05) compared to placebo with estimate treatment effects -1.7 and -2.1 kg, respectively. Minor decreases in mean weights and waist circumference across three treatment groups were observed throughout all study visits.

The HDB treatment group demonstrated a consistent positive effect in reduction of total cholesterol, LDL cholesterol, and triglycerides and an increase in HDL cholesterol. At Week 16, the HDB treatment group showed a statistically significant decrease (p=0.02) in mean triglyceride values and a significant increase in HDL cholesterol levels (p=0.05) compared to placebo.

Minor changes in mean hs-CRP and urate levels from baseline across three treatment groups were observed at Visits 4 and 7; none of the treatment effects for LDB and HDB treatment groups compared to the placebo in change of hs-CRP and urate were statistically significant.

Safety Results: Of the 60 treated subjects, 41 (LDB, 18/24; HDB, 16/24; Placebo, 7/12) experienced 104 all-causality AEs (LDB, 47; HDB, 36; Placebo, 21). Of the 41 subjects experienced 104 AEs, 32 (LDB, 14/24; HDB, 12/24; Placebo, 6/12) experienced 60 AEs (LDB, 28; HDB, 19; Placebo, 13) that were considered possibly- or probably-related to study treatments. The most commonly experienced AEs, flatulence (LDB, 29.2%; HDB, 29.2%; Placebo, 16.7%), abdominal distension (LDB, 25.0%; HDB, 16.7%; Placebo, 8.3%), and diarrhea (LDB, 16.7%; HDB, 12.5%; Placebo, 8.3%), which were possibly related to study drug. All of the AEs were mild or moderate in severity except for two events, osteosarcoma and flatulence, that were rated as severe. One of the severe events, osteosarcoma, was reported as a serious adverse event (SAE); the subject discontinued from the study due to this unrelated SAE. Additionally, one subject who received LDB, experienced moderate

abdominal pain and diarrhea which were considered possibly related to treatment by the investigator and discontinued from the study. These gastrointestinal AEs resolved in 6 days.

The majority of laboratory safety test results for complete blood count (hemoglobin, hematocrit, platelet, WBC), liver function tests (bilirubin, ALP, and ALT) and renal function (serum sodium, potassium, urea, creatinine) were within normal ranges. None of the abnormal values were clinically significant nor reported as an AE.

Questionnaire survey results for QOL, Appetite, International Physical Activity, and Dietary showed no remarkable differences except the HDB treatment group had a statistically significant mean increase from baseline in "Days doing vigorous physical activities" compared to placebo ($p=0.03$) at Visit 4; and the placebo group had a significant mean increase in the Social Relationship Domain total score from baseline at Visit 4, compared to the LDB and HDB treatment groups ($p<0.01$ and $p=0.03$, respectively).

Conclusion: This Phase 2, double-blind, randomized, placebo-controlled, proof of concept study examined glucose-lowering effects of BTI320, a propriety fractionated mannan, in Chinese subjects with pre-diabetes. A total of 60 eligible subjects were enrolled and randomly assigned to BTI320 8 g (24), BTI320 4 g (24) and placebo (12). Fifty-seven (57) subjects completed the 16-week study.

The changes in serum fructosamine levels from baseline to 4 weeks were -5.2, -9.4, and -8.8 µmol/L in subjects receiving low dose BTI320, high dose BTI320, and placebo, respectively. The estimated mean differences in change in fructosamine levels were not significant for comparison between intervention with BTI320 and placebo. This is not a surprising finding in that the study subjects were at high risk for diabetes but still able to regulate glucose metabolism. That there was no spike in fructosamine levels and a trend to lower fructosamine levels while on BTI320 at Week 4 supports its ability to reduce postprandial glucose excursion through the breakdown and lower absorption of glucose through the gut.

Management of post-prandial sugar spikes is critical for the prevention of diabetes, and treatment with BTI320 4 g significantly reduced post-prandial glucose AUC in 1 hour ($p<0.01$), 2 hours ($p=0.01$) and 3 hours ($p=0.02$) post meal and post-meal maximum glucose ($p=0.01$), secondary endpoints of the study. Additionally, BTI320 8 g may provide benefit in reducing serum triglyceride and increase HDL cholesterol.

Overall, BTI320 was relatively well tolerated and no hypoglycemic symptoms or events were reported in the study. The most common side-effects possibly associated with BTI320 were abdominal distension, flatulence, and diarrhea occurring in approximately 20-30% of treated subjects. Most of these were mild to moderate in severity. No deaths occurred in the study.

Given the ease of administration and high levels of tolerance, BTI320 has the potential to be used as an adjunct to lifestyle modification for diabetes prevention. Future research will be required to test the feasibility and effectiveness of BTI320 as part of a larger program for diabetes prevention.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: Abbreviations and Specialty Terms

Abbreviation or Specialty Term	Explanation
AE	Adverse event
ALP	Alkaline Phosphatase
ALT	Alkaline Aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AUC	Area under the curve
AUC_180	AUC for blood glucose above 180 mg/dL (10 mmol/L)
BMI	Body mass index
BP	Blood pressure
CGMS	Continuous glucose monitoring system
CI	Confidence interval
CREC	Clinical Research Ethics Committee
CRF	Case report form
DBP	Diastolic blood pressure
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
FPG	Fasting plasma glucose
GCP	Good Clinical Practice
GLP-1	Glucagon-like peptide-1
HbA_{1c}	Glycated hemoglobin
HDB	High dose (8 grams) BTI320
HDL	High-density lipoprotein
hs-CRP	High-sensitivity C-reactive protein
ICF	Informed Consent form
ICH	International Conference on Harmonization
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IQR	Inter-quartile range
IRB	Institutional Review Board
ISI	Insulin sensitivity index
ITT	Intent-to-treat
LDB	Low dose (4 grams) BTI320
LDL	Low-density lipoprotein
MAGE	Mean amplitude of glucose excursion
MBG	Mean blood glucose
MPMG	Mean post-meal maximum glucose
MTT	Meal tolerance test
OGTT	Oral glucose tolerance test
PP	Per-protocol (evaluable)
%CV	Percent coefficient of variation
QOL	Quality of life
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Statistical analysis report
SBP	Systolic blood pressure
SD	Standard deviation

ULN	Upper limit of normal
WHOQOL-BREF	World Health Organization Quality of Life – abbreviated form of WHOQOL-100

5. ETHICS

5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

This protocol and the Informed Consent Form (ICF) were reviewed and approved by the appropriate Institutional Review Board (IRB) associated with the study site. Any additional protocol amendments were approved by the IRB prior to their implementation. A copy of the letter, signed by either the Chairman of the IRB or the Director General of the hospital, to the Principal Investigator indicating IRB approval of the protocol was received by the sponsor or designee and maintained in the study file prior to study initiation. A list of IRBs consulted and the name of the committee Chair(s) are included in the study report (Appendix 16.1.3). Drug supply was not shipped to the study site until the sponsor or designee received this documentation.

5.2 Ethical Conduct of the Study

This study was conducted in full compliance with the International Conference on Harmonization (ICH) guidelines, including Good Clinical Practice (GCP), and any other applicable local laws and regulations (e.g., 21 Code of Federal Regulations parts 50, 54, 56, and 812, 45 CFR 46). Compliance with these standards provides assurance that the rights, safety, and well-being of the patients in the study are protected.

The Principal Investigator at the investigational site was to ensure that the study was conducted in full compliance with the protocol and any applicable guidelines and standards and was responsible for contacts with study personnel and IRB.

5.3 Patient Information and Consent

The risks and benefits of participating in this study were explained to each potential patient prior to entering the study. The informed consent was written in language(s) readily understood by the patient. The informed consent was approved by the IRB prior to study initiation, performance of any study procedure and dispensing of the study drug. The Principal Investigator or his/her designee obtained a signed and witnessed ICF for each patient. Receipt of the signed ICF was documented in the Case Report Form (CRF) and a copy retained by the Investigator. A copy of the signed ICF was given to each patient.

6. INVESTIGATORS AND ADMINISTRATIVE STRUCTURE

6.1 Principal Investigator(s)

The Principal Investigator was Prof. Andrea Luk at the Chinese University of Hong Kong Prince of Wales Hospital. The Principal Investigator's *curriculum vitae* is presented in Appendix 16.1.

6.2 Clinical Research Personnel

Name	Title / Company	Role
Dr. Andrea Luk	Principal Investigator / The Chinese University of Hong Kong, Prince of Wales Hospital	Chief Medical Officer / Director of Clinical Operations
Karen Lee	Clinical Project Manager / SugarDown Company Limited	Clinical Operations Manager
Clinical Research Pharmacy operated by a team of pharmacists	Pharmacist / The Chinese University of Hong Kong Prince of Wales Hospital	Drug Safety Officer / Drug Safety Monitor
Marc Chong, PhD	Statistician / Center of Clinical Research and Biostatistics, The Chinese University of Hong Kong	Statistical Analyst / Data Analyst
Daisy Sun, MS	Medical Writer / Target Health Inc.	Author of the Clinical Study Report
David R Luke, PharmD	Sr Director, Clinical & Scientific Affairs / Target Health Inc.	Medical Writer & Reviewer
Vanessa Hayes, JD	Consultant / Target Health Inc.	QC/QA

7. INTRODUCTION

7.1 Background

In a recent national survey, 11% of adults in China have diabetes and 50% have pre-diabetes defined by a fasting plasma glucose (FPG) of 5.6-6.9 mmol/L and/or a 2-hour plasma glucose of 7.8-11.0 mmol/L using the 75 g oral glucose tolerance test (OGTT) and/or a glycated hemoglobin (HbA_{1c}) of 5.7-6.4% (Xy *et al*, 2013; Yang *et al*, 2010). Depending on the presence of other risk factors, the annual conversion rate of pre-diabetes to a diagnosis of diabetes averages 3-10% with pre-diabetes associated with 1.5-2.0 fold increased risk for cardiovascular disease (lnzucchi and Sherman, 2005). Once diabetes is established, life expectancy is reduced by 6 years if not diagnosed, treated, or controlled, particularly in young-to-middle aged subjects who will face long disease durations of diabetes (Seshasai *et al*, 2011).

In the Hong Kong Diabetes Registry, depending on control of glucose and other risk factors, 3-10% of Chinese subjects with diabetes may die or develop a major event every year including heart disease, stroke, kidney failure, and/or all-site cancer (Chan *et al*, 2011; Chan *et al*, 2009). One study predicted new onset chronic kidney disease (CKD) in almost 6,000 Chinese patients with Type 2 diabetes (Luk *et al*, 2008).

Besides glycemic control as defined by HbA_{1c}, post-prandial hyperglycemia and glycemic variability have also been shown to predict cardiovascular and renal events in both pre-diabetic and diabetic patients (Luk *et al*, 2013; Chon *et al*, 2013; Kong *et al*, 2014). Genetic variants discovered in large-scale epidemiological studies, including those from China and specifically Hong Kong, have been found to be associated with beta (β) cell dysfunction which can be further exacerbated by glucotoxicity and lipotoxicity, often due to co-existing obesity, thus giving rise to early onset diabetes (Tam *et al*, 1997; Luk *et al*, 2013). Several studies, including those from Asian populations, indicate that subjects with pre-diabetes exhibit reduced early-phase insulin secretions, resulting in postprandial hyperglycemia which can impose metabolic stress on the β-cells leading to eventual β-cell failure (Gastaldelli *et al*, 2004; Ma *et al*, 2013; Matthews *et al*, 1985).

BTI320, also known as PAZ320 and SUGARDOWN®, is derived from galactomannan which acts by blocking key carbohydrate hydrolyzing enzymes, including amylase, maltose, lactose, and sucrose, in the gastrointestinal tract. BTI320 also binds to ingested polysaccharides, thereby slowing absorption with each meal, reducing post-prandial glucose excursion (Trask *et al*, 2014). As a secondary benefit, galactomannan is an appetite suppressant which facilitates meal portion control. The mechanism of action for BTI320 is similar to Acarbose®, an alpha glucosidase inhibitor, which has been shown to improve glycemic control and has been approved for prevention of diabetes in China (Yang *et al*, 2001, Chan *et al*, 1998). SUGARDOWN® is currently distributed as a dietary supplement.

The effects of BTI320 on post-prandial glucose parameters were examined in one Phase 1 and one Phase 2 study. In the former, 10 healthy volunteer subjects consumed single doses of 6 and 12 g BTI320 on separate occasions (Trask *et al*, 2013). Plasma glucose and insulin levels were measured at baseline and at regular time intervals up to 120 minutes after a standard meal of white rice containing 50 g carbohydrates. Compared to the placebo arm, both glucose and

insulin area under curve (AUC) values were markedly reduced with pre-meal consumption of BTI320, independent of dose.

The phase 2 study enrolled 24 subjects (23 Caucasians, 1 Asian) with Type 2 diabetes treated concurrently with anti-diabetic medications or insulin (Trask *et al*, 2013, Trask *et al*, 2014). In this 7-day, open-label, sequential, dose-escalation study, subjects received, on separate days, 8 and 16 g of BTI320. The glucose AUC value over the 3-hour period post ingestion and the 2-hour post-prandial glucose excursion were measured and compared to the BTI320 placebo. The 2-hour post-prandial glucose excursion test was derived from continuous glucose monitoring system (CGMS); both tests were measured after ingestion of a standard meal of 75 g of jasmine rice. The glucose AUC and the 2-hour post-prandial glucose excursion values were reduced in 47% and 75%, respectively, of the subjects taking BTI320 compared with placebo.

Randomized controlled trials demonstrated that intensive lifestyle intervention targeting weight loss of at least 7% of body weight and increased physical activity to at least 150 minutes per week of moderate intensity exercise prevent or delay the onset of Type 2 diabetes in people with pre-diabetes (Knowler *et al*, 2002, Tuomilehto *et al*, 2001, Pan *et al*, 1997). Trials of pharmacological products including metformin, acarbose, and rosiglitazone have also demonstrated efficacy at reducing conversion rate to Type 2 diabetes (Knowler *et al*, 2002, Gerstein *et al*, 2006, Chiasson *et al*, 2002). However, side effects and costs have limited wide-spread use of anti-diabetic drugs in the pre-diabetes population.

Where HbA_{1c} is the 'gold standard' and commonly used to monitor long term glycemic control and guide medication adjustments, it can only reflect the change in fasting glucose and blood glucose level over a past 3-month period. A monitoring system that records and provides blood glucose level information in real time would therefore precisely monitor the efficacy in post-prandial glucose reduction and explore the safety in hypoglycemic event aversion of anti-diabetic drugs. To date, CGMS is the only method to capture the time when blood glucose is 'in range' by highlighting the magnitude of glycemic excursions, and capturing hypoglycemic excursions. CGMS helps Type 2 diabetes patients identify changing glucose levels in real time and help them manage their daily glucose levels to avoid hypoglycemia and improve diabetes control.

It has been demonstrated in prior glycemic index self-controlled trials with high body mass index individuals, based on the prior literature and studies, that the addition of BTI320 may reduce the total glycose load in a high glycemic meal. Additionally, it may aid in the control of blood glucose levels in people with dysglycemia including those with diabetes, pre-diabetes, and metabolic syndrome.

8. STUDY OBJECTIVES

8.1 Study Objectives

8.1.1 Primary Objective

- To compare the effect of high dose BTI320 (HDB, 8 g) and low dose BTI320 (LDB, 4 g) with placebo on serum fructosamine in subjects at high risk for diabetes (pre-diabetic).

8.1.2 Secondary Objectives

- To compare the effect of HDB and LDB with placebo on CGMS parameters in subjects at high risk for diabetes.
- To compare the effect of HDB and LDB with placebo on HbA_{1c} in subjects at high risk for diabetes.

9. INVESTIGATIONAL PLAN

9.1 Overall Study Design

This was a Phase 2, single-center, randomized, double-blind, placebo-controlled, 3-treatment arm pilot study to evaluate the efficacy and safety of BTI320 in the treatment of high-risk subjects with pre-diabetes (blood sugar levels that were above normal but not reaching diabetic range).

Assuming the screen failure is 67%, i.e., screen 3 subjects to have 1 subject randomized, at least 180 Chinese subjects were to be screened to achieve the target number of 60 subjects randomized. Subjects were recruited and randomized into High-Dose BTI320 (HDB) three times daily, Low-Dose BTI320 (LDB) three times daily, or placebo in a 2:2:1 ratio:

- HDB 8 g three times daily (n=24)
- LDB 4 g three times daily (n=24)
- Placebo three times daily (n=12)

A total of 7 visits was scheduled for this 16-week study. Subjects were followed closely for 30 ± 7 days after study.

9.2 Discussion of the Study Design, Including the Choice of Control Groups

The hypothesis for this placebo-controlled study was that treatment with BTI320 is safe and efficacious in reducing postprandial hyperglycemia and glycemic variability, as measured by CGMS, in subjects at high risk for diabetes, which may enhance β-cell preservation and serve as a potential treatment option for pre-diabetes.

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

Subjects who met all of the following criteria were eligible for enrollment:

1. Adult subjects ≥ 18–70 years of age
2. Chinese ethnicity
3. High risk subject with pre-diabetes as defined by meeting at least 2 of the following criteria:
   - FPG ≥ 5.6-6.9 mmol/l and/or 2-hour PG ≥ 7.8-11.0 mmol/l during 75 g OGTT
   - HbA_{1c} ≥ 5.7-6.4%
   - At least one of the following risk factors:
     - History of gestational diabetes

- Family history of diabetes in first degree relative
- Two or more components of the metabolic syndrome:
  - Triglyceride ≥ 1.7 mmol/L
  - Blood pressure (BP) ≥130/80 mmHg
  - High-density lipoprotein cholesterol (HDL-cholesterol) <1.3 mmol/L in women or <1.1 mmol/L in men
  - Waist circumference ≥80 cm in women or ≥ 90 cm in men.
  - Subjects on anti-hypertensive agent for treatment of hypertension or a lipid lowering drug for the treatment of hyperlipidemia were respectively considered to have one component of the metabolic syndrome.

4. A female subject of childbearing potential who is sexually active with a non-sterilized male partner agrees to use routinely adequate and effective contraception to avoid pregnancy during the study period and up to 30 days after the final visit.
5. Able and willing to consistently record food diary to facilitate CGMS evaluation
6. Signed informed consent prior to the initiation of any study-related procedures.

9.3.2 Exclusion Criteria

Subjects who met any of the following criteria were excluded from the study:

1. Subject has received anti-diabetic agents within 6 weeks prior to screening visit
2. On dietary supplement known to affect glucose or galactose metabolism
3. History of acute cardiovascular disease including myocardial infarction, acute coronary syndrome, or stroke which required hospitalization in the last 12 months.
4. Significant renal impairment with estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2
5. Known lactose or galactose intolerance
6. History of an eating disorder
7. Pregnant or lactating female subjects
8. Subjects with gastrointestinal disease that may interfere with absorption of the investigational product
9. Subject has received any investigational product within 30 days of randomization visit
10. Reduced life expectancy or any condition considered by the investigator as unsuitable for enrollment into study.

9.3.3 Removal of Subjects from Therapy or Assessment

A subject could be withdrawn/discontinued from the study at any time if the subject, the investigator, or the Sponsor felt that it was not in the subject's best interest to continue. All subjects were free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice. Reasonable attempts were made by the Investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study was specified in the subject's source document.

The possible reasons for study treatment discontinuation are: the subject experienced an adverse

event (AE) that requires early termination because continued participation imposes an unacceptable risk to the subject's health; the subject was unwilling to continue because of the AE experienced; other reasons include major protocol deviation, lost to follow-up, voluntary withdrawal, study termination, or the subject was found to be pregnant.

All subjects who discontinued study treatment were requested to return to the clinic for an early discontinuation visit as soon as possible and then were encouraged to complete all remaining scheduled visits and procedures.

9.4 Treatments

9.4.1 Treatments Administered

Study drug was supplied by SugarDown Company Limited as a chewable tablet containing 4 g BTI320. Control product was a placebo tablet of same appearance and taste to the study drug. All subjects were instructed to take 2 chewable tablets prior to meal ingestion:

- HDB: consists of 2 active chewable tablets
- LDB: consists of 1 active chewable tablet and 1 placebo chewable tablet
- Placebo: consists of 2 placebo chewable tablets

Study drugs were stored at the drug storage facility of the Diabetes and Endocrine Research Centre. The storage was maintained at room temperature between 15 – 25^{o}C and protected from light.

9.4.2 Identity of Investigational Product(s)

BTI-320 is a non-systemic, non-toxic, chewable tablet.

9.4.3 Method of Assigning Patients to Treatment Groups

Randomization was performed after the investigator confirmed that the subject met all inclusion criteria. Upon randomization, each eligible subject was assigned a subject randomization number (01, 02, 03 …) in consecutive order which corresponded to one of the three study intervention arms (HDB, LDB, or placebo). The allocation of study intervention to each subject was by a pre-determined randomization number using computation procedures.

9.4.4 Selection of Doses in the Study

The effect of BTI320 on postprandial glucose parameters was examined in one Phase 1 (10 healthy volunteers) study. Subjects consumed single doses of 6 g and 12 g of BTI320 on separate occasions; both glucose and insulin area under curve (AUC) were reduced with pre-meal consumption of BTI320 at both doses. The effect of BTI320 on post-prandial glucose parameters was also examined in one Phase 2 (n=24), 7-day, open-label, sequential dose-escalation study. Subjects received, on separate days, 8 g and 16 g of BTI320. The glucose AUC was reduced in 47% and 2-hour post-prandial glucose excursion reduced in 75% of subjects taking BTI320. Among the non-responders, a paradoxical increase in both of these glycemic parameters was observed.

9.4.5 Selection and Timing of Dose for Each Patient

Study drug was to be taken prior to each meal ingestion.

9.4.6 Blinding

The subjects, investigators, and site personnel involved in the study were blinded to the assignment of the investigational drug. The coding of the investigational drug remained blinded throughout the study period and could not be broken by the investigator unless information concerning the investigational drug was necessary for the medical treatment of the subject.

9.4.7 Prior and Concomitant Therapy

All subjects were maintained on the same medications throughout the entire study period, as medically feasible, with no introduction of new acute or chronic therapies. All medications were allowed except for medications noted in the exclusion criteria as described above, including anti-diabetic agents and dietary supplements known to affect glucose or galactose metabolism.

9.4.8 Treatment Compliance

Subjects were required to bring study medication containers to each clinic visit regardless of whether the study medication container was empty. Compliance with the study drug was calculated based on the number of doses of study drug taken as determined by counts of returned tablets, and the number of main meals consumed. Thus, the subject who only consumed two main meals per day would be expected to take four study drug tablets (two before each meal) for the day. The subject was asked to record the number of main meals (breakfast, lunch, dinner) consumed between Visits 3 and 4, Visits 4 and 5, Visits 5 and 6, and Visits 6 and 7.

Study drug was returned to the Sponsor or its designee for destruction according to local laws after completion of drug accountability and reconciliation at study closure.

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and Safety Measurements Assessed and Flow Chart

9.5.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint was the change in serum fructosamine in subjects treated with HDB and LDB compared with placebo from baseline to Week 4.

9.5.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints were:

- Changes in subjects treated with HDB and LDB compared with placebo from baseline to Week 4 and Week 16 in continuous glucose monitoring system (CGMS) parameters as follows:
    - AUC post-prandial glucose at 1 hour, 2 hours and 3 hours
    - Mean post-meal maximum glucose (MPMG)
    - Mean amplitude of glucose excursion (MAGE)

- Mean blood glucose (MBG)

- Changes in HbA_{1c} in subjects treated with HDB and LDB compared with placebo from baseline to Week 16.
- Changes in fructosamine in subjects treated with HDB and LDB compared with placebo from baseline to Week 8, Week 12, and Week 16.
- Changes in subjects treated with HDB and LDB compared with placebo from baseline to Week 4 and Week 16 during standard meal tolerance test (MTT) in AUC of glucose, insulin, and C-peptide from 0 minute to 15, 30, 60, 90, and 120 minutes, as well as changes in glucagon-like peptide-1 (GLP-1).
- Proportion of subjects with impaired fasting glucose or impaired glucose tolerance at 30-day post-treatment compared to baseline in HDB, LDB and placebo groups.

9.5.1.3 Other Secondary Endpoints

The other secondary endpoint was between-group and within-group comparisons with repeated measures from baseline to Week 4 and Week 16:

- Blood pressure, waist circumference, body weight.
- Serum lipids, highly-sensitive C-reactive protein (hs-CRP) and urate.
- Quality of life (QOL), food satiety, nutritional intake and exercise.

9.5.1.4 Safety Endpoints

9.5.1.4.1 Adverse Events (AE)

An adverse event (AE) is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, disease or exacerbation of a pre-existing condition temporally associated with the use of a medicinal (test) product.

The intensity of AEs must be recorded during the course of the event including the start and stop dates for each change in intensity.

- Mild: does not interfere with usual activity.
- Moderate: mild to moderate interferes with usual activity
- Severe: interferes significantly with usual activity.

The following guidance was used in determining the relationship between AE and study drug:

Term	Definition
Definitely	Previously known toxicity of the study drug, or an event that follows a reasonable temporal sequence from administration of the study drug, that follows a known or expected response pattern to the study drug, that is confirmed by stopping the dosage of the drug, and that is not explained by any other reasonable hypothesis
Probably	An event that follows a reasonable temporal sequence from administration of the study drug; that follows a known or expected response pattern to the study drug; that is confirmed by stopping or reducing the dosage of the study drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions

Possibly	An event that follows a reasonable temporal sequence from administration of the study drug; that follows a known or expected response pattern to the study drug; but that could readily have been produced by a number of other factors
Unrelated	An event that can be determined with certainty to have no relationship to the study drug

The outcome of AEs was recorded during the course of the study in the eCRF:

- Recovered/Resolved
- Not Recovered /Not Resolved

9.5.1.4.2 Serious Adverse Events (SAE)

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

1. Results in death
2. Is life threatening
3. Requires in-patient hospitalization or prolongation of existing hospitalization
4. Results in persistent disability/incapacity
5. Leads to a congenital anomaly/birth defect
6. Is an important medical event based on investigator judgment

A SAE report had to be generated and reported to Clinical Research Ethics Committee (CREC) and Sponsor within 24 hours of first onset or notification of the event.

9.5.1.4.3 Clinical Laboratory Evaluations

Clinical Biochemistry and Hematology

Fructosamine was measured at Visits 2, 4, 5, 6, and 7, and HbA_{1c} was recorded at Visit 1 (Screening) and Visit 7. Lipid panel (total cholesterol, triglyceride, HDL-cholesterol, and LDL-cholesterol), urate, and complete blood count were measured at Visits 1, 4, and 7. Highly sensitive CRP (hs-CRP) was measured at Visits 2, 4, and 7. Renal and liver function tests were measured at Visits 1, 4, 5, 6, and 7.

An additional 30 mL of venous blood from the subjects at Visits 1, 4, and 7 were collected for future analysis of relevant biomarkers including DNA and RNA extraction.

Oral Glucose Tolerance Test (OGTT)

An OGTT was done at Visit 1 (Screening) to determine subject's eligibility to proceed into the study (Matsuda and DeFronzo, 1999; Phillips *et al*, 1994). Prior to attend the screening visit OGTT, the subject was instructed to have at least 8 hours of overnight fasting after ingesting three days of a normal diet. Plasma glucose was taken at 0 minutes and 120 minutes in relation to the glucose challenge which was prepared by dissolving 75 g anhydrous glucose in 250 mL water and consumed within 5 minutes. The OGTT was repeated at the 30-Day Post-Treatment Visit.

Standard Meal Tolerance Test (MTT)

A standard MTT was performed at Visits 2, 4 and 7. Subjects were instructed to fast for at least 10 hours prior to this visit. Blood samples for glucose, insulin, C-peptide and GLP-1 were taken at 0, 15, 30, 60, 90, and 120 minutes following the standard meal provided by the site. This

consisted of a fixed caloric meal close to 500 kcal including snack and drink tailored for the study.

Continuous Glucose Monitoring System (CGMS)

Continuous glucose monitoring for a 72-hour period was done during 3 periods in this study. Subjects had the CGMS device installed at Visit 2, Visit 4, and 3 days prior to Visit 7. The CGMS sensor was installed in the subcutaneous layer of the abdomen by using a dedicated 'sensertor'. The insertion site was away from waist line regions where there would be anticipated movement which could lead to inadvertent detachment of the sensor during the monitoring period. The sensor was activated once the CGMS sensor was correctly inserted.

Subjects were instructed to calibrate the CGMS device using the provided glucometer. Calibration involved testing of capillary blood glucose levels at least 3 times daily during the 72-hour monitoring period, preferably pre-meal and at bedtime. A food diary was also recorded during the CGMS monitoring in which the subject was given a standard food diary sheet to record the times when meals were taken and what food was consumed during each meal.

9.5.1.4.4 Vital Signs

Blood pressure was taken at Visit 1 (Screening) and at Visits 2 – 7, and at the 30-Day Post-Treatment visit.

9.5.1.4.5 Anthropometric Measures, Including Body Weight

Anthropometric parameters including body height, body weight and waist circumference were measured at Visit 1 (Screening). Body weight was additionally measured at all subsequent Visits 2 - 7, and 30-Day Post-Treatment Visit. Waist circumference was measured at Visits 4 and 7.

9.5.1.4.6 Questionnaires

Questionnaires on health-related quality of life (World Health Organization Quality of Life [WHOQOL]-BREF), appetite (Hill and Blundell), physical activity (International Physical Activity Questionnaire Short Last 7 Days Self-Administered Format), and dietary survey (Food Frequency Questionnaire) were administered at Visits 2, 4 and 7.

Table 2: Schedule of Evaluations

	Visit 1 (-7-14 days)	Visit 2 (-3 days)	Visit 3 (RV*)	Visit 4 (Week 4)	Visit 5 (Week 8)	Visit 6 (Week 12)	Visit 7 (Week 16)	Follow up (30-day post-treatment)
Window period		±7 days	0	±5 days	±5 days	±5 days	±5 days	±7 days
Consent	✓							
Randomization			✓					
Body weight / BP	✓	✓	✓	✓	✓	✓	✓	✓
Height	✓							
Waist	✓			✓			✓	
Physical examination		✓					✓	
72-hour CGMS		✓		✓			✓**	
Fructosamine		✓		✓	✓	✓	✓	
HbA_{1c}	✓						✓	
OGTT	✓							✓
MTT		✓		✓			✓	
Urate	✓			✓			✓	
hs-CRP		✓		✓			✓	
Lipid panel	✓			✓			✓	
Renal / liver function	✓			✓	✓	✓	✓	
Complete blood count	✓			✓			✓	
Questionnaires		✓		✓			✓	
Adverse events		✓	✓	✓	✓	✓	✓	✓
Compliance check (# of main meals)				✓	✓	✓	✓	
Drug dispensed			✓	✓	✓	✓		

*Randomization visit: At the end of the CGMS monitoring period, subjects returned for removal of the CGMS device. Data from the subject's CGMS device were downloaded and recorded. If ≥ 30% of the values were missing, CGMS monitoring for the 72 hours was repeated.
** Performed 3 days prior to Visit 7.

9.5.2 Appropriateness of Measurements

All measurements analyzed are appropriate for evaluation of post-prandial hyperglycemia in high risk subjects with pre-diabetes.

9.5.3 Primary Efficacy Endpoint

Change in serum fructosamine in subjects treated with LDB and HDB compared to placebo from baseline to Week 4.

9.5.4 Drug Concentration Measurements - Pharmacokinetic Assessments

NA

9.6 Data Quality Assurance

9.6.1 Source Data and Records

The Investigator prepared and maintained adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

The Sponsor supplied the study site with access to electronic CRF (eCRF) data capture. The Sponsor made arrangements to train appropriate site staff in its use. These forms were used to transmit the information collected in the performance of this study to the Sponsor. Study site staff entered data from source documents corresponding to a subject's visit into the eCRF when the information corresponding to that visit was available.

9.6.2 Reporting of Results

The Investigator was responsible for the collection and reporting of all clinical, safety and laboratory data entered onto the eCRFs and source documents. The Investigator had to ensure that information collected and reported are accurate, authentic, complete, consistent, legible, timely, and available when required. The eCRFs had to be signed by the Investigator or by an authorized staff member to attest that the data contained in the eCRFs were true. Any corrections to entries made in the eCRFs and source documents were dated, initialed and explained (if necessary) and not to obscure the original entry.

9.6.3 Confidentiality of Subject Data

Subjects were not identified by name in the study database or on any study document to be collected by the Sponsor, but were identified by a subject number

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

All data were expressed as mean ± standard deviation (SD) or mean (inter-quartile range [IQR]) as appropriate.

9.7.1.1 Study Populations

Two subject populations were analyzed:

- Intention-to-treat (ITT): All subjects who received at least one dose of BTI320 were included in the safety analysis.
- Per protocol (PP): subjects who have taken ≥ 70% of the assigned treatment were included in the efficacy analysis.

9.7.1.2 Efficacy Analyses

9.7.1.2.1 Primary Efficacy Analyses

The Primary endpoint was the change of serum fructosamine between study interventions and placebo from baseline to Week 4.

- Fructosamine measurements: Mean, median, SD, IQR, and 95% confidence interval by treatment arms
- Change of fructosamine from baseline by treatment arms:
  1. Mean, median, SD, and IQR
  2. Comparisons of treatment effects: Analysis of variance (ANOVA) and post-hoc

paired t-tests. Non-parametric tests (Kruskal-Wallis test and Wilcoxon signed-rank test) were used if normal assumption was violated.

3. Treatment effects: Mixed effect model adjusted with age, sex, and baseline measurement

9.7.1.2.2 Secondary Efficacy Analyses

9.7.1.2.2.1 Serum Fructosamine at Week 8, Week 12, and Week 16

The secondary endpoint was the change of serum fructosamine between study interventions and placebo from baseline to Week 8, Week 12, and Week 16.

- Fructosamine measurements: Mean, median, SD, IQR, and 95% confidence interval over scheduled visits by treatment arms
- Change of fructosamine levels from baseline by treatment arms:
  1. Mean, median, SD, and IQR over scheduled visits
  2. By visit comparisons of treatment effects: Analysis of variance (ANOVA) and post-hoc paired t-tests. Non-parametric tests (Kruskal-Wallis test and Wilcoxon signed-rank test) were used if normal assumption was violated.
  3. Treatment effects over time: Mixed effect model adjusted with age, sex, and baseline measurement
  4. Mean plot with SD bars over scheduled visits

9.7.1.2.2.2 Clinical Glucose Monitoring System (CGMS)

MBG 1-hour AUC, 2-hour AUC, 3-hour AUC, 24-hour AUC_180, 72-hour AUC_180, MPMG, MAGE, SD, and %CV: Mean, median, SD, and IQR over scheduled visits by treatment arms

Change of CGMS parameters from baseline by treatment arms:

- Mean, median, SD, and IQR over scheduled visits
- Comparisons of treatment effects at Visits 4 and 7: Analysis of covariance (ANCOVA) adjusted with age, sex and baseline measurements; post-hoc paired t-tests and Wilcoxon signed-rank test if normality assumption could not be held
- Mean plots with SD bars over scheduled visits

9.7.1.2.2.3 Glycosylated Hemoglobin (HbA_{1c})

- HbA_{1c}: Mean, median, SD, IQR, and 95% confidence interval at Visit 7 by treatment arms
- Change of HbA_{1c} from baseline to Visit 7:
  1. Comparisons of treatment effects at Visit 7: ANCOVA adjusted with age, sex and baseline measurements; post-hoc paired t-tests and Wilcoxon signed-rank test if normality assumption could not be held.

9.7.1.2.2.4 Standard Meal Tolerance Test (MTT)

AUC of glucose, insulin, C-peptide, and GLP-1: Mean, median, SD, and IQR over scheduled

visits by treatment arms

Change of MTT parameters from baseline by treatment arms:

- Mean, median, SD, and IQR over scheduled visits
- Comparisons of treatment effects at Visits 4 and 7: ANCOVA adjusted with age, sex and baseline measurements; post-hoc paired t-tests and Wilcoxon signed-rank test if normality assumption could not be held
- Mean plots with SD bars over scheduled visits

9.7.1.2.2.5 Oral Glucose Tolerance Test (OGTT)

Impaired glucose tolerance and impaired fasting glucose: Count of patients (N) and proportion at Visit 7

Change of impaired glucose tolerance from baseline by treatment groups:

- Count of patients (N) and proportion
- Comparisons of treatment effects at Visit 7: Logistic regression adjusted with age, sex and baseline measurements

9.7.1.2.3 Other Secondary Analyses

9.7.1.2.3.1 Blood pressure and anthropometric measures

Blood pressure, body weight, body mass index (BMI), and waist circumference: Mean, median, SD, and IQR over scheduled visits by treatment arms

Change in blood pressure and anthropometric measures from baseline by treatment arms:

- Mean, median, SD, and IQR over scheduled visits
- By visit comparisons of treatment effects: ANOVA and post-hoc paired t-tests
- Treatment effects over time (weight and BMI): Mixed effect model adjusted with age, sex, and baseline FPG

9.7.1.2.3.2 Serum lipids, highly sensitive C-reactive protein (hs-CRP), and urate

Serum lipids (total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol), hs-CRP and urate: Mean, median, SD, and IQR over scheduled visits by treatment arms

Change of serum lipids, hs-CRP, and urate from baseline:

- Mean, median, SD, and IQR over scheduled visits by treatment arms
- Comparisons of treatment effects at Visits 4 and 7: ANCOVA adjusted with age, sex and baseline measurements; post-hoc paired t-tests

9.7.1.3 Safety Analysis

9.7.1.3.1 Adverse Events (AEs)

- Possibly related and probably related to study drugs: Count of patients (N) and proportion over study visits

- SAE: Count of patients (N) and proportion over study visits

9.7.1.3.2 Demographics and Baseline Characteristics

- Age: Mean, median, SD, and inter-quartile range (IQR) by treatment arms
- Gender, ethnicity, and race: Count of patients (N) and proportion by treatment arms
- Medical history: Count of patients (N) and proportion categorized by medical histories. Rare terms were grouped into "Other".

All of the above baseline characteristics and the details of eligibility criteria were listed subject by subject. The baseline information reported either from Visit 1, 2, or 3 in which the latest data collected before any treatment taken.

9.7.1.3.3 Anthropometric Measures

Blood pressure, body height, weight, BMI, and waist circumference: Mean, median, SD, and IQR by treatment arms

9.7.1.3.4 Physical Examination

Cardiovascular, respiratory, abdominal, central nervous system, musculoskeletal, and skin: Abnormal count of patients (N) and proportion by treatment arms

9.7.1.3.5 CGMS measurements

MBG, 1-hour AUC, 2-hour AUC, 3-hour AUC, 24-hour AUC_180, 72-hour AUC_180, MPMG, MAGE, SD, and %CV: Mean, median, SD, and IQR by treatment arms.

9.7.1.3.6 Clinical Laboratory Results

Renal (serum sodium, potassium, creatinine, blood urea nitrogen) and liver function (bilirubin, alkaline phosphatase, alanine aminotransferase): Mean, median, SD, and IQR by treatment arms.

Complete blood count (hemoglobin, hematocrit, platelet count, and white blood cell count): Mean, median, SD, and IQR by treatment arms.

Fructosamine, HbA_{1c}, AUC of glucose, insulin, C-peptide, GLP-1, serum lipids (total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol), hs-CRP, and urate: Mean, median, SD, and IQR by treatment arms.

9.7.1.3.7 Vital Signs

Systolic and diastolic blood pressures: Mean, median, SD, and IQR by treatment arms.

9.7.1.3.8 Oral Glucose Tolerance Test (OGTT)

Impaired glucose tolerance and impaired fasting glucose: Count of patients (N) and proportion by treatment arms

9.7.1.3.9 World Health Organization Quality of Life – Abbreviated (WHOQOL-BREF)

Overall Quality of Life and General Health, Physical Health Domain, Psychological Domain,

Social relationships Domain, Environment Domain: Mean, median, SD, and IQR over scheduled visits by treatment arms.

Change of Overall Quality of Life and General Health, Physical Health Domain, Psychological Domain, Social relationships Domain, Environment Domain from baseline by treatment arms:

- Mean, median, SD, and IQR over scheduled visits
- Comparisons of treatment effects at Visits 4 and 7: ANCOVA adjusted with age, sex and baseline measurements; post-hoc paired t-tests

9.7.1.3.10 Appetite, physical activity, and dietary survey

Appetite, physical activity, and dietary survey: Mean, median, SD, and IQR over scheduled visits by treatment arms.

Change of Appetite, physical activity, and dietary survey from baseline by treatment arms:

- Mean, median, SD, and IQR over scheduled visits
- Comparisons of treatment effects at Visits 4 and 7: ANCOVA adjusted with age, sex and baseline measurements; post-hoc paired t-tests

9.7.1.3.11 Concomitant Medications

All concomitant medications administered during the study and the corresponding ongoing profile were listed.

9.7.1.3.12 Treatment Compliance

Compliance with the study drug was calculated based on doses of study drugs taken as determined by counts of returned tablets, and the number of main meals consumed. Thus, subject who only consumed two main meals per day would be expected to take four study drug tablets (two before each meal) for the day.

$$\text{Drug compliance} = \frac{\text{(Number of study drug tablets taken during intervention period / 2)}}{\text{Number of main meals consumed during intervention period}}$$

9.7.1.4 Data Handling

Subjects who were found to be not eligible for randomization due to failure to meet the inclusion criteria were documented in the CRF and their data were not used for main analysis. In the study, subjects were free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice. The reason for the subject's withdrawal from the study was specified in the subject's source document. Their data were used for analysis in accordance to the criteria of analysis populations. No imputation of values for missing data was performed.

A p-value <0.05 (2-tailed) was considered significant for 2-group comparisons. For multiple group comparisons (high dose *versus* control; low dose *versus* control; high dose *versus* low dose), Bonferroni correction was applied with a p-value <0.017 (=0.05 significant level / 3 groups) considered as significant.

9.7.1.5 Interim Analysis

Interim analyses were conducted when the first 10 randomized subjects completed Visit 4. The purpose of the interim analysis was to ensure that there was an adequate post-prandial glucose excursion and to assess subject adherence in taking the study drug.

9.7.2 Determination of Sample Size

Fructosamine was used as a primary endpoint for comparing placebo to each of the two treatment arms. Assuming that a mean of 273 µmol/L with a SD of 22.5 µmol/L will be found in the placebo arm, then a 10% change in baseline fructosamine would be detected using a two-sided 5% level test with 80% power and 11 patients per arm. The study would have >80% power for the comparisons using 12 subjects in the control group versus 24 subjects in the study treatment groups.

9.8 Changes in the Conduct of the Study or Planned Analyses

Three protocol amendments were issued:

Version 2: 6Oct2014

Version 3: 23Jan2015

Version 4: 22Sep2015

10. STUDY PATIENTS

10.1 Disposition of Subjects

A total of 77 subjects were screened and 60 subjects were eligible for enrollment (Data Listing 2.1, Appendix 16.2.1). Of the 60 subjects, 12, 24, and 24 were randomly assigned to placebo, LDB, and HDB, respectively. Of the 24 subjects who received LDB, 2 (8%) discontinued from the study due to adverse event. Of the 24 subjects who received HDB, 1 (4%) withdrew consent. Fifty-seven (57) subjects completed the study (Table 3).

Table 3: Patient Disposition - ITT Population

Variables		Placebo	4 grams BTI320	8 grams BTI320
Disposition	Adverse event	0 (0.0)	2 (8.3)	0 (0.0)
	Completed	12 (100.0)	22 (91.7)	23 (95.8)
	Withdrawal by subject	0 (0.0)	0 (0.0)	1 (4.2)

Reference: Statistical Table 2.1 (Section 14)

10.2 Protocol Deviations

Five (5) subjects (SG01_16, SG01_17, SG01_30, SG01_41 and SG01_56) were excluded from the PP population due to overall compliance rates <70% of the assigned treatment (Data Listing 3.2.2, Appendix 16.2.2).

11. EFFICACY EVALUATION

11.1 Data Sets Analyzed

In this study, the safety analysis was performed using the ITT data set (n=60, HDB, 24; LDB, 24; Placebo, 12). Of the 60 treated subjects, 55 (HDB, 24; LDB, 19; Placebo, 12) had taken ≥70% of their assigned treatment and were included in PP population (Data Listing 2.2, Appendix 16.2.3).

Statistical output tables referenced to but not included in the text are presented in Section 14. Individual subject data listings are presented in Appendix 16.2.

11.2 Demographic and Other Baseline Characteristics

11.2.1 Demographics

Demographic characteristics are summarized in Table 4. Of the 60 ITT subjects, the mean age ranged from 54.1 to 58.5 years (median 56.5 to 60.0 years) among the three treatment groups. There was a similar proportion of male and female subjects in the HDB and LDB treatment groups, however, the majority of subjects in the placebo group were female (75.0%). In addition, the mean weight for the HDB and LDB treatment groups (71.0 and 74.2 kg) was higher

compared to the placebo group (63.9 kg).

Individual subject demographics can be found in Data Listing 1.1 (Appendix 16.2.4).

Table 4: Summary of Demographics / Anthropometric Measures (ITT Population)

Variables		Placebo	4 grams BTI320	8 grams BTI320
Age (years)	N	12	24	24
	Mean (SD)	57.1 (10.9)	54.1 (8.6)	58.5 (8.5)
	Median (IQR)	60.0 (6.5)	56.5 (13.0)	60.0 (14.0)
Sex n(%)	F	9 (75.0)	11 (45.8)	12 (50.0)
	M	3 (25.0)	13 (54.2)	12 (50.0)
Height (cm)	Mean (SD)	157.87 (9.96)	162.58 (9.30)	161.93 (10.57)
	Median (IQR)	154.30 (10.65)	160.95 (12.60)	163.70 (17.90)
BMI (kg/m2)	Mean (SD)	25.09 (4.33)	28.04 (5.81)	26.85 (4.41)
	Median (IQR)	24.35 (4.20)	27.00 (8.15)	26.40 (6.15)
Weight (kg)	Mean (SD)	63.88 (19.98)	74.24 (16.88)	71.00 (16.23)
	Median (IQR)	56.30 (12.55)	71.00 (22.10)	69.90 (19.50)
Waist Circumference (cm)	Mean (SD)	88.03 (15.73)	94.97 (15.62)	90.55 (9.14)
	Median (IQR)	82.85 (12.90)	90.65 (24.80)	89.50 (12.55)

Reference: Statistical Tables 1.1 and 1.3 (Section 14)

11.2.2 Other Baseline Characteristics

11.2.2.1 Medical History

Medical history results are summarized and presented in Statistical Table 1.2 (Section 14). The most common medical histories were hypertension (HDB, 54.2%; LDB, 45.8%; Placebo, 58.3% of subjects), dyslipidemia (HDB, 41.7%; LDB, 25.0%; Placebo, 33.3% of subjects), and obesity (HDB, 20.8%; LDB, 16.7%; Placebo, 25.0% of subjects). Subjects in HDB and LDB treatment groups had greater ongoing medical histories in gastroesophageal reflux disease and sleep apnea syndrome.

Individual subject medical history results can be found in Data Listing 1.2 (Appendix 16.2.4).

11.2.2.2 Vital Signs

Vital sign results are summarized and presented in Statistical Table 1.4 (Section 14). At the baseline visit, the majority of subjects had normal vital signs: the mean systolic blood pressure ranged between 121.7 (±13.2) - 127.8 (±8.7) mmHg and the mean diastolic blood pressure ranged between 78.4 (±6.8) - 80.4 (±7.3) mmHg. Individual subject data for vital signs can be found in Data Listings 7.1.1 and 7.1.2 (Appendix 16.2.7).

11.2.2.3 Physical Examination

At the screening visit, the most commonly observed abnormal physical examination results were in the abdominal body system (HDB, 29.2%; LDB, 20.8%; Placebo, 33.3% of subjects) and skin system (HDB, 12.5%; LDB, 16.7%; Placebo, 8.3% of subjects) (Statistical Table 1.5, Section 14). Individual subject data for physical examination can be found in Data Listing 1.3 (Appendix 16.2.4).

11.2.2.4 CGMS measurements

Most of baseline CGMS measurements showed no remarkable difference across groups (Statistical Table 1.6, Section 14). Individual subject data can be found in Data Listing 6.2 series (Appendix 16.2.6).

11.2.2.5 Fructosamine

The mean serum fructosamine levels at baseline (Visit 2) were similar across the HDB, LDB, and placebo study groups, 272.2 (±20.2), 268.5 (±18.3) and 278.9 (±22.0) µmol/L, respectively (Statistical Table 1.7, Section 14). Individual subject data can be found in Data Listing 5.1 (Appendix 16.2.6).

11.2.2.6 Laboratory Assessments

Laboratory assessment results at the baseline visit (complete blood count, renal and liver function, HbA_{1c}, MTT, IGT (impaired glucose tolerance), and IFG (Impaired fasting glucose), serum lipids, hs-CRP and urate are summarized in Statistical Tables 1.8 - 1.13 (Section 14). Individual subject data can be found in Data Listings 6.3, 6.4, 6.5, 7.2, 8.1, 8.2 series (Appendix 16.2.8).

11.2.2.7 Questionnaires

WHOQOL-BREF, food frequency, appetite and international physical activity questionnaires are summarized in Statistical Tables 1.14 - 1.17 (Section 14). Individual subject data can be found in Data Listings 9.1 - 9.2 series (Appendix 16.2.6).

11.2.2.8 Previous and Current Medications

All concomitant medications recorded at Visit 1 (Screening) are presented in Data Listing 4.1 (Appendix 16.2.7).

11.3 Measurements of Treatment Compliance

Individual subject data for exposure to treatment, drug compliance by visit and overall compliance can be found in Data Listings 3.1 - 3.2 series (Appendix 16.2.5).

11.4 Efficacy Results and Tabulations of Individual Patient Data

11.4.1 Analysis of Efficacy

11.4.1.1 Primary Efficacy

11.4.1.1.1 Fructosamine

The mean serum fructosamine levels at baseline (Visit 2) and Visit 4 (Week 4) and the change from baseline at Week 4 are summarized in Table 5. The mean reductions of serum fructosamine level from baseline at Week 4 for the LDB (-5.2 µmol/L, p=0.46) and HDB (-9.4 µmol/L, p=0.88) treatment groups showed no statistically significant differences compared to the placebo (-8.8 µmol/L) group.

The mean change of serum fructosamine level from baseline at Week 4 adjusted for baseline measurements, age and gender (ANCOVA analysis) also showed no statistically significant treatment effects in the LDB and HDB treatment groups compared to the placebo group, the estimated effects of LDB and HDB were 2.46 (95% CI: -6.3, 11.2) and -1.57 (95% CI: -10.3, 7.1) µmol/L with p= 0.57 and 0.72, respectively (Statistical Table 5.1.3, Section 14). Similar results were observed in the PP population, the estimated effects of LDB and HDB were 0.86 (95% CI: -7.8, 9.6) and -1.88 (95% CI: -10.2, 6.4) µmol/L with p= 0.84 and 0.65, respectively (Statistical Tables P5.1.1 - P5.1.3, Section 14).

Table 5: Serum fructosamine

Fructosamine (µmol/L)		Placebo	4 grams BTI320	8 grams BTI320
Visit 2 (-3 days)	N	12	24	24
	Mean (SD)	279 (22)	269 (18)	272 (20)
	Median (IQR)	276 (32)	271 (18)	271 (28)
	95% CI	(265, 293)	(261, 276)	(264, 281)
Visit 4 (week 4)	N	12	23	24
	Mean (SD)	270 (25)	263 (20)	263 (19)
	Median (IQR)	269 (40)	269 (25)	261 (28)
	95% CI	(254, 286)	(255, 272)	(255, 271)
Change of fructosamine (µmol/L) from baseline at Visit 4 (week 4)	Mean (SD)	-8.8 (12.5)	-5.2 (14.1)	-9.4 (8.9)
	Median (IQR)	-8.0 (16.5)	-6.0 (19.0)	-9.5 (10.5)
	p-value		0.46	0.88

95% CI: 95% confidence intervals for the mean values
p-value: The univariate p-values of treatment groups were obtained by t-tests comparing the changes to the placebo group
Reference: Statistical Tables 5.1.1 and 5.1.2.

11.4.1.2 Secondary Efficacy

11.4.1.2.1 Fructosamine

The mean serum fructosamine levels at baseline and Visits 5 (Week 8), 6 (Week 12) and 7 (Week 16) and the change from baseline at Visits 5, 6 and 7 are summarized in Statistical Tables 6.1.1 and 6.1.2 (Section 14). There were no statistically significant differences in the mean reductions of serum fructosamine level from baseline at Visits 5, 6 and 7 in comparison of the LDB and HDB treatment groups to the placebo group (p=0.42 - 1.00, respectively).

For the mean change of serum fructosamine level from baseline at Visits 5, 6 and 7 adjusted for baseline measurements, age and gender, the LDB and HDB treatment groups also showed no statistically significantly treatment effects compared to the placebo group (p= 0.30 - 0.87, respectively) (Statistical Table 6.1.3, Section 14). Overall decreases observed using mixed effect model analysis comparing the outcome values adjusted for repeated measures, age, and gender were -5.48 (95% CI: -17.7, 6.7; p= 0.37) and -7.27 (95% CI: -19.4, 4.8; p=0.23) µmol/L for the LDB and HDB groups, respectively compared to the placebo group (Statistical Table 6.1.4, Section 14).

Similar results were observed for the PP population (Statistical Tables P6.1.1 - P6.1.3, Section 14). The overall estimate of change in fructosamine using mixed effect model analysis were -5.88 (95% CI: -19.1, 7.3, p=0.38) and -7.39 (95% CI: -19.9, 5.1; p=0.24) µmol/L for the LDB and HDB groups, respectively compared to the placebo group (Statistical Table P6.1.4, Section 14).

11.4.1.2.2 CGMS Measurements

There was no significant difference in comparison of the LDB and HDB treatment groups to the placebo group in the mean change from baseline in all CGMS parameters evaluated at Visit 4 (Week 4) and Visit 7 (Week 16) which included 1-hour AUC, 2-hour AUC, 3-hour AUC, 24-hour AUC_180, 72-hour AUC_180, MPMG, MBG, MAGE, SD, and %CV (Statistical Tables 6.2.1.1 to 6.2.10.3, Section 14). Adjusted for baseline covariates, the LDB and HDB treatment groups had more decreases in most CGMS parameters compared to placebo.

PP population showed similar findings in CGMS analysis (Statistical Tables P6.2.1.1 to P6.2.10.3, Section 14).

11.4.1.2.3 CGMS Measurements by Meal Type and Meal Days Within Visits

CGMS measurements, which include post-prandial glucose AUC, MBG, SD, %CV at 1 hour, 2 hours and 3 hours, and PMG are summarized by meal type (breakfast, lunch or dinner) and meal days within visits (Statistical Tables S6.2.1.1 to S6.2.3.3, Section 14). Taking into consideration the within and between subject variability, changes in CGMS parameters were analyzed using linear mixed models to determine treatment effects adjusted for repeated measurements between and within visits, and the baseline covariates of age and gender.

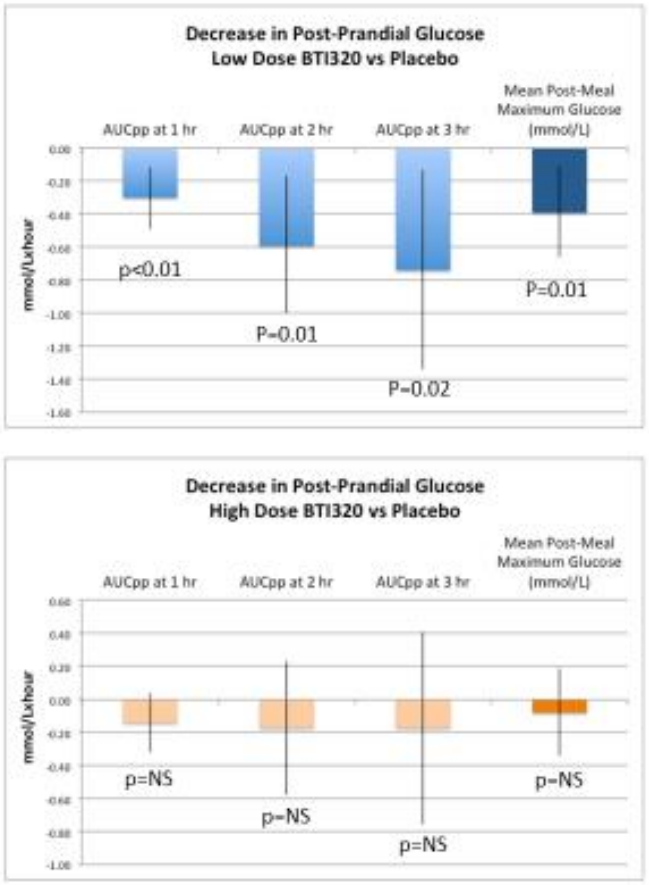
The repeated measures analysis showed that the LDB treatment group demonstrated statistically significant differences in lowering mean post-prandial glucose levels and post-meal glucose over meals within visits compared to the placebo group at 1, 2, and 3 hour post meal (Table 6; Figure 1).

Table 6: Post-prandial Glucose - AUC at 1, 2, and 3 hour (mmol/L*h) and PMG - Over Meals within Visits

PP Glucose	Treatment effects	Estimate	95%CI of estimate	p-value*
AUC at 1 hour	4 grams BTI320	-0.30	(-0.48, -0.11)	<0.01
	8 grams BTI320	-0.14	(-0.32, 0.04)	0.13
AUC at 2 hour	4 grams BTI320	-0.59	(-1.01, -0.18)	0.01
	8 grams BTI320	-0.17	(-0.57, 0.24)	0.42
AUC at 3 hour	4 grams BTI320	-0.74	(-1.35, -0.14)	0.02
	8 grams BTI320	-0.17	(-0.75, 0.42)	0.57
PMG	4 grams BTI320	-0.39	(-0.67, -0.12)	0.01
	8 grams BTI320	-0.08	(-0.35, 0.18)	0.54

*p-value: The p-values of treatment effects (reference to placebo) were obtained by mixed effect model analysis comparing the outcome values adjusted with repeated measures, age, and gender.
Reference: Statistical Tables S6.2.1.2, S6.2.2.2, S6.2.3.2 and S6.2.8.2.

Figure 1: Post-prandial Glucose - AUC at 1, 2, and 3 hour (mmol/L*h) and PMG



Supplementary analyses results showed that the LDB treatment group demonstrated the similar significantly positive treatment effects compared to the placebo group in CGMS measurements

for MBG, PMG and MPMG over meal days by visits or within visits (Statistical Tables S6.2.4.1 to S6.2.9.2, Section 14). Additionally, the LDB treatment group also showed a statistically significant (p=0.03) low SD at 24 hour compared to the placebo group (Statistical Table S6.2.13.2, Section 14).

11.4.1.2.4 HbA_{1c}

The mean HbA_{1c} levels were similar at Visit 1 (-7 to -14 days) and Visit 7 (Week 16), the three groups remained within the defined glycated hemoglobin (HbA_{1c}) range (5.7-6.4%). The LDB and HDB treatment groups showed no statistically significant differences in mean changes of HbA_{1c} levels from baseline at Week 16 compared to the placebo group (Statistical Tables 6.3.1 - 6.3.3, Section 14). The same results were observed for the PP analysis (Statistical Tables P6.3.1 - P6.3.3, Section 14).

11.4.1.2.5 MTT measurements

The results of changes in AUC of glucose, insulin and C-peptide from 0 (baseline) to 15, 30, 60, 90, and 120 minutes, and changes in glucagon-like peptide-1 (GLP-1) from baseline to Week 4 and Week 16 during the standard meal tolerance test (MTT) are summarized in Statistical Tables 6.4.1.1 to 6.4.4.3 and Figure 6.4.1 to 6.4.4, Section 14). Subjects treated with HDB and LDB showed less decrease in AUC values of 120-min glucose and C-peptide from baseline compared with placebo at Week 16. None of the differences were statistically significant, except for the LDB treatment group at Week 4 that showed a significant mean increase in 120-min AUC of C-peptide from baseline compared to the placebo group (p=0.04) (Statistical Table 6.4.3.2, Section 14). At Week 16 (Visit 7), dose dependent results were observed in 120-min AUC of plasma glucose (Statistical Table 6.4.1.2, Section 14), C-peptide (Statistical Table 6.4.3.2, Section 14) and GLP-1 (Statistical Table 6.4.4.2, Section 14).

Similar results were observed for the PP analysis (Statistical Tables P6.4.1.1 to P6.4.4.3, Section 14).

11.4.1.2.6 Oral glucose tolerance test (OGTT) - IGT and IFG

The distribution of subjects with pre-diabetes with normal glucose tolerance, IFG, IGT, or IFG and IGT is presented in Table 7. A greater number of subjects with no change in IFG, IGT, or no worsening to normal glucose levels was observed at 30 days post Week 16 in the HDB treatment group (21, 91.3%) than either the LDB (17, 77.3%) or placebo (8, 66.7%) treatment groups.

Logistic regression analysis adjusted for age and gender showed treatment effects (referenced to placebo) of -0.14 (p=0.87) and -1.45 (p=0.14) for the HDB and LDB treatment groups and odds ratios of 0.87 and 0.24 respectively on the change from IFG/IGT or worsened to normal glucose levels (Statistical Table 6.5.3, Section 14).

Similar results were observed for the PP analysis (Statistical Tables P6.5.1 to P6.5.3, Section 14). No significant association was found between pre-diabetes conditions and any of the treatment groups in both ITT and PP analysis.

Table 7: OGTT - IGT and IFG: Baseline and follow-up - ITT (N=60)

OGTT, n(%)		Placebo	4 grams BTI320	8 grams BTI320
Visit 1 (-7-14 Days)	IFG and IGT	4 (33.3)	4 (16.7)	7 (29.2)
	Impaired fasting glucose (IFG)	0 (0.0)	3 (12.5)	1 (4.2)
	Impaired glucose tolerance (IGT)	5 (41.7)	10 (41.7)	8 (33.3)
	Normal glucose tolerance	3 (25.0)	7 (29.2)	8 (33.3)
Follow Up Visit (30 Days Post Visit 7)	IFG and IGT	1 (8.3)	3 (13.6)	6 (26.1)
	Impaired fasting glucose (IFG)	2 (16.7)	2 (9.1)	4 (17.4)
	Impaired glucose tolerance (IGT)	3 (25.0)	4 (18.2)	4 (17.4)
	Normal glucose tolerance	6 (50.0)	10 (45.5)	7 (30.4)
	Type 2 diabetes	0 (0.0)	3 (13.6)	2 (8.7)
Proportion changes of IGT and IFG at Follow up visit (30 Days Post Visit 7)	Change from IFG/IGT or worsen to normal glucose levels	4 (33.3)	5 (22.7)	2 (8.7)
	No change from IFG/IGT or worsen to normal glucose levels	8 (66.7)	17 (77.3)	21 (91.3)

Normal glucose levels: Fasting plasma glucose (FPG) < 5.6 mmol/L and PG OGTT 2 hours < 7.8 mmol/L
Impaired fasting glucose (IFG): FPG between 5.6 mmol/L and 6.9 mmol/L, and OGTT 2 hours < 7.8 mmol/L
Impaired glucose tolerance (IGT): FPG < 5.6 mmol/L and OGTT 2 hours between 7.8 mmol/L and 11.0 mmol/L
IFG and IGT: FPG between 5.6 mmol/L and 6.9 mmol/L and OGTT 2 hours between 7.8 mmol/L and 11.0 mmol/L
Type 2 diabetes: FPG > 6.9 mmol/L or OGTT 2 hours > 11.0 mmol/L. Reference: Statistical Tables 6.5.1 and 6.5.2.

11.4.1.3 Other Secondary Analyses

11.4.1.3.1 Blood pressure and anthropometric measures

The mean SBP and DBP values are summarized in Statistical Tables 7.1.1.1 to 7.1.2.4 (Section 14). The majority of SBP and DBP values measured were within the normal reference range; very few subjects had SBP or DBP values increased transiently above the upper limit of normal (ULN, SBP 139 mmHg; DBP 89 mmHg) during the study (Data Listing 7.1.1, Appendix 16.2). Only one subject (SG01_05) in the HDB treatment group had high SBPs throughout the study: 168 mmHg at baseline, 166 mmHg at Visit 4, 154 mmHg at Visit 7, and 168 mmHg at the follow up visit. Apart from this one subject, the highest mean SBP and DBP were <130 mmHg and <82 mmHg, respectively, overall; the mean changes in SBP and DBP were minor throughout all visits. The LDB and HDB estimated treatment effects (active to placebo) adjusted for repeated measurements, age, and gender in SBP were -4.4 (95% CI: -10.3, 1.5) and -3.0 (95% CI: -8.8, 2.8) mmHg respectively, whereas DBP differences were 0.9 (95% CI: -4.7, 2.9) and -0.6 (95% CI: -4.4, 3.2) mmHg.

Minor decreases in mean weight across study groups were observed throughout all study visits (Statistical Tables 7.1.3.1 to 7.1.3.4, Section 14). The LDB treatment group showed a statistically significant decrease in mean weight at Visit 7 (p=0.03) and approached a significant decrease at the follow-up visit (p=0.05) compared to placebo with estimated treatment effects -1.7 and -2.1 kg, respectively (ANCOVA analysis).

Minor decreases in mean waist circumference with all treatment groups were also observed throughout the study visits (Statistical Tables 7.1.4.1 to 7.1.4.3, Section 14).

Similar mean changes in SBP and DBP values across all study groups were observed in PP analyses (Statistical Tables P7.1.1.4 and P7.1.2.4, Section 14).

In the PP analysis, the LDB treatment group also showed a significant mean weight decrease compared to placebo at Visit 7 (estimated treatment effect -1.9 kg, p=0.03) and 30 days post Week 16 (estimated treatment effect -2.4 kg, p=0.04) (Statistical Table P7.1.3.3, Section 14).

11.4.1.3.2 Serum lipids, hs-CRP, and Urate

Serum lipid parameters are summarized in Statistical Tables 7.2.1.1 to 7.2.4.3 (Section 14). Although there was a minor change in most of the serum lipid results, the HDB treatment group demonstrated a consistent positive effect in reduction of total cholesterol, LDL, and triglyceride values with a coincident increase in HDL cholesterol. At Week 16, the HDB treatment group showed a statistically significant decrease (p=0.02) in mean triglycerides with treatment effects of -0.49 mmol/L (95% CI: -0.92, -0.6) and a significant increase in HDL cholesterol levels (p=0.05) with treatment effects of 0.13 mmol/L (95% CI: 0.00, 0.26) compared to placebo. Similar results of serum lipids in PP population are summarized in Statistical Tables P7.2.1.1 to P7.2.4.3 (Section 14).

Minor changes in mean hs-CRP and urate levels from baseline were observed at Visits 4 and 7 with all three treatment groups; none of the treatment effects for LDB and HDB treatment groups compared to the placebo were statistically significant (Statistical Tables 7.2.5.1 to 7.2.6.3, Section 14). Analysis results for hs-CRP and urate in PP population are presented in Statistical Tables P7.2.5.1 to P7.2.6.3 (Section 14).

11.4.2 Statistical/analytical issues

ANCOVA model was used to compare the difference in all efficacy analysis parameter changes from baseline between LDB, HDB, and placebo. Baseline measurements, age, and gender were used as adjustments for covariates.

11.4.3 Drug dose, drug concentration, and relationships to response

Not applicable.

11.4.4 Drug-drug and drug-disease interactions

Not applicable.

11.4.5 By-Patient displays

See Appendix 16.2 for individual subject data.

11.4.6 Summary of Efficacy

The primary efficacy analysis results showed that the three treatment groups resulted in non-significant mean decrease in fructosamine level after 4 weeks of treatment: -8.8, -5.2, and -9.4 µmol/L change in the placebo, LDB, and HDB treatment groups, respectively. The estimated

treatments effects adjusting for baseline measurements, age, and gender (ANCOVA) were 2.46 (95%CI: -6.3 to 11.2) and -1.57 (95% CI: -10.3 to 7.1) for the LDB and HDB treatment groups, respectively.

Similarly, minor mean decreases in baseline serum fructosamine level were observed in the secondary efficacy comparison of the LDB and HDB treatment groups to the placebo group after 8, 12, and 16 weeks of treatment. After adjusting for visit effects and baseline covariates, the estimated treatment effects were -5.5 (95% CI: -17.7 to 6.7) for LDB and -7.3 (95% CI: -19.4 to 4.8).

There was no significant difference with the LDB and HDB treatment groups compared to the placebo group in the mean change from baseline in all CGMS parameters evaluated at Visit 4 (Week 4) and Visit 7 (Week 16). However, when adjusted for repeated measurements the LDB treatment group demonstrated statistically significant differences in lowering mean post-prandial glucose levels and post-meal glucose compared to placebo at 1, 2, and 3 hour post-meal and overall post-meal glucose with p-values ranging from <0.01 to 0.02. Subjects treated with HDB and LDB resulted in less decreases in AUCs of 120-min glucose and C-Peptide values in the standard meal tolerance test (MTT) compared with placebo at Week 16. None of the differences were statistically significant except for the LDB treatment group at Week 4 which resulted in a significant mean increase in AUC 120-min C-Peptide from baseline compared to the placebo group (p=0.04). Dose-dependent results were observed at Week 16 (Visit 7) in AUC 120-min plasma glucose, C-Peptide, and GLP1 biomarkers.

Results of the oral glucose tolerance test showed a greater number of subjects in the HDB treatment group (21, 91.3%) with no change in IFG, IGT or worsened to normal glucose levels at 30 days post Week 16 than either the LDB (17, 77.3%) or placebo (8, 66.7%) treatment groups. The mean HbA_{1c} levels were similar among the three treatment groups at Visit 1 (-7 to -14 days) and Visit 7 (Week 16); all remained within the defined HbA_{1c} range of 5.7 – 6.4%. The LDB and HDB treatment groups showed no statistically significant differences in mean changes of HbA_{1c} levels from baseline to Week 16 similar to the placebo group.

The majority of systolic and diastolic BP values measured were within the normal reference range. Overall, the highest mean SBP was <130 mmHg and the highest mean DBP was <82 mmHg; the mean changes in SBP and DBP were minor throughout all visits.

The LDB treatment group showed a statistically significant decrease in mean weight at Visit 7 (treatment effect -1.7 kg; p=0.03), which also approached significance at the follow-up visit (treatment effect -2.1 kg; p=0.05) compared to placebo with estimate treatment effects of -0.1 and -0.2 kg, respectively. There were no significant changes in body weight in the HDB treatment group. Minor decreases in mean weights and waist circumference across three treatment groups were observed throughout all study visits.

The HDB treatment group demonstrated a consistent positive effect in reduction of total cholesterol, LDL cholesterol and triglycerides and an increase in HDL cholesterol. At Week 16, the HDB treatment group showed a statistically significant decrease (p=0.02) in mean triglyceride and approached a significant increase in HDL cholesterol levels (p=0.05) compared to placebo.

Minor changes in mean hs-CRP and urate levels from baseline across three treatment groups

were observed at Visits 4 and 7; none of the treatment effects for LDB and HDB treatment groups compared to the placebo in change of hs-CRP and urate were statistically significant.

12. SAFETY EVALUATIONS

12.1 Extent of Exposure

Subject exposures to treatments are summarized in Statistical Table 3.1 (Section 14). Greater than 90% of the subjects in each of the treatment groups completed all 7 visits and the follow-up visit. The average drug compliances calculated by half of the number of administered tablets divided by the number of meals ingested between two visits were high (92.3% to 99.7%; Table 8). The means of overall compliance were greater than 95% across the three treatment groups.

Table 8: Extent of Exposure

Compliance (%)		Placebo	4 grams BTI320	8 grams BTI320
Between Visit 3 and 4	N	12	21	24
	Mean (SD)	92.3 (15.3)	96.2 (12.2)	95.1 (8.3)
	Median (IQR)	100.0 (12.2)	100.0 (12.8)	100.0 (14.0)
Between Visit 4 and 5	N	11	19	23
	Mean (SD)	96.5 (6.2)	98.9 (16.7)	95.0 (8.6)
	Median (IQR)	98.8 (0.0)	98.8 (2.4)	98.8 (3.7)
Between Visit 5 and 6	N	11	18	22
	Mean (SD)	99.7 (0.8)	97.9 (4.7)	98.9 (6.0)
	Median (IQR)	100.0 (0.0)	100.0 (0.0)	100.0 (0.0)
Between Visit 6 and 7	N	11	17	22
	Mean (SD)	97.9 (4.8)	97.4 (4.2)	98.4 (3.4)
	Median (IQR)	100.0 (2.6)	100.0 (5.4)	100.0 (5.1)
All Visits*	N	12	21	24
	Mean (SD)	97.0 (4.2)	95.3 (15.3)	95.8 (6.4)
	Median (IQR)	98.9 (5.4)	99.1 (6.6)	96.8 (5.6)

*Overall compliance is calculated by half of the number of tablets (A+B) taken divided by number of meals taken in a whole study period
Reference: Statistical Table 3.2.1: Study Outcomes - Drug compliance - Week 4, week 8, week 12, and week 16
Statistical Table 3.2.2: Study Outcomes - Drug compliance - Overall

12.2 Adverse Events

12.2.1 Brief Summary of Adverse Events (AEs)

All-cause AEs experienced during the study are summarized in Table 8.2.8.1 (Section 14). Of the 60 treated subjects, 41 (LDB, 18/24; HDB, 16/24; Placebo, 7/12) experienced 104 all-causality AEs (LDB, 47; HDB, 36; Placebo, 21). Of the 41 subjects who experienced 104 AEs, 32 subjects

(LDB, 14/24; HDB, 12/24; Placebo, 6/12) experienced 60 AEs (LDB, 28; HDB, 19; Placebo, 13) which were considered possibly- or probably-related to study treatments (Table 9; Data Listing 8.3.1, Appendix 16.2). All of the AEs were mild to moderate in severity except for two events, osteosarcoma and flatulence, which were considered severe. One of the severe events, osteosarcoma, was reported as SAE (Data Listing 8.3.4, Appendix 16.2.7).

The most commonly occurring AEs, flatulence (LDB, 29.2%; HDB, 29.2%; placebo, 16.7%), abdominal distension (LDB, 25.0%; HDB, 16.7%; placebo, 8.3%), and diarrhea (LDB, 16.7%; HDB, 12.5%; placebo, 8.3%), were possibly treatment-related and more frequently reported in the LDB and HDB treatment groups compared with the group.

Table 9: Possibly and probably treatment related AEs

Adverse events Dictionary-Derived Term n(%)		Placebo	4 grams BTI320	8 grams BTI320
Possibly related AEs	Abdominal distension	1 (8.3%)	6 (25.0%)	4 (16.7%)
	Abdominal pain	2 (16.7%)	2 (8.3%)	1 (4.2%)
	Abdominal pain upper	0 (0%)	1 (4.2%)	0 (0%)
	Constipation	0 (0%)	0 (0%)	1 (4.2%)
	Decreased appetite	0 (0%)	1 (4.2%)	0 (0%)
	Defecation urgency	0 (0%)	1 (4.2%)	0 (0%)
	Diarrhea	1 (8.3%)	4 (16.7%)	3 (12.5%)
	Flatulence	2 (16.7%)	7 (29.2%)	7 (29.2%)
	Frequent bowel movements	5 (41.7%)	4 (16.7%)	2 (8.3%)
	Gastroenteritis	0 (0%)	1 (4.2%)	0 (0%)
	Tooth fracture	1 (8.3%)	0 (0%)	0 (0%)
Probably related AEs	Diarrhea	1 (8.3%)	1 (4.2%)	0 (0%)
	Flatulence	0 (0%)	0 (0%)	1 (4.2%)

Reference: Statistical Table 8.2.8.2.

12.2.2 Display of Adverse Events

Table 9 summarizes the number of subjects with treatment related AEs by dictionary-derived term. Statistical Table 8.2.8.1 summarizes number of subjects with AEs by dictionary-derived term.

12.2.3 Analysis of Adverse Events

Overall, the most frequently experienced AEs were abdominal distension and flatulence in subjects who received LDB (25.0% and 29.2% of subjects, respectively) and HDB (16.7% and 33.3% of subjects, respectively) relative to the placebo group (8.3% and 16.7% of subjects, respectively). Most of the abdominal distension and flatulence events were considered possibly- or probably-related to treatment (Statistical Table 8.2.8.1, Section 14; Table 9). Frequent bowel movements occurred in 41.7% of placebo treated subjects which was higher than those reported in the of LDB (16.7%) and HDB (8.3%) treatment groups. All frequent bowel movement events were considered possibly-related to treatment (Table 9).

12.2.4 Listing of Adverse Events by Subject

Adverse Events by subject are listed in the following listings in Appendix 16.2.7:

- All AEs (by dictionary-derived term) are provided in Data Listing 8.3.1
- AE possibly related to study drug is provided in Data Listing 8.3.2
- AE probably related to study drug is provided in Data Listing 8.3.3
- SAE is provided in Data Listing 8.3.4

12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1 Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No deaths occurred during the study. Two subjects (SG01_41 and SG01_56) discontinued from study due to AEs while 2 other subjects temporarily discontinued from the study due to AEs; subject SG01_30 had study drug temporarily interrupted for 2 days and subject SG01_55 completed the study (Data Listing 8.3.1, Appendix 16.2.7).

12.3.2 Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

One subject (SG01_41) in the LDB treatment group was diagnosed with an osteosarcoma at left distal femur (serious adverse event) who discontinued from the study due to this SAE which was considered by the Investigator to not be related to study medication (Data Listing 8.3.1, Appendix 16.2.7).

Additionally, one subject (SG01_56) also in the LDB treatment group experienced a moderate abdominal pain and diarrhea which was considered possibly-related to treatment by the Investigator. The subject discontinued the study due to the gastrointestinal AEs and both GI events recovered in 6 days after reporting the AEs (Data Listing 8.3.1, Appendix 16.2.7).

12.4 Clinical Laboratory Evaluation

12.4.1 Listing of Individual Laboratory Measurements by Subject and Each Abnormal Laboratory Value

Laboratory safety test results for hemoglobin, hematocrit, platelet, white blood cell (WBC),

sodium, potassium, urea, creatinine, bilirubin, alkaline phosphatase (ALP), and alanine aminotransferase (ALT) at Visits 1, 4 and 7 are summarized in Statistical Tables 8.1.1 to 8.2.7 (Section 14).

12.4.2 Evaluation of laboratory Results

12.4.2.1 Complete blood count

There were no remarkable differences observed in mean hemoglobin, hematocrit, platelet, and WBC counts at Visits 1, 4, and 7 across the three treatment groups (Statistical Tables 8.1.1 to 8.1.4, Section 14).

12.4.2.2 Renal and liver function

There were no remarkable differences observed in the mean values in liver function test parameters of bilirubin, ALP, and ALT (Statistical Tables 8.2.5 to 8.2.7, Section 14) and urinalysis of serum sodium, potassium, urea, creatinine (Statistical Tables 8.2.1 to 8.2.4, Section 14) at Visits 1, 4 and 7 across the three treatment groups; all mean values were within normal laboratory test levels. There were very few subjects with transient abnormal ALT values and none of the values were 3X above the ULN. One subject (SG01_41) in the LDB treatment group had abnormal ALP test results at the screening visit (291 IU/L) and Visit 4 (722 IU/L), which led to an outlier mean value in Statistical Table 8.2.6 (Section 14; Data Listing 8.2.6, Appendix 16.2.8).

12.5 Questionnaire Analyses

12.5.1 WHOQOL-BREF

There were no statistically significant changes in mean total scores in the WHOQOL-BREF questionnaire in Physical Health and Psychological Domains, the mean total scores among the three treatment groups at Visits 2, 4 and 7 for Physical Health Domain ranged between 11.9 to 12.9, and for Psychological Domain ranged between 11.7 to 13.2 (Statistical Tables 9.1.1.1 - 9.1.2.3, Section 14).

There was a mean increase in the Social Relationship Domain total score from baseline in the placebo group at Visit 4, which was significantly higher than the mean change in total domain score observed in the LDB and HDB treatment groups ($P<0.01$ and $P=0.03$, respectively) (Statistical Table 9.1.3.2, Section 14). Additionally, the ANCOVA analysis showed that the HDB group had a mean increase in the Social Relationship Domain total score from baseline at Visit 7, which approached a statistically significant increase ($P=0.05$) compared to the placebo group with estimated treatment effects of 1.1 (95% CI: -0.0, 2.3) (Statistical Tables 9.1.3.1 - 9.1.3.3, Section 14). There were no statistically significant differences in the mean total scores of Environment Domain among the three treatment groups at Visits 2, 4, and 7 (range: 13.8 to 15.4) (Statistical Tables 9.1.4.1 - 9.1.4.3, Section 14).

12.5.2 Appetite

Individual question scores from the Appetite Questionnaire Questions 1 to 6 were summarized in Statistical Tables 9.2.1.1 - 9.2.1.6 (Section 14). The changes in appetite mean scores from

baseline at Week 4 and Week 16 were minor and similar across the three treatment groups (Statistical Tables 9.2.1.7 - 9.2.1.8, Section 14).

12.5.3 International Physical activity

Individual question scores from International Physical activity questionnaire Questions 1 to 7 were summarized in Statistical Tables 9.2.2.1 - 9.2.2.7 (Section 14). The changes in International Physical Activity Questions 1 to 7 mean total scores from baseline at Week 4 and Week 16 were minor and similar across the three treatment groups, except for Question 1 at Week 4, in which the HDB treatment group had a statistically significant increase in "Days doing vigorous physical activities" compared to placebo (-0.3 ± 0.8 *vs.* -1.0 ± 0.0 days; p=0.03). Similarly, 16 weeks of therapy resulted in an increase in activity in the HDB treatment group (+0.5 ± 1.3 days) compared with placebo (-1.0 ± 1.4 days; p=0.26) and LDB (0.0 ± 0.0) (Statistical Table 9.2.2.8, Section 14).

12.5.4 Dietary survey

The food frequency questionnaire results for each dietary survey parameter are summarized in Statistical Tables 9.2.3.1 - 9.2.3.19 (Section 14). No statistically significant differences from baseline were observed at Week 4 and Week 16 between the LDB and HDB treatment and placebo group (Statistical Tables 9.2.3.20 - 9.2.3.21, Section 14).

The placebo group had the largest mean decrease from baseline in dietary calories, protein, carbohydrate, dietary fiber, sugar (total), trans fat, calcium, copper, iron, magnesium, phosphorus, potassium, sodium and zinc at Week 4 and Week 16, followed by the LDB treatment group, while the HDB treatment group showed stable or less change in these dietary parameters at the Week 4 and Week 16 (Statistical Tables 9.2.3.20 - 9.2.3.21, Section 14).

12.6 Other Observations Related to Safety

12.6.1 Concomitant Medications

Data Listing 4.1 lists the information of concurrent medications (Appendix 16.2.7). The most commonly prescribed drugs for hypertension were amlodipine, atenolol, lisinopril, and losartan; simvastatin and rosuvastatin for dyslipidemia; and famotidine for subjects with gastrointestinal disorders.

12.7 Safety Conclusions

Of the 60 treated subjects, 41 (LDB, 18/24; HDB, 16/24; Placebo, 7/12) experienced 104 all causality AEs (LDB, 47; HDB, 36; Placebo, 21). Of the 41 subjects experienced 104 AEs, 32 (LDB, 14/24; HDB, 12/24; Placebo, 6/12) experienced 60 AEs (LDB, 28; HDB, 19; Placebo, 13) that were considered possibly or probably related to study treatments. The most commonly experienced AEs, flatulence (LDB, 29.2%; HDB, 29.2%; Placebo, 16.7%), abdominal distension (LDB, 25.0%; HDB, 16.7%; Placebo, 8.3%), and diarrhea (LDB, 16.7%; HDB, 12.5%; Placebo, 8.3%), which were possibly related to study drug were more frequently reported events in the LDB and HDB treatment groups. All of the AEs were mild or moderate in severity except for two events, osteosarcoma and flatulence, that were rated severe. One of the severe events, osteosarcoma, was reported as SAE, the subject discontinued from the study due to this unrelated

SAE. Additionally, one subject who received LDB experienced moderate abdominal pain and diarrhea which were considered possibly related to treatment by the investigator and discontinued from the study due to the gastrointestinal AEs, which resolved in 6 days.

The majority of laboratory safety test results for complete blood count (hemoglobin, hematocrit, platelet, WBC), liver function (bilirubin, ALP and ALT) and renal function (serum sodium, potassium, urea, creatinine) were within normal range, none of the abnormal values were clinically significant nor reported as an AE.

Questionnaire survey results for QOL, Appetite, International Physical Activity, and Dietary showed no remarkable differences except the HDB treatment group had a statistically significant mean increase from baseline in "Days doing vigorous physical activities" compared to placebo ($p=0.03$) at Visit 4. The placebo group had a significant mean increase in the Social Relationship Domain total score from baseline at Visit 4, compared with the LDB and HDB treatment groups ($P<0.01$ and $P=0.03$, respectively).

13. DISCUSSION AND OVERALL CONCLUSIONS

This phase 2, double blind, randomized, placebo-controlled, proof of concept study examined glucose-lowering effects of BTI320, a propriety fractionated mannan, in Chinese subjects with pre-diabetes. A total of sixty (60) eligible subjects were enrolled and randomly assigned to BTI320 8 g (24), BTI320 4 g (24) and placebo (12). Fifty-seven (57) subjects completed the 16-week study.

With no significant differences detected (normal range fructosamine) in subjects treated with BTI320 and placebo, the primary efficacy endpoint (change in baseline serum fructosamine to Week 4) was registered without an increase. As a non-systemic agent, it would be anticipated to observe little change unless the daily exposure of blood glucose was unregulated as in early stage onset of metabolic dysfunction with blood sugar increases that are sustained outside appropriate normal ranges.

However, significant attenuation of postprandial hyperglycemia and multiple CGM glycemic variability parameters were observed in subjects receiving low dose (4 g) BTI320 compared with placebo. Similarly, treatment with 4 g BTI320 significantly reduced post-prandial glucose AUC in 1 hour ($p<0.01$), 2 hours ($p=0.01$), and 3 hours ($p=0.02$) and post-meal maximum glucose ($p=0.01$). Reductions were also observed in the high dose (8 g) group albeit not reaching statistical significance. Minor decreases in serum fructosamine level or HbA_{1c} from baseline were also observed in both treatment groups at up to 16 weeks of intervention when compared to placebo.

It is speculated that BTI320 works by predominately suppressing postprandial glucose excursion, slowing down the rate of glucose excursion, as well as reducing the absolute amount absorbed, thereby preventing hyperglycemia without the risk of hypoglycemia. However, since changes in serum fructosamine and HbA_{1c} comprise of both fasting and post-prandial periods of glycemia, the observed effect of BTI320 might not be of sufficient magnitude to translate into changes of significance. We speculated that a minor or no change in serum fructosamine in this prediabetic population indicates a slow down or possible delay in diabetes progression. It is hypothesized that the selected prediabetic population in this study may have limited the study power to demonstrate significant effects on glycemic measures such as fructosamine and HbA_{1c} compared

with testing in a population with diagnosed diabetes.

In this study, differences were observed in baseline factors including variability in dietary intake among the treatment groups. For instance, placebo subjects overall had higher intakes of calories, sugar, and fat at baseline compared with subjects in the active treatment groups. Such imbalances in risk factors may have contributed to the robust placebo effect observed for the primary efficacy endpoint. When linear mixed models were used to adjust for intersubject variability and intrasubject variability by repeated measures, statistically significant treatment effects in CGMS parameters were observed in the low dose BTI320 group compared to placebo. Further research in the prediabetic population should take this variability into consideration in the choice of study design and analytical methods in an effort to adequately balance risk factors and confounders.

It is also interesting to note that dose response was not observed as treatment with high dose BTI320 did not show statistical efficacy in the reduction of both blood glucose and body weight, although it may provide benefit in reducing serum triglyceride and increasing HDL-cholesterol. The combination of small sample size and inter-individual variability with respect to meal content, meal size, and post-prandial glucose absorption might have limited the study power to conclusively examine the efficacy of BTI320. Furthermore, it is also possible that the lower dose is the optimal dose in terms of delaying glucose absorption in the gastrointestinal tract and that the higher dose does not produce additional benefits.

Overall, BTI320 was relatively well tolerated and importantly, no hypoglycemic symptoms or events were reported in the study. The majority of adverse events reported, such as abdominal distension and increased flatulence, were all gastrointestinal symptoms, likely as a result of increased bacterial digestion of complex carbohydrates in the colon producing flatulence.

BTI320 significantly reduced postprandial hyperglycemia and glycemic variability, as measured by CGMS in subjects at high risk for diabetes. Treatment with low doses of BTI320 significantly attenuated post-prandial rise in blood glucose at 1, 2 and 3 hours post meal and reduced body weight. Given the ease of administration and high levels of tolerance, BTI320 has the potential to be used as an adjunct to lifestyle modification for diabetes prevention. Future research is required to test the feasibility and effectiveness of BTI320 as part of a larger program for diabetes prevention.

14. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 Demographic Data Summary Figures and Tables

Number	Title	Population
1.2	Demographics and other baseline characteristics - Major ongoing medical history	ITT
1.4	Demographics and other baseline characteristics - Vital signs	ITT
1.5	Demographics and other baseline characteristics - Physical exam	ITT
1.6	Demographics and other baseline characteristics - CGMS measurements	ITT
1.7	Demographics and other baseline characteristics - Fructosamine	ITT
1.8	Demographics and other baseline characteristics - HbA_{1c}	ITT
1.9	Demographics and other baseline characteristics - MTT 120-min AUC	ITT
1.10	Demographics and other baseline characteristics - IGT and IFG	ITT
1.11	Demographics and other baseline characteristics - Serum lipids	ITT
1.12	Demographics and other baseline characteristics - hs-CRP and urate	ITT
1.13	Demographics and other baseline characteristics - Complete blood count, renal and liver function	ITT
1.14	Demographics and other baseline characteristics - WHOQOL-BREF	ITT
1.15	Demographics and other baseline characteristics - Appetite	ITT
1.16	Demographics and other baseline characteristics - International physical activity	ITT
1.17	Demographics and other baseline characteristics – food frequency questionnaire	ITT
3.1	Study Outcomes - Exposure to treatment	ITT

14.2 Efficacy Summary Tables

Number	Title	Population
5.1.3	Primary Analyses - Change of fructosamine (ANCOVA analysis - From baseline to week 4)	ITT
6.1.1	Secondary Analyses – Fructosamine (Baseline, week 8, week 12, and week 16)	ITT
6.1.2	Secondary Analyses - Change of fructosamine (Univariate analysis - From baseline to week 8, week 12, and week 16)	ITT
6.1.3	Secondary Analyses - Change of fructosamine (ANCOVA analysis - From baseline to week 8, week 12, and week 16)	ITT
6.1.4	Secondary Analyses - Change of fructosamine (Repeated measures analysis - Over visits)	ITT
6.2.1.1	Secondary Analyses - CGMS measurements - AUC at 1 hour (Baseline, week 4, and week 16)	ITT
6.2.1.2	Secondary Analyses - CGMS measurements - Change of 1-hour AUC (Univariate analysis - From baseline to week 4, and week 16)	ITT
6.2.1.3	Secondary Analyses - CGMS measurements - Change of 1-hour AUC (ANCOVA analysis - From baseline to week 4, and week 16)	ITT
6.2.2.1	Secondary Analyses - CGMS measurements - AUC at 2 hour (Baseline, week 4, and week 16)	ITT
6.2.2.2	Secondary Analyses - CGMS measurements - Change of 2-hour AUC (Univariate analysis - From baseline to week 4, and week 16)	ITT
6.2.2.3	Secondary Analyses - CGMS measurements - Change of 2-hour AUC (ANCOVA analysis - From baseline to week 4, and week 16)	ITT
6.2.3.1	Secondary Analyses - CGMS measurements - AUC at 3 hour (Baseline, week 4, and week 16)	ITT
6.2.3.2	Secondary Analyses - CGMS measurements - Change of 3-hour AUC (Univariate analysis - From baseline to week 4, and week 16)	ITT
6.2.3.3	Secondary Analyses - CGMS measurements - Change of 3-hour AUC (ANCOVA analysis - From baseline to week 4, and week 16)	ITT
6.2.4.1	Secondary Analyses - CGMS measurements – AUC_180 during the 24 hour period (Baseline, week 4, and week 16)	ITT
6.2.4.2	Secondary Analyses - CGMS measurements - Change of 24-hour AUC_180 (Univariate analysis - From baseline to week 4, and week 16)	ITT
6.2.4.3	Secondary Analyses - CGMS measurements - Change of 24-hour AUC_180 (ANCOVA analysis - From baseline to week 4, and week 16)	ITT
6.2.5.1	Secondary Analyses - CGMS measurements – AUC_180 during the 72 hour period (Baseline, week 4, and week 16)	ITT
6.2.5.2	Secondary Analyses - CGMS measurements - Change of 72-hour AUC_180 (Univariate analysis - From baseline to week 4, and week 16)	ITT
6.2.5.3	Secondary Analyses - CGMS measurements - Change of 72-hour AUC_180 (ANCOVA analysis - From baseline to week 4, and week 16)	ITT
6.2.6.1	Secondary Analyses - CGMS measurements – MPMG (Baseline, week 4, and week 16)	ITT
6.2.6.2	Secondary Analyses - CGMS measurements - Change of MPMG (Univariate analysis - From baseline to week 4, and week 16)	ITT
6.2.6.3	Secondary Analyses - CGMS measurements - Change of MPMG (ANCOVA analysis - From baseline to week 4, and week 16)	ITT
6.2.7.1	Secondary Analyses - CGMS measurements – MBG (Baseline, week 4, and week 16)	ITT
6.2.7.2	Secondary Analyses - CGMS measurements - Change of MBG (Univariate analysis - From baseline to week 4, and week 16)	ITT
6.2.7.3	Secondary Analyses - CGMS measurements - Change of MBG (ANCOVA	ITT

Number	Title	Population
	analysis - From baseline to week 4, and week 16)	
6.2.8.1	Secondary Analyses - CGMS measurements – SD (Baseline, week 4, and week 16)	ITT
6.2.8.2	Secondary Analyses - CGMS measurements - Change of SD (Univariate analysis - From baseline to week 4, and week 16)	ITT
6.2.8.3	Secondary Analyses - CGMS measurements - Change of SD (ANCOVA analysis - From baseline to week 4, and week 16)	ITT
6.2.9.1	Secondary Analyses - CGMS measurements – CV (Baseline, week 4, and week 16)	ITT
6.2.9.2	Secondary Analyses - CGMS measurements - Change of CV (Univariate analysis - From baseline to week 4, and week 16)	ITT
6.2.9.3	Secondary Analyses - CGMS measurements - Change of CV (ANCOVA analysis - From baseline to week 4, and week 16)	ITT
6.2.10.1	Secondary Analyses - CGMS measurements – MAGE (Baseline, week 4, and week 16)	ITT
6.2.10.2	Secondary Analyses - CGMS measurements - Change of MAGE (Univariate analysis - From baseline to week 4, and week 16)	ITT
6.2.10.3	Secondary Analyses - CGMS measurements - Change of MAGE (ANCOVA analysis - From baseline to week 4, and week 16)	ITT
6.3.1	Secondary Analyses - HbA_{1c} (Baseline and week 16)	ITT
6.3.2	Secondary Analyses - Change of HbA_{1c} (Univariate analysis - From baseline to week 16)	ITT
6.3.3	Secondary Analyses - Change of HbA_{1c} (ANCOVA analysis - From baseline to week 16)	ITT
6.4.1.1	Secondary Analyses - MTT - 120-min AUC of glucose level (Baseline, week 4, and week 16)	ITT
6.4.1.2	Secondary Analyses - MTT - Change of 120-min glucose AUC (Univariate analysis - From baseline to week 4, and week 16)	ITT
6.4.1.3	Secondary Analyses - MTT - Change of 120-min glucose AUC (ANCOVA analysis - From baseline to week 4, and week 16)	ITT
6.4.2.1	Secondary Analyses - MTT - 120-min AUC of insulin (Baseline, week 4, and week 16)	ITT
6.4.2.2	Secondary Analyses - MTT - Change of 120-min insulin AUC (Univariate analysis - From baseline to week 4, and week 16)	ITT
6.4.2.3	Secondary Analyses - MTT - Change of 120-min insulin AUC (ANCOVA analysis - From baseline to week 4, and week 16)	ITT
6.4.3.1	Secondary Analyses - MTT - 120-min AUC of C-Peptide (Baseline, week 4, and week 16)	ITT
6.4.3.2	Secondary Analyses - MTT - Change of 120-min C-Peptide AUC (Univariate analysis - From baseline to week 4, and week 16)	ITT
6.4.3.3	Secondary Analyses - MTT - Change of 120-min C-Peptide AUC (ANCOVA analysis - From baseline to week 4, and week 16)	ITT
6.4.4.1	Secondary Analyses - MTT - 120-min AUC of GLP1 (Baseline, week 4, and week 16)	ITT
6.4.4.2	Secondary Analyses - MTT - Change of 120-min GLP1 AUC (Univariate analysis - From baseline to week 4, and week 16)	ITT
6.4.4.3	Secondary Analyses - MTT - Change of 120-min GLP1 AUC (ANCOVA analysis - From baseline to week 4, and week 16)	ITT
6.5.3	Secondary Analyses - Change of IGT and IFG (Logistic regression analysis - From baseline to follow-up)	ITT
7.1.1.1	Other Secondary Analyses – SBP (Baseline, week 4, week 8, week 12, week 16, and follow-up)	ITT

Number	Title	Population
7.1.1.2	Other Secondary Analyses - Change of SBP (Univariate analysis - From baseline to week 4, week 8, week 12, week 16, and follow-up)	ITT
7.1.1.3	Other Secondary Analyses - Change of SBP (ANCOVA analysis - From baseline to week 4, week 8, week 12, week 16, and follow-up)	ITT
7.1.1.4	Secondary Analyses - Change of SBP	ITT
7.1.2.1	Other Secondary Analyses – DBP (Baseline, week 4, week 8, week 12, week 16, and follow-up)	ITT
7.1.2.2	Other Secondary Analyses - Change of DBP (Univariate analysis - From baseline to week 4, week 8, week 12, week 16, and follow-up)	ITT
7.1.2.3	Other Secondary Analyses - Change of DBP (ANCOVA analysis - From baseline to week 4, week 8, week 12, week 16, and follow-up)	ITT
7.1.2.4	Secondary Analyses - Change of DBP	ITT
7.1.3.1	Other Secondary Analyses – Weight (Baseline, week 4, week 8, week 12, week 16, and follow-up)	ITT
7.1.3.2	Other Secondary Analyses - Change of weight (Univariate analysis - From baseline to week 4, week 8, week 12, week 16, and follow-up)	ITT
7.1.3.3	Other Secondary Analyses - Change of weight (ANCOVA analysis - From baseline to week 4, week 8, week 12, week 16, and follow-up)	ITT
7.1.3.4	Secondary Analyses - Change of weight	ITT
7.1.4.1	Other Secondary Analyses - Waist circumference (Baseline, week 4, week 8, week 12, week 16, and follow-up)	ITT
7.1.4.2	Other Secondary Analyses - Change of waist circumference (Univariate analysis - From baseline to week 4, week 8, week 12, week 16, and follow-up)	ITT
7.1.4.3	Other Secondary Analyses - Change of waist circumference (ANCOVA analysis - From baseline to week 4, week 8, week 12, week 16, and follow-up)	ITT
7.2.1.1	Other Secondary Analyses - Total cholesterol (Baseline, week 4, and week 16)	ITT
7.2.1.2	Other Secondary Analyses - Change of total cholesterol (Univariate analysis - From baseline to week 4 and week 16)	ITT
7.2.1.3	Other Secondary Analyses - Change of total cholesterol (ANCOVA analysis - From baseline to week 4, and week 16)	ITT
7.2.2.1	Other Secondary Analyses - LDL cholesterol (Baseline, week 4, and week 16)	ITT
7.2.2.2	Other Secondary Analyses - Change of LDL cholesterol (Univariate analysis - From baseline to week 4 and week 16)	ITT
7.2.2.3	Other Secondary Analyses - Change of LDL cholesterol (ANCOVA analysis - From baseline to week 4, and week 16)	ITT
7.2.3.1	Other Secondary Analyses - HDL cholesterol (Baseline, week 4, and week 16)	ITT
7.2.3.2	Other Secondary Analyses - Change of HDL cholesterol (Univariate analysis - From baseline to week 4 and week 16)	ITT
7.2.3.3	Other Secondary Analyses - Change of HDL cholesterol (ANCOVA analysis - From baseline to week 4, and week 16)	ITT
7.2.4.1	Other Secondary Analyses – Triglyceride (Baseline, week 4, and week 16)	ITT
7.2.4.2	Other Secondary Analyses - Change of triglyceride (Univariate analysis - From baseline to week 4 and week 16)	ITT
7.2.4.3	Other Secondary Analyses - Change of triglyceride (ANCOVA analysis - From baseline to week 4, and week 16)	ITT
7.2.5.1	Other Secondary Analyses - hs-CRP (Baseline, week 4, and week 16)	ITT
7.2.5.2	Other Secondary Analyses - Change of hs-CRP (Univariate analysis - From baseline to week 4 and week 16)	ITT
7.2.5.3	Other Secondary Analyses - Change of hs-CRP (ANCOVA analysis - From baseline to week 4, and week 16)	ITT
7.2.6.1	Other Secondary Analyses – Urate (Baseline, week 4, and week 16)	ITT
7.2.6.2	Other Secondary Analyses - Change of urate (Univariate analysis - From baseline	ITT

Number	Title	Population
	to week 4 and week 16)	
7.2.6.3	Other Secondary Analyses - Change of urate (ANCOVA analysis - From baseline to week 4, and week 16)	ITT

14.2.1 Supplementary Tables

Number	Title	Population
6.2.1.1	Secondary Analyses - CGMS measurements - AUC at 1 hour (mmol/L*h) - Meals sequence by days and visits	ITT
6.2.1.3	Secondary Analyses - CGMS measurements - AUC at 1 hour (mmol/L*h)	ITT
6.2.1.4	Secondary Analyses - CGMS measurements - AUC at 1 hour (mmol/L*h)	ITT
6.2.2.1	Secondary Analyses - CGMS measurements - AUC at 2 hour (mmol/L*h) - Meals sequence by days and visits	ITT
6.2.2.3	Secondary Analyses - CGMS measurements - AUC at 2 hour (mmol/L*h)	ITT
6.2.2.4	Secondary Analyses - CGMS measurements - AUC at 2 hour (mmol/L*h)	ITT
6.2.3.1	Secondary Analyses - CGMS measurements - AUC at 3 hour (mmol/L*h) - Meals sequence by days and visits	ITT
6.2.3.3	Secondary Analyses - CGMS measurements - AUC at 3 hour (mmol/L*h)	ITT
6.2.4.1	Secondary Analyses - CGMS measurements - MBG at 1 hour (mmol/L) - Meals sequence by days and visits	ITT
6.2.4.2	Secondary Analyses - CGMS measurements - MBG at 1 hour (mmol/L) – Repeated measures analysis - Over meals within visits	ITT
6.2.5.1	Secondary Analyses - CGMS measurements - MBG at 2 hour (mmol/L) - Meals sequence by days and visits	ITT
6.2.5.2	Secondary Analyses - CGMS measurements - MBG at 2 hour (mmol/L) – Repeated measures analysis - Over meals within visits	ITT
6.2.6.1	Secondary Analyses - CGMS measurements - MBG at 3 hour (mmol/L) - Meals sequence by days and visits	ITT
6.2.6.2	Secondary Analyses - CGMS measurements - MBG at 3 hour (mmol/L) – Repeated measures analysis - Over meals within visits	ITT
6.2.7.1	Secondary Analyses - CGMS measurements - MBG at 24 hour (mmol/L) - Meals days by visits	ITT
6.2.7.2	Secondary Analyses - CGMS measurements - MBG at 24 hour (mmol/L) – Repeated measures analysis - Over meal days within visits	ITT
6.2.8.1	Secondary Analyses - CGMS measurements - PMG (mmol/L) - Meals sequence by days and visits	ITT
6.2.9.1	Secondary Analyses - CGMS measurements - MPMG at 24 hour (mmol/L) - Meals days by visits	ITT
6.2.9.2	Secondary Analyses - CGMS measurements - MPMG at 24 hour (mmol/L) – Repeated measures analysis - Over meal days within visits	ITT
6.2.10.1	Secondary Analyses - CGMS measurements - SD at 1 hour (mmol/L) - Meals sequence by days and visits	ITT
6.2.10.2	Secondary Analyses - CGMS measurements - SD at 1 hour (mmol/L) – Repeated measures analysis - Over meals within visits	ITT
6.2.11.1	Secondary Analyses - CGMS measurements - SD at 2 hour (mmol/L) - Meals sequence by days and visits	ITT
6.2.11.2	Secondary Analyses - CGMS measurements - SD at 2 hour (mmol/L) – Repeated measures analysis - Over meals within visits	ITT
6.2.12.1	Secondary Analyses - CGMS measurements - SD at 3 hour (mmol/L) - Meals sequence by days and visits	ITT
6.2.12.2	Secondary Analyses - CGMS measurements - SD at 3 hour (mmol/L) – Repeated measures analysis - Over meals within visits	ITT

6.2.13.1	Secondary Analyses - CGMS measurements - SD at 24 hour (mmol/L) - Meals days by visits	ITT
6.2.13.2	Secondary Analyses - CGMS measurements - SD at 24 hour (mmol/L) – Repeated measures analysis - Over meal days within visits	ITT
6.2.14.1	Secondary Analyses - CGMS measurements - CV at 1 hour (mmol/L) - Meals sequence by days and visits	ITT
6.2.14.2	Secondary Analyses - CGMS measurements - CV at 1 hour (mmol/L) – Repeated measures analysis - Over meals within visits	ITT
6.2.15.1	Secondary Analyses - CGMS measurements - CV at 2 hour (mmol/L) - Meals sequence by days and visits	ITT
6.2.15.2	Secondary Analyses - CGMS measurements - CV at 2 hour (mmol/L) – Repeated measures analysis - Over meals within visits	ITT
6.2.16.1	Secondary Analyses - CGMS measurements - CV at 3 hour (mmol/L) - Meals sequence by days and visits	ITT
6.2.16.2	Secondary Analyses - CGMS measurements - CV at 3 hour (mmol/L) – Repeated measures analysis - Over meals within visits	ITT
6.2.17.1	Secondary Analyses - CGMS measurements - CV at 24 hour (mmol/L) - Meals days by visits	ITT
6.2.17.2	Secondary Analyses - CGMS measurements - CV at 24 hour (mmol/L) – Repeated measures analysis - Over meal days within visits	ITT

14.2.2 PP Tables

Number	Title	Population
5.1.1	Primary Analyses - Fructosamine	PP
5.1.2	Primary Analyses - Change of fructosamine (Univariate analysis - From baseline to week 4)	PP
5.1.3	Primary Analyses - Change of fructosamine (ANCOVA analysis - From baseline to week 4)	PP
6.1.1	Secondary Analyses - Fructosamine	PP
6.1.2	Secondary Analyses - Change of fructosamine (Univariate analysis - From baseline to week 8, week 12, and week 16)	PP
6.1.3	Secondary Analyses - Change of fructosamine (ANCOVA analysis - From baseline to week 8, week 12, and week 16)	PP
6.1.4	Secondary Analyses - Change of fructosamine (Repeated measures analysis - Over visits)	PP
6.2.1.1	Secondary Analyses - CGMS measurements - AUC at 1 hour 9 Baseline, week 4, and week 16)	PP
6.2.1.2	Secondary Analyses - CGMS measurements - Change of 1-hour AUC (Univariate analysis - From baseline to week 4 and week 16)	PP
6.2.1.3	Secondary Analyses - CGMS measurements - Change of 1-hour AUC (ANCOVA analysis - From baseline to week 4, and week 16)	PP
6.2.2.1	Secondary Analyses - CGMS measurements - AUC at 2 hour (Baseline, week 4, and week 16)	PP
6.2.2.2	Secondary Analyses - CGMS measurements - Change of 2-hour AUC (Univariate analysis - From baseline to week 4, and week 16)	PP
6.2.2.3	Secondary Analyses - CGMS measurements - Change of 2-hour AUC (ANCOVA analysis - From baseline to week 4, and week 16)	PP
6.2.3.1	Secondary Analyses - CGMS measurements - AUC at 3 hour (Baseline, week 4, and week 16)	PP
6.2.3.2	Secondary Analyses - CGMS measurements - Change of 3-hour AUC (Univariate analysis - From baseline to week 4, and week 16)	PP
6.2.3.3	Secondary Analyses - CGMS measurements - Change of 3-hour AUC	PP

Number	Title	Population
	(ANCOVA analysis - From baseline to week 4, and week 16)	
6.2.4.1	Secondary Analyses - CGMS measurements – AUC_180 during the 24 hour period (Baseline, week 4, and week 16)	PP
6.2.4.2	Secondary Analyses - CGMS measurements - Change of 24-hour AUC_180 (Univariate analysis - From baseline to week 4, and week 16)	PP
6.2.4.3	Secondary Analyses - CGMS measurements - Change of 24-hour AUC_180 (ANCOVA analysis - From baseline to week 4, and week 16)	PP
6.2.5.1	Secondary Analyses - CGMS measurements - AUC_180 during the 72 hour period (Baseline, week 4, and week 16)	PP
6.2.5.2	Secondary Analyses - CGMS measurements - Change of 72-hour AUC_180 (Univariate analysis - From baseline to week 4, and week 16)	PP
6.2.5.3	Secondary Analyses - CGMS measurements - Change of 72-hour AUC_180 (ANCOVA analysis - From baseline to week 4, and week 16)	PP
6.2.6.1	Secondary Analyses - CGMS measurements – MPMG (Baseline, week 4, and week 16)	PP
6.2.6.2	Secondary Analyses - CGMS measurements - Change of MPMG (Univariate analysis - From baseline to week 4, and week 16)	PP
6.2.6.3	Secondary Analyses - CGMS measurements - Change of MPMG (ANCOVA analysis - From baseline to week 4, and week 16)	PP
6.2.7.1	Secondary Analyses - CGMS measurements – MBG (Baseline, week 4, and week 16)	PP
6.2.7.2	Secondary Analyses - CGMS measurements - Change of MBG (Univariate analysis - From baseline to week 4, and week 16)	PP
6.2.7.3	Secondary Analyses - CGMS measurements - Change of MBG (ANCOVA analysis - From baseline to week 4, and week 16)	PP
6.2.8.1	Secondary Analyses - CGMS measurements – SD (Baseline, week 4, and week 16)	PP
6.2.8.2	Secondary Analyses - CGMS measurements - Change of SD (Univariate analysis - From baseline to week 4, and week 16)	PP
6.2.8.3	Secondary Analyses - CGMS measurements - Change of SD (ANCOVA analysis - From baseline to week 4, and week 16)	PP
6.2.9.1	Secondary Analyses - CGMS measurements – CV (Baseline, week 4, and week 16)	PP
6.2.9.2	Secondary Analyses - CGMS measurements - Change of CV (Univariate analysis - From baseline to week 4, and week 16)	PP
6.2.9.3	Secondary Analyses - CGMS measurements - Change of CV (ANCOVA analysis - From baseline to week 4, and week 16)	PP
6.2.10.1	Secondary Analyses - CGMS measurements – MAGE (Baseline, week 4, and week 16)	PP
6.2.10.2	Secondary Analyses - CGMS measurements - Change of MAGE (Univariate analysis - From baseline to week 4, and week 16)	PP
6.2.10.3	Secondary Analyses - CGMS measurements - Change of MAGE (ANCOVA analysis - From baseline to week 4, and week 16)	PP
6.3.1	Secondary Analyses - HbA_{1c} (Baseline and week 16)	PP
6.3.2	Secondary Analyses - Change of HbA_{1c} (Univariate analysis - From baseline to week 16)	PP
6.3.3	Secondary Analyses - Change of HbA_{1c} (ANCOVA analysis - From baseline to week 16)	PP
6.4.1.1	Secondary Analyses - MTT - 120-min AUC of glucose level (Baseline, week 4, and week 16)	PP
6.4.1.2	Secondary Analyses - MTT - Change of 120-min glucose AUC (Univariate analysis - From baseline to week 4, and week 16)	PP

Number	Title	Population
6.4.1.3	Secondary Analyses - MTT - Change of 120-min glucose AUC (ANCOVA analysis - From baseline to week 4, and week 16)	PP
6.4.2.1	Secondary Analyses - MTT - 120-min AUC of insulin (Baseline, week 4, and week 16)	PP
6.4.2.2	Secondary Analyses - MTT - Change of 120-min insulin AUC (Univariate analysis - From baseline to week 4, and week 16)	PP
6.4.2.3	Secondary Analyses - MTT - Change of 120-min insulin AUC (ANCOVA analysis - From baseline to week 4, and week 16)	PP
6.4.3.1	Secondary Analyses - MTT - 120-min AUC of C-Peptide (Baseline, week 4, and week 16)	PP
6.4.3.2	Secondary Analyses - MTT - Change of 120-min C-Peptide AUC (Univariate analysis - From baseline to week 4, and week 16)	PP
6.4.3.3	Secondary Analyses - MTT - Change of 120-min C-Peptide AUC (ANCOVA analysis - From baseline to week 4, and week 16)	PP
6.4.4.1	Secondary Analyses - MTT - 120-min AUC of GLP1 (Baseline, week 4, and week 16)	PP
6.4.4.2	Secondary Analyses - MTT - Change of 120-min GLP1 AUC (Univariate analysis - From baseline to week 4, and week 16)	PP
6.4.4.3	Secondary Analyses - MTT - Change of 120-min GLP1 AUC (ANCOVA analysis - From baseline to week 4, and week 16)	PP
6.5.1	Secondary Analyses - IGT and IFG (Baseline and follow-up)	PP
6.5.2	Secondary Analyses - Change of IGT and IFG (Univariate analysis - From baseline to follow-up)	PP
6.5.3	Secondary Analyses - Change of IGT and IFG (Logistic regression analysis - From baseline to follow-up)	PP
7.1.1.1	Secondary Analyses – SBP Baseline, week 4, week 8, week 12, week 16, and follow-up	PP
7.1.1.2	Secondary Analyses - Change of SBP (Univariate analysis - From baseline to week 4, week 8, week 12, week 16, and follow-up)	PP
7.1.1.3	Secondary Analyses - Change of SBP (ANCOVA analysis - From baseline to week 4, week 8, week 12, week 16, and follow-up)	PP
7.1.1.4	Secondary Analyses - Change of SBP (Repeated measures analysis - Over visits)	PP
7.1.2.1	Other Secondary Analyses – DBP Baseline, week 4, week 8, week 12, week 16, and follow-up	PP
7.1.2.2	Other Secondary Analyses - Change of DBP (Univariate analysis - From baseline to week 4, week 8, week 12, week 16, and follow-up)	PP
7.1.2.3	Other Secondary Analyses - Change of DBP (ANCOVA analysis - From baseline to week 4, week 8, week 12, week 16, and follow-up)	PP
7.1.2.4	Secondary Analyses - Change of DBP (Repeated measures analysis - Over visits)	PP
7.1.3.1	Other Secondary Analyses – Weight (Baseline, week 4, week 8, week 12, week 16, and follow-up)	PP
7.1.3.2	Other Secondary Analyses - Change of weight (Univariate analysis - From baseline to week 4, week 8, week 12, week 16, and follow-up)	PP
7.1.3.3	Other Secondary Analyses - Change of weight (ANCOVA analysis - From baseline to week 4, week 8, week 12, week 16, and follow-up)	PP
7.1.3.4	Other Secondary Analyses - Change of weight (Repeated measures analysis - Over visits)	PP
7.1.4.1	Other Secondary Analyses - Waist circumference (Baseline, week 4, and week 16)	PP
7.1.4.2	Other Secondary Analyses - Waist circumference (Univariate analysis - From	PP

Number	Title	Population
	baseline to week 4, and week 16)	
7.1.4.3	Other Secondary Analyses - Waist circumference (ANCOVA analysis - From baseline to week 4, and week 16)	PP
7.2.1.1	Other Secondary Analyses - Total cholesterol (Baseline, week 4, and week 16)	PP
7.2.1.2	Other Secondary Analyses - Change of total cholesterol (Univariate analysis - From baseline to week 4, and week 16)	PP
7.2.1.3	Other Secondary Analyses - Change of total cholesterol (ANCOVA analysis - From baseline to week 4, and week 16)	PP
7.2.2.1	Other Secondary Analyses - LDL cholesterol (Baseline, week 4, and week 16)	PP
7.2.2.2	Other Secondary Analyses - Change of LDL cholesterol (Univariate analysis - From baseline to week 4, and week 16)	PP
7.2.2.3	Other Secondary Analyses - Change of LDL cholesterol (ANCOVA analysis - From baseline to week 4, and week 16)	PP
7.2.3.1	Other Secondary Analyses - HDL cholesterol (Baseline, week 4, and week 16)	PP
7.2.3.2	Other Secondary Analyses - Change of HDL cholesterol (Univariate analysis - From baseline to week 4, and week 16)	PP
7.2.3.3	Other Secondary Analyses - Change of HDL cholesterol (ANCOVA analysis - From baseline to week 4, and week 16)	PP
7.2.4.1	Other Secondary Analyses – Triglyceride (Baseline, week 4, and week 16)	PP
7.2.4.2	Other Secondary Analyses - Change of triglyceride (Univariate analysis - From baseline to week 4, and week 16)	PP
7.2.4.3	Other Secondary Analyses - Change of triglyceride (ANCOVA analysis - From baseline to week 4, and week 16)	PP
7.2.5.1	Other Secondary Analyses - hs-CRP (Baseline, week 4, and week 16)	PP
7.2.5.2	Other Secondary Analyses - Change of hs-CRP (Univariate analysis - From baseline to week 4, and week 16)	PP
7.2.5.3	Other Secondary Analyses - Change of hs-CRP (ANCOVA analysis - From baseline to week 4, and week 16)	PP
7.2.6.1	Other Secondary Analyses – Urate (Baseline, week 4, and week 16)	PP
7.2.6.2	Other Secondary Analyses - Change of urate (Univariate analysis - From baseline to week 4, and week 16)	PP
7.2.6.3	Other Secondary Analyses - Change of urate (ANCOVA analysis - From baseline to week 4, and week 16)	PP

14.2.3 Figures

Number	Title	Population
6.4.1	Secondary Analyses - MTT - 120-min AUC of glucose level	ITT
6.4.2	Secondary Analyses - MTT - 120-min AUC of insulin	ITT
6.4.3	Secondary Analyses - MTT - 120-min AUC of C-Peptide	ITT
6.4.4	Secondary Analyses - MTT - 120-min AUC of GLP1	ITT

14.3 Safety Data Summary Figures and Tables

14.3.1 Displays of Adverse Events

Number	Title	Population
3.1	Study Outcomes - Exposure to treatment	ITT
8.2.8.1	Safety Analyses - AE	ITT
9.1.1.1	Questionnaire Analyses - WHOQOL-BREF Physical health domain (Baseline, week 4, and week 16)	ITT
9.1.1.2	Other Secondary Analyses - Change of WHOQOL-BREF physical health domain (Univariate analysis - From baseline to week 4 and week 16)	ITT
9.1.1.3	Other Secondary Analyses - Change of WHOQOL-BREF physical health domain (ANCOVA analysis - From baseline to week 4, and week 16)	ITT
9.1.2.1	Questionnaire Analyses - WHOQOL-BREF Psychological domain (Baseline, week 4, and week 16)	ITT
9.1.2.2	Other Secondary Analyses - Change of WHOQOL-BREF psychological domain (Univariate analysis - From baseline to week 4 and week 16)	ITT
9.1.2.3	Other Secondary Analyses - Change of WHOQOL-BREF psychological domain (ANCOVA analysis - From baseline to week 4, and week 16)	ITT
9.1.3.1	Questionnaire Analyses - WHOQOL-BREF Social relationships domain (Baseline, week 4, and week 16)	ITT
9.1.3.2	Other Secondary Analyses - Change of WHOQOL-BREF social relationships domain (Univariate analysis - From baseline to week 4 and week 16)	ITT
9.1.3.3	Other Secondary Analyses - Change of WHOQOL-BREF social relationships domain (ANCOVA analysis - From baseline to week 4, and week 16)	ITT
9.1.4.1	Questionnaire Analyses - WHOQOL-BREF Environment domain (Baseline, week 4, and week 16)	ITT
9.1.4.2	Other Secondary Analyses - Change of WHOQOL-BREF environment domain (Univariate analysis - From baseline to week 4 and week 16)	ITT
9.1.4.3	Other Secondary Analyses - Change of WHOQOL-BREF environment domain (ANCOVA analysis - From baseline to week 4, and week 16)	ITT
9.2.1.1	Questionnaire Analyses - Appetite Q1	ITT
9.2.1.2	Questionnaire Analyses - Appetite Q2	ITT
9.2.1.3	Questionnaire Analyses - Appetite Q3	ITT
9.2.1.4	Questionnaire Analyses - Appetite Q4	ITT
9.2.1.5	Questionnaire Analyses - Appetite Q5	ITT
9.2.1.6	Questionnaire Analyses - Appetite Q6	ITT
9.2.1.7	Other Secondary Analyses - Change of appetite (Univariate analysis - From baseline to week 4)	ITT
9.2.1.8	Other Secondary Analyses - Change of appetite (Univariate analysis - From baseline to week 16)	ITT
9.2.2.1	Questionnaire Analyses - International physical activity Q1	ITT
9.2.2.2	Questionnaire Analyses - International physical activity Q2	ITT
9.2.2.3	Questionnaire Analyses - International physical activity Q3	ITT
9.2.2.4	Questionnaire Analyses - International physical activity Q4	ITT
9.2.2.5	Questionnaire Analyses - International physical activity Q5	ITT
9.2.2.6	Questionnaire Analyses - International physical activity Q6	ITT
9.2.2.7	Questionnaire Analyses - International physical activity Q7	ITT
9.2.2.8	Other Secondary Analyses - Change of international physical activity (Univariate	ITT

Number	Title	Population
	analysis - From baseline to week 4)	
9.2.2.9	Other Secondary Analyses - Change of international physical activity (Univariate analysis - From baseline to week 16)	ITT
9.2.3.1	Questionnaire Analyses - FFQ Calories	ITT
9.2.3.2	Questionnaire Analyses - FFQ Protein	ITT
9.2.3.3	Questionnaire Analyses - FFQ Carbohydrate	ITT
9.2.3.4	Questionnaire Analyses - FFQ Dietary fiber	ITT
9.2.3.5	Questionnaire Analyses - FFQ Sugar	ITT
9.2.3.6	Questionnaire Analyses - FFQ Fat	ITT
9.2.3.7	Questionnaire Analyses - FFQ Saturated fat	ITT
9.2.3.8	Questionnaire Analyses - FFQ Trans fat	ITT
9.2.3.9	Questionnaire Analyses - FFQ Cholesterol	ITT
9.2.3.10	Questionnaire Analyses - FFQ Vitamin C	ITT
9.2.3.11	Questionnaire Analyses - FFQ Calcium	ITT
9.2.3.12	Questionnaire Analyses - FFQ Copper	ITT
9.2.3.13	Questionnaire Analyses - FFQ Iron	ITT
9.2.3.14	Questionnaire Analyses - FFQ Magnesium	ITT
9.2.3.15	Questionnaire Analyses - FFQ Manganese	ITT
9.2.3.16	Questionnaire Analyses - FFQ Phosphorus	ITT
9.2.3.17	Questionnaire Analyses - FFQ Potassium	ITT
9.2.3.18	Questionnaire Analyses - FFQ Sodium	ITT
9.2.3.19	Questionnaire Analyses - FFQ Zinc	ITT
9.2.3.20	Other Secondary Analyses - Change of food frequency (Univariate analysis - From baseline to week 4)	ITT
9.2.3.21	Other Secondary Analyses - Change of food frequency (Univariate analysis - From baseline to week 16)	ITT

14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events

No deaths occurred during the study. Data Listing 8.3.1 presents subjects who experienced a SAE or discontinued from the study due to AE(s) (Appendix 16.2).

14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

14.3.3.1 Subjects discontinued from the study due to an AE

One subject (SG01_56), a 53 year old male with ongoing gout and *tinea pedis*, was randomized to the 4 g BTI320 treatment group. This subject completed Visit 3 with a total of 18 meals. On 18Sep2015, he experienced moderate abdominal pain and diarrhea which was considered possibly-related to treatment by the Investigator. The subject discontinued the study on 24Sep2015 due to the gastrointestinal AEs and both events were considered recovered in 6 days (Data Listing 8.3.1, Appendix 16.2).

14.3.4 Laboratory Value Listing

Number	Title	Population
8.1.1	Safety Analyses – Hemoglobin	ITT
8.1.2	Safety Analyses – Hematocrit	ITT
8.1.3	Safety Analyses – Platelet	ITT
8.1.4	Safety Analyses - White blood cell	ITT
8.2.1	Safety Analyses - Sodium	ITT
8.2.2	Safety Analyses - Potassium	ITT
8.2.3	Safety Analyses - Urea	ITT
8.2.4	Safety Analyses - Creatinine	ITT
8.2.5	Safety Analyses - Bilirubin	ITT
8.2.6	Safety Analyses - ALP	ITT
8.2.7	Safety Analyses - ALT	ITT

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