

PHASE IIA CLINICAL TRIAL PROTOCOL: PIT-OST-01

Evaluation of a Synchronized Multivariant HPMC Formulation for Accelerated Cortical Bridging and Callus Mineralization in Upper and Lower Extremity Diaphyseal Fractures

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ABSTRACT

Delayed fracture healing and osteolytic complications present clinical challenges in orthopedics. PIT-OST-01 is an oral, vegan, multi-component therapeutic stack developed under the PhytoIntelligence 3.4 framework. It is designed to upregulate Runx2/BMP-2 expression and control post-traumatic inflammatory osteolysis. This randomized, double-blind, placebo-controlled trial will evaluate the safety, tolerability, and radiographic efficacy of PIT-OST-01 in adults presenting with acute, non-displaced or minimally displaced diaphyseal fractures of the upper or lower extremity.

1. INTRODUCTION AND OBJECTIVES

Fractures of the humerus, radius, ulna, femur, or tibia (broken arms or legs) require coordinated physiological repair. Delayed healing occurs in 5–10% of patients, resulting in severe morbidity. Preclinical and pharmacokinetic models indicate that PIT-OST-01 upregulates osteoblastic type I collagen, osterix, and **Runx2** while suppressing **NF-κB** osteoclastogenesis.

The primary objective is to evaluate whether daily administration of PIT-OST-01 significantly reduces the time to cortical bridging and clinical union compared to placebo. Secondary objectives include safety profiling, quantitative assessment of callus density, and pain trajectory kinetics.

2. TRIAL DESIGN

This is a Phase IIA, multi-center, randomized, double-blind, placebo-controlled, parallel-group clinical trial. Participants will be randomized in a 1:1 ratio to receive either PIT-OST-01 or an identical organic placebo capsule twice daily for 12 weeks, alongside standard orthopedic immobilization.

3. PATIENT SELECTION AND ENROLLMENT CRITERIA

3.1 Inclusion Criteria

To participate, subjects must meet all the following criteria:

1. Males or non-pregnant, non-lactating females aged 18 to 65 years.
2. Diagnosed with an acute, closed, isolated, non-displaced or minimally displaced (not requiring surgical fixation) diaphyseal fracture of a long bone (tibia, fibula, femur, humerus, radius, or ulna) within 72 hours of injury.
3. Consented to standardized orthopedic immobilization (casting or bracing).
4. Capable of understanding and providing written informed consent.

3.2 Exclusion Criteria

Subjects displaying any of the following will be excluded:

1. Open, infected, or pathological fractures (e.g., secondary to bone malignancy or severe osteoporosis with bone mineral density T-score ≤ -3.0).
2. History of metabolic bone disease (e.g., Paget's disease, osteomalacia, hyperparathyroidism).
3. Chronic use of systemic corticosteroids, immunosuppressants, or anti-resorptive medications (bisphosphonates, denosumab).
4. Concurrent use of potent CYP3A4 substrates with narrow therapeutic indices (e.g., cyclosporine, tacrolimus).
5. Known hypersensitivity to any of the botanical components of PIT-OST-01.

4. INVESTIGATIONAL PRODUCT AND ADMINISTRATION

The active investigational product, PIT-OST-01, is formulated as a single 750 mg organic, vegan hypromellose (HPMC) capsule containing:

- **Node 1 (Icaritin Nanocrystals):** 230 mg
- **Node 2 (*Cissus quadrangularis* Extract):** 180 mg [Metabolic Flux Enhancer]
- **Node 3 (Curcumin BCM-95):** 110 mg
- **Node 4 (*Boswellia serrata* SLBSP):** 85 mg
- **Node 5 (trans-Resveratrol):** 65 mg
- **Node 6 (Piperine):** 15 mg
- **Node 7 (Naringin):** 10 mg [Vascular Coupling/Osteogenic Adjuvant]
- **Excipient (USP-MCC):** 55 mg

4.1 Dosing Schedule

Patients will orally self-administer one HPMC capsule twice daily (morning and evening, 12 hours apart) with 250 mL of water immediately following a meal, to ensure optimal micellar lipid absorption of lipophilic actives. Total daily active dose equals 1390 mg.

5. EFFICACY AND SAFETY ENDPOINTS

5.1 Primary Efficacy Endpoint

The primary endpoint is the **Time to Radiographic Union**, defined as the first post-randomization visit where radiographic cortical bridging is visible in at least 3 out of 4 cortices on high-resolution anteroposterior and lateral radiographs, evaluated by an independent, blinded central radiological review committee utilizing the Radiographic Union Scale for Tibial Fractures (RUST) or equivalent validated anatomical scoring system.

5.2 Secondary Efficacy Endpoints

The secondary endpoints include:

1. **Time to Clinical Union:** Defined as painless full weight-bearing on the affected extremity (for lower limbs) or pain-free resisted motion (for upper limbs), assessed at bi-weekly clinical evaluations.
2. **Quantitative Callus Density:** Percentage change in trabecular bone mineral density within the callosal margin, measured via peripheral quantitative computed tomography (pQCT) at weeks 4, 8, and 12.
3. **Pain Trajectory:** Progression of local visual analog scale (VAS) pain scores recorded in daily patient electronic diaries.
4. **Functional Recovery Metrics:** Short Form-36 (SF-36) and extremity-specific functional indices (e.g., Lower Extremity Functional Scale) assessed at weeks 6 and 12.

5.3 Safety Endpoints

The safety parameters will consist of:

1. Incidence and severity of all Treatment-Emergent Adverse Events (TEAEs) classified using MedDRA terms.
2. Comprehensive clinical laboratory evaluations (hepatic enzymes ALT/AST, renal function serum creatinine, coagulation markers PT/INR, and blood calcium) performed at baseline, week 4, and week 12.

6. STATISTICAL ANALYSIS PLAN

The sample size calculation is based on an assumed control time-to-union of 14 weeks (± 3 weeks). To detect a 20% reduction in healing time (to 11.2 weeks) with 80% statistical power ($\beta = 0.20$) and a two-sided significance level of $\alpha = 0.05$, assuming a 15% drop-out rate, a total of 120 subjects (60 per arm) will be enrolled. Primary analysis of the time-to-union will be conducted using the Kaplan-Meier survival analysis with the log-rank test. Functional score and bone density differences will be analyzed using a mixed-effects model for repeated measures (MMRM).

Keywords: PIT-OST-01, Cortical Bridging, Diaphyseal Fracture, Runx2, HPMC Formulation, PhytoIntelligence, Clinical Trial Protocol

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