A Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Study to Evaluate the Efficacy and Safety of Fuling Yunhua Granules and Dihuang Baoyuan Granules in Patients with Type 2 Diabetes Mellitus Whose Glycemic Control Remains Inadequate after Diet and Exercise Intervention

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1. Study Objectives

Primary Objective

To evaluate the efficacy of the combination therapy with Dihuang Baoyuan Granules (Formula B) and Fuling Yunhua Granules (Formula A) in patients with type 2 diabetes mellitus (T2DM) whose glycemic control is still inadequate after dietary and exercise interventions.

Secondary Objective

To assess the safety of the combination therapy with Formula B and Formula A in the same patient population.

Exploratory Objective

To evaluate glycemic control after discontinuation of the combination therapy in T2DM patients whose glycemic control was initially inadequate despite diet and exercise interventions. (Note: Results from this exploratory phase may not be included in the final study report.)

2. Study Methods and Design

2.1 Study Design

This study adopts a multicenter, randomized, double-blind, placebo-controlled design comprising four phases: a screening period (up to 2 weeks), a baseline period (1 week), a 12-week treatment period, and a 1-week post-treatment follow-up period.

Seventy-two eligible subjects will enter a 1-week baseline period, during which 7-day continuous glucose monitoring (CGM) data will be collected. Subsequently, subjects will be randomized in a 2:1:2:1 ratio to four treatment arms for 12 weeks of treatment.

An interim analysis is planned after approximately 30 subjects have completed 4 weeks of treatment and corresponding data are available. Based on 4-week CGM-derived time-in-range (TIR) changes from baseline, the Independent Data Monitoring Committee (IDMC) will decide whether to expand enrollment. If recommended by the IDMC, the principal investigator may increase sample size (to 30 subjects per active arm and 15 per matching placebo arm) to obtain more robust efficacy and safety data.

To further assess post-discontinuation glycemic control, an exploratory follow-up phase is added. After completing the Week-12 treatment and the Week-13 follow-up visit (Visit 11), subjects whose HbA1c < 6.5 % may opt into an 11-week exploratory follow-up by signing an additional informed consent form, resulting in a total follow-up of 12 weeks (1 week routine follow-up plus 11 weeks exploratory). Subjects entering this follow-up will not receive study drugs. Those who decline or do not meet criteria will complete the study at Visit 11 (see Figure 1).

Statistical analyses (excluding exploratory endpoints) will be performed after all randomized subjects have completed the 12-week treatment and Visit 11. Throughout the study, investigators will provide dietary advice and exercise guidance according to the 2020 Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes.

2.2 Study Population and Selection Criteria

Target Population

Adults with T2DM whose glycemic control remains suboptimal despite diet and exercise therapy. T2DM diagnosis follows the

2020 WHO criteria (Attachment 12.1). Subjects will be recruited from outpatient clinics at participating centers via newspaper, internet, and poster advertisements between August and November 2024.

Inclusion Criteria

1) Aged 18－75 years (inclusive), any sex.

2) Diagnosed with T2DM ≥ 8 weeks per 2020 WHO criteria.

3) Glycemic control attempted with diet and exercise alone for ≥ 3 months before screening, or cumulative use of antihyperglycemic drugs ≤ 2 weeks within 3 months and none within 1 month before screening.

4) BMI ≥ 19 kg/m².

5) HbA1c ≥ 7.0 % and < 10.5 % at screening.

6) Fasting plasma glucose (FPG) < 13.9 mmol/L at screening.

7) Able to understand study procedures, willing to comply with the protocol, and has signed informed consent form (ICF).

Exclusion Criteria

1) Diabetes other than T2DM (type 1, gestational, or specific

types).

2) History of acute diabetic complications (DKA, hyperosmolar hyperglycemic state, or lactic acidosis) within 6 months.

3) Unstable or treated chronic diabetic complications (proliferative retinopathy, severe neuropathy, intermittent claudication) within 6 months.

4) ⩾ 3 level-3 hypoglycemic episodes within 6 months (definitions in Attachment 12.2).

5) Systemic corticosteroids (oral, IV, intra-articular) for ⩾ 7 cumulative days within 3 months.

6) Severe infection within 3 months.

7) Malignancy (except cured basal-cell carcinoma or cervical carcinoma in situ) within 5 years.

8) Major cardiovascular events within 6 months (NYHA class III - IV heart failure, MI, CABG/PCI, significant arrhythmias, ACS, TIA, or stroke).

9) Diseases affecting drug absorption, distribution, metabolism, or excretion within 6 months (IBD, peptic ulcer, GI bleeding, major GI surgery such as gastrectomy or intestinal resection).

10) Uncontrolled thyroid dysfunction despite stable

medication.

11) Hypertension with SBP > 160 mmHg or DBP > 100 mmHg despite ≥ 4 weeks of treatment.

12) Organ transplant or severe autoimmune disease.

13) Clinically relevant drug hypersensitivity or atopic disorders (asthma, urticaria, eczema).

14) Major surgery within 6 months or planned surgery that could interfere with study completion.

15) Laboratory abnormalities at screening:

- ALT or AST > 2.5× ULN
- eGFR < 60 mL/min/1.73 m² (CKD-EPI)
- TBIL > 1.5× ULN
- TG > 5.7 mmol/L
- Fasting C-peptide < 0.8 ng/mL (0.26 nmol/L)

16) Positive HBsAg (unless HBV-DNA < lower limit and not on anti-HBV therapy), anti-HCV, anti-HIV, or syphilis antibody.

17) Blood donation or blood loss > 400 mL within 3 months.

18) Pregnant, lactating, or of reproductive potential unwilling to use effective contraception.

19) Alcohol, tobacco, or drug abuse within 3 months.

20) Participation in another interventional trial within 3

months.

21) Hypersensitivity to study drug components.

22) Any condition considered unsuitable by the investigator.

Withdrawal Criteria

1) Poor adherence affecting efficacy/safety assessment after counseling.

2) AE/SAE necessitating discontinuation.

3) Investigator believes continuation would harm the subject.

4) Pregnancy.

5) Major protocol deviation affecting results.

6) Withdrawal of consent.

7) Lost to follow-up.

8) Death.

9) Other reasons.

Subjects may withdraw at any time. Upon withdrawal, no further study drug is given, but safety follow-up continues until events resolve or are explained. Detailed records must be entered into the eCRF.

Exploratory Phase Selection Criteria

Inclusion

1) Completed 12-week treatment and Visit 11 with HbA1c < 6.5 %.

2) No antihyperglycemic drugs between Visit 10 and signing additional consent.

3) Willing and able to sign supplementary ICF.

Exclusion

Any condition deemed unsuitable by the investigator.

2.3 Treatment Arms and Controls

2.3.1 Investigational Products

- Fuling Yunhua Granules (Formula A)

  Specification: 12 g/sachet; 1 g ≈ 4.77 g crude herb.

  Shelf-life: 18 months.

  Storage: Sealed, 10–30 °C.

- Dihuang Baoyuan Granules (Formula B)

  Specification: 18 g/sachet; 1 g ≈ 3.95 g crude herb.

  Shelf-life: 18 months.

  Storage: Sealed, 10–30 °C.

• Placebo Control

A-formula and B-formula matching placebos identical in appearance, odor, and packaging but containing no active ingredients.

All investigational products are supplied by Beijing Jingyi Hesheng Pharmaceutical Technology Co., Ltd.

2.3.2 Dosing Regimen

Subjects take four sachets daily: one before each meal and one 2 h after dinner, for 12 weeks.

2.3.3 Concomitant Medications

Permitted

1) Stable treatment of hypertension, dyslipidemia, etc.

2) Symptomatic treatment for AEs.

Prohibited (from consent to end of follow-up)

1) Any antihyperglycemic agents other than study drug or rescue therapy.

2) Systemic corticosteroids (inhaled/topical allowed), growth hormone.

3) Other investigational drugs.

During exploratory follow-up, prohibited agents additionally include study drugs and any antihyperglycemics.

Rescue Therapy

If FPG > 13.9 mmol/L, metformin may be initiated at 0.5 g twice daily, titrated to 1 g twice daily as tolerated. Subjects remain on study drug unless withdrawal is indicated. Rescue decisions and potential study discontinuation are at investigator discretion.

Exploratory Phase: If FPG ≥ 8.0 mmol/L without apparent cause, investigator may schedule unscheduled testing; withdrawal from exploratory phase if judged necessary.

2.3.4 Drug Accountability

Per GCP (2020), study drugs are stored, dispensed, and reconciled by designated pharmacy staff; all movements are

documented. Unused drug and packaging must be returned. At study end, all materials are returned to the sponsor for destruction. Labels state "For Clinical Research Use Only" and include required details.

2.3.5 Treatment Compliance

Compliance (%) = (actual dose taken / planned dose) × 100. Accurate dosing records are maintained in the eCRF, including dates, times, doses, and reasons for missed/reduced doses.

2.4 Randomization and Blinding

2.4.1 Randomization

A non-blinded statistician independent of the study uses SAS 9.4+ to generate a block randomization list. Subjects are randomized 2:1:2:1 via an Interactive Web Response System (IWRS). Randomization parameters and seed are archived.

2.4.2 Blinding

Double-blind: subjects, investigators, and blinded study staff remain unaware of treatment assignment.

2.4.3 Unblinding

Planned

a) Final database lock after all subjects complete Visit 11.

b) Interim analysis after 30 subjects complete 4 weeks; data are unblinded only for IDMC review.

Emergency unblinding for SAEs or life-threatening events is allowed via IWRS; the decision rests with the PI. Sponsor must be notified within 24 h; unblinded subject must discontinue study drug but remain in follow-up.

2.5 Endpoints

Efficacy

Primary

• Change in HbA1c from baseline to Week 12.

Secondary (Week 12)

• Change in FPG, fasting C-peptide.

• Proportion achieving HbA1c < 7 % and < 6.5 %.

• CGM-derived 7-day TIR, TBR, TAR, MAGE, GMI, CV, SD, MODD.

• Changes in fasting lipids (TC, LDL-C, HDL-C, TG), SBP, DBP,

uric acid, body weight.

Safety

AEs, physical exam, laboratory tests (hematology, urinalysis, biochemistry), vital signs, 12-lead ECG.

Exploratory (12 weeks after stopping BAB/ABA therapy)

- Proportion with HbA1c < 6.5 %.
- GMI increase < 0.4 % (Weeks 23–25 vs exploratory baseline).
- Changes in 14-day CGM metrics, HbA1c, FPG, C-peptide, lipids, BP, uric acid.

Exploratory baseline = Visit 10 values; CGM baseline = Weeks 11–13 data.