**Title:** Effect of BI 1358894 on cholecystokinin-tetrapeptide (CCK-4)–induced anxiety, panic symptoms, and stress biomarkers: a Phase I randomized trial in healthy males

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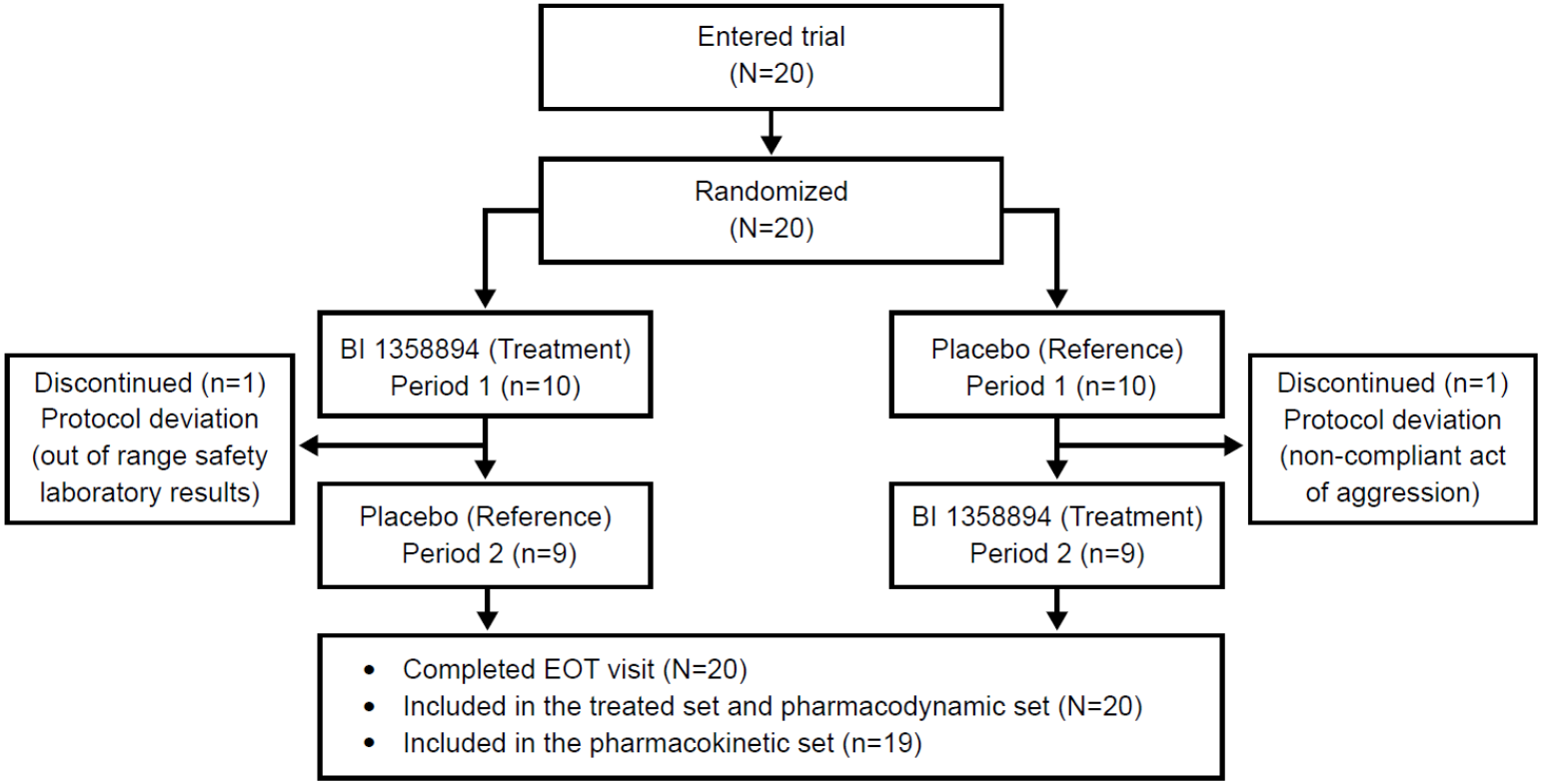
**Online Resources**

**Online Resource 1: Participant disposition.**




EOT, end of treatment.

**Online Resource 2: Participant demographic data.**

| **Subjects** | **N (%)** |
|---|---|
| Treated | 20 (100) |
| Male | 20 (100) |
| Ethnicity | |
| American Indian or Alaskan Native | 1 (5) |
| Asian | 1 (5) |
| Black or African American | 1 (5) |
| Hispanic/Latino | 1 (5) |
| White | 16 (80) |
| Smoking | |
| Smoker | 4 (20) |
| Former smoker | 5 (25) |
| Never smoked | 11 (55) |
| Mean age (SD; years) | 26.7 (9.5) |
| Mean body mass index (SD; $kg/m^2$) | 23.0 (2.8) |

SD, standard deviation.

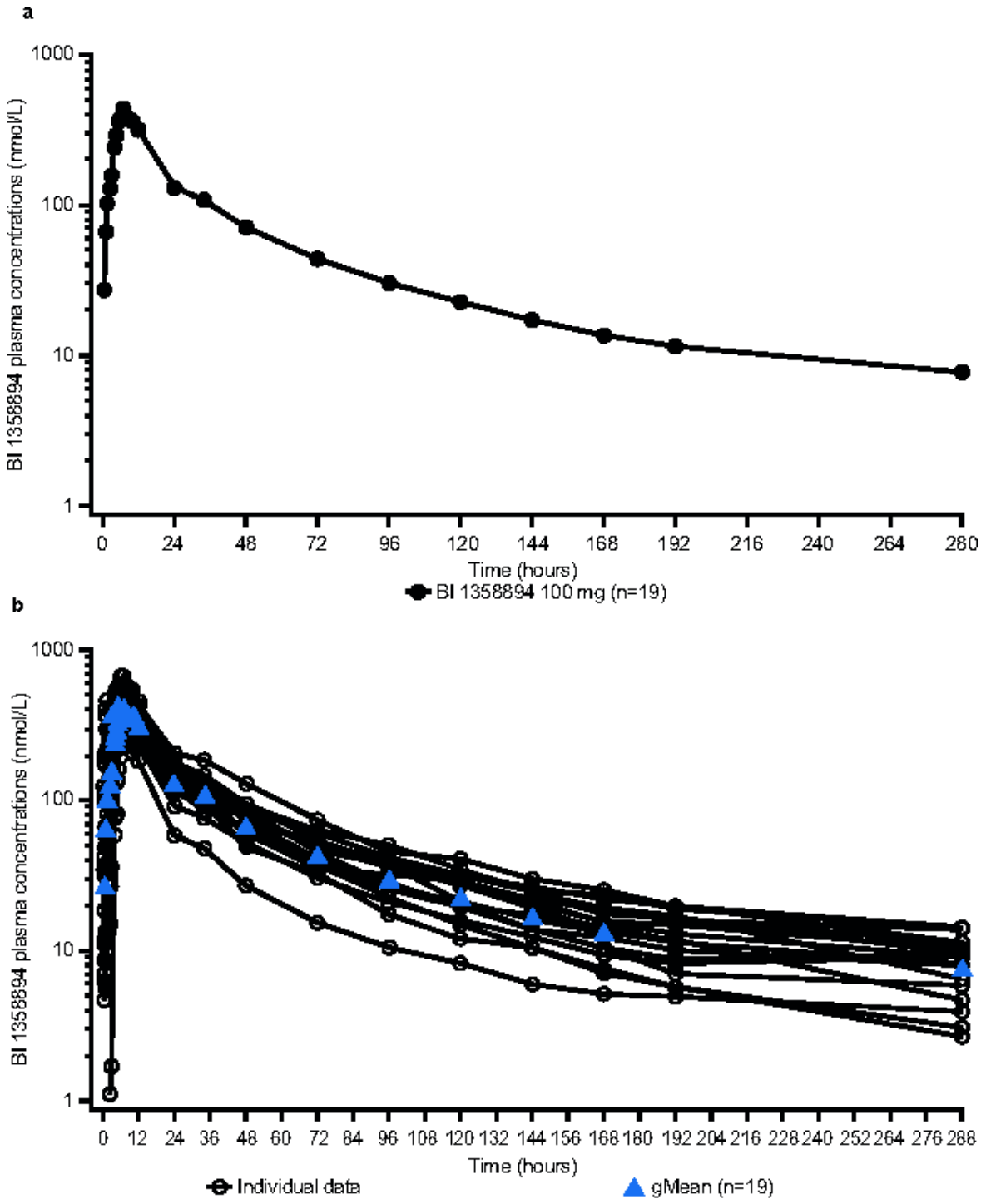
**Online Resource 3: Summary of PSS and EVAS pharmacodynamic parameters.**

| Endpoint | Placebo (N=19) | | BI 1358894 (N=19) | |
|---|---|---|---|---|
| | Mean | SD | Mean | SD |
| PSS sum intensity score | | | | |
| $E_{base}$ | 0.21 | 0.42 | 0.26 | 0.56 |
| $E_{max}$ | 30.40 | 12.40 | 22.20 | 12.40 |
| $AUEC_{4.75\text{-}5.5}$ (h) | 6.99 | 2.95 | 5.35 | 3.11 |
| $t_{max}$ (h)[a] | 5.08 | 5.08–5.08 | 5.08 | 5.08–5.08 |
| Change from baseline of PSS sum intensity score | | | | |
| $AUEC_{4.75\text{-}5.5}$ (h) | 6.84 | 2.98 | 5.15 | 3.05 |
| $t_{max}$ (h)[a] | 5.08 | 5.08–5.08 | 5.08 | 5.08–5.08 |
| PSS total number of symptoms[b] | | | | |
| $E_{base}$ | 0.21 | 0.42 | 0.26 | 0.56 |
| $E_{max}$ | 12.60 | 3.37 | 11.00 | 3.54 |
| $AUEC_{4.75\text{-}5.5}$ (h) | 3.22 | 1.05 | 2.97 | 1.21 |
| $t_{max}$ (h)[a] | 5.08 | 5.08–5.08 | 5.08 | 5.08–5.08 |
| Change from baseline in PSS total number of symptoms[b] | | | | |
| $E_{max}$ | 12.40 | 3.30 | 10.70 | 3.45 |
| $AUEC_{4.75\text{-}5.5}$ (h) | 3.06 | 1.03 | 2.77 | 1.18 |
| $t_{max}$ (h)[a] | 5.08 | 5.08–5.08 | 5.08 | 5.08–5.08 |
| EVAS score | | | | |
| $E_{base}$ (mm) | 5.21 | 6.48 | 5.79 | 7.61 |
| $E_{max}$ (mm) | 72.40 | 12.60 | 58.50 | 19.80 |
| $AUEC_{4.75\text{-}5.5}$ (h·mm) | 19.50 | 4.30 | 17.80 | 6.59 |
| $t_{max}$ (h)[a] | 5.08 | 5.08–5.08 | 5.08 | 5.08–5.08 |
| Change from baseline in EVAS score | | | | |
| $E_{max}$ (mm) | 67.20 | 13.60 | 52.70 | 20.00 |
| $AUEC_{4.75\text{-}5.5}$ (h·mm) | 15.60 | 4.13 | 13.50 | 5.58 |
| $t_{max}$ (h)[a] | 5.08 | 5.08–5.08 | 5.08 | 5.08–5.08 |

[a]Median and range (minimum–maximum) are displayed instead of mean and SD.
[b]Number of symptoms rated ≥1 (i.e., not absent).

$AUEC_{4.75-5.5}$, area under the concentration-time curve of the analyte in plasma over the time interval 4:45 h to 5:30 h; CI, confidence interval; $E_{base}$, baseline score (4:45 h); $E_{max}$, maximum PSS/EVAS score, number of symptoms or change from baseline; EVAS, emotional faces visual analog scale; PSS, Panic Symptom Scale; $t_{max}$, time from dosing to maximum PSS/EVAS score, number of symptoms or change from baseline.

**Online Resource 4:** (a) Geometric mean plasma concentration-time profiles of BI 1358894 after a single oral administration of BI 1358894 100 mg (semi-log scale) and (b) Individual and geometric mean plasma concentration-time profiles of BI 1358894 after a single oral administration of BI 1358894 100 mg (semi-log scale).



**Online Resource 5:** Pharmacokinetic parameters of BI 1358894 in plasma following a single oral administration of 100 mg BI 1358894.

| | BI 1358894 (N=19) | |
|---|---|---|
| | gMean | gCV (%) |
| $AUC_{0\text{-}tz}$ [h·nmol/L] | 13,700 | 23.0 |
| $AUC0_{\text{-}\infty}$ [h·nmol/L] | 15,000 | 23.7 |
| $\%AUC_{tz\text{-}\infty}$ [%] | 7.5 | 59.6 |
| $AUC_{4.75\text{-}5.5}$ [h·nmol/L] | 248.0 | 39.0 |
| $C_{max}$ [nmol/L] | 469 | 20.1 |
| $t_{max}$ [h][a] | 7.0 | 1.5–12.0 |
| $t_{½}$ [h] | 112.0 | 23.7 |
| $MRT_{ex}$ | 89.0 | 28.7 |
| CL/F [mL/min] | 212.0 | 23.7 |
| $V_z$/F [L] | 2,050 | 32.9 |

[a]Median and range (minimum–maximum) are displayed instead of gMean and gCV (%).

$AUC_{0\text{-}tz,}$ Area under the concentration-time curve of the analyte in plasma over the time interval from zero to the last quantifiable data point; $AUC_{0\text{-}\infty}$, area under the concentration-time curve from zero to infinity; $\%AUC_{tz\text{-}\infty,}$ percentage $AUC_{tz\text{-}\infty}$; $AUEC_{4.75\text{-}5.5}$, area under the concentration-time curve of the analyte in plasma over the time interval 4:45 h to 5:30 h; CL/F, apparent clearance of the analyte in the plasma after extravascular administration; $C_{max}$, maximum measured concentration of the analyte in plasma; $MRT_{ex}$, mean residence time of the analyte in the body to excretion; $t_{max}$, time to maximum concentration; $t_{½}$, half-life; $V_z$/F, apparent volume of distribution during the terminal phase after extravascular administration.

**Online Resource 6:** Overall summary of participants with TEAEs[a].

| | Placebo N (%) | BI 1358894 N (%) | Total on-treatment N (%) |
|---|---|---|---|
| Number of subjects | 19 (100) | 19 (100) | 20 (100) |
| Any AE | 10 (52.6) | 14 (73.7) | 19 (95.0) |
| Drug-related AEs[b] | 5 (26.3) | 11 (57.9) | 13 (65.0) |
| Other significant AEs[c] | 0 | 0 | 0 |
| AEs leading to discontinuation of trial medication | 0 | 0 | 0 |
| AEs of severe intensity | 0 | 0 | 0 |
| AESIs | 0 | 0 | 0 |
| SAEs | 0 | 0 | 0 |

[a]A participant may be counted in more than one category. [b]The investigator assessed the possible causal relationship between an AE and the trial medication. [c]According to European Medicines Agency ICH E3. AE, adverse event; AESI, adverse event of special interest; SAE, severe adverse event; TEAE, treatment emergent adverse event.