**SUPPLEMENTAL TABLE 1** General data for the phase II, III and IV clinical trials

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| --- | --- | --- | --- | --- | --- |
|  | **Phase IIa** | | **Phase IIIa** | **Phase IVa** | |
| **Study timeline** | February 2005 to June 2005 | | June 2005 to September 2005 | April 2013 to June 2014 | |
| **Registration number** | 2004L02887 | | 2004L02887 | | 2011LS00817 |
| **Registration authority** | State Food and Drug Administration (SFDA) | | | | |
| **Study design** | Multicenter, double-blind, parallel controlled | Multicenter, double-blind, parallel controlled | | Multicenter, open, single-arm registration | |
| **Number of casesb** | *N* = 238 (10 mL ginkgolide, *n* = 80; 6 mL ginkgolide, *n* = 79; control, *n* = 79) | | *N* = 476 (10 mL ginkgolide, *n* = 357; control, *n* = 119) | *N* = 3652 | |
| **Trial accomplishment** | 10 mL ginkgolide: enrolled, *n* = 80; drop-off, *n* = 0; rejected, *n* = 1; valid, *n* = 79  6 mL ginkgolide: enrolled, *n* = 79; drop-off, *n* = 0; rejected, *n* = 3; valid, *n* = 76  Control: enrolled, *n* = 79, drop-off, *n* = 1; rejected, *n* = 2; valid, *n* = 76 | | 10 mL ginkgolide: enrolled, *n* = 357; drop-off, *n* = 8; rejected, *n* = 24; valid, *n* = 325  Control group: enrolled, *n* = 119; drop-off, *n* = 4; rejected, *n* = 4; valid, *n* = 111 | Enrolled, *n* = 3652; drop-off, *n* = 300; valid, *n* = 3352 | |
| **Diagnostic criteria** | In accordance with the diagnostic criteria for ischemic stroke in Western medicine: acute onset; symptoms and signs maintained for more than a few hours; cerebral hemorrhage and other diseases excluded by cerebral CT or MRI; cerebral infarction lesion shown in cerebral CT or MRI | | | | |
| **Inclusion criteria** | (1) Ischemic stroke diagnosed in accordance with the diagnostic criteria used in Western medicine; (2) onset 7 days to 6 months previously; (3) no disturbance of consciousness; (4) written informed consent provided by patient; (5) for the phase II/III study, 5 ≤ NIHSS score ≤ 22 (no NIHSS score restriction in the phase IV study); (6) for the phase II/III study, age 30­–75 years (no age restriction in the phase IV study) | | | | |
| **Exclusion criteria** | (1) Cerebral embolism caused by brain tumor, trauma, rheumatic heart disease, coronary heart disease or other heart diseases with atrial fibrillation; (2) allergy to ginkgo preparations, glycerol or ethanol or patients with an allergic constitution; (3) pregnancy, breastfeeding or planning to become pregnant; (4) alanine transaminase or aspartate transaminase ≥ 2.5 times the upper limit of normal (5) creatinine ≥ 1.5 times the upper limit of normal; (6) hemorrhagic tendency or severe hemorrhage had occurred within previous 3 months; (7) physical or mental disability as prescribed by law; (8) recently participated in other clinical trials | | | | |
| **Intervention methods** | 10 mL ginkgolide group: ginkgolide intravenous infusion, 10 mL/time, 1 time/day  6 mL ginkgolide group: ginkgolide intravenous infusion, 6 mL/time, 1 time/day  Control group: shuxuening intravenous infusion, 20 mL/time, 1 time/day | | 10 mL ginkgolide group: ginkgolide intravenous infusion, 10 mL/time, 1 time/day  Control group: shuxuening intravenous infusion, 20 mL/time, 1 time/day | Ginkgolide intravenous infusion, 10 mL/time, 1 time/day | |
| **Drop-off criteria** | (1) Serious adverse events occurred; (2) the disease was exacerbated or symptoms appeared that might affect the experimental observations; (3) poor adherence to therapy or reluctance to continue participating in the clinical trial | | | | |
| **Rejection criteria** | (1) Patients not selected in line with the inclusion criteria; (2) patients not administrated the study drug or not recorded after administration | | | | |
| **Withdrawal criteria** | (1) Patients were able to withdraw from the study at any time; (2) disease was exacerbated during the trial or symptoms appeared that might affect the experimental observations; (3) use of drugs that were prohibited during the study | | | | |
| **Leading units** | The Traditional Chinese Medicine Hospital of Xinjiang Uyghur Autonomous Region | | The Traditional Chinese Medicine Hospital of Xinjiang Uyghur Autonomous Region | | The Second Affiliated Hospital of Tianjing College of Traditional Chinese Medicine |
| **Participating units** | First Affiliated Hospital, JiLin; First Affiliated Hospital, Heilongjiang University of Chinese Medicine; Second Affiliated Hospital, Heilongjiang University of Chinese Medicine; First Affiliated Hospital, Guangxi Traditional Chinese Medicine | | First Affiliated Hospital, JiLin; First Affiliated Hospital, Heilongjiang University of Chinese Medicine; Second Affiliated Hospital, Heilongjiang University of Chinese Medicine; First Affiliated Hospital, Guangxi Traditional Chinese Medicine | | 82 centers including: Affiliated Hospital, Liaoning College of Chinese Medicine; First Affiliated Hospital, Tianjing College of Traditional Chinese Medicine; First Affiliated Hospital, Guiyang Medical College; First Affiliated Hospital, Yunnan University of Traditional Chinese Medicine; First Affiliated Hospital, Henan University of Traditional Chinese Medicine; Beijing Tiantan Hospital, Capital Medical University;West China Hospital, Sichuan University; Xiyuan Hospital, China Academy of Chinese Medical Sciences; Tangdu Hospital, Fourth Military Medical University; Sichuan Provincial Traditional Chinese Medicine Hospital; First Hospital of Jilin University; Third Affiliated Hospital, Zhongshan University; No. 1 Affiliated Hospital, Guangzhou University of Traditional Chinese Medicine; Xiangya School of Medicine, CSU |

Note: a The results of the phase II, III and IV clinical studies have not been previously published. b The number of cases was determined according to the minimum number of cases in the phase II, III and IV clinical studies, as specified by the State Food and Drug Administration.

**SUPPLEMENTAL TABLE 2** Incidence of study drug-related adverse events in the post-marketing (phase IV) study

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Adverse event** | **Number of cases (*N* = 3652)** | | | **Adverse event** | **Number of cases (*N* = 3652)** | | |
| **Frequency** | ***n*** | **Incidence(%)** | **Frequency** | ***n*** | **Incidence(%)** |
| **Examinations** | 18 | 16 | 0.44 | **Gastrointestinal diseases** | 22 | 16 | 0.44 |
| Elevated γ-glutamyl transferase | 2 | 2 | 0.05 | Flatulence | 1 | 1 | 0.03 |
| Increased alanine aminotransferase | 1 | 1 | 0.03 | Nausea | 6 | 6 | 0.16 |
| Prolonged partial thromboplastin time | 1 | 1 | 0.03 | Regurgitation | 1 | 1 | 0.03 |
| Increased liver enzymes | 1 | 1 | 0.03 | Diarrhea | 1 | 1 | 0.03 |
| Hematuria positive | 1 | 1 | 0.03 | Retching | 1 | 1 | 0.03 |
| Elevated aspartate transaminase | 1 | 1 | 0.03 | Dry mouth | 2 | 2 | 0.05 |
| Normal fibrin D-dimer | 1 | 1 | 0.03 | Vomiting | 6 | 6 | 0.16 |
| Elevated serum creatine phosphokinase MB | 1 | 1 | 0.03 | Projectile vomiting | 1 | 1 | 0.03 |
| Elevated serum creatine phosphokinase | 2 | 2 | 0.05 |  |  |  |  |
| Elevated blood urea | 1 | 1 | 0.03 | Epigastric discomfort | 3 | 2 | 0.06 |
| Elevated blood pressure | 6 | 6 | 0.16 |  |  |  |  |
| **Nervous system diseases** | 48 | 43 | 1.18 | **Musculoskeletal and connective tissue diseases** | 5 | 4 | 0.11 |
| Numbness | 1 | 1 | 0.03 | Rigidity | 1 | 1 | 0.03 |
| Cerebral infarction | 1 | 1 | 0.03 | Pain in the neck | 1 | 1 | 0.03 |
| Numbness of upper limb | 1 | 1 | 0.03 | General arthralgia | 1 | 1 | 0.03 |
| Drowsiness | 2 | 2 | 0.05 | Pain of upper limb | 1 | 1 | 0.03 |
| Head discomfort | 1 | 1 | 0.03 | Limb pain | 1 | 1 | 0.03 |
| Giddiness | 3 | 3 | 0.08 |  |  |  |  |
| Headache | 11 | 11 | 0.3 |  |  |  |  |
| Dizziness | 27 | 27 | 0.74 |  |  |  |  |
| Fullness of head | 1 | 1 | 0.03 |  |  |  |  |
| **Diseases of skin and subcutaneous tissue** | 57 | 46 | 1.26 | **Systemic disease and response at administration site** | 60 | 48 | 1.31 |
| Maculopapular rash | 3 | 3 | 0.08 | Fever | 2 | 2 | 0.05 |
| Idrosis | 1 | 1 | 0.03 | Tiredness | 12 | 12 | 0.33 |
| Allergic dermatitis | 1 | 1 | 0.03 | Facial tidal fever | 1 | 1 | 0.03 |
| Erythema | 7 | 6 | 0.16 | Fatigue | 1 | 1 | 0.03 |
| Local itching | 8 | 7 | 0.19 | Weariness | 1 | 1 | 0.03 |
| Facial redness | 1 | 1 | 0.03 | General pyrexia | 5 | 5 | 0.14 |
| Dryness of the skin | 1 | 1 | 0.03 | Erythema at infusion site | 5 | 3 | 0.08 |
| Dermatitis | 1 | 1 | 0.03 | Phlebitis at infusion site | 3 | 2 | 0.05 |
| Erythrasma | 15 | 15 | 0.41 | Discomfort of the chest | 1 | 1 | 0.03 |
| Papular erythrasma | 1 | 1 | 0.03 | Chest tightness | 8 | 8 | 0.22 |
| Erythrasma of human trunk | 1 | 1 | 0.03 | Blushing at injection site | 6 | 6 | 0.16 |
| General redness | 4 | 4 | 0.11 | Redness at injection site | 2 | 2 | 0.05 |
| Urticaria | 3 | 3 | 0.08 | Pyrexia at injection site | 7 | 7 | 0.19 |
| Pruritus | 10 | 10 | 0.27 | Pain at injection site | 6 | 6 | 0.16 |
| **Vascular and lymphatic diseases** | 69 | 69 | 1.89 | **Eye disorders** | 5 | 4 | 0.11 |
| Hypotension | 2 | 2 | 0.05 | Conjunctival hyperemia | 2 | 2 | 0.05 |
| Facial flushing | 63 | 63 | 1.73 | Conjunctival edema | 1 | 1 | 0.03 |
| Skin flushing | 3 | 3 | 0.08 | Clouded vision | 1 | 1 | 0.03 |
| Pruritus | 1 | 1 | 0.03 | Discomfort of the eyes | 1 | 1 | 0.03 |
| **Mental diseases** | 5 | 5 | 0.14 | **Cardiac diseases** | 9 | 9 | 0.25 |
| Anxiety | 2 | 2 | 0.05 | Coronary artery disease | 1 | 1 | 0.03 |
| Insomnia | 1 | 1 | 0.03 | Palpitations | 7 | 7 | 0.19 |
| Gastrointestinal somatization disorders | 1 | 1 | 0.03 | Sinus tachycardia | 1 | 1 | 0.03 |
| Excitatory state | 1 | 1 | 0.03 |  |  |  |  |
| **Immune system diseases** | 2 | 2 | 0.05 | **Respiratory system, thoracic and mediastinal diseases** | 1 | 1 | 0.03 |
| Erythrasma | 1 | 1 | 0.03 |
| Pruritus | 1 | 1 | 0.03 | Irritation of the throat | 1 | 1 | 0.03 |
| **Sum** | 301 | 189 | 5.18 |  |  |  |  |