Clinical Trial Protocol

A multicenter, randomized, double-blinded, placebo-controlled phase III clinical study to evaluate the efficacy and safety of Liraglutide Injection in the intervention of obese or overweight adult patients with associated metabolic abnormalities

Protocol No.: JSWB-LRG2020-301

Clinical phase: III

Drug name: Liraglutide Injection

Sponsor

Wanbang Biopharmaceuticals

No.6 Yangshan Road, Jinshanqiao Economic Zone, Xuzhou-221004, Jiangsu Province, China.

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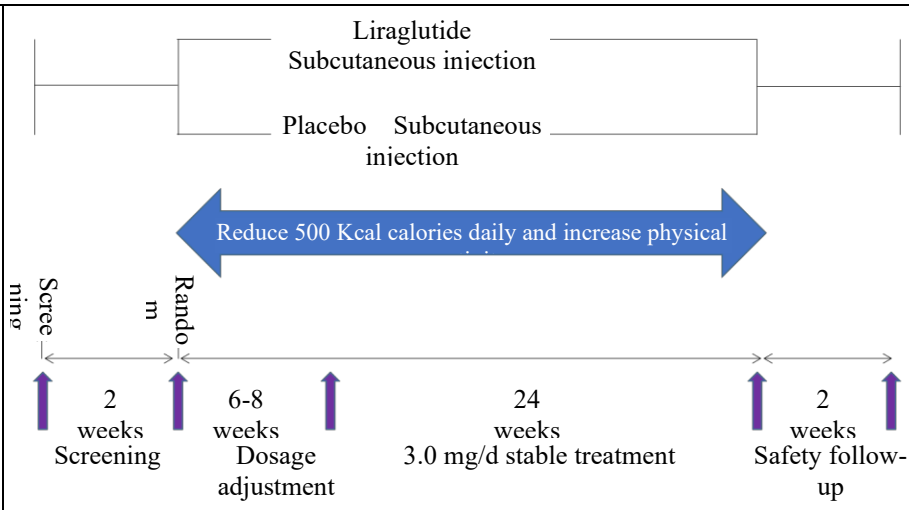
Protocol Summary

Investigational drug	Liraglutide Injection	**Registration classification**	Biology - Class 7
Study title	A multicenter, randomized, double-blinded, placebo-controlled phase III clinical study to evaluate the efficacy and safety of Liraglutide Injection in the intervention of obese or overweight adult patients with associated metabolic abnormalities		
Clinical study approval No.	CXSL1900149		
Sponsor	Wanbang Biopharmaceuticals		
Trial site	Zhongshan Hospital, Fudan University		
PI:	Professor Xiaoying Li		
Trial phase	III		
Study objective	**Primary study objective** To evaluate the body weight loss effect of Liraglutide Injection compared with placebo in obese or overweight adult patients with related metabolic abnormalities (hypertension, dyslipidemia or type 2 diabetes). **Secondary study objective:** ● To observe the effect of Liraglutide Injection on waist circumference, blood pressure, blood lipid, blood glucose and other metabolic index and quality of life compared with placebo; ● To evaluate the safety and tolerance of Liraglutide Injection.		
Trial design	This is a multicenter, randomized, double-blind, placebo-controlled phase III clinical trial. The total study duration will be about 34~36 weeks, including a 2-week screening period, a 6~8-week dosage adjustment period, a 24-week stable treatment period and a 2-week safety follow-up period. Subjects with obesity or overweight with related metabolic disorders will be subcutaneously injected with 3.0 mg Liraglutide Injection or placebo every day. Changes in body weight from baseline for Liraglutide Injection will be compared with placebo at the end of treatment. In the course of the trial, the subjects will be weighed on an empty stomach and blood samples will be collected according to the protocol, and the efficacy and safety will be evaluated. All subjects will be given medication on the basis of reduced calorie diet guidance (reduced by about 500 kcal/day) and increased physical exercise.		

	
Subject population	Obese or overweight adult patients with associated metabolic abnormalities
Sample size	Total 291 subjects will be enrolled as planned, and about 414 subjects will be included in the study as expected considering the dropouts.
Inclusion criteria	1) Those voluntarily participating and signing the ICF. 2) Those aged 18-70 years old (including 18 and 70 years old), without restriction on male and female 3) Those failing to control their body weight in previous diet therapy alone. 4) Those voluntarily following the medication, diet and exercise requirements decided by the investigators. 5) Those with a stable body weight (patient reported body weight change < 5 kg) in last 3 months. 6) Those with BMI ≥ 30 kg/m^2 (obese) or BMI ≥ 27 kg/m^2 (overweight) accompanied by at least one treated or untreated related metabolic abnormality (hypertension, dyslipidemia, type 2 diabetes). Those with untreated hypertension defined as SBP ≥ 140 mmHg or DBP ≥ 90 mmHg; untreated dyslipidemia defined as LDL-C ≥ 4.1 mmol/L, TG ≥ 1.7 mmol/L, TC ≥ 5.7 mmol/L or HDL-C < 1.0 mmol/L in male and < 1.3 mmol/L in female. 7) Those with type 2 diabetes should additionally meet the following inclusion criteria: a) Those diagnosed as type 2 diabetes according to WHO (1999) Diagnostic and Classification Criteria at the time of screening; b) Those receiving diet and exercise therapy alone, or receivig metformin, sulfonylureas, glycosidase inhibitors and glinides alone or in combination on the basis of diet and exercise therapy, with their treatment remaining stable at least 3 months before screening (with original documents such as prescriptions provided); c) Those with HbA1c of 7.0-10.0% (inclusive); d) Those with FPG < 13.3 mmol/L (240 mg/dL).
Exclusion criteria	Subjects who meet one of the following exclusion criteria will be excluded. 1) Those with type 1 diabetes or secondary diabetes.

	2)	Those with acute metabolic complications such as diabetic ketoacidosis or hyperglycemia (coma) within 6 months before screening.
	3)	Those with 2 or more severe hypoglycemia events (hypoglycemia with severe cognitive impairment and need other measures to help them recover) without obvious inducement within 3 months before screening.
	4)	Those receiving GLP-1 receptor agonist, DPP-4 inhibitors, SGLT-2 inhibitor, or insulin therapy within 3 months prior to screening.
	5)	Those with obesity caused by endocrine diseases such as Cushing's syndrome.
	6)	Patients taking drugs that can significantly increase weight in the 3 months before screening, including systemic glucocorticoid (except cumulative or continuous use of less than 14 days).
	7)	Those using OTC weight-loss drugs or appetite inhibitors (including traditional Chinese medicine as weight-loss drugs) within 1 month before screening, or use prescription weight-loss drugs (such as fentanyl, sibutramine, orlistat) or lipid dissolving injection (such as fat dissolving needle) within 3 months before screening.
	8)	Those with binge eating behavior in the past, that is, eating a large amount of food in a short period of time with a sense of loss of control.
	9)	Those who have treated or plan to treat obesity (during the trial) with surgery or body weight loss devices.
	10)	Those with a past or family history of MTC (grandparents, parents, siblings), or those whose genetic diseases are prone to induce MTC and MEN2.
	11)	Those with thyroid nodules of unknown etiology at the time of screening which is considered clinically significant by the investigator (calcitonin is more than 50 pg/ml, which is only allowed to be retested once).
	12)	Those with a past history or found to have hyperthyroidism or hypothyroidism or subclinical hypothyroidism at the time of screening [TSH > 6 mIU/L].
	13)	Those with history of pancreatic cancer, acute or chronic pancreatitis, or with acute or chronic pancreatitis at the time of screening, or having blood amylase or lipase ≥ 3 times ULN.
	14)	Those with acute gallbladder disease (cholecystitis, gallstone) more than 2 times in 1 year before screening.
	15)	Those with MDD, anxiety disorder or other mental illnesses or with the PHQ-9 score ≥ 15 at screening
	16)	Those with the following cardiovascular and cerebrovascular diseases within 6 months before screening: decompensated cardiac insufficiency (NYHA Class III-IV), UA or AMI, CVA or stroke.
	17)	Those with a history of heart valve replacement, CABG or other PTCA including percutaneous coronary intervention.
	18)	Those who fail to control their blood pressure effectively, with SBP ≥ 160 mmHg or DBP ≥ 100 mmHg.
	19)	Those with a history of malignancy in the past 5 years, not including cervical epithelial carcinoma, squamous cell carcinoma or basal cell carcinoma of skin that have been clinically cured within 5 years.
	20)	Those with known proliferative retinopathy or maculopathy.
	21)	Those with a history of major surgical operations (intrathoracic, intracranial, intraperitoneal, etc.) within 6 months, or planning to perform operations that may interfere with the completion or compliance of the study.
	22)	Those with a history of organ transplantation.
	23)	Those with ADIS or syphilis at the time of screening, or whose serum virological test shows hepatitis C virus antibody or hepatitis B surface antigen and hepatitis B core antibody are positive at the time of screening.
	24)	Those with AST or ALT > 3.0-fold ULN, or total bilirubin > 2.0-fold ULN at the time of screening.
	25)	Those with eGFR < 60 mL/min/1.73 m^2 at the time of screening.
	26)	Those with a history of drug abuse (heavy and repeated use of dependent drugs or substances not related to medical purposes, including addictive and habitual

<table>
<tr><td></td><td>drugs, causing physical and mental dependence) in 5 years before screening and alcohol dependence (long-term heavy drinking, causing physical and mental dependence, male drinking more than 14 units of alcohol per week, and female drinking more than 7 units per week) (1 unit alcohol = 360 mL beer or 45 mL spirits with 40% alcohol content or 150 mL wine)].
27) Female who are known to be pregnant (determined by pregnancy test at the time of screening) or who are breast-feeding or who plan a pregnancy during the study and are unwilling to take effective contraceptive measures (including partners).
28) Those participating in other intervention clinical trials within 3 months prior to screening.
29) Those known to be allergic to GLP-1 receptor agonist.
30) Those with any serious systemic diseases as determined by the investigator, or other diseases as believed by the investigator to be possible to interfere with the results of this study or abnormal laboratory tests with clinical significance.
31) Those who, according to the opinion of investigators, are not suitable to participate in clinical trials, including those who are physically or psychologically unable to comply with the protocol.</td></tr>
<tr><td>Stratified standard</td><td>Based on stratified randomization, stratifying factors included baseline BMI < 30 kg/m^2 and ≥ 30 kg/m^2， presence and absence of type 2 diabetes. The number of enrolled patients with type 2 diabetes should not exceed 17% of the total number.</td></tr>
<tr><td>Rescue therapy criteria</td><td>If the fasting blood glucose of patients with type 2 diabetes exceeds the following standard (at least 2 times, one of which should be fasting venous blood glucose), the combination of hypoglycemic drugs can be gradually increased to the maximum prescription dose. If the blood glucose is still out of control, other hypoglycemic treatments (metformin, sulfonylureas, glycosidase inhibitors or glinides) permitted by this protocol should be allowed to be increased, which will determined by the investigator.
● Baseline - Week 6: FPG > 13.3 mmol/L (240 mg/dL)
● Week 7~Week 30: FPG > 11.1 mmol/L (200 mg/dL)
Rescue therapy will affect the evaluation of body weight and response indicators, so the body weight and blood glucose efficacy analysis will only include the measured values before rescue therapy.</td></tr>
<tr><td>Administration regimen</td><td>Investigational drug: Liraglutide Injection (BID), by subcutaneous injection, with the injection site to be at the abdomen, thigh or upper arm as selected. Dosage adjustment is not required when injection site and injection time change. The initial dose of Liraglutide Injection should be 0.6 mg per day. The dose escalation protocol should be based on the table below to reduce the likelihood of gastrointestinal symptoms. At Week 7, the dose should be increased to 3.0 mg per day. A subject failing to tolerate the target dose of 3.0 mg may try the dose of 2.4 mg and try to increase the dose to 3.0 mg again within 2 weeks. If the subject is still unable to tolerate such dose (3.0 mg), the drug must be discontinued and the treatment must be terminated.
Control drug: placebo, which should be used as above.
Dose increment protocol for the investigational drug
<table>
<tr><th>Week</th><th>Daily dose</th></tr>
<tr><td>Week 1</td><td>0.6 mg</td></tr>
<tr><td>Week 2</td><td>1.2 mg</td></tr>
<tr><td>Weeks 3~4</td><td>1.8 mg</td></tr>
<tr><td>Weeks 5~6</td><td>2.4 mg</td></tr>
<tr><td>Week 7</td><td>3.0 mg</td></tr>
</table></td></tr>
<tr><td>Study cycle</td><td>Screening period: 2 weeks
Treatment period: 30~32 weeks (about 6~8 weeks of dosage adjustment period, 24 weeks of stable treatment period)
Safety follow-up period: 2 weeks</td></tr>
</table>

	The study cycle will be about 34~36 weeks.
Response evaluation indicator	Primary endpoint: 1) The percentage of body weight loss from baseline at the end of treatment; 2) The proportion of subjects whose body weight will decrease by ≥ 5% from baseline level at the end of treatment; Secondary endpoint: 1) Changes in waist circumference of the subjects at the end of treatment; 2) Changes in blood pressure level (diastolic pressure and systolic pressure) and pulse of the subjects at the end of treatment; 3) The changes in blood lipid levels (triglyceride, total cholesterol, low density lipoprotein cholesterol, and high density lipoprotein cholesterol) of the subjects at the end of treatment; 4) The change of blood glucose level (insulin, fasting blood-glucose) of the subjects at the end of treatment; 5) The changes in HbA1c of patients with type 2 diabetes at the end of treatment; 6) The absolute body weight loss of the subjects at the end of treatment; 7) The proportion of subjects with body weight loss > 10% at the end of treatment; 8) Effect of changes in body weight of the patients to the IWQOL-lite at the end of treatment
Response evaluation criteria	The product can be considered to be effective in body weight control when the following conditions are met simultaneously after 30-32 weeks of treatment: ✧ The difference in mean body weight loss between the experimental group and the placebo group is at least 5%, and the difference is statistically significant. ✧ The proportion of subjects losing more than 5% of their body weight from baseline in the experimental group should be at least 35%, which should be about 2 times as much as that in the placebo group. In addition to that, the difference between the two groups should be statistically significant.
Safety evaluation index	It is used to evaluate the safety and immunogenicity of the investigational drug following subcutaneous injection. ● Incidence rate of AEs, AEs during treatment, serious and non-SAEs ● Incidence rate of gastrointestinal reactions: including nausea, diarrhea, vomiting, constipation, abdominal pain and dyspepsia ● Incidence rate of hypoglycemic events: proportion of subjects and incidence rate of hypoglycemic events in each category ● Early withdrawal due to AEs: including stopping treatment due to nausea and vomiting ● Changes in vital signs ● Changes in physical examination ● Changes in 12 lead ECG ● Changes in clinical laboratory examination parameters (blood routine, urine routine, blood biochemistry (liver function, kidney function, TSH, calcitonin, amylase, lipase, etc.)) ● Changes in PHQ-9 ● Incidence rate of Liraglutide antibody

Sample size calculation	According to the statistical requirements of placebo-controlled superiority trial, the main reponse indicator of this study is the mean weight loss percentage of subjects compared with baseline at the end of treatment and the proportion of subjects with body weight loss ≥ 5% at the end of treatment, and the two indicators will be the synergistic response indicators. According to the response evaluation criteria, the product can be considered effective for body weight control if the following two conditions are met simultaneously at the end of treatment: response indicator (1) The difference in mean body weight loss between the experimental group and the placebo group should be at least 5%, with the difference to be statistically significant. With the bilateral test α=0.05 and the power as 90% and without considering the shedding, the random proportion of experimental group: placebo group is 2:1, the required sample size is 102 cases in the experimental group and 51 cases in the placebo group, with a total sample size of 153 cases Response indicator (2) The proportion of subjects with body weight loss ≥ 5% from baseline in the experimental group should be at least 35%, which is about 2 times the body weight loss rate of subjects in the placebo group, with the difference between the two groups to be statistically significant. With the bilateral test α= 0.05 and the power as 90% and without considering the shedding, the random proportion of experimental group: placebo group is 2:1, the required sample size is 194 cases in the experimental group and 97 cases in the placebo group, with a total sample size of 291 cases. According to the above response evaluation criteria, the above 2 response indicators should be met at the same time in order to succeed in the trial. Therefore, 291 cases of the larger sample size required to achieve statistical significance of the 2 indicators are taken as the effective sample size required for the synergistic response indicator. Taking into account the shedding factors, it is estimated that about 414 subjects will be included according to the 30% shedding rate.
Statistical analysis	The software of SAS 9.4 or above will be used for analysis. The safety data set will be used for safety analysis, and the data from the full analysis set and the per protocol set will be used for the analysis of efficacy. The analysis of the primary endpoint will be based on the full analysis set. **Collaborative main evaluation indicator of the study 1:** The percentage of subjects in the experimental group who lost body weight compared with baseline at the end of treatment. Superiority test hypothesis 1: ● H_0:The difference in the mean change in body weight between the Liraglutide Injection group and the placebo group at the end of treatment compared with the baseline period is < 5%; ● H_1:The difference between the Liraglutide Injection group and the placebo group at the end of treatment compared with baseline body weight change was ≥ 5%. **Collaborative main evaluation indicator of the study 2:** The proportion of subjects whose body weights decrease by ≥ 5% from baseline at the end of treatment. Superiority test hypothesis 2: ● H_0:The proportion of subjects who lost more than 5% of their body weight from baseline is less than 35% in the experimental group, or the proportion of subjects in the experimental group lost body weight 2 times as much as that in the placebo group, or there is no statistical significant difference between the two groups. ● H_1: The proportion of subjects with body weight loss ≥ 5% from baseline in the experimental group is greater than or equal to 35%, which is 2 times as much as that in the placebo group, and there is a statistical significant difference between the two groups. The above two statistical test hypotheses are based on two-sided test, and at the significance level of α= 0.05, the two collaborative primary endpoints should reach statistical significance at the same time. The safety evaluation indexes include physical examination, vital signs, electrocardiogram, laboratory examination, immunogenicity, mental health assessment and AEs. The immunogenicity evaluation indicator is the incidence rate of Liraglutide antibody.