Clinical trial results:
Targeted Use of Placebo Effects Decreases Experimental Itch in Atopic Dermatitis Patients: A Randomized Controlled Trial
German: Nutzen des Placeboeffektes bei atopischer Dermatitis - Steigerung der pharmakologischen Wirkung bei Juckreiz durch Klassische Konditionierung und Erwartungsprozesse: Eine randomisierte kontrollierte Studie

Summary

EudraCT number	2008-008474-31
Trial protocol	DE
Global end of trial date	16 March 2014

Results information

Result version number	v1 (current)
This version publication date	04 September 2022
First version publication date	04 September 2022

Trial information

Trial identification

Sponsor protocol code	PlacItch

Additional study identifiers

ISRCTN number	ISRCTN12345678
ClinicalTrials.gov id (NCT number)	NCT02094287
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Charité - Universitätsmedizin Berlin
Sponsor organisation address	Charitéplatz 1, Berlin, Germany, 10117
Public contact	Prof. Margitta Worm, Charité - Universitätsmedizin Berlin, Dpt. of Dermatology, Division of Allergy and Immunology, margitta.worm@charite.de
Scientific contact	Prof. Margitta Worm, Charité - Universitätsmedizin Berlin, Dpt. of Dermatology, Division of Allergy and Immunology, margitta.worm@charite.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 March 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 March 2014
Global end of trial reached?	Yes
Global end of trial date	16 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The study is initiated in the indication of atopic dermatitis to study the impact of placebo effects in the treatment of pruritus. Classical conditioning and expectation via instructions/anticipation maintain the effect of placebo.

Protection of trial subjects:

All clinical tests (blood draw, skin prick test, questionnaires) and therapeutic interventions (infusion and instruction) were performed according to defined SOPs and clinical standards.
An patient insurance in accordance with the Medicines Act, Section 40, Paragraph 3 was provided for the probands for travel to the study center and for potential therapeutic side effects.
As no specific e.g. painful procedures were performed, no specific procedures were required.

Background therapy:

All participants suffered from atopic dermatitis and received their individual background therapies.
To explore the potential mediation role of expectation in driving itch re- duction (NRS 0–10; 0 = no itch, 10 = maximum itch) after conditioning, we performed a mediation analysis.24 The variable "conditioning" (yes/no) was treated as the independent variable , whereas the average delta score of the mean of "itch intensity ratings" of experimen- tal itch stimuli (NRS 0–10) from T1 baseline to T2, testing phase, and after intervention T2, was treated as dependent variable, "itch reduction baseline-T2" (criterion, Y). Expectations were assessed on day 2 (T2) at the beginning of the experiment (before infusion T2) by asking "Based on your current experience with our experimental itch stimulus, what itch relief on the NRS 0–10 do you expect from the following infusion?" Patients should provide two scores to indicate the expected itch relief. Reinforced expecta tion (average delta score between the current itch intensity rating and the predicted itch intensity rating with regard to experimental itch stimuli) was treated as the mediator (M) in mediation models. In this model, we calcu- lated the total effect of conditioning on itch reduction without mediator variable (c), the effect of the relationship between conditioning and itch reduction with the additional impact of expectation (c'), the direct effect of X to Mi (a), the direct effect of Mi to Y (b), and the indirect effect of X via Mi to Y (ab). IBM SPSS Statistics 21 software (IBM, Armonk, NY) was used in the per-protocol analysis. For the mediation analyses the macro "PROCESS" 3.5 by Andrew F. Hayes24 was used.

Evidence for comparator: -

Actual start date of recruitment	03 September 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 102

Worldwide total number of subjects	102
EEA total number of subjects	102

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	102
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment via the in-house outpatients clinic

Pre-assignment

Screening details:

Participants with a severity index (SCORing Atopic Dermatitis (SCORAD)) below 50 points, had no acute eczema on their forearms, were free of past or current psychiatric and neurological disorders, and received neither systemic treatments for skin diseases nor used topical treatments on their arms in the previous 4 and 2 weeks, respectively.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	OPEN-DRUG+INST

Arm description:

openly infused dimetindene (drug) in full sight with information

Arm type	Experimental
Investigational medicinal product name	Dimetindene
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Infusion

Dosage and administration details:

15-minute infusion (dimetindene)

Arm title	OPEN-DRUG+INST+COND

Arm description:

openly infused drug with an additional classical conditioning learning experience

Arm type	Experimental
Investigational medicinal product name	Dimetindene
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Infusion

Dosage and administration details:

15-minute infusion (dimetindene)

Arm title	HIDDEN-DRUG

Arm description:

infused drug without any information or sight

Arm type	control group 1

Investigational medicinal product name	Dimetindene
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Infusion

Dosage and administration details:
15-minute infusion (dimetindene)

Arm title	PLAC+INST+COND

Arm description:
placebo infusion (saline) declared as dimetindene and also experienced the conditioning experience

Arm type	control goup 2
Investigational medicinal product name	Saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Infusion

Dosage and administration details:
15 minutes infusion of saline

Number of subjects in period 1	OPEN-DRUG+INST	OPEN-DRUG+INST+COND	HIDDEN-DRUG
Started	26	26	24
Completed	26	26	24

Number of subjects in period 1	PLAC+INST+COND
Started	26
Completed	26

Baseline characteristics

Reporting groups	
Reporting group title	OPEN-DRUG+INST
Reporting group description:	
openly infused dimetindene (drug) in full sight with information	
Reporting group title	OPEN-DRUG+INST+COND
Reporting group description:	
openly infused drug with an additional classical conditioning learning experience	
Reporting group title	HIDDEN-DRUG
Reporting group description:	
infused drug without any information or sight	
Reporting group title	PLAC+INST+COND
Reporting group description:	
placebo infusion (saline) declared as dimetindene and also experienced the conditioning experience	

Reporting group values	OPEN-DRUG+INST	OPEN-DRUG+INST+COND	HIDDEN-DRUG
Number of subjects	26	26	24
Age categorical Units: Subjects			
Adults (18-64 years)	26	26	24
Age continuous Units: years			
arithmetic mean	30.69	28.81	32.58
standard deviation	± 10.77	± 9.71	± 12.84
Gender categorical Units: Subjects			
Female	17	18	17
Male	9	8	7
SCORAD score			
Severity of atopic dermatitis			
Units: points			
arithmetic mean	27.29	29.03	21.97
standard deviation	± 10.84	± 12.46	± 7.05
IgE values			
Total IgE values in LU/mL			
Units: LU/mL			
arithmetic mean	437	1714	1286
standard deviation	± 1122	± 5863	± 3603

Reporting group values	PLAC+INST+COND	Total	
Number of subjects	26	102	
Age categorical Units: Subjects			
Adults (18-64 years)	26	102	
Age continuous Units: years			
arithmetic mean	30.62		

standard deviation	± 9.37	-	

Gender categorical Units: Subjects			
Female	19	71	
Male	7	31	
SCORAD score			
Severity of atopic dermatitis			
Units: points			
arithmetic mean	23.18		
standard deviation	± 8.90	-	
IgE values			
Total IgE values in LU/mL			
Units: LU/mL			
arithmetic mean	457		
standard deviation	± 1001	-	

End points

End points reporting groups

Reporting group title	OPEN-DRUG+INST
Reporting group description:	
openly infused dimetindene (drug) in full sight with information	
Reporting group title	OPEN-DRUG+INST+COND
Reporting group description:	
openly infused drug with an additional classical conditioning learning experience	
Reporting group title	HIDDEN-DRUG
Reporting group description:	
infused drug without any information or sight	
Reporting group title	PLAC+INST+COND
Reporting group description:	
placebo infusion (saline) declared as dimetindene and also experienced the conditioning experience	

Primary: Change of itch ratings

End point title	Change of itch ratings
End point description:	
Primary treatment effects were estimated using generalized linear models: three repeated mea- sures analyses of variance (ANOVAs) with the within-subject factor "phase" (baseline, and testing phase T1 and T2) and between-subject factor "group" (HIDDEN-DRUG, OPEN-DRUG+INST, OPEN-DRUG+INST+COND, PLAC+INST+COND); η2 values were used as measures of effect sizes. Planned comparisons of the interaction ef- fects "phase * group" were conducted via orthogonal contrasts, with r as the effect size. Post hoc pairwise comparisons of treatment groups after the intervention were conducted via independent t-tests, with P = 0.025 as a Bonferroni-corrected criterion for significance. Difference scores between measurement phases (difference from baseline to T1, and difference from baseline to T2) were calculated and compared via a multivariate analysis of variance (MANOVA) with five a priori nonorthogonal contrasts on factor "group" to estimate the effects of placebo effects.	
End point type	Primary
End point timeframe:	
from the baseline measurement to T1 and T2.	

End point values	OPEN-DRUG+INST	OPEN-DRUG+INST+COND	HIDDEN-DRUG	PLAC+INST+COND
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	26	24	26
Units: score				
arithmetic mean (standard deviation)				
Baseline -itch	5.91 (± 1.37)	6.10 (± 1.68)	5.27 (± 1.62)	5.77 (± 1.60)
T1 - itch	3.19 (± 2.02)	2.28 (± 2.27)	4.20 (± 2.19)	2.64 (± 1.91)
T2 -itch	2.75 (± 1.82)	1.03 (± 1.32)	3.63 (± 2.10)	2.06 (± 1.76)

Attachments (see zip file)	Chart_Itch intensity and wheal sizes at different time points.jpg Experimental substances_Figure_1_200124.tiff DISPOSITION OF PATIENTS_Figure_2_200124.tiff

Statistical analyses

Statistical analysis title	open drug + Inst vs. Hidden drug
Comparison groups	OPEN-DRUG+INST v HIDDEN-DRUG
Number of subjects included in analysis	50
Analysis specification	Post-hoc
Analysis type	superiority[1]
P-value	< 0.002
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Variability estimate	Standard error of the mean

Notes:

[1] - three repeated measures analyses of variance (ANOVAs) with the within-subject factor "phase" (baseline, and testing phase T1 and T2) and between-subject factor "group" (HIDDEN-DRUG, OPEN-DRUG+INST, OPEN-DRUG+INST+COND, PLAC+INST+COND); η2 values were used as measures of effect sizes.

Statistical analysis title	Plac+Inst+Cond vs. hidden drug
Comparison groups	PLAC+INST+COND v HIDDEN-DRUG
Number of subjects included in analysis	50
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0
Method	ANOVA

Statistical analysis title	open drug+Inst+Cond vs. open drug +Inst
Comparison groups	OPEN-DRUG+INST+COND v OPEN-DRUG+INST
Number of subjects included in analysis	52
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.075
Method	ANOVA

Secondary: Change of wheal size

End point title	Change of wheal size

End point description:

End point type	Secondary

End point timeframe:

from the baseline measurement to T1 and T2

End point values	OPEN-DRUG+INST	OPEN-DRUG+INST+COND	HIDDEN-DRUG	PLAC+INST+COND
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	26	24	26
Units: mm²				
arithmetic mean (standard deviation)				
baseline - wheal size	29.27 (± 11.14)	29.88 (± 15.07)	30.21 (± 6.56)	32.42 (± 13.38)
T1 - wheal size	13.69 (± 5.64)	16.85 (± 10.75)	18.71 (± 7.69)	23.50 (± 10.25)
T2 - wheal size	14.88 (± 5.52)	12.81 (± 6.71)	21.54 (± 7.44)	23.62 (± 8.48)

Attachments (see zip file)	Itch intensity and wheal sizes at different times/Chart_Itch

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: from baseline to T2	
Assessment type	Systematic

Dictionary used	
Dictionary name	own
Dictionary version	1

Frequency threshold for reporting non-serious adverse events: 1 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No AEs have been reported.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 July 2012	We submitted an BfArm-Amendment to add a relevant inclusion criterion, namely a baseline itch NRS value of ≥ 3. In addition, we increased the number of cases by 40 in this amendment because we wanted to do an additional investigation, namely microdialysis, in a small sample. Extension of duration of study by two years. Resumption of recruitment (September 2012).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The selection of study groups was clinically and feasibility oriented. The group PLAC+INST (placebo group without conditioning)were not used for ethical reasons.
The histamine prick-test application without any treatment seemed us not justifiable.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/33894061