Bioequivalence and safety evaluation of two preparations of metformin hydrochloride sustained-release tablets (Boke® and Glucophage®-XR) in healthy Chinese volunteers: a randomised phase I clinical trial

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Table S1. AE occurred in 3 participants who withdrew due to AE

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Serial number | The name of the AE | Relationship with drugs | Time of occurrence (after oral) | Duration | Severity (Level) | Value | Intervention | Reasons for withdrawal of participants |
| 1003 | Diarrhea | Possibly related | 6 h 6 min | 10 min | 1 | NA | No | AE did not return to normal or NCS before the 2nd period of administration. The participant did not meet the inclusion and exclusion criteria, and, thus, was withdrawn from the trial. |
| Alanine aminotransferase (↑) | Possibly related | 6 D 5 min | 14D 29min | 3 | 109→608→339→73→25 U/L | Oral silybin capsule 70 mg/tablet, tid |
| γ-glutamyl-transferase (↑) | Possibly related | 6 D 5 min | 14D 29min | 3 | 6→261→173→84→47 U/L (NCS) |
| Gallbladder silt stone | Unlikely related | 8 D 51 min | UK | NA | NA | No |
| Vaginitis | Unlikely related | 8D1h40min | UK | NA | NA | No |
| 1015 | Abdominal pain | Possibly related | 16 h 32min | 6 h | 1 | NA | No | The last blood sample for bilirubin exam was collected 1 h 13 min before administration of the 2nd period. Although the results returned to normal, the report was obtained after the scheduled time for the 2nd administration time, and, thus, the participant was withdrawn. |
| Diarrhea | Possibly related | 2D11h32min | 8 min | 1 | NA | No |
| Blood bilirubin ↑ | Possibly related | 2 D | 4D22h 47min | 2 | Screen time 23.4 (NCS) → P1: 25.1 → 27.8 → 31.1 → 35 → 23.7 umol/L (NCS) | No |
| Blood unbound bilirubin (↑) | Possibly related | 2 D | 4D 8h  26min | 2 | Screen time 7.5 (NCS) → P1:8.2 →9.0→ 8.0 → 11.2 → 7.9 umol/L (NCS) | No |
| Conjugated bilirubin (↑) | Possibly related | 2 D | 3D22h 47min | 2 | Screen time15.9(NCS)→P1:16.9→18.8→23.1 →23.8→15.8 umol/L (NCS) | No |
| Urine ketone bodies (+) | Possibly related | 2D 17min | 4D10h 45min | 1 | 1+→1+→3+→1+→- | No |
| Blood unbound bilirubin (↑) | Blood unbound bilirubin (↑) | Possibly related | 2 h 54 min | 10 min | 1 | NA | No | The participant was withdrawn from the 2nd period of the trial because of not meeting the inclusion and exclusion criteria due to drug use. |
| Blood unbound bilirubin (↑) | Possibly related | 6D20h44min | 2D 3h5min | 2 | White blood cell 12.46×109/L CS; Review 4.40 Normal  Blood lymphocyte percentage (LY%) 7.3% CS; Review 42.0% normal  Blood monocytes (MO#) 1.1×109/L CS; Review 0.48 normal  Blood neutrophils (NE#) 10.4×109/L CS; Review 2.0 Normal | 2017-12-13: Oral volavol (cefuroxime axetil tablets) 0.5G bid  2017-12-13~14: Oral Tylenol (acetaminophen sustained release tablet) 0.65g  2017-12-13~14: Oral cefdinir dispersible tablets 0.1g 3 times/day  2017-12-13~14: Oral vitamin C yinqiao tablets 2 tablets tid  2017-12-13~14: Oral lotus Qingwen capsule 4 tablets tid |
| Blood unbound bilirubin (↑) | Possibly related | 2 D | 2D23h 19min | 1 | 8.8→6.8 μmol/L | No |

Table S2. Detail of all adverse events during the trail

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Serial number | Time of administration | Adverse events | Severity | Date and time of occurrence/end | Drug | Relationship with drugs |
| 1003 | 2017-12-06 08:04 | Diarrhea | 1 | 2017-12-06 14:10/2017-12-06 14:20 | R | probably related |
| 2017-12-06 08:04 | Alanine aminotransferase (↑) | 3 | 2017-12-12 08:09/2017-12-26 08:38 | R | probably related |
| 2017-12-06 08:04 | γ-glutamyl-transferase (↑) | 3 | 2017-12-12 08:09/2017-12-26 08:38 | R | probably related |
| 2017-12-06 08:04 | Gallbladder silt stone | 1 | 2017-12-14 08:55/ UK | R | unlikely related |
| 2017-12-06 08:04 | Vaginitis | 1 | 2017-12-14 09:44/ UK | R | unlikely related |
| 1004 | 2017-12-13 08:06 | Hypertriglyceridemia | 1 | 2017-12-15 08:06/2017-12-18 08:20 | R | probably related |
| 1006 | 2017-12-06 08:10 | Blood unbound bilirubin (↑) | 1 | 2017-12-08 08:10/2017-12-11 08:33 | R | probably related |
| 2017-12-13 08:10 | Blood bilirubin (↑) | 1 | 2017-12-15 08:10/2017-12-18 08:02 | T | probably related |
| 2017-12-13 08:10 | Blood unbound bilirubin (↑) | 1 | 2017-12-15 08:10/2017-12-18 08:02 | T | probably related |
| 2017-12-13 08:10 | Conjugated bilirubin (↑) | 1 | 2017-12-15 08:10/2017-12-18 08:02 | T | probably related |
| 1008 | 2017-12-06 08:14 | Hypertriglyceridemia | 1 | 2017-12-08 08:14/2017-12-11 08:35 | R | probably related |
| 2017-12-06 08:14 | Serum creatine phosphokinase (↑) | 1 | 2017-12-08 08:14/2017-12-11 08:35 | R | probably related |
| 1009 | 2017-12-06 08:16 | Hyperuricemia | 1 | 2017-12-08 08:16/2017-12-11 08:36 | R | probably related |
| 1015 | 2017-12-06 08:28 | Abdominal pain | 1 | 2017-12-07 01:00/2017-12-10 07:00 | T | probably related |
| 2017-12-06 08:28 | Diarrhea | 1 | 2017-12-08 20:00/2017-12-08 20:08 | T | probably related |
| 2017-12-06 08:28 | Blood bilirubin (↑) | 2 | 2017-12-08 08:28/2017-12-13 07:15 | T | probably related |
| 2017-12-06 08:28 | Blood unbound bilirubin (↑) | 2 | 2017-12-08 08:28/2017-12-12 16:54 | T | probably related |
| 2017-12-06 08:28 | Conjugated bilirubin (↑) | 2 | 2017-12-08 08:28/2017-12-13 07:15 | T | probably related |
| 2017-12-06 08:28 | Urine ketone bodies (+) | 1 | 2017-12-08 08:45/2017-12-12 19:30 | T | probably related |
| 1016 | 2017-12-06 08:30 | Diarrhea | 1 | 2017-12-10 15:00/2017-12-10 15:10 | R | probably related |
| 2017-12-13 08:30 | Abdominal pain | 1 | 2017-12-13 18:58/2017-12-13 20:10 | T | probably related |
| 2017-12-13 08:30 | Diarrhea | 1 | 2017-12-13 19:58/2017-12-13 20:10 | T | probably related |
| 1017 | 2017-12-06 08:32 | Diarrhea | 1 | 2017-12-06 14:35/2017-12-06 14:38 | T | probably related |
| 2017-12-06 08:32 | Blood in the urine | 1 | 2017-12-08 08:13/2017-12-12 09:26 | T | probably related |
| 1027 | 2017-12-06 08:52 | Hyperuricemia | 1 | 2017-12-08 08:52/2017-12-11 08:38 | T | probably related |
| 1029 | 2017-12-06 08:56 | Diarrhea | 1 | 2017-12-06 13:21/2017-12-06 13:27 | R | probably related |
| 1033 | 2017-12-06 09:04 | Hypertriglyceridemia | 1 | 2017-12-08 09:04/2017-12-11 08:41 | R | probably related |
| 1034 | 2017-12-06 09:06 | Hypertriglyceridemia | 2 | 2017-12-08 09:06/2017-12-11 08:43 | T | probably related |
| 1035 | 2017-12-13 09:08 | Blood unbound bilirubin (↑) | 1 | 207-12-15/09:08 - 2017-12-18/08:05 | R | probably related |
| 1036 | 2017-12-13 09:10 | Blood unbound bilirubin (↑) | 2 | 2017-12-15 09:10/2018-01-12 11:15 | T | probably related |
| 2017-12-13 09:10 | Conjugated bilirubin (↑) | 2 | 2017-12-15 09:10/2018-01-12 11:15 | T | probably related |
| 2017-12-13 09:10 | Blood bilirubin (↑) | 2 | 2017-12-15 09:10/2018-01-12 11:15 | T | probably related |
| 2017-12-13 09:10 | Upper respiratory tract infection | 3 | 2018-01-01 15:00/2018-01-07 11:00 | T | unlikely related |
| 1040 | 2017-12-13 09:18 | Neutrophil count (↑) | 1 | 2017-12-15 14:05/2017-12-18 09:41 | R | probably related |
| 1043 | 2017-12-13 09:24 | Upper respiratory tract infection | 1 | 2017-12-15 07:00/2017-12-20 08:50 | T | probably related |
| 1044 | 2017-12-06 09:26 | Abdominal pain | 1 | 2017-12-06 12:20/2017-12-06 12:30 | T | probably related |
| 2017-12-06 09:26 | Upper respiratory tract infection | 2 | 2017-12-13 06:10/2017-12-15 09:15 | T | probably related |
| 2017-12-06 09:26 | Blood unbound bilirubin (↑) | 1 | 2017-12-08 09:26/2017-12-11 08:45 | T | probably related |
| 1046 | 2017-12-13 09:30 | Abdominal distension | 1 | 2017-12-13 11:30/2017-12-13 13:58 | R | probably related |
| 1047 | 2017-12-06 09:32 | Hyperuricemia | 1 | 2017-12-08 09:32/2017-12-12 16:48 | T | probably related |
| 2017-12-13 09:32 | Hyperuricemia | 1 | 2017-12-15 09:32/2017-12-18 08:07 | R | probably related |

Drug specifications of Boke®



