# Corticotropin-Releasing Factor Type 1 Receptor Antagonism Is Ineffective for Women with Posttraumatic Stress Disorder

## *Supplemental Information*

## SUPPLEMENTARY TEXT

DNA extraction and genotyping

DNA isolation from whole EDTA blood was performed with a magnetic bead based technology using the PerkinElmer Chemagic 360 extraction robot. Quality and quantity of the extracted DNA was assessed using the Epoch Microplate Spectrophotometer (BioTek). We excluded relatives of individual subjects from the whole sample (n = 3, Pi_Hat ≥ 0.0625) based on mean identity by descent in PLINK (1). For the genome wide analyses referring the population stratification, we only included individuals with a sample-wise call rate ≥ 0.98 and SNPs with call rate ≥ 0.98, Hardy Weinberg equilibrium test (HWE) p-value ≥ $1\times10^{-5}$ and MAF ≥ 0.05, allowing for a total of 575,455 markers in 86 individuals. To correct for population stratification in an ethnically mixed sample, principal components (PC) for genetic background were calculated from all genotypes for each of the individuals using Genome-wide Complex Trait Analysis (**Figure S8**).

# SUPPLEMENTARY TABLES

## Table S1. CONSORT Checklist

| Section/Topic | Item No | Checklist item | Reported on page No. |
|---|---|---|---|
| **Title and abstract** | | | |
| | 1a | Identification as a randomised trial in the title | Prevented by character limit |
| | 1b | Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts) | 2-3 |
| **Introduction** | | | |
| Background and objectives | 2a | Scientific background and explanation of rationale | 4-6 |
| | 2b | Specific objectives or hypotheses | 5-6 |
| **Methods** | | | |
| Trial design | 3a | Description of trial design (such as parallel, factorial) including allocation ratio | 6 |
| | 3b | Important changes to methods after trial commencement (such as eligibility criteria), with reasons | n/a |
| Participants | 4a | Eligibility criteria for participants | 6-7 |
| | 4b | Settings and locations where the data were collected | 6 |
| Interventions | 5 | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered | 7 |
| Outcomes | 6a | Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed | 8-9 |
| | 6b | Any changes to trial outcomes after the trial commenced, with reasons | n/a |

| | | | |
|---|---|---|---|
| Sample size | 7a | How sample size was determined | Ref. 34 |
| | 7b | When applicable, explanation of any interim analyses and stopping guidelines | n/a |
| Randomisation: | | | |
| Sequence generation | 8a | Method used to generate the random allocation sequence | 7 |
| | 8b | Type of randomisation; details of any restriction (such as blocking and block size) | 7 |
| Allocation concealment mechanism | 9 | Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned | 7 |
| Implementation | 10 | Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions | 7 |
| Blinding | 11a | If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how | 7 |
| | 11b | If relevant, description of the similarity of interventions | n/a |
| Statistical methods | 12a | Statistical methods used to compare groups for primary and secondary outcomes | 8-9 |
| | 12b | Methods for additional analyses, such as subgroup analyses and adjusted analyses | 9 |
| **Results** | | | |
| Participant flow (a diagram is strongly recommended) | 13a | For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome | 10 |
| | 13b | For each group, losses and exclusions after randomisation, together with reasons | Fig S1 |
| Recruitment | 14a | Dates defining the periods of recruitment and follow-up | 6 |
| | 14b | Why the trial ended or was stopped | n/a |
| Baseline data | 15 | A table showing baseline demographic and clinical characteristics for each group | 27 |

| | | | |
|---|---|---|---|
| Numbers analysed | 16 | For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups | 10 |
| Outcomes and estimation | 17a | For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval) | 10-11 |
| | 17b | For binary outcomes, presentation of both absolute and relative effect sizes is recommended | 10 |
| Ancillary analyses | 18 | Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory | 11-13 |
| Harms | 19 | All important harms or unintended effects in each group (for specific guidance see CONSORT for harms) | 13, Tables S3,S4 |
| **Discussion** | | | |
| Limitations | 20 | Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses | 14-17 |
| Generalisability | 21 | Generalisability (external validity, applicability) of the trial findings | 14-17 |
| Interpretation | 22 | Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence | 14-17 |
| **Other information** | | | |
| Registration | 23 | Registration number and name of trial registry | 6 |
| Protocol | 24 | Where the full trial protocol can be accessed, if available | 6 |
| Funding | 25 | Sources of funding and other support (such as supply of drugs), role of funders | 17-18 |

**Table S2. Ethnicity and allele frequency of CRF1 SNP rs110402**

| Race | GG | AG/AA | Total |
|---|---|---|---|
| White | 18 | 33 | 51 |
| Black | 14 | 14 | 28 |
| Other | 1 | 6 | 7 |
| **Total** | 33 | 53 | 86 |

**Table S3. Spontaneously reported adverse events**

| Adverse Event | GSK561679 | Placebo | Total |
|---|---|---|---|
| Headache | 25 | 24 | 49 |
| Nausea | 19 | 11 | 30 |
| Insomnia | 6 | 11 | 17 |
| Diarrhea | 6 | 9 | 15 |
| Upper Resp. Tract Infection | 8 | 7 | 15 |
| Sedation | 5 | 8 | 13 |
| Dizziness | 7 | 4 | 11 |
| Rash | 2 | 8 | 10 |
| Vomiting | 4 | 6 | 10 |
| Dyspepsia | 4 | 5 | 9 |
| Constipation | 2 | 5 | 7 |
| Dry Mouth | 5 | 2 | 7 |
| Irritability | 3 | 4 | 7 |
| Pruritis | 4 | 3 | 7 |
| Abdominal Pain | 1 | 5 | 6 |
| Arthralgia | 5 | 1 | 6 |
| Cough | 2 | 4 | 6 |
| Depression Worsening | 2 | 3 | 5 |
| Neck Pain | 3 | 2 | 5 |
| Rhinitis Allergic | 2 | 3 | 5 |
| Sinusitis | 1 | 4 | 5 |
| Vision Blurred | 2 | 3 | 5 |
| Contusion | 0 | 4 | 4 |
| Disturbance in Attention | 1 | 3 | 4 |
| Hypersensitivity | 1 | 3 | 4 |
| Migraine | 3 | 1 | 4 |
| Muscle spasm | 1 | 3 | 4 |
| Myalgia | 1 | 3 | 4 |
| Palpitations | 2 | 2 | 4 |
| Abdominal Distension | 0 | 3 | 3 |
| Flatulence | 0 | 3 | 3 |
| Hot Flush | 0 | 3 | 3 |
| Non-Cardiac Chest Pain | 0 | 3 | 3 |
| Oropharyngeal Pain | 0 | 3 | 3 |
| Tinnitus | 3 | 0 | 3 |

All $p > .05$

**Table S4. Patient Rated Inventory of Side Effects (PRISE) symptom counts**

| Symptom | Placebo n (%) | GSK561679 n (%) | p-value |
|---|---|---|---|
| Anxiety | 50 (77) | 54 (86) | p < 0.29 |
| Blurred Vision | 21 (32) | 15 (24) | p < 0.38 |
| Chest Pain | 13 (2) | 9 (14) | p < 0.53 |
| Constipation | 16 (25) | 17 (27) | p < 0.92 |
| Decreased Energy | 54 (83) | 51 (81) | p < 0.93 |
| Diarrhea | 20 (31) | 22 (35) | p < 0.62 |
| Difficulty Sleeping | 59 (91) | 58 (92) | p < 0.99 |
| Difficulty Urinating | 1 (2) | 0 (0) | p < 0.99 |
| Dizziness | 31 (47) | 24 (38) | p < 0.27 |
| Dizziness on Standing | 23 (35) | 19 (3) | p < 0.66 |
| Dry Mouth | 22 (34) | 22 (35) | p > 0.99 |
| Dry Skin | 29 (45) | 25 (4) | p < 0.70 |
| Fatigue | 55 (85) | 47 (75) | p < 0.15 |
| Frequent Urination | 21 (32) | 16 (25) | p < 0.50 |
| General Malaise | 25 (38) | 22 (35) | p < 0.82 |
| Headache | 51 (78) | 45 (71) | p < 0.47 |
| Blurred Vision | 21 (32) | 15 (24) | p < 0.38 |
| Chest Pain | 13 (2) | 9 (14) | p < 0.53 |
| Constipation | 16 (25) | 17 (27) | p < 0.92 |
| Decreased Energy | 54 (83) | 51 (81) | p < 0.93 |
| Diarrhea | 20 (31) | 22 (35) | p < 0.62 |
| Difficulty Sleeping | 59 (91) | 58 (92) | p < 0.99 |
| Difficulty Urinating | 1 (2) | 0 (0) | p < 0.99 |
| Increased Perspiration | 19 (29) | 13 (21) | p < 0.36 |
| Itching | 28 (43) | 27 (43) | p > 0.99 |
| Loss of Sexual Desire | 28 (43) | 32 (51) | p < 0.49 |
| Menstrual Irregularity | 11 (17) | 9 (14) | p < 0.87 |
| Nausea/Vomiting | 26 (4) | 28 (44) | p < 0.74 |
| Painful Urination | 6 (9) | 1 (2) | p < 0.11 |
| Palpitation | 18 (28) | 20 (32) | p < 0.76 |
| Poor Concentration | 53 (82) | 53 (84) | p < 0.88 |
| Poor Coordination | 16 (25) | 17 (27) | p < 0.76 |
| Rash | 9 (14) | 8 (13) | p > 0.99 |
| Restlessness | 42 (65) | 40 (63) | p > 0.99 |
| Ringing in Ears | 18 (28) | 15 (24) | p < 0.76 |
| Sleeping Too Much | 19 (29) | 11 (17) | p < 0.17 |
| Tremors | 11 (17) | 2 (3) | **p < 0.02** |
| Trouble Achieving Orgasm | 11 (17) | 7 (11) | p < 0.45 |

Bolded value is p<.05

## SUPPLEMENTARY FIGURES

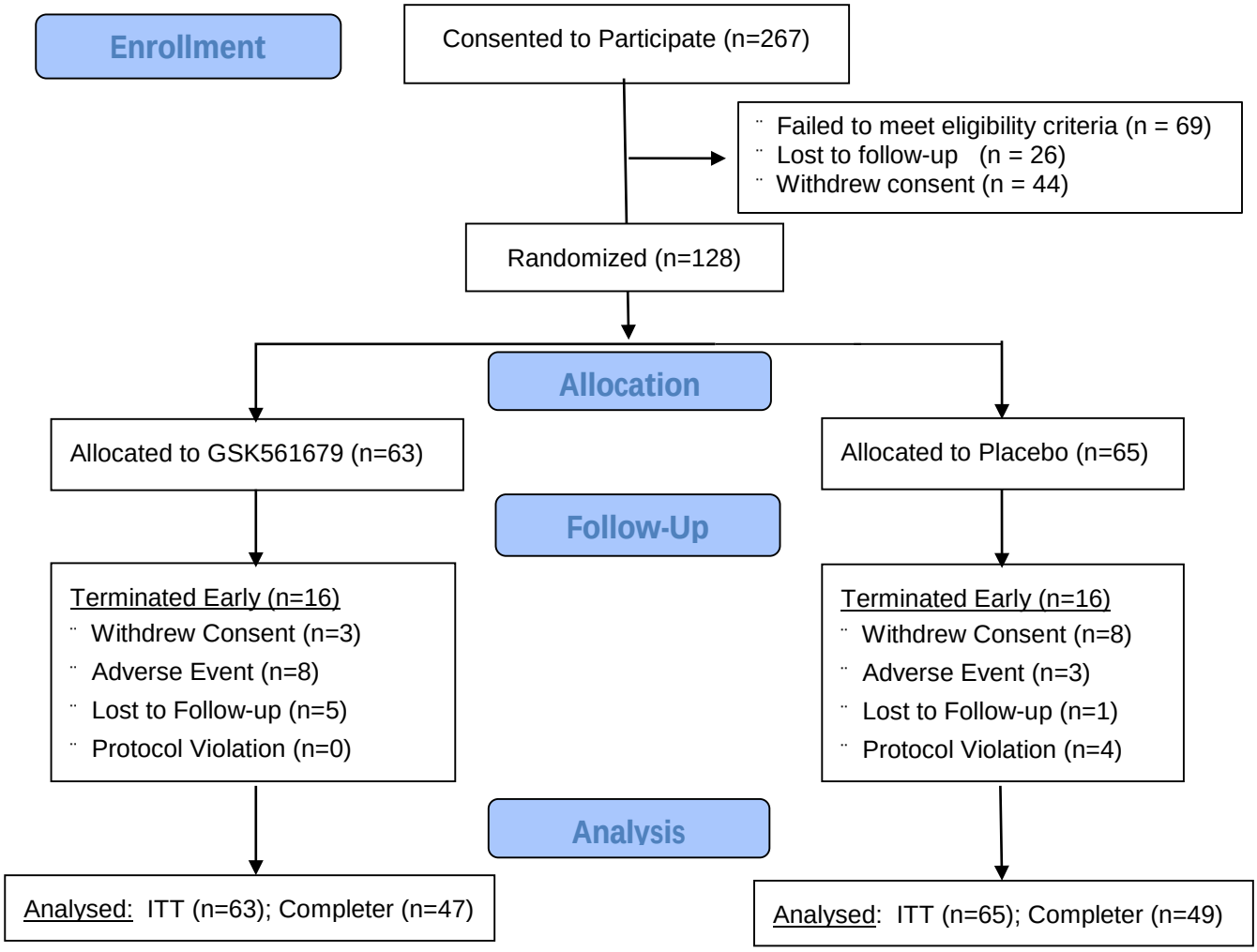


**Figure S1: CONSORT flow diagram**

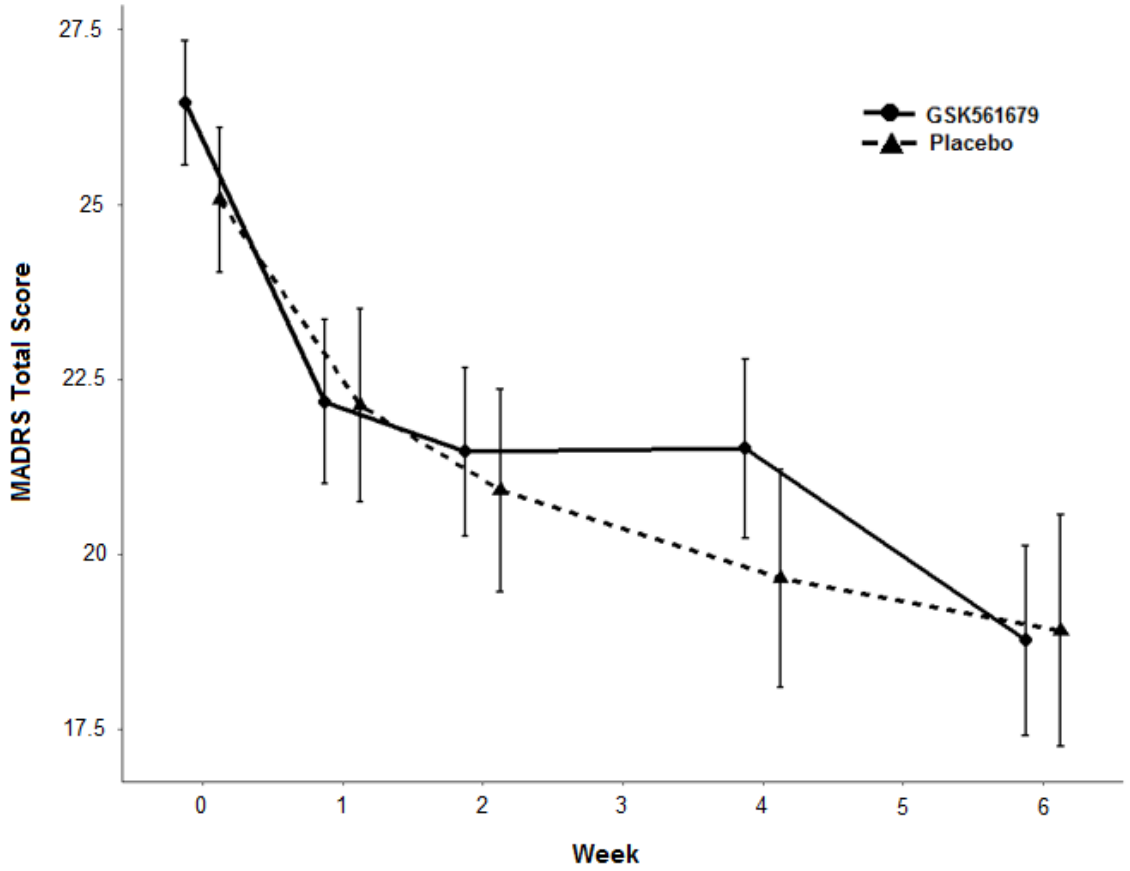


**Figure S2: Change in MADRS scores over time**

S.E. bars represent ± 1 S.E.

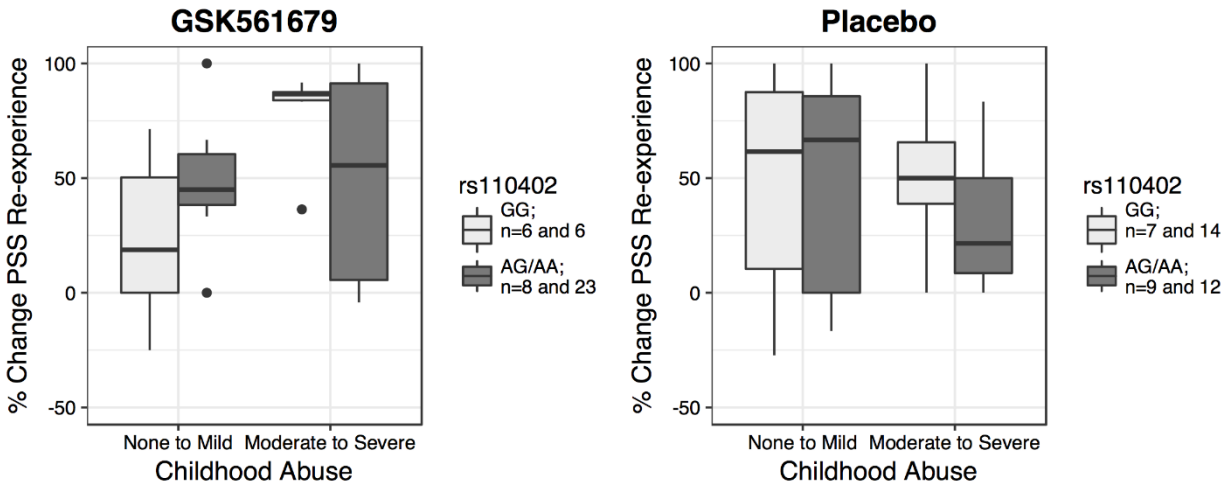


**Figure S3: Significant interaction effect of rs110402 and childhood abuse on percent change in PSS re-experiencing score**

The boxplots describe the mean % change of PSS re-experiencing score in abused and non-abused patients treated with GSK561679 or placebo. GG carriers are shown in light grey and AA/AG in dark grey. Black dots indicate outliers. rs110402 A carrier status by childhood abuse exposure showed a significant interaction effect on PSS re-experiencing score % change over treatment in subjects treated with GSK561679 (-ß=-2.472; p=0.006) but not in subjects treated with placebo (ß=-0.075; p=0.92). rs110402 GG carriers exposed to child abuse displayed the highest % change of PSS symptoms following GSK561679 treatment.

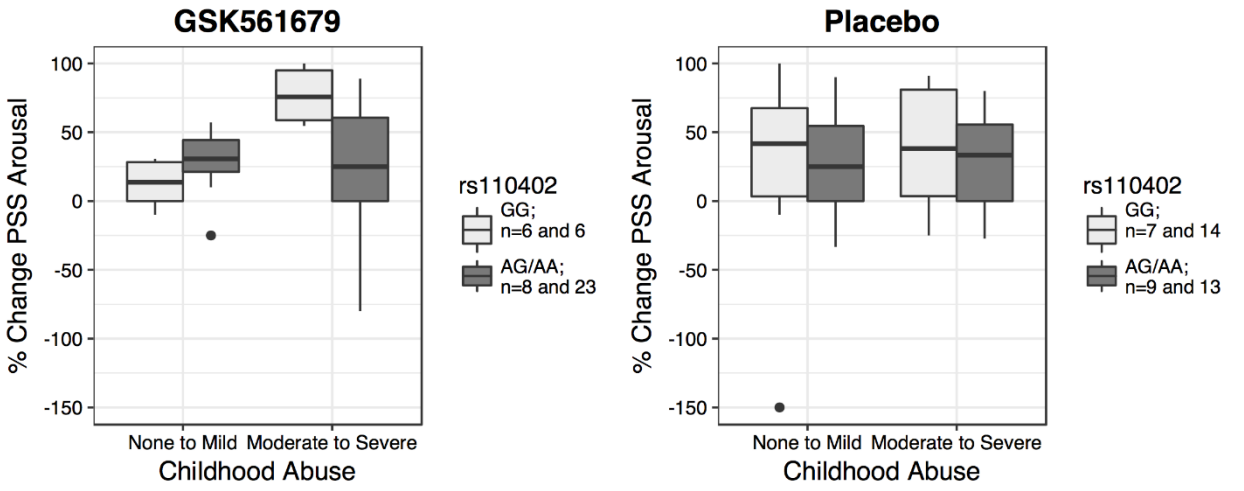


**Figure S4: Significant interaction effect of rs110402 and childhood abuse on percent change in PSS arousal score**

The boxplots describe the mean % change of PSS arousal score in abused and non-abused patients treated with GSK561679 or placebo. GG carriers are shown in light grey and AA/AG in dark grey. Black dots indicate outliers. rs110402 A carrier status by childhood abuse exposure showed a significant interaction effect on PSS arousal score % change over treatment in subjects treated with the GSK561679 (ß=-2.034; p= 0.019) but not in subjects treated with placebo (ß=0.054; p=0.94). rs110402 GG carriers exposed to child abuse displayed the highest % change of PSS symptoms following GSK561679 treatment.

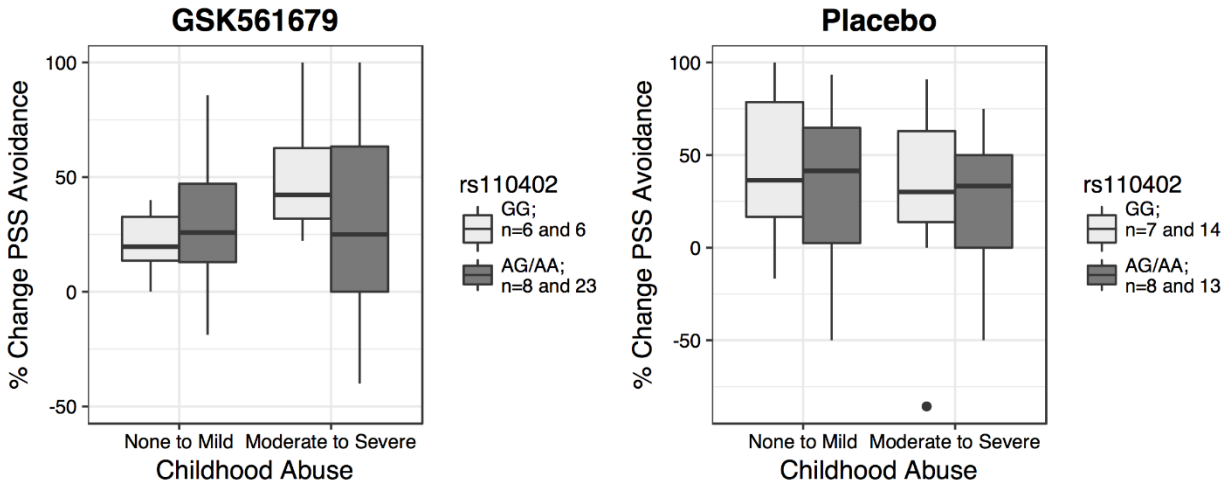


**Figure S5: Lack of interaction effect of rs110402 and childhood abuse on percent change in PSS avoidance score**

The boxplots describe the mean % change of PSS avoidance score in abused and non-abused patients treated with GSK561679 or placebo. GG carriers are shown in light grey and AA/AG in dark grey. Black dots indicate outliers. rs110402 A carrier status by childhood abuse exposure showed no significant interaction effect on PSS avoidance score % change over treatment in subjects treated with either GSK561679 (ß=-0.945; p=0.36) or placebo (ß=0.565; p=0.44).

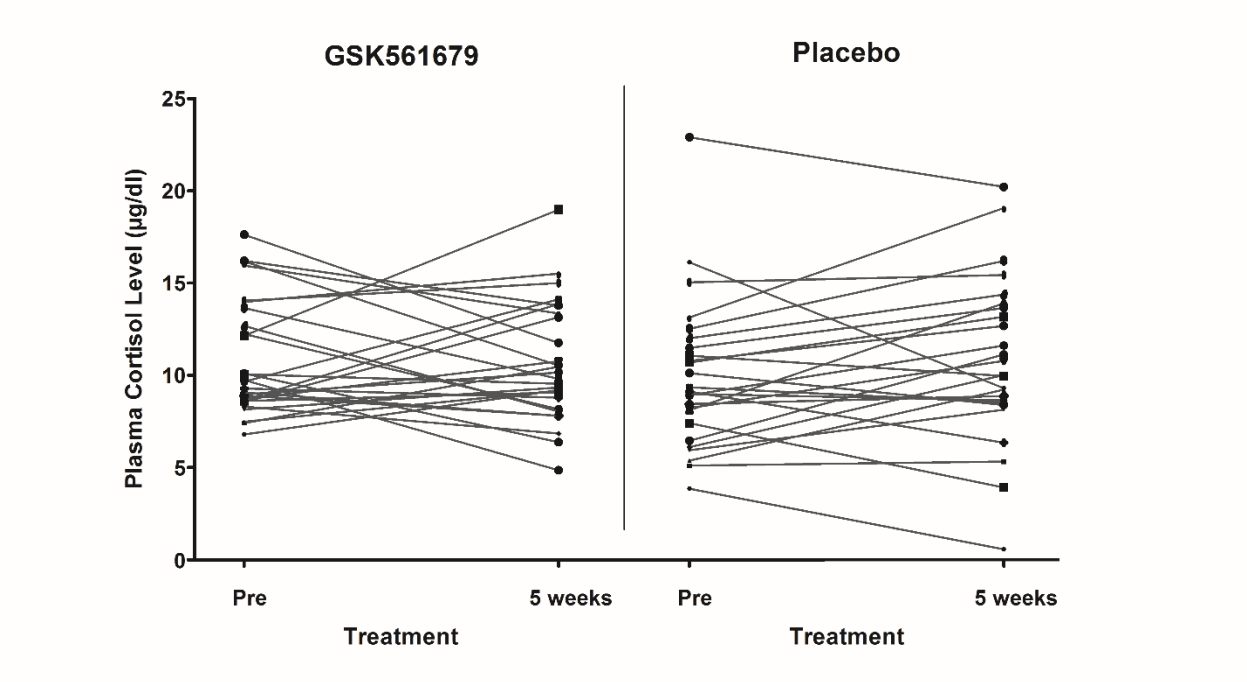


**Figure S6. Lack of effect of GSK561679 and placebo on morning cortisol**

Non-significant change in morning cortisol from baseline to week 5 between patients treated with GSK561679 or placebo ($p<.05$).

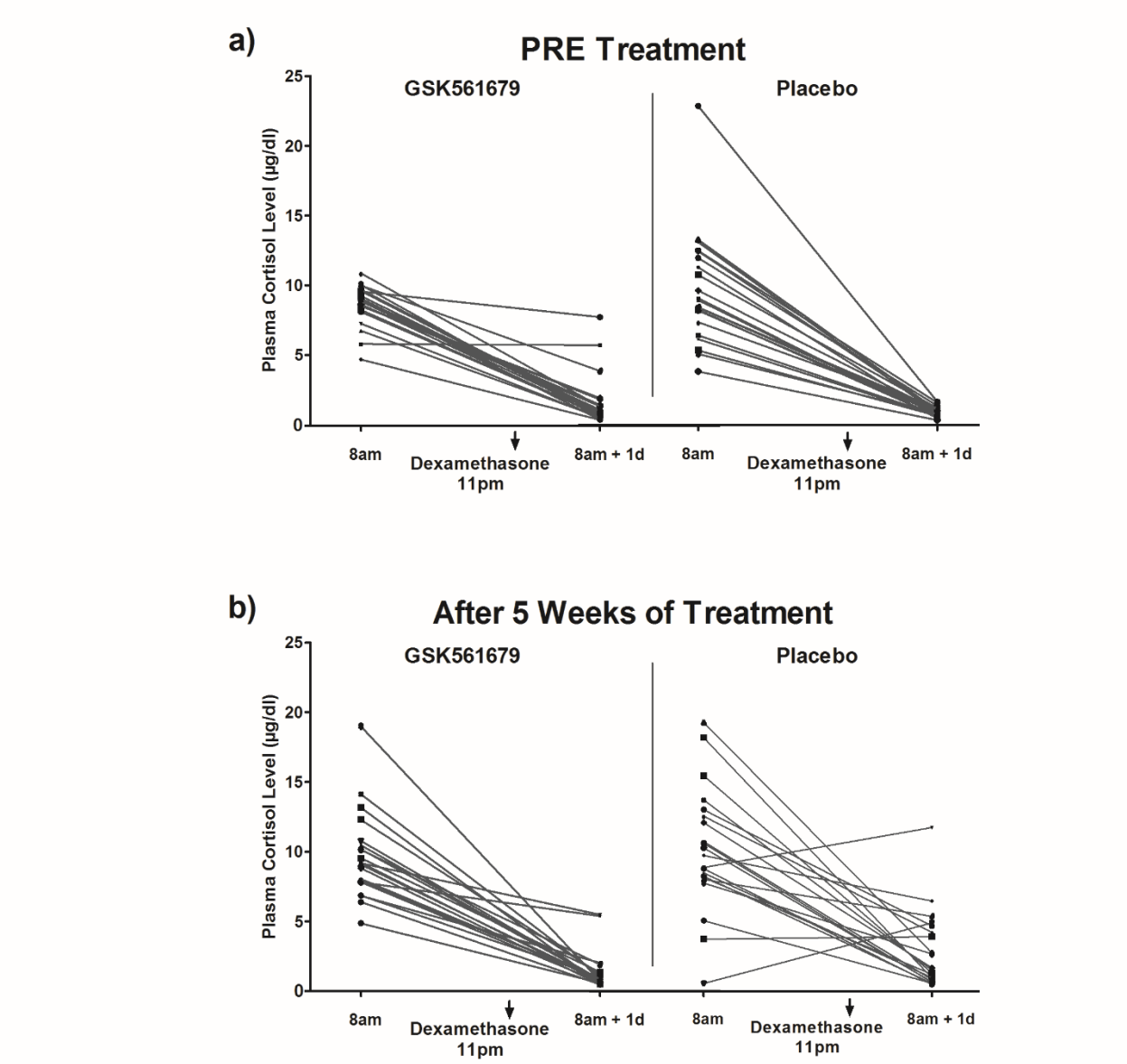


**Figure S7: Lack of effect of GSK561679 on change in morning plasma cortisol levels after dexamethasone suppression**

Change of 8:00am plasma cortisol levels before and after administration of 0.5mg dexamethasone in subjects treated with the GSK561679 or placebo. a) Pre-treatment; b) after 5 weeks of treatment. At both time points no significant difference was observed between the two treatments groups ($p>0.05$ for all; Pre-treatment: n= 36 GSK561679, 33 placebo; 5 weeks after treatment: n= 29 GSK561679, 26 placebo).

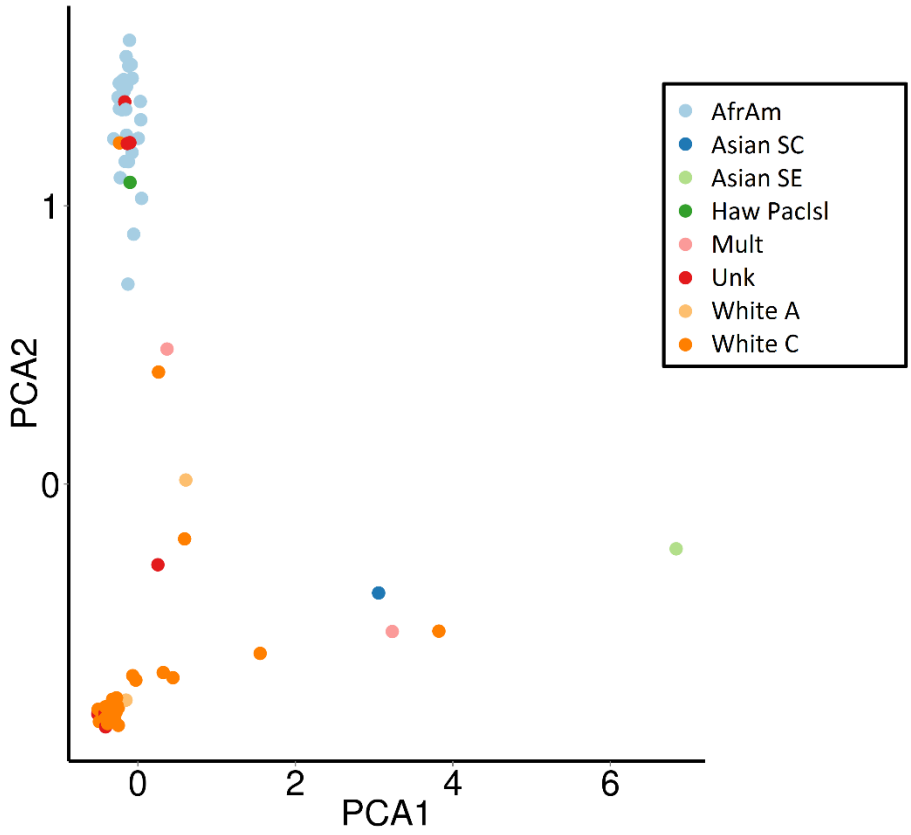


**Figure S8: PCA Plot**

PCA plot of samples shows good concordance between self-reported ethnicity (legend) and estimated ethnicity by principal component analysis. African-American (AfrAm), Asian South Central (Asian SC), Asian South East (Asian SE), Hawaiian Pacific Islands (Haw PacIsl) Multiple (Mult), Unknown (Unk), White Arabic (White A), White Caucasian (White C).

## SUPPLEMENTARY REFERENCE

1. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, et al. (2007): PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet* 81: 559-575.