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ORIGINAL PAPER

Open-label, randomized, multiple-center, parallel study comparing glycemic responses and safety profiles of Glucerna versus Fresubin in subjects of type 2 diabetes mellitus

Wei-Qing Wang · Yi-Fei Zhang · Da-Jin Zhou · Zhi-Min Liu · Xu Hong · Ming-Cai Qiu · Yong-Quan Shi · Pei-Jin Xia · Jin Lu · Mao-Jing Xu · Liang An · Wei Feng · Peng Zhang · J. Schwamman · Guang Ning

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Abstract Since the increase of prevalence of type 2 diabetes mellitus (T-2DM), the replacing quickly absorbed carbohydrates with a fat source rich in monounsaturated fatty acid to provide improved glycemic control in these patients has become an important assistant therapy. In the present study, we compared glycemic response and safety of two nutritional products, Glucerna and Fresubin, in Chinese subjects with T-2DM. Overall, 203 T-2DM subjects were randomly assigned (1:1) to either Glucerna or Fresubin. The primary endpoint was the adjusted area under the curve (adj-AUC) for plasma glucose at 0–240 min. Blood samples were collected at 0, 30, 60, 90, 120, 180, and 240 min to compare the adjusted area under the curve (AUC) for the change in plasma glucose or insulin from 0 to 240 min. Adjusted peak values and times of glucose and insulin responses and adjusted glucose and insulin values were collected at the same time points. Safety parameters were also evaluated. The adjusted AUC for the change in plasma glucose in the Glucerna group was significantly lower than in Fresubin group (5.60 ± 5.88 mmol/l*h vs. 7.97 ± 6.32 mmol/l*h, $P = 0.0061$), as was the adjusted peak value of glucose (3.51 ± 2.04 mmol/l vs. 4.69 ± 1.99 mmol/l, $P < 0.0001$). Glucerna subjects had a longer adjusted peak time to insulin response compared to Fresubin subjects (105.00 ± 43.4 min vs. 88.81 ± 37.69 min, $P = 0.0050$). Glucerna subjects also experienced more gradual changes in glucose and insulin values. In conclusion, Glucerna provided better control of postprandial plasma glucose and insulin levels in Chinese subjects with T-2DM. Variation of postprandial glucose tended to be relatively stable after patients took Glucerna. Study results suggest that Glucerna may be beneficial in the reduction of postprandial glycemia.

Keywords Glucerna · Fresubin · Type 2 diabetes mellitus · Glucose response test

W.-Q. Wang and Y.-F. Zhang contributed equally to this work.

W.-Q. Wang · Y.-F. Zhang · G. Ning (✉)
Shanghai Clinical Center for Endocrine and Metabolic Diseases, Shanghai Institute of Endocrinology and Metabolism, Division of Endocrine and Metabolic Diseases in E-Institute of Shanghai Universities, Ruijin Hospital, Shanghai Jiaotong University Medical School, Ruijin 2nd Road 197, Shanghai 200025, P.R. China
e-mail: guangning@medmail.com.cn

D.-J. Zhou · Y.-Q. Shi · P.-J. Xia
Department of Endocrinology, Chang Hai Hospital, Shanghai 200433, P.R. China

Z.-M. Liu · J. Lu · M.-J. Xu
Department of Endocrinology, Chang Zheng Hospital, 200003 Shanghai, P.R. China

X. Hong · L. An · W. Feng
Department of Endocrinology, You Yi Hospital, Beijing 100050, P.R. China

M.-C. Qiu · P. Zhang
Department of Endocrinology, General Hospital, Tianjin 300052, P.R. China

J. Schwamman
Abbott, Abbott Park, IL, USA

Introduction

The current estimate for the worldwide incidence of diabetes is 194 million people, with projections of 333 million people afflicted by 2025 [1]. In 1993, results from the Diabetes Control and Complications Trial (DCCT) were published [2] and since that time, numerous clinical studies have demonstrated the relationship between glucose

control and improved outcomes in diabetic subjects. In addition to anti-hyperglycemic medications, clinicians have begun stressing the importance of nutritional supplement that emphasizes glucose and insulin response patterns that more closely mimic response seen in the non-diabetic population. A significant amount of research has demonstrated that replacing quickly absorbable carbohydrates with a fat source rich in monounsaturated fatty acid provides improved glycemic control in subjects with diabetes [3–10].

In this study, we compared an experimental nutritional product Glucerna (Abbott) with Fresubin Diabetes (Sino-Swed Pharmaceutical Corporation), a nutritional formula currently marketed in China for glucose control. The nutrients containing in these two products were listed in Table 1. The purpose of the study was to evaluate the safety and efficacy of both products in terms of plasma glucose and insulin response and the incidence of adverse events in Chinese subjects with type 2 diabetes mellitus (T-2DM).

Table 1 Study drug nutrients (per 100 ml)

Nutrient	Unit	Control	Experimental
Energy	kcal	90	99
Protein	g	3.40	4.18
Fat	g	3.20	5.44
Carbohydrate	g	12.0	8.14
Total dietary fiber	g	1.5	1.44
Moisture	g	89.0	84.9
Carnitine	mg	na	7.8
Taurine	mg	na	11
Inositol	mg	na	84
Vitamins			
Vitamin A	IU	na	546
Vitamin A (palmitate)	IU	200	266
Vitamin A (betacarotene)	IU	na	280
Vitamin D_3	IU	14	28
Vitamin E	IU	0.75	3.2
Vitamin K_1	μg	5	5.6
Vitamin C	mg	4.5	11
Folic acid	μg	10	42
Nutrient	Unit	Fresubin®	Glucerna®
Vitamin B_1	mg	0.1	0.16
Vitamin B_2	mg	0.13	0.18
Vitamin B_6	mg	0.12	0.21
Vitamin B_{12}	μg	0.2	0.30
Niacin	mg	0.9	1.7
Panthothenic acid	mg	0.35	0.75
Biotin	μg	10	4.0
Choline	mg	20	42
Minerals			
Sodium	mg	63	93
Potassium	mg	107	130
Chloride	mg	64	125
Calcium	mg	60	70
Phosphorus	mg	47	65
Magnesium	mg	20	20
Iron	mg	1	1.3
Zinc	mg	0.75	1.2
Manganese	mg	0.2	0.35
Copper	μg	100	140
Iodine	μg	10	11
Selenium	μg	3.75	4.9
Chromium	μg	5	7.0
Molybdenum	μg	10	10

Results

Subject demographics and baseline characteristics

Overall, 211 subjects were enrolled into the study. Of these subjects, three subjects in the experimental group discontinued prematurely due to the occurrence of an adverse event; two subjects discontinued for other reasons. In the control group one subject discontinued due to the occurrence of an adverse event and two others were lost to follow up. A total of 203 subjects (102 in the experimental group and 101 in the control group) comprised the intent-to-treat population. Subjects in both treatment groups were comparable with regards to demographic and baseline characteristics. Mean age in the experimental group was 55.83 ± 8.21 years compared with 55.77 ± 8.28 years in the control group. No differences were seen between treatment groups with respect to body weight, body mass index (BMI), or sex. Finger stick blood glucose at baseline was 7.38 ± 1.52 mmol/l in the experimental group compared with 7.32 ± 1.77 mmol/l in the control group. Mean consumption of study products was similar between treatment groups on days 5 through 7. No clinically meaningful differences were observed between treatment groups with regards to anti-hyperglycemic or other concomitant medications. Subject demographics and baseline characteristics are presented in Table 2.

Few deviations from the protocol were observed throughout the study. A total of five subjects in the experimental group and four subjects in the control had protocol deviations. All but two deviations were due to subjects not consuming the total amount of study product. The remaining two deviations both occurred in the experimental group: one subject failed to take anti-hyperglycemic medication for three consecutive days and

Table 2 Subject demographics and baseline characteristics

	Glucerna ($N = 102$)	Fresubin ($N = 101$)
Sex (number % of subjects)		
Male	51 (50%)	48 (47.52%)
Female	52 (50%)	53 (52.48%)
Age (years)		
Mean (SD)	55.82 (8.21)	55.77 (8.28)
Range	30.66–70.11	32.35–70.38
Body mass index (kg/m^2)		
Mean (SD)	25.11 (3.16)	25.36 (3.34)
Range	17.00–36.90	18.30–34.60
Finger stick blood glucose (mmol/l)		
Mean (SD)	7.38 (1.52)	7.32 (1.77)
Range	4.68–11.77	4.57–11.77
Anti-hyperglycemic medications (number % of subjects)		
Alpha glucosidase inhibitors	34 (33.33%)	31 (30.69%)
Biguanides	64 (62.75%)	54 (53.47%)
Sulfonamides, urea derivatives	73 (71.57%)	67 (66.34%)
Traditional Chinese anti-hyperglycemics	14 (13.73%)	12 (11.88%)
Other concomitant medications		
Renin–angiotensin system agents	15 (14.71%)	11 (10.89%)
Antihypertensives	15 (14.71%)	10 (9.90%)
Calcium channel blockers	6 (5.88%)	13 (12.87%)
Other traditional Chinese medications	25 (25.49%)	19 (19.80%)
Vitamins	15 (14.71%)	9 (8.91%)
Study drug intake		
Mean (SD)	497.06 (18.4)	511.14 (7.05)
Range	375.00–512.5	450.0–512.5

one subject underwent the glucose response test (GRT) 20 min late.

Primary and secondary analysis

Results of the primary analysis indicated that subjects in the experimental group had a lower mean adjusted area under the curve (adj-AUC) for plasma glucose over 0–240 min compared with subjects in the control group. The difference between treatment groups was statistically significant (5.60 ± 5.88 mmol/l*h vs. 7.97 ± 6.32 mmol/l*h, $P = 0.0061$, respectively). Among the secondary endpoints, significant differences between treatment groups favoring the experimental group were detected for the mean adjusted peak value for glucose (3.51 ± 2.04 mmol/l vs. 4.69 ± 1.99 mmol/l, $P < 0.0001$) and for the mean adjusted time to peak insulin response (105.00 ± 43.4 min vs. 88.81 ± 37.69 min, $P = 0.0050$). Results for the remaining secondary endpoints were not significantly different between two groups (Table 3 and Fig. 1a, b).

Glucose and insulin were measured at designated time points (0, 30, 60, 90, 120, 180, and 240 min) and compared between groups. Results indicated that subjects in the experimental group experienced a more gradual increase in glucose values at all study measurement time points. Similarly, insulin response was more gradual in the experimental compared with response in the control group. Insulin response times peaked at approximately 90 min in the control group, but at 120 min in the experimental group (Fig.1a, b and Table 4). Glucose values were significantly lower at the 30, 60, and 90 min time points in the experimental group compared to the control group ($P < 0.0001$, $P < 0.0001$, and $P = 0.0006$, respectively). Similarly, insulin values were significantly lower at the 30, 60, and 180 min time points in the experimental group compared to the control group ($P = 0.0192$, $P = 0.0143$, and $P = 0.0407$, respectively).

Safety analysis

The overall incidence of adverse events was similar between treatment groups, as was the incidence of adverse events considered possibly or probably related to study drug. The majority of observed events in either treatment group were associated with the gastrointestinal system, with a similar distribution of events seen between treatment

Table 3 Primary and secondary study endpoints

Endpoint	Experimental group ($N = 102$)	Control group ($N = 101$)	P-value[a]
Mean (SD) adj-AUC of plasma glucose at 0–240 min (mmol/l*h)	5.60 (5.88)	7.97 (6.32)	0.0061
Mean (SD) adj-AUC of insulin response at 0–240 min (μIU/ml*h)	45.54 (41.40)	51.02 (43.97)	0.3613
Mean (SD) adjusted peak value for glucose (mmol/l)	3.51 (2.04)	4.69 (1.99)	<0.0001
Mean (SD) adjusted peak value for insulin (μIU/ml)	26.56 (19.18)	31.96 (22.66)	0.0684
Mean (SD) adjusted time to peak plasma glucose (min)	87.94 (36.38)	79.31 (29.57)	0.0651
Mean (SD) adjusted time to peak insulin response (min)	105 (43.4)	88.81 (37.69)	0.0050

[a] P-value from paired t-test

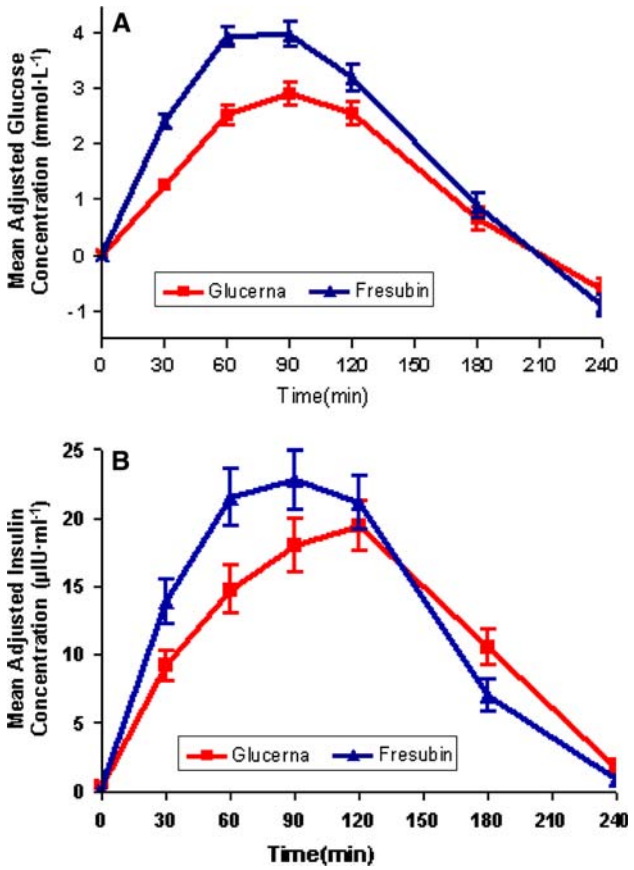

Fig. 1 (**a**) Mean adjusted plasma glucose over time and (**b**) mean adjusted plasma insulin over time

groups (Table 5). The most commonly reported adverse events were constipation, diarrhea, flatulence, nausea, and distension. Only one adverse event considered to be of severe intensity was reported among all treated subjects. No deaths or serious adverse events were reported, and a total of four subjects discontinued treatment due to the occurrence of an adverse event.

Sensory evaluation

A sensory evaluation was conducted at Visit 1 to determine the acceptability of study products in an effort to identify potential compliance issues that could occur during the study. Prior to randomization, all eligible subjects completed a sensory evaluation of both products. Results were similar and no statistically significant differences were observed between treatment groups. Both Glucerna and Fresubin Diabetes were generally well tolerated and no subjects discontinued from the study due to intolerance to study products.

Discussion

Since publication of information from the DCCT [2] and the United Kingdom Prospective Diabetes Study Group (UKPDS 33) [11], clinicians have recognized the importance of glycemic control in treating the diabetic patient. A growing body of evidence has emphasized the role that medical nutritional therapy (MNT) plays in increasing control over glucose and insulin response and in improving patient outcomes and long-term prognosis [12–14]. In 1987, the National Institutes of Health Consensus Development Conference [4] published information on the relationship of diet and exercise to glycemic response and insulin resistance. Research into causes and treatments for diabetes mellitus have only increased in the interim, and in January of 2004 the American Diabetes Association (ADA) published its comprehensive guidelines for the nutritional management of type 1 and 2 diabetes. It was recommended in these guidelines that the diabetic patient should limit intake of carbohydrate, that ingested carbohydrate should come from complex sources, and that carbohydrate and monounsaturated fats should comprise 60–70% of energy intake [11].

The role of carbohydrates in insulin resistance and glucose response has been well studied in recent years. Recommendations on structuring carbohydrate intake are provided by the ADA and the European Association for the Study of Diabetes (EASD). Until recently, these guidelines cautioned against supplanting dietary carbohydrate with fats due to the increased risk of cardiovascular events in diabetic patients [13, 15]. However, research in this area

Table 4 Glucose and insulin response on study day 8

	Experimental group ($N = 102$)	Control group ($N = 101$)	P-value[a]
Mean (SD) plasma glucose (mmol/l) at			
30 min	1.26 (0.96)	2.40 (1.35)	<0.0001
60 min	2.52 (1.70)	3.93 (1.76)	<0.0001
90 min	2.90 (2.12)	3.99 (2.31)	0.0006
120 min	2.55 (2.20)	3.20 (2.53)	0.0545
180 min	0.65 (1.99)	0.88 (2.28)	0.4643
240 min	−0.62 (1.95)	−0.92 (1.89)	0.2682
Mean (SD) insulin response (μIU/ml) at			
30 min	8.84 (11.40)	13.50 (16.36)	0.0192
60 min	14.40 (17.47)	21.15 (21.22)	0.0143
90 min	17.60 (20.01)	22.44 (21.58)	0.0991
120 min	19.06 (19.07)	20.78 (19.93)	0.5315
180 min	10.19 (13.06)	6.63 (11.55)	0.0407
240 min	1.25 (6.34)	0.53 (4.97)	0.3645

[a] P-value from independent-samples t-test

Table 5 Most commonly reported adverse events—>10% of subjects in either treatment group

System organ preferred term	Glucerna ($N = 100$)	Fresubin ($N = 73$)
Gastrointestinal tract		
Constipation	9 (9.0%)	11 (15.07%)
Diarrhea	15 (15.00%)	6 (8.22%)
Flatulence	15 (15.0%)	14 (19.18%)
Nausea	15 (15.00%)	12 (16.44%)
General disorders and administration site conditions		
Distension NOS	9 (9.0%)	12 (16.44%)

suggests that replacing simple carbohydrates (i.e., those that are quickly absorbed) with a fat source rich in monounsaturated fatty acid (MUFA) results in improved glycemic response and a concomitant favorable insulin response. This research has further demonstrated that MUFA as an energy source does not negatively impact cardiovascular outcomes and improves cardiovascular disease risk profile [5, 10, 16, 17].

Postprandial blood glucose is increasingly becoming a specific management goal and treatment target with regards to the diabetic chronic complications. Postprandial glucose levels correlate to plasma glucose levels, which are predictive of overall glycemic control. Results from the DECODE study conducted in Europe demonstrated a greater association of increased mortality risk with blood glucose levels 2 h after a glucose load than that seen with fasting plasma glucose levels [18]. Investigators noted that postprandial hyperglycemia increased the risk of cardiovascular mortality [19]. Further, results from the Diabetes Intervention Study [20] showed that postprandial blood glucose was a significant predictor of subsequent heart attack, demonstrating the importance of postprandial hyperglycemia management.

In the current study we compared an experimental nutritional product (Glucerna, Abbott) to the marketed product in China (Fresubin Diabetes, Sino-Swed Pharmaceuticals) in Chinese subjects with type 2 diabetes. Glucerna is a carbohydrate reduced, modified-fat liquid formula that has been shown to be safe in reducing postprandial glycemic response in healthy or diabetic subjects, and in subjects with stress-induced hyperglycemia [16, 17, 21–24]. Fresubin Diabetes is a dietary supplement used for glucose control in China; however, its benefit to type 2 diabetes patients was not definitely confirmed till now [25]. The primary endpoint was the comparison of adj-AUC of plasma glucose values in either treatment group through 240 min during a GRT. Secondary evaluations included insulin response, glucose and insulin peak response and peak times, and glucose and insulin values at designated time points.

Results of the primary analysis indicated that subjects receiving Glucerna had a lesser adj-AUC plasma glucose compared with subjects receiving Fresubin Diabetes ($P = 0.0061$). This result supports the premise that the high MUFA content of Glucerna promotes a more controlled postprandial plasma glucose compared to that of the currently available product in China. Further, the carbohydrate content of Glucerna is lower than that of Fresubin Diabetes. Subjects in our study consumed approximately 40 g of carbohydrate per serving compared with 66 g in the Fresubin Diabetes treatment group. It is reasonable to assume that the lower carbohydrate content and beneficial MUFA composition of Glucerna contributed significantly to the improved glycemic/insulin response seen in the experimental group. Secondary to this finding, comparison of insulin response in either treatment group indicated a

decrease in adj-AUC insulin among Glucerna-treated subjects, although this finding was not statistically significant ($P = 0.3501$).

Other secondary endpoints provide additional support for these findings. Comparison of the mean adjusted peak value for glucose favored Glucerna as subjects receiving Fresubin Diabetes experienced greater peak glucose values ($P < 0.0001$). In contrast, subjects receiving Glucerna had a greater mean time to peak insulin response than did subjects in the Fresubin Diabetes group ($P = 0.0050$).

When plotted, the more gradual glucose and insulin response experienced in the Glucerna group is clearly demonstrated over time. Subjects receiving Glucerna had lower peak glucose values, which were attained 30 min after peak values were observed in Fresubin Diabetes subjects. Similarly, insulin response over time was characterized by lesser insulin values in the Glucerna group, a lesser peak insulin value, and a peak insulin value that was attained 30 min later than that observed in the Fresubin Diabetes group. While the decline in plasma glucose in both groups was similar after peak values were attained, subjects in the Fresubin Diabetes group demonstrated a more precipitous drop in insulin following peak values.

The principal weaknesses of the study were the open-label design and the lack of formal analysis for the determination of sample size. Nutritional studies are notoriously difficult to conduct for numerous reasons; compliance being key among these reasons. However, it was felt that the short time period allotted (8 days) with unsupervised study product consumption occurring on only three of those days would mitigate compliance as a potential issue. However, the study was conducted as an open-label trial through necessity. Fresubin Diabetes is a marketed product in China. Therefore, it was unrealistic to expect that all eligible diabetic subjects would have had no prior exposure to the product. Furthermore, subjects sampled both products prior to randomization in order to ensure acceptability during the study. Since the study products do not taste or appear the same, blinding would have no effect, as subjects would have been able to determine identity through prior exposure. With regards to sample size, it was determined that 200 subjects (100 per treatment arm) would be sufficient to detect differences between treatment groups, though this was not calculated formally. Results bear out this premise; however, future studies could require additional subjects based on number of endpoints and potential for dropouts during longer term trials.

Outcomes of this study clearly demonstrate the beneficial nutritional profile of Glucerna compared to Fresubin Diabetes in Chinese diabetic patients and tend to reflect international recommendations of greater glucose control. Use of Glucerna as a morning meal replacement resulted in lower adj-AUC glucose and insulin values, prolonged glucose and insulin responses over time, with a subsequently decreased insulin response over 6 h of a GRT period. Results of our study strongly suggest that a medical nutritional product that provides improved glucose control and insulin response should be considered in the overall therapeutic approach to treatment of T-2DM.

Materials and methods

Subjects

We conducted a randomized, open-label, multi-center, parallel group study in five centers in China. Subjects were randomized (1:1) to one of two study groups: experimental formula (Glucerna) or control group (Fresubin Diabetes). Eligible subjects included adults (18–70 years) with T-2DM for at least 6 months who had stable glycemic control (subjects had to be taking the same prescribed anti-diabetes medications for at least 1 month and have finger stick blood glucose between 80 mg/dl [4.4 mmol/l] and 220 mg/dl [12.2 mmol/l] at visit 1). Female subjects could not be pregnant or lactating. Significant exclusion criteria included the following: subject required exogenous insulin for glucose control; history of significant cardiovascular event; active malignancy; history of acute complications due to T-2DM; end stage renal disease; history of organ transplant; metabolic, gastrointestinal, or hepatic disease; BMI $\geq$ 40, and finger stick blood glucose test $\geq$250 mg/dl at visit 2. Study sites and locations in China are as follows: Rui Jin Hospital, Shanghai; Chang Zheng Hospital, Shanghai; Chang Hai, Shanghai; You Yi Hospital, Beijing; and General Hospital, Tianjin.

Sealed envelopes containing subject treatment assignments were provided to each site. Randomization schedules were unique to each site and each study center obtained a group of codes for numbering subjects. Subjects were numbered in the order they entered the study. Eligible subjects were given a treatment number corresponding to the sealed envelopes and the treatment assignment contained within.

Research designs

This study was conducted from October 20, 2004, until December 30, 2004. The study protocol was approved by the Independent Ethics Committee of Rui Jin Hospital, Shanghai Jiaotong University School of Medicine. The length of the study was 8 days for each subject, and subjects in either treatment group underwent two clinical visits (visit 1/day 1 and visit 2/day 8). Visit 1/day 1 and visit 2/day 8 were conducted at the enrolling site; subjects maintained their normal schedules on days 2 through 7. Results

from the visit 1 procedures served as baseline values. On visit 1/day 1, subjects underwent screening for eligibility at each enrolling site. After having study procedures explained, subjects provided written informed consent and underwent randomization. Study product and subject diaries were then dispensed. Visit 1 procedures included medical history, vital signs, a complete physical examination, clinical laboratory tests, and a finger stick blood glucose test (Abbott Medisense Optimum™ meter). Laboratory testing included a complete blood count with differential, BUN, creatinine, total bilirubin, AST ALT, alkaline phosphatase, sodium, chloride, HDL, LDL, triglycerides, total protein, glucose, albumin, HCO_3, HbA_{1c}, and urinalysis.

Subjects abstained from study product on days 2, 3, and 4, and were instructed to carefully record anti-hyperglycemic medications, gastrointestinal symptoms, and adverse events within the diaries provided. On days 5, 6, and 7, subjects replaced their usual breakfast with 500 ml of their assigned study product. Subjects recorded product intake in addition to anti-hyperglycemic medications, gastrointestinal symptoms, and adverse events within their diaries.

On study day 8, subjects were instructed to fast for 10 (±2) hours prior to returning to the clinic. Subjects were also instructed not to take anti-hyperglycemic medication prior to visit 2 on day 8. During the study visit, investigators collected a finger stick blood glucose test, checked vital signs, conducted an abbreviated physical exam, collected and reviewed subject diaries, collected blood and urine samples for laboratory testing, and conducted a GRT. Subjects consumed either 500 ml of Glucerna or 550 ml of Fresubin Diabetes, depending on their randomized assignment, within 10 min of conduct of the GRT. Safety data concerning adverse events were also collected at this time.

Study products

The experimental product was Glucerna (Abbott, Abbott Park, USA), a liquid for oral intake with 496 kcal per 500 ml of product. Similarly, Fresubin Diabetes (Sino-Swed Pharmaceutical Corporation, China) is a liquid for oral intake with 495 kcal per 550 ml of product. Both products were stored at room temperature.

Glucose response test

At visit 2, a catheter needle was inserted in a retrograde manner into a dorsal hand vein in each subject and maintained with 0.05% heparin. Fasting blood was drawn for clinical laboratory tests and for fasting glucose and insulin values for the GRT at the zero (0) time point. Immediately following the fasting blood draw, the study drug (500 ml of experimental product or 550 ml of control product; approximately equivalent caloric values) was given to each subject. Time 0 was recorded as the first sip of study product which was consumed within 10 min. Subsequent blood samples were obtained at the following scheduled times: 30, 60, 90, 120, 180, and 240 min (±5 min at each time point). Plasma samples were analyzed for glucose and insulin.

The primary endpoint was the adj-AUC for plasma glucose at 0–240 min. Secondary endpoints included adj-AUC for plasma insulin at 0–240 min, the adjusted peak value of plasma glucose and plasma insulin, the adjusted peak time of plasma glucose and plasma insulin, and the adjusted glucose and insulin values at 0, 30, 60, 90, 120, 180, and 240 min. All the adjusted values of plasma glucose or insulin were obtained from values at one time point minus fasting value of glucose or insulin. Therefore, all the fasting values of plasma glucose and insulin were adjusted as zero.

Statistical analysis

Statistical tests were two-tailed and conducted at the 0.05 significance level, and *P*-values were rounded to four decimal places. The difference of adj-AUC between the two treatment arms was analyzed using one-way ANOVA. An analysis of covariance (ANCOVA model) was applied for comparison with factors for treatment groups, center, and baseline glucose. Between-group differences of the secondary efficacy variables described above were analyzed by Independent-Samples *t*-test or by a Wilcoxon rank-sum test. The AUC was adjusted by the measured value of time 0. The adj-AUC was calculated by the measured value at each point of GRT minus the measured value of time 0. The randomization sequence was created by the sponsor's statistical contract research organization (Gleneagles International, PR China) with oversight approval of the sponsor. A sample size of 200 subjects was considered sufficient to detect significant differences between the study products for the efficacy variables measured.

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