Supplementary material

Neurocart test battery

The Neurocart test battery consisted of the following tests and endpoints, most of which have shown effects of both CNS depressants (Groeneveld et al., 2016) and stimulants (Wilhelmus et al., 2017; Baakman et al., 2019). For eye movement analysis (van Steveninck et al., 1991; Van Steveninck et al., 1997), the time in which the eyes are in smooth pursuit of the target (%), saccadic peak velocity (degrees/second), saccadic inaccuracy (%) and saccadic reaction time (seconds) were measured. The body sway meter (Wright, 1971) measured body movements in a single plane, providing a measure of postural stability (mm). In the adaptive tracking test (Borland and Nicholson, 1984) a circle moves randomly about a screen. The subject must try to keep a dot inside the moving circle by operating a joystick. If this effort is successful, the speed of the moving circle increases. Conversely, the velocity is reduced if the test subject cannot maintain the dot inside the circle. The percentage of the time that the subject is able to keep the dot in the circle is recorded. In the finger tapping test (Andrew, 1977) the volunteer is instructed to tap as quickly as possible with the index finger and to rest the wrist on the table. The number of taps per 10 seconds is recorded. In the stop signal task (Logan et al., 1984), the stop signal test an arrow pointing either to the left or to the right is displayed in the middle of a computer screen. Response instructions are to respond as quickly and accurately as possible to the direction in which the arrow is pointing (by pressing a corresponding button). The total correct responses for, the total missed responses, the mean response time of both the stop and the go signal and the mean signal delay for the stop signal were recorded. Finally, subjective mood and drug effects were measured using the Bond and Lader visual analogue scale (VAS) (Bond and Lader, 1974) and Bowdle VAS (Bowdle et al., 1998). Out of the 16 VAS scales in the Bond and Lader VAS three summary scales were calculated for alertness, mood and calmness and out of the 13 VAS scales of the Bowdle VAS the three summary scales external perception, internal perception and feeling high were calculated.

Contrasts used in the analysis of the PD effects of JNJ-54175446

For the exploration of the PD effects of JNJ-54175446 at steady state on the dexamphetamine challenge in comparison to placebo, the following contrasts were calculated according to supplemental table 1.
((m21-24 - m5-8) condition 3 + (m13-16 - m5-8) condition 4) vs ((m21-24 - m5-8) condition 1 + (m13-16 - m5-8) condition 2) = green –blue vs orange-yellow
to
((m21-24 - m5-8) condition 11 + (m13-16 - m5-8) condition 12) vs ((m21-24 - m5-8) condition 1 + (m13-16 - m5-8) condition 2)

Supplemental table 1: JNJ-54175446, placebo (plac) and dexamphetamine challenge (ch) conditions and their corresponding time of measurements (m). Measurement 1-4, 9-12, 17-20 are pre-challenge, measurement 5-8, 13-16 and 21-24 are post challenge; Day -5 measurements 1-4 are covariates.

		Time: measurement 1 to 24					
	Condition (trt/ch/ch)	Day -5 m 1-4	Day -5 m 5-8	Day 7 m 9-12	Day 7 m 13-16	Day 10 m 17-20	Day 10 m 21-24
1	Placebo/Plac/Amph	Pre ch	Amph ch	Pre ch	Plac ch	Pre ch	Amph ch
2	Placebo/Amph/Plac	Pre ch	Amph ch	Pre ch	Amph ch	Pre ch	Plac ch
3	JNJ-54175446/Plac/Amph	Pre ch	Amph ch	Pre ch	Plac ch	Pre ch	Amph ch
4	JNJ-54175446/Amph/Plac	Pre ch	Amph ch	Pre ch	Amph ch	Pre ch	Plac ch

To explore the PD effects of JNJ-54175446 at steady state under non-challenged conditions in comparison to placebo the following contrasts were calculated according to supplementary table 2.

(m9-20 condition 3 + m9-12 and 17-24 condition 4) vs (m9-20 condition 1+m9-12 and 17-24 condition 2) = yellow vs pink

to

(m9-20 condition 11 + m9-12 and 17-24 condition 12) vs (m9-20 condition 1 + m9-12 and 17-24 condition 2)

Supplemental table 2: JNJ-54175446, placebo (plac) and challenge (ch) conditions and their corresponding time of measurements (m). Measurement 1-4, 9-12, 17-20 are pre-challenge, measurement 5-8, 13-16 and 21-24 are post challenge; Day -5 measurements 1-4 are covariates.

		Time: measurement 1 to 24					
	Condition (trt/ch/ch)	Day -5 m 1-4	Day -5 m 5-8	Day 7 m 9-12	Day 7 m 13-16	Day 10 m 17-20	Day 10 m 21-24
1	Placebo/Plac/Amph	Pre ch	Amph ch	Pre ch	Plac ch	Pre ch	Amph ch
2	Placebo/Amph/Plac	Pre ch	Amph ch	Pre ch	Amph ch	Pre ch	Plac ch
3	JNJ-54175446/Plac/Amph	Pre ch	Amph ch	Pre ch	Plac ch	Pre ch	Amph ch
4	JNJ-54175446/Amph/Plac	Pre ch	Amph ch	Pre ch	Amph ch	Pre ch	Plac ch

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	Cover page
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	2-3
	2b	Specific objectives or hypotheses	3
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	4-5
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	4-6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	4-6
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	4
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	4
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	4
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	4
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	4
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	4

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	4
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	7
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	8
	13b	For each group, losses and exclusions after randomisation, together with reasons	8 & fig. 2
Recruitment	14a	Dates defining the periods of recruitment and follow-up	8
	14b	Why the trial ended or was stopped	Not applicable
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	8
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	8
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)	8-10
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	8-10
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	8-10
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	10
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	11-13
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	11-13
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11-13
Other information			
Registration	23	Registration number and name of trial registry	8 and abstract
Protocol	24	Where the full trial protocol can be accessed, if available	NA
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	13

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.