Clinical trial results:
Exploratory, controlled, randomized, observer-blind intrainidividual clinical trial to evaluate the efficacy and the tolerability of topically applied 0.1% tyrothricin (Tyrosur® Gel) in patients with mild to severe facial papulopustular acne.

Summary

EudraCT number	2013-001716-30
Trial protocol	DE
Global end of trial date	13 March 2014

Results information

Result version number	v1 (current)
This version publication date	04 September 2021
First version publication date	04 September 2021

Trial information

Trial identification

Sponsor protocol code	CRC-ACNE-AC-04

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Charité-Universitätsmedizin Berlin
Sponsor organisation address	Charitéplatz 1, Berlin, Germany, 10117
Public contact	Dr. Kathrin Hillmann, Charité-Universitätsmedizin Berlin Dept. of Dermatology Clinical Research Center for HairSkin Scie, 0049 30450518499, kathrin.hillmann@charite.de
Scientific contact	Dr. Kathrin Hillmann, Charité-Universitätsmedizin Berlin Dept. of Dermatology Clinical Research Center for HairSkin Scie, 0049 30450518499, kathrin.hillmann@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	07 July 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this trial is to evaluate the efficacy and the tolerability of topically applied 0.1% tyrothricin (Tyrosur® Gel) in patients with mild to severe facial papulopustular acne in comparison to a combination of clindamycin and benzoyl peroxide or to benzoyl peroxide alone.

Protection of trial subjects:

The medical history of the patient was documented with special emphasis on other skin diseases, like e.g. eczema or contact dermatitis. Furthermore the patient were subjected to a clinical examination in order to measure e.g. the blood pressure and pulse rate and to examine for skin status. Additionally adverse events, serious adverse events and local intolerances were recorded throughout the whole treatment period.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 October 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 24
Worldwide total number of subjects	24
EEA total number of subjects	24

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)	24
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment started on the 17th of September 2013. Subjects were recruited through IEC approved advertisements in the Berlin subway, CRC subject database, CRC homepage, digital Charité intranet notice board, leaflets and addressing patients during consulting hours for acne at the Department for Dermatology at the Charité.

Pre-assignment

Screening details:

27 people were pre-screened. Screening criterium included 18-25 year old female or males with Fitzpatrick Skin phototype I-III with mild to severe facial papulopustular acne, comparable in appearance on both sides of the face. Female subjects must have had a negative pregnancy test as well as a reliable contraception method.

Pre-assignment period milestones

Number of subjects started	24
Number of subjects completed	24

Period 1

Period 1 title	Inclusion
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Investigator[1]

Blinding implementation details:

In this clinical trial, a single blind concept was chosen. The investigators were blinded to the study medication and had neither access to the randomization list nor to the drug accountability log and were not present during product application. Product application was conducted solely by the study nurses. Due to original, unblinded packaging of the products, subjects and responsible study nurses were not blinded to the study medication.

Arms

Are arms mutually exclusive?	No
Arm title	0.1 % Tyrothricin

Arm description:

Over 24 consecutive days every subject (n=24) received 0.1% tyrothricin (Tyrosur® Gel) applied to one half of the face, which was assigned according to randomization. This was compared to either a combination of clindamycin and benzoyl peroxide (Duac Acne Gel) or to benzoyl peroxide alone, which was applied to the other side of the face, in patients with mild to severe facial papulopustular acne.

Arm type	Experimental
Investigational medicinal product name	Tyrosur Gel
Investigational medicinal product code	
Other name	0.1% Tyrothricin
Pharmaceutical forms	Gel
Routes of administration	Topical

Dosage and administration details:

On 24 consecutive days, the study products were applied topically according to the randomization list once daily in the evening at the study center on the related areas of patient´s face over a trial period of 25 days by the study nurse. Every patient received treatment with 0.1% tyrothricin (Tyrosur® Gel) on one half of the face in a thin layer. The side of the face treated with 0.1% tyrothricin (Tyrosur® Gel) was randomized.No application was performed in the direct area around the eyes and on the lips of the patients.

Arm title	Clindamycin + BPO

Arm description:

Over 24 consecutive days, 12 subjects randomly assigned to group 1 received the combination of Clindamycin + BPO (Duac Acne Gel). This was applied to the other half of the face that was not randomly assigned to 0.1% Tyrothricin.

Arm type	Active comparator
Investigational medicinal product name	Duac Acne Gel
Investigational medicinal product code	
Other name	Clindamycin and BPO
Pharmaceutical forms	Gel
Routes of administration	Topical

Dosage and administration details:

On 24 consecutive days, the study products were applied topically according to the randomization list once daily in the evening at the study center on the related areas of patient´s face over a trial period of 25 days by the study nurse. On the other half of the patient's face, not assigned to Tyrosur Gel, a combination of clindamycin and BPO (Duac Acne Gel®) was applied in a thin layer on the related areas according to randomization. No application was performed in the direct area around the eyes and on the lips of the patients.

Arm title	BPO 5%

Arm description:

Over 24 consecutive days, 12 subjects randomly assigned to group 2 received Benzoyl peroxide 5% alone (Aknefug Oxid mild 5%). This was applied to the other half of the face that was not randomly assigned to 0.1% Tyrothricin.

Arm type	Active comparator
Investigational medicinal product name	BPO 5%
Investigational medicinal product code	
Other name	Aknefug Oxid mild 5%
Pharmaceutical forms	Gel
Routes of administration	Topical

Dosage and administration details:

On 24 consecutive days, the study products were applied topically according to the randomization list once daily in the evening at the study center on the related areas of patient´s face over a trial period of 25 days by the study nurse. On the other half of the patient's face, not allocated to Tyrosur Gel, BPO 5% alone (Aknefug Oxid mild 5%®) was applied in a thin layer on the related areas according to randomization. No application was performed in the direct area around the eyes and on the lips of the patients.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: This was an investigator blinded study. The subject could not be blinded as he/she saw which product was on which facial side

Number of subjects in period 1	0.1 % Tyrothricin	Clindamycin + BPO	BPO 5%
Started	24	12	12
Inclusion/exclusion	24	12	12
Physical examination of skin	24	12	12
Vital parameters	24	12	12
Urine pregnancy test	24	12	12
Concomitant medication	24	12	12
Application of trial medication	24	12	12
Lesion count	24	12	12
Fluorescence intensity (Visipor)	24	12	12
Sebum content (Sebumeter)	24	12	12

ISGA	24	12	12
Photodocumentation and lesion counting	24	12	12
Local tolerability of the skin	24	12	12
Adverse events	24	12	12
Completed	24	12	12

Period 2

Period 2 title	Visit 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Investigator[2]

Blinding implementation details:

In this clinical trial, a single blind concept was chosen. The investigators were blinded to the study medication and had neither access to the randomization list nor to the drug accountability log and were not present during product application. Product application was conducted solely by the study nurses. Due to original, unblinded packaging of the products, subjects and responsible study nurses were not blinded to the study medication.

Arms

Are arms mutually exclusive?	No
Arm title	0.1% Tyrothricin

Arm description:

Over 24 consecutive days every subject (n=24) received 0.1% tyrothricin (Tyrosur® Gel) applied to one half of the face, which was assigned according to randomization. This was compared to either a combination of clindamycin and benzoyl peroxide (Duac Acne Gel) or to benzoyl peroxide alone, which was applied to the other side of the face, in patients with mild to severe facial papulopustular acne.

Arm type	Experimental
Investigational medicinal product name	Tyrosur Gel
Investigational medicinal product code	
Other name	0.1% Tyrothricin
Pharmaceutical forms	Gel
Routes of administration	Topical

Dosage and administration details:

On 24 consecutive days, the study products were applied topically according to the randomization list once daily in the evening at the study center on the related areas of patient´s face over a trial period of 25 days by the study nurse. Every patient received treatment with 0.1% tyrothricin (Tyrosur® Gel) on one half of the face in a thin layer. The side of the face treated with 0.1% tyrothricin (Tyrosur® Gel) was randomized.No application was performed in the direct area around the eyes and on the lips of the patients.

Arm title	Clindamcin + BPO

Arm description:

Over 24 consecutive days, 12 subjects randomly assigned to group 1 received the combination of Clindamycin + BPO (Duac Acne Gel). This was applied to the other half of the face that was not randomly assigned to 0.1% Tyrothricin.

Arm type	Active comparator

Investigational medicinal product name	Duac Acne Gel
Investigational medicinal product code	
Other name	Clindamycin and BPO
Pharmaceutical forms	Gel
Routes of administration	Topical

Dosage and administration details:

On 24 consecutive days, the study products were applied topically according to the randomization list once daily in the evening at the study center on the related areas of patient´s face over a trial period of 25 days by the study nurse. On the other half of the patient's face, not assigned to Tyrosur Gel, a combination of clindamycin and BPO (Duac Acne Gel®) was applied in a thin layer on the related areas according to randomization. No application was performed in the direct area around the eyes and on the lips of the patients.

Arm title	BPO 5%

Arm description:

Over 24 consecutive days, 12 subjects randomly assigned to group 2 received Benzoyl peroxide 5% alone (Aknefug Oxid mild 5%). This was applied to the other half of the face that was not randomly assigned to 0.1% Tyrothricin.

Arm type	Active comparator
Investigational medicinal product name	BPO 5%
Investigational medicinal product code	
Other name	Aknefug Oxid mild 5%
Pharmaceutical forms	Gel
Routes of administration	Topical

Dosage and administration details:

On 24 consecutive days, the study products were applied topically according to the randomization list once daily in the evening at the study center on the related areas of patient´s face over a trial period of 25 days by the study nurse. On the other half of the patient's face, not allocated to Tyrosur Gel, BPO 5% alone (Aknefug Oxid mild 5%®) was applied in a thin layer on the related areas according to randomization. No application was performed in the direct area around the eyes and on the lips of the patients.

Notes:

[2] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: This was an investigator blinded study. The subject could not be blinded as he/she saw which product was on which facial side

Number of subjects in period 2	0.1% Tyrothricin	Clindamcin + BPO	BPO 5%
Started	24	12	12
Physical examination of skin	24	12	12
Concomitant medication	24	12	12
Application of trial medication	24	12	12
Lesion count	24	12	12
Fluorescence intensity (Visiopor)	24	12	12
Sebum content (Sebumeter)	24	12	12
ISGA	24	12	12
Photodocumentation and lesion counting	24	12	12
Local tolerability of the skin	24	12	12
Adverse events	24	12	12
Completed	24	12	12

Period 3

Period 3 title	Visit 3
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Investigator[3]

Blinding implementation details:

In this clinical trial, a single blind concept was chosen. The investigators were blinded to the study medication and had neither access to the randomization list nor to the drug accountability log and were not present during product application. Product application was conducted solely by the study nurses. Due to original, unblinded packaging of the products, subjects and responsible study nurses were not blinded to the study medication.

Arms

Are arms mutually exclusive?	No
Arm title	0.1% Tyrothricin

Arm description:

Over 24 consecutive days every subject (n=24) received 0.1% tyrothricin (Tyrosur® Gel) applied to one half of the face, which was assigned according to randomization. This was compared to either a combination of clindamycin and benzoyl peroxide (Duac Acne Gel) or to benzoyl peroxide alone, which was applied to the other side of the face, in patients with mild to severe facial papulopustular acne.

Arm type	Experimental
Investigational medicinal product name	Tyrosur Gel
Investigational medicinal product code	
Other name	0.1% Tyrothricin
Pharmaceutical forms	Gel
Routes of administration	Topical

Dosage and administration details:

On 24 consecutive days, the study products were applied topically according to the randomization list once daily in the evening at the study center on the related areas of patient´s face over a trial period of 25 days by the study nurse. Every patient received treatment with 0.1% tyrothricin (Tyrosur® Gel) on one half of the face in a thin layer. The side of the face treated with 0.1% tyrothricin (Tyrosur® Gel) was randomized.No application was performed in the direct area around the eyes and on the lips of the patients.

Arm title	Clindamycin + BPO

Arm description:

Over 24 consecutive days, 12 subjects randomly assigned to group 1 received the combination of Clindamycin + BPO (Duac Acne Gel). This was applied to the other half of the face that was not randomly assigned to 0.1% Tyrothricin.

Arm type	Active comparator
Investigational medicinal product name	Duac Acne Gel
Investigational medicinal product code	
Other name	Clindamycin and BPO
Pharmaceutical forms	Gel
Routes of administration	Topical

Dosage and administration details:

On 24 consecutive days, the study products were applied topically according to the randomization list once daily in the evening at the study center on the related areas of patient´s face over a trial period of 25 days by the study nurse. On the other half of the patient's face, not assigned to Tyrosur Gel, a combination of clindamycin and BPO (Duac Acne Gel®) was applied in a thin layer on the related areas according to randomization. No application was performed in the direct area around the eyes and on the lips of the patients.

Arm title	BPO 5%

Arm description:

Over 24 consecutive days, 12 subjects randomly assigned to group 2 received Benzoyl peroxide 5% alone (Aknefug Oxid mild 5%). This was applied to the other half of the face that was not randomly assigned to 0.1% Tyrothricin.

Arm type	Active comparator
Investigational medicinal product name	BPO 5%
Investigational medicinal product code	
Other name	Aknefug Oxid mild 5%
Pharmaceutical forms	Gel
Routes of administration	Topical

Dosage and administration details:

On 24 consecutive days, the study products were applied topically according to the randomization list once daily in the evening at the study center on the related areas of patient´s face over a trial period of 25 days by the study nurse. On the other half of the patient's face, not allocated to Tyrosur Gel, BPO 5% alone (Aknefug Oxid mild 5%®) was applied in a thin layer on the related areas according to randomization. No application was performed in the direct area around the eyes and on the lips of the patients.

Notes:

[3] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: This was an investigator blinded study. The subject could not be blinded as he/she saw which product was on which facial side

Number of subjects in period 3	0.1% Tyrothricin	Clindamycin + BPO	BPO 5%
Started	24	12	12
Physical examination of the skin	24	12	12
Concomitant medication	24	12	12
Application of trial medication	24	12	12
Lesion count	24	12	12
Fluorescence intensity (Visiopor)	24	12	12
Sebum content (Sebumeter)	24	12	12
ISGA	24	12	12
Photodocumentation and lesion counting	24	12	12
Local tolerability of the skin	24	12	12
Adverse events	24	12	12
Completed	23	11	12
Not completed	1	1	0
Adverse event, non-fatal	1	1	-

Period 4

Period 4 title	Visit 4
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Investigator[4]

Blinding implementation details:

In this clinical trial, a single blind concept was chosen. The investigators were blinded to the study medication and had neither access to the randomization list nor to the drug accountability log and were not present during product application. Product application was conducted solely by the study nurses. Due to original, unblinded packaging of the products, subjects and responsible study nurses were not blinded to the study medication.

Arms

Are arms mutually exclusive?	No
Arm title	0.1% Tyrothricin

Arm description:

Over 24 consecutive days every subject (n=24) received 0.1% tyrothricin (Tyrosur® Gel) applied to one half of the face, which was assigned according to randomization. This was compared to either a combination of clindamycin and benzoyl peroxide (Duac Acne Gel) or to benzoyl peroxide alone, which was applied to the other side of the face, in patients with mild to severe facial papulopustular acne.

Arm type	Experimental
Investigational medicinal product name	Tyrosur Gel
Investigational medicinal product code	
Other name	0.1% Tyrothricin
Pharmaceutical forms	Gel
Routes of administration	Topical

Dosage and administration details:

On 24 consecutive days, the study products were applied topically according to the randomization list once daily in the evening at the study center on the related areas of patient´s face over a trial period of 25 days by the study nurse. Every patient received treatment with 0.1% tyrothricin (Tyrosur® Gel) on one half of the face in a thin layer. The side of the face treated with 0.1% tyrothricin (Tyrosur® Gel) was randomized.No application was performed in the direct area around the eyes and on the lips of the patients.

Arm title	Clindamycin + BPO

Arm description:

Over 24 consecutive days, 12 subjects randomly assigned to group 1 received the combination of Clindamycin + BPO (Duac Acne Gel). This was applied to the other half of the face that was not randomly assigned to 0.1% Tyrothricin.

Arm type	Active comparator
Investigational medicinal product name	Duac Acne Gel
Investigational medicinal product code	
Other name	Clindamycin and BPO
Pharmaceutical forms	Gel
Routes of administration	Topical

Dosage and administration details:

On 24 consecutive days, the study products were applied topically according to the randomization list once daily in the evening at the study center on the related areas of patient´s face over a trial period of 25 days by the study nurse. On the other half of the patient's face, not assigned to Tyrosur Gel, a combination of clindamycin and BPO (Duac Acne Gel®) was applied in a thin layer on the related areas according to randomization. No application was performed in the direct area around the eyes and on the lips of the patients.

Arm title	BPO 5%

Arm description:

Over 24 consecutive days, 12 subjects randomly assigned to group 2 received Benzoyl peroxide 5% alone (Aknefug Oxid mild 5%). This was applied to the other half of the face that was not randomly assigned to 0.1% Tyrothricin.

Arm type	Active comparator

Investigational medicinal product name	BPO 5%
Investigational medicinal product code	
Other name	Aknefug Oxid mild 5%
Pharmaceutical forms	Gel
Routes of administration	Topical

Dosage and administration details:

On 24 consecutive days, the study products were applied topically according to the randomization list once daily in the evening at the study center on the related areas of patient´s face over a trial period of 25 days by the study nurse. On the other half of the patient's face, not allocated to Tyrosur Gel, BPO 5% alone (Aknefug Oxid mild 5%®) was applied in a thin layer on the related areas according to randomization. No application was performed in the direct area around the eyes and on the lips of the patients.

Notes:

[4] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: This was an investigator blinded study. The subject could not be blinded as he/she saw which product was on which facial side

Number of subjects in period 4	0.1% Tyrothricin	Clindamycin + BPO	BPO 5%
Started	23	11	12
Physical examination of the skin	23	11	12
Concomitant medication	23	11	12
Application of trial medication	23	11	12
Lesion count	23	11	12
Fluorescence intensity (Visiopor)	23	11	12
Sebum content (Sebumeter)	23	11	12
ISGA	23	11	12
Photodocumentation and lesion counting	23	11	12
Local tolerability of the skin	23	11	12
Adverse events	23	11	12
Completed	23	11	12

Period 5

Period 5 title	Visit 5
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Investigator[5]

Blinding implementation details:

In this clinical trial, a single blind concept was chosen. The investigators were blinded to the study medication and had neither access to the randomization list nor to the drug accountability log and were not present during product application. Product application was conducted solely by the study nurses. Due to original, unblinded packaging of the products, subjects and responsible study nurses were not blinded to the study medication.

Arms

Are arms mutually exclusive?	No

Arm title	0.1% Tyrothricin

Arm description:

Over 24 consecutive days every subject (n=24) received 0.1% tyrothricin (Tyrosur® Gel) applied to one half of the face, which was assigned according to randomization. This was compared to either a combination of clindamycin and benzoyl peroxide (Duac Acne Gel) or to benzoyl peroxide alone, which was applied to the other side of the face, in patients with mild to severe facial papulopustular acne.

Arm type	Experimental
Investigational medicinal product name	Tyrosur Gel
Investigational medicinal product code	
Other name	0.1% Tyrothricin
Pharmaceutical forms	Gel
Routes of administration	Topical

Dosage and administration details:

On 24 consecutive days, the study products were applied topically according to the randomization list once daily in the evening at the study center on the related areas of patient´s face over a trial period of 25 days by the study nurse. Every patient received treatment with 0.1% tyrothricin (Tyrosur® Gel) on one half of the face in a thin layer. The side of the face treated with 0.1% tyrothricin (Tyrosur® Gel) was randomized.No application was performed in the direct area around the eyes and on the lips of the patients.

Arm title	Clindamycin + BPO

Arm description:

Over 24 consecutive days, 12 subjects randomly assigned to group 1 received the combination of Clindamycin + BPO (Duac Acne Gel). This was applied to the other half of the face that was not randomly assigned to 0.1% Tyrothricin.

Arm type	Active comparator
Investigational medicinal product name	Duac Acne Gel
Investigational medicinal product code	
Other name	Clindamycin and BPO
Pharmaceutical forms	Gel
Routes of administration	Topical

Dosage and administration details:

On 24 consecutive days, the study products were applied topically according to the randomization list once daily in the evening at the study center on the related areas of patient´s face over a trial period of 25 days by the study nurse. On the other half of the patient's face, not assigned to Tyrosur Gel, a combination of clindamycin and BPO (Duac Acne Gel®) was applied in a thin layer on the related areas according to randomization. No application was performed in the direct area around the eyes and on the lips of the patients.

Arm title	BPO 5%

Arm description:

Over 24 consecutive days, 12 subjects randomly assigned to group 2 received Benzoyl peroxide 5% alone (Aknefug Oxid mild 5%). This was applied to the other half of the face that was not randomly assigned to 0.1% Tyrothricin.

Arm type	Active comparator
Investigational medicinal product name	BPO 5%
Investigational medicinal product code	
Other name	Aknefug Oxid mild 5%
Pharmaceutical forms	Gel
Routes of administration	Topical

Dosage and administration details:

On 24 consecutive days, the study products were applied topically according to the randomization list once daily in the evening at the study center on the related areas of patient´s face over a trial period of 25 days by the study nurse. On the other half of the patient's face, not allocated to Tyrosur Gel, BPO 5% alone (Aknefug Oxid mild 5%®) was applied in a thin layer on the related areas according to randomization. No application was performed in the direct area around the eyes and on the lips of the patients.

Notes:

[5] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: This was an investigator blinded study. The subject could not be blinded as he/she saw which product was on which facial side

Number of subjects in period 5	0.1% Tyrothricin	Clindamycin + BPO	BPO 5%
Started	23	11	12
Physical examination of skin	23	11	12
Concomitant medication	23	11	12
Application of trial medication	23	11	12
Lesion count	23	11	12
Fluorescence intensity (Visiopor)	23	11	12
Sebum content (Sebumeter)	23	11	12
ISGA	23	11	12
Photodocumentation and lesion count	23	11	12
Local tolerability of the skin	23	11	12
Adverse events	23	11	12
Completed	23	11	12

Period 6

Period 6 title	Visit 6
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Investigator[6]

Blinding implementation details:

In this clinical trial, a single blind concept was chosen. The investigators were blinded to the study medication and had neither access to the randomization list nor to the drug accountability log and were not present during product application. Product application was conducted solely by the study nurses. Due to original, unblinded packaging of the products, subjects and responsible study nurses were not blinded to the study medication.

Arms

Are arms mutually exclusive?	No
Arm title	0.1% Tyrothricin

Arm description:

Over 24 consecutive days every subject (n=24) received 0.1% tyrothricin (Tyrosur® Gel) applied to one half of the face, which was assigned according to randomization. This was compared to either a combination of clindamycin and benzoyl peroxide (Duac Acne Gel) or to benzoyl peroxide alone, which was applied to the other side of the face, in patients with mild to severe facial papulopustular acne.

Arm type	Experimental

Investigational medicinal product name	Tyrosur Gel
Investigational medicinal product code	
Other name	0.1% Tyrothricin
Pharmaceutical forms	Gel
Routes of administration	Topical

Dosage and administration details:

On 24 consecutive days, the study products were applied topically according to the randomization list once daily in the evening at the study center on the related areas of patient´s face over a trial period of 25 days by the study nurse. Every patient received treatment with 0.1% tyrothricin (Tyrosur® Gel) on one half of the face in a thin layer. The side of the face treated with 0.1% tyrothricin (Tyrosur® Gel) was randomized.No application was performed in the direct area around the eyes and on the lips of the patients.

Arm title	Clindamycin + BPO

Arm description:

Over 24 consecutive days, 12 subjects randomly assigned to group 1 received the combination of Clindamycin + BPO (Duac Acne Gel). This was applied to the other half of the face that was not randomly assigned to 0.1% Tyrothricin.

Arm type	Active comparator
Investigational medicinal product name	Duac Acne Gel
Investigational medicinal product code	
Other name	Clindamycin and BPO
Pharmaceutical forms	Gel
Routes of administration	Topical

Dosage and administration details:

On 24 consecutive days, the study products were applied topically according to the randomization list once daily in the evening at the study center on the related areas of patient´s face over a trial period of 25 days by the study nurse. On the other half of the patient's face, not assigned to Tyrosur Gel, a combination of clindamycin and BPO (Duac Acne Gel®) was applied in a thin layer on the related areas according to randomization. No application was performed in the direct area around the eyes and on the lips of the patients.

Arm title	BPO 5%

Arm description:

Over 24 consecutive days, 12 subjects randomly assigned to group 2 received Benzoyl peroxide 5% alone (Aknefug Oxid mild 5%). This was applied to the other half of the face that was not randomly assigned to 0.1% Tyrothricin.

Arm type	Active comparator
Investigational medicinal product name	BPO 5%
Investigational medicinal product code	
Other name	Aknefug Oxid mild 5%
Pharmaceutical forms	Gel
Routes of administration	Topical

Dosage and administration details:

On 24 consecutive days, the study products were applied topically according to the randomization list once daily in the evening at the study center on the related areas of patient´s face over a trial period of 25 days by the study nurse. On the other half of the patient's face, not allocated to Tyrosur Gel, BPO 5% alone (Aknefug Oxid mild 5%®) was applied in a thin layer on the related areas according to randomization. No application was performed in the direct area around the eyes and on the lips of the patients.

Notes:

[6] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: This was an investigator blinded study. The subject could not be blinded as he/she saw which product was on which facial side

Number of subjects in period 6	0.1% Tyrothricin	Clindamycin + BPO	BPO 5%
Started	23	11	12
Physical examination of skin	23	11	12
Concomitant medication	23	11	12
Application of trial medication	23	11	12
Lesion count	23	11	12
Fluorescence intensity (Visiopor)	23	11	12
Sebum content (Sebumeter)	23	11	12
ISGA	23	11	12
Photodocumentation and lesion count	23	11	12
Local tolerability of the skin	23	11	12
Adverse events	23	11	12
Completed	23	11	12

Period 7

Period 7 title	Visit 7
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Investigator[7]

Blinding implementation details:

In this clinical trial, a single blind concept was chosen. The investigators were blinded to the study medication and had neither access to the randomization list nor to the drug accountability log and were not present during product application. Product application was conducted solely by the study nurses. Due to original, unblinded packaging of the products, subjects and responsible study nurses were not blinded to the study medication.

Arms

Are arms mutually exclusive?	No
Arm title	0.1% Tyrothricin

Arm description:

Over 24 consecutive days every subject (n=24) received 0.1% tyrothricin (Tyrosur® Gel) applied to one half of the face, which was assigned according to randomization. This was compared to either a combination of clindamycin and benzoyl peroxide (Duac Acne Gel) or to benzoyl peroxide alone, which was applied to the other side of the face, in patients with mild to severe facial papulopustular acne.

Arm type	Experimental
Investigational medicinal product name	Tyrosur Gel
Investigational medicinal product code	
Other name	0.1% Tyrothricin
Pharmaceutical forms	Gel
Routes of administration	Topical

Dosage and administration details:

On 24 consecutive days, the study products were applied topically according to the randomization list once daily in the evening at the study center on the related areas of patient´s face over a trial period of

25 days by the study nurse. Every patient received treatment with 0.1% tyrothricin (Tyrosur® Gel) on one half of the face in a thin layer. The side of the face treated with 0.1% tyrothricin (Tyrosur® Gel) was randomized.No application was performed in the direct area around the eyes and on the lips of the patients.

Arm title	Clindamycin + BPO

Arm description:

Over 24 consecutive days, 12 subjects randomly assigned to group 1 received the combination of Clindamycin + BPO (Duac Acne Gel). This was applied to the other half of the face that was not randomly assigned to 0.1% Tyrothricin.

Arm type	Active comparator
Investigational medicinal product name	Duac Acne Gel
Investigational medicinal product code	
Other name	Clindamycin and BPO
Pharmaceutical forms	Gel
Routes of administration	Topical

Dosage and administration details:

On 24 consecutive days, the study products were applied topically according to the randomization list once daily in the evening at the study center on the related areas of patient´s face over a trial period of 25 days by the study nurse. On the other half of the patient's face, not assigned to Tyrosur Gel, a combination of clindamycin and BPO (Duac Acne Gel®) was applied in a thin layer on the related areas according to randomization. No application was performed in the direct area around the eyes and on the lips of the patients.

Arm title	BPO 5%

Arm description:

Over 24 consecutive days, 12 subjects randomly assigned to group 2 received Benzoyl peroxide 5% alone (Aknefug Oxid mild 5%). This was applied to the other half of the face that was not randomly assigned to 0.1% Tyrothricin.

Arm type	Active comparator
Investigational medicinal product name	BPO 5%
Investigational medicinal product code	
Other name	Aknefug Oxid mild 5%
Pharmaceutical forms	Gel
Routes of administration	Topical

Dosage and administration details:

On 24 consecutive days, the study products were applied topically according to the randomization list once daily in the evening at the study center on the related areas of patient´s face over a trial period of 25 days by the study nurse. On the other half of the patient's face, not allocated to Tyrosur Gel, BPO 5% alone (Aknefug Oxid mild 5%®) was applied in a thin layer on the related areas according to randomization. No application was performed in the direct area around the eyes and on the lips of the patients.

Notes:

[7] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: This was an investigator blinded study. The subject could not be blinded as he/she saw which product was on which facial side

Number of subjects in period 7	0.1% Tyrothricin	Clindamycin + BPO	BPO 5%
Started	23	11	12
Physical examination of skin	23	11	12
Concomitant medication	23	11	12
Application of trial medication	23	11	12
Lesion count	23	11	12

Fluorescence intensity (Visiopor)	23	11	12
Sebum content (Sebumeter)	23	11	12
ISGA	23	11	12
Photodocumentation and lesion counting	23	11	12
Local tolerability of the skin	23	11	12
Adverse events	23	11	12
Completed	23	11	12

Period 8

Period 8 title	Visit 8
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Investigator[8]

Blinding implementation details:

In this clinical trial, a single blind concept was chosen. The investigators were blinded to the study medication and had neither access to the randomization list nor to the drug accountability log and were not present during product application. Product application was conducted solely by the study nurses. Due to original, unblinded packaging of the products, subjects and responsible study nurses were not blinded to the study medication.

Arms

Are arms mutually exclusive?	No
Arm title	0.1% Tyrothricin

Arm description:

Over 24 consecutive days every subject (n=24) received 0.1% tyrothricin (Tyrosur® Gel) applied to one half of the face, which was assigned according to randomization. This was compared to either a combination of clindamycin and benzoyl peroxide (Duac Acne Gel) or to benzoyl peroxide alone, which was applied to the other side of the face, in patients with mild to severe facial papulopustular acne.

Arm type	Experimental
Investigational medicinal product name	Tyrosur Gel
Investigational medicinal product code	
Other name	0.1% Tyrothricin
Pharmaceutical forms	Gel
Routes of administration	Topical

Dosage and administration details:

On 24 consecutive days, the study products were applied topically according to the randomization list once daily in the evening at the study center on the related areas of patient´s face over a trial period of 25 days by the study nurse. Every patient received treatment with 0.1% tyrothricin (Tyrosur® Gel) on one half of the face in a thin layer. The side of the face treated with 0.1% tyrothricin (Tyrosur® Gel) was randomized.No application was performed in the direct area around the eyes and on the lips of the patients.

Arm title	Clindamycin + BPO

Arm description:

Over 24 consecutive days, 12 subjects randomly assigned to group 1 received the combination of Clindamycin + BPO (Duac Acne Gel). This was applied to the other half of the face that was not randomly assigned to 0.1% Tyrothricin.

Arm type	Active comparator

Investigational medicinal product name	Duac Acne Gel
Investigational medicinal product code	
Other name	Clindamycin and BPO
Pharmaceutical forms	Gel
Routes of administration	Topical

Dosage and administration details:

On 24 consecutive days, the study products were applied topically according to the randomization list once daily in the evening at the study center on the related areas of patient´s face over a trial period of 25 days by the study nurse. On the other half of the patient's face, not assigned to Tyrosur Gel, a combination of clindamycin and BPO (Duac Acne Gel®) was applied in a thin layer on the related areas according to randomization. No application was performed in the direct area around the eyes and on the lips of the patients.

Arm title	BPO 5%

Arm description:

Over 24 consecutive days, 12 subjects randomly assigned to group 2 received Benzoyl peroxide 5% alone (Aknefug Oxid mild 5%). This was applied to the other half of the face that was not randomly assigned to 0.1% Tyrothricin.

Arm type	Active comparator
Investigational medicinal product name	BPO 5%
Investigational medicinal product code	
Other name	Aknefug Oxid mild 5%
Pharmaceutical forms	Gel
Routes of administration	Topical

Dosage and administration details:

On 24 consecutive days, the study products were applied topically according to the randomization list once daily in the evening at the study center on the related areas of patient´s face over a trial period of 25 days by the study nurse. On the other half of the patient's face, not allocated to Tyrosur Gel, BPO 5% alone (Aknefug Oxid mild 5%®) was applied in a thin layer on the related areas according to randomization. No application was performed in the direct area around the eyes and on the lips of the patients.

Notes:

[8] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: This was an investigator blinded study. The subject could not be blinded as he/she saw which product was on which facial side

Number of subjects in period 8	0.1% Tyrothricin	Clindamycin + BPO	BPO 5%
Started	23	11	12
Physical examination of skin	23	11	12
Vital parameters	23	11	12
Urine pregnancy test	23	11	12
Concomitant medication	23	11	12
Application of trial medication	23	11	12
Lesion count	23	11	12
Fluorescence intensity (Visiopor)	23	11	12
Sebum content (Sebumeter)	23	11	12
ISGA	23	11	12
Photodocumentation and lesion count	23	11	12
Local tolerability of the skin	23	11	12
Adverse events	23	11	12

Completed	23	11	12

Baseline characteristics

Reporting groups	
Reporting group title	0.1 % Tyrothricin

Reporting group description:

Over 24 consecutive days every subject (n=24) received 0.1% tyrothricin (Tyrosur® Gel) applied to one half of the face, which was assigned according to randomization. This was compared to either a combination of clindamycin and benzoyl peroxide (Duac Acne Gel) or to benzoyl peroxide alone, which was applied to the other side of the face, in patients with mild to severe facial papulopustular acne.

Reporting group title	Clindamycin + BPO

Reporting group description:

Over 24 consecutive days, 12 subjects randomly assigned to group 1 received the combination of Clindamycin + BPO (Duac Acne Gel). This was applied to the other half of the face that was not randomly assigned to 0.1% Tyrothricin.

Reporting group title	BPO 5%

Reporting group description:

Over 24 consecutive days, 12 subjects randomly assigned to group 2 received Benzoyl peroxide 5% alone (Aknefug Oxid mild 5%). This was applied to the other half of the face that was not randomly assigned to 0.1% Tyrothricin.

Reporting group values	0.1 % Tyrothricin	Clindamycin + BPO	BPO 5%
Number of subjects	24	12	12
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
18-25 years	24	12	12
Age continuous Units: years			
arithmetic mean	20.7	21.3	20.2
full range (min-max)	18 to 25	18 to 25	19 to 23
Gender categorical Units: Subjects			
Female	15	7	8
Male	9	5	4

Reporting group values	Total		
Number of subjects	24		
Age categorical Units: Subjects			
In utero	0		

Preterm newborn infants (gestational age < 37 wks)	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)	0		
From 65-84 years	0		
85 years and over	0		
18-25 years	24		
Age continuous			
Units: years			
arithmetic mean			
full range (min-max)	-		
Gender categorical			
Units: Subjects			
Female	15		
Male	9		

End points reporting groups

Reporting group title	0.1 % Tyrothricin

Reporting group description:

Over 24 consecutive days every subject (n=24) received 0.1% tyrothricin (Tyrosur® Gel) applied to one half of the face, which was assigned according to randomization. This was compared to either a combination of clindamycin and benzoyl peroxide (Duac Acne Gel) or to benzoyl peroxide alone, which was applied to the other side of the face, in patients with mild to severe facial papulopustular acne.

Reporting group title	Clindamycin + BPO

Reporting group description:

Over 24 consecutive days, 12 subjects randomly assigned to group 1 received the combination of Clindamycin + BPO (Duac Acne Gel). This was applied to the other half of the face that was not randomly assigned to 0.1% Tyrothricin.

Reporting group title	BPO 5%

Reporting group description:

Over 24 consecutive days, 12 subjects randomly assigned to group 2 received Benzoyl peroxide 5% alone (Aknefug Oxid mild 5%). This was applied to the other half of the face that was not randomly assigned to 0.1% Tyrothricin.

Reporting group title	0.1% Tyrothricin

Reporting group description:

Over 24 consecutive days every subject (n=24) received 0.1% tyrothricin (Tyrosur® Gel) applied to one half of the face, which was assigned according to randomization. This was compared to either a combination of clindamycin and benzoyl peroxide (Duac Acne Gel) or to benzoyl peroxide alone, which was applied to the other side of the face, in patients with mild to severe facial papulopustular acne.

Reporting group title	Clindamcin + BPO

Reporting group description:

Over 24 consecutive days, 12 subjects randomly assigned to group 1 received the combination of Clindamycin + BPO (Duac Acne Gel). This was applied to the other half of the face that was not randomly assigned to 0.1% Tyrothricin.

Reporting group title	BPO 5%

Reporting group description:

Over 24 consecutive days, 12 subjects randomly assigned to group 2 received Benzoyl peroxide 5% alone (Aknefug Oxid mild 5%). This was applied to the other half of the face that was not randomly assigned to 0.1% Tyrothricin.

Reporting group title	0.1% Tyrothricin

Reporting group description:

Over 24 consecutive days every subject (n=24) received 0.1% tyrothricin (Tyrosur® Gel) applied to one half of the face, which was assigned according to randomization. This was compared to either a combination of clindamycin and benzoyl peroxide (Duac Acne Gel) or to benzoyl peroxide alone, which was applied to the other side of the face, in patients with mild to severe facial papulopustular acne.

Reporting group title	Clindamycin + BPO

Reporting group description:

Over 24 consecutive days, 12 subjects randomly assigned to group 1 received the combination of Clindamycin + BPO (Duac Acne Gel). This was applied to the other half of the face that was not randomly assigned to 0.1% Tyrothricin.

Reporting group title	BPO 5%

Reporting group description:

Over 24 consecutive days, 12 subjects randomly assigned to group 2 received Benzoyl peroxide 5% alone (Aknefug Oxid mild 5%). This was applied to the other half of the face that was not randomly assigned to 0.1% Tyrothricin.

Reporting group title	0.1% Tyrothricin

Reporting group description:

Over 24 consecutive days every subject (n=24) received 0.1% tyrothricin (Tyrosur® Gel) applied to one half of the face, which was assigned according to randomization. This was compared to either a

combination of clindamycin and benzoyl peroxide (Duac Acne Gel) or to benzoyl peroxide alone, which was applied to the other side of the face, in patients with mild to severe facial papulopustular acne.

Reporting group title	Clindamycin + BPO

Reporting group description:

Over 24 consecutive days, 12 subjects randomly assigned to group 1 received the combination of Clindamycin + BPO (Duac Acne Gel). This was applied to the other half of the face that was not randomly assigned to 0.1% Tyrothricin.

Reporting group title	BPO 5%

Reporting group description:

Over 24 consecutive days, 12 subjects randomly assigned to group 2 received Benzoyl peroxide 5% alone (Aknefug Oxid mild 5%). This was applied to the other half of the face that was not randomly assigned to 0.1% Tyrothricin.

Reporting group title	0.1% Tyrothricin

Reporting group description:

Over 24 consecutive days every subject (n=24) received 0.1% tyrothricin (Tyrosur® Gel) applied to one half of the face, which was assigned according to randomization. This was compared to either a combination of clindamycin and benzoyl peroxide (Duac Acne Gel) or to benzoyl peroxide alone, which was applied to the other side of the face, in patients with mild to severe facial papulopustular acne.

Reporting group title	Clindamycin + BPO

Reporting group description:

Over 24 consecutive days, 12 subjects randomly assigned to group 1 received the combination of Clindamycin + BPO (Duac Acne Gel). This was applied to the other half of the face that was not randomly assigned to 0.1% Tyrothricin.

Reporting group title	BPO 5%

Reporting group description:

Over 24 consecutive days, 12 subjects randomly assigned to group 2 received Benzoyl peroxide 5% alone (Aknefug Oxid mild 5%). This was applied to the other half of the face that was not randomly assigned to 0.1% Tyrothricin.

Reporting group title	0.1% Tyrothricin

Reporting group description:

Over 24 consecutive days every subject (n=24) received 0.1% tyrothricin (Tyrosur® Gel) applied to one half of the face, which was assigned according to randomization. This was compared to either a combination of clindamycin and benzoyl peroxide (Duac Acne Gel) or to benzoyl peroxide alone, which was applied to the other side of the face, in patients with mild to severe facial papulopustular acne.

Reporting group title	Clindamycin + BPO

Reporting group description:

Over 24 consecutive days, 12 subjects randomly assigned to group 1 received the combination of Clindamycin + BPO (Duac Acne Gel). This was applied to the other half of the face that was not randomly assigned to 0.1% Tyrothricin.

Reporting group title	BPO 5%

Reporting group description:

Over 24 consecutive days, 12 subjects randomly assigned to group 2 received Benzoyl peroxide 5% alone (Aknefug Oxid mild 5%). This was applied to the other half of the face that was not randomly assigned to 0.1% Tyrothricin.

Reporting group title	0.1% Tyrothricin

Reporting group description:

Over 24 consecutive days every subject (n=24) received 0.1% tyrothricin (Tyrosur® Gel) applied to one half of the face, which was assigned according to randomization. This was compared to either a combination of clindamycin and benzoyl peroxide (Duac Acne Gel) or to benzoyl peroxide alone, which was applied to the other side of the face, in patients with mild to severe facial papulopustular acne.

Reporting group title	Clindamycin + BPO

Reporting group description:

Over 24 consecutive days, 12 subjects randomly assigned to group 1 received the combination of Clindamycin + BPO (Duac Acne Gel). This was applied to the other half of the face that was not randomly assigned to 0.1% Tyrothricin.

Reporting group title	BPO 5%

Reporting group description:

Over 24 consecutive days, 12 subjects randomly assigned to group 2 received Benzoyl peroxide 5% alone (Aknefug Oxid mild 5%). This was applied to the other half of the face that was not randomly assigned to 0.1% Tyrothricin.

Reporting group title	0.1% Tyrothricin

Reporting group description:

Over 24 consecutive days every subject (n=24) received 0.1% tyrothricin (Tyrosur® Gel) applied to one half of the face, which was assigned according to randomization. This was compared to either a combination of clindamycin and benzoyl peroxide (Duac Acne Gel) or to benzoyl peroxide alone, which was applied to the other side of the face, in patients with mild to severe facial papulopustular acne.

Reporting group title	Clindamycin + BPO

Reporting group description:

Over 24 consecutive days, 12 subjects randomly assigned to group 1 received the combination of Clindamycin + BPO (Duac Acne Gel). This was applied to the other half of the face that was not randomly assigned to 0.1% Tyrothricin.

Reporting group title	BPO 5%

Reporting group description:

Over 24 consecutive days, 12 subjects randomly assigned to group 2 received Benzoyl peroxide 5% alone (Aknefug Oxid mild 5%). This was applied to the other half of the face that was not randomly assigned to 0.1% Tyrothricin.

Primary: Inflammatory lesion count

End point title	Inflammatory lesion count

End point description:

At the screening / inclusion visit the inflammatory lesions (papules and pustules, nodules and cysts) in the patient´s face (forehead, cheeks and region of the chin) excluding the nasal region were counted by the investigator. Each side of the face was assessed separately. The counting was repeated on Day 4 and 8 ± 1d (visit 2, 3), Day 12 and 15 ± 1d (visit 4, 5), Day 18 and 22 ± 1d (visit 6, 7), and Day 25 ± 1d (visit 8). The absolute change or the reduction of inflammatory lesion count between the inclusion visit and each subsequent visit was determined. Finally, the change in inflammatory lesion counts over all measurement time points was considered.

End point type	Primary

End point timeframe:

Over 25 consecutive days. The count of lesion numbers occured only on Day 4 and 8 ± 1d (visit 2, 3), Day 12 and 15 ± 1d (visit 4, 5), Day 18 and 22 ± 1d (visit 6, 7), and Day 25 ± 1d (visit 8).

End point values	0.1 % Tyrothricin	Clindamycin + BPO	BPO 5%	0.1% Tyrothricin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	12	12	23
Units: Lesion count (n)				
arithmetic mean (confidence interval 95%)	21.5 (16 to 27.1)	23.1 (13.5 to 32.7)	19.9 (13.3 to 26.5)	17.8 (13.2 to 22.5)

End point values	0.1% Tyrothricin	Clindamycin + BPO	Clindamycin + BPO	BPO 5%
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	11	11	12

Units: Lesion count (n)				
arithmetic mean (confidence interval 95%)	13.8 (10.4 to 17.3)	13.9 (9.3 to 16.9)	10.8 (5.8 to 15.7)	14.1 (10.1 to 18.1)

End point values	BPO 5%			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Lesion count (n)				
arithmetic mean (confidence interval 95%)	9.8 (6.8 to 12.7)			

Statistical analyses

Statistical analysis title	wilcoxon test
Comparison groups	0.1 % Tyrothricin v Clindamycin + BPO v BPO 5% v 0.1% Tyrothricin v 0.1% Tyrothricin v Clindamycin + BPO v Clindamycin + BPO v BPO 5% v BPO 5%
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Primary: Non-inflammatory lesion count

End point title	Non-inflammatory lesion count

End point description:

At screening / inclusion visit the non-inflammatory lesions (open and closed comedones) in the patient´s face (forehead, cheeks and region of the chin) excluding the nasal region were counted by the investigator. Each side of the face was assessed separately. The counting was repeated on Day 4 and 8 ± 1d (visit 2, 3), Day 12 and 15 ± 1d (visit 4, 5), Day 18 and 22 ± 1d (visit 6, 7), and Day 25 ± 1d (visit 8). Then the absolute change or the reduction of noninflammatory lesion count between the inclusion visit and each subsequent visit was determined respectively. Finally, the change in non-inflammatory lesion counts over all measurement time points was considered.

End point type	Primary

End point timeframe:

The counting was conducted at the inclusion visit, and repeated on Day 4 and 8 ± 1d (visit 2, 3), Day 12 and 15 ± 1d (visit 4, 5), Day 18 and 22 ± 1d (visit 6, 7), and Day 25 ± 1d (visit 8).

End point values	0.1 % Tyrothricin	Clindamycin + BPO	BPO 5%	0.1% Tyrothricin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	12	12	12
Units: Lesion count				
arithmetic mean (confidence interval 95%)	34.5 (27.8 to 41.3)	37.5 (25.7 to 49.3)	35.5 (24.7 to 46.3)	31.1 (25.3 to 37.0)

End point values	0.1% Tyrothricin	Clindamycin + BPO	Clindamycin + BPO	BPO 5%
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	11	11	12
Units: Lesion count				
arithmetic mean (confidence interval 95%)	28.0 (23.2 to 32.9)	30.7 (23.0 to 38.5)	21.4 (15.2 to 27.7)	25.2 (18.1 to 32.2)

End point values	BPO 5%			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Lesion count				
arithmetic mean (confidence interval 95%)	18.8 (14.1 to 23.4)			

Statistical analyses

Statistical analysis title	Wilcoxon test
Comparison groups	0.1 % Tyrothricin v Clindamycin + BPO v BPO 5% v 0.1% Tyrothricin v 0.1% Tyrothricin v Clindamycin + BPO v Clindamycin + BPO v BPO 5% v BPO 5%
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: Investigator’s Static Global Assessment (ISGA)

End point title	Investigator’s Static Global Assessment (ISGA)

End point description:

Treatment success was determined by the improvement in ISGA. At inclusion visit and at each following visit (2 - 8) the investigator assessed the acne severity by using the ISGA 6-point scale. Only patients with an Investigator´s Static Global Assessment Score (ISGA) of 2 to 4 will were enrolled in the trial. Each side of the face was assessed separately. Finally, the absolute and relative ISGA score change between inclusion and each subsequent visit was determined. According to the recommendation of the U.S. Food and Drug Administration (FDA) the ISGA score was also dichotomized.

Treatment success was defined as improvement by at least two grades from the baseline score. Subjects were discontinued from the trial by the investigator at any time if the ISGA increased for one or more grades from baseline.

End point type	Secondary

End point timeframe:

At inclusion visit and at each following visit (2 - 8) the investigator assessed the acne severity by using the ISGA 6-point scale.

End point values	0.1 % Tyrothricin	Clindamycin + BPO	BPO 5%	0.1% Tyrothricin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	12	12	23
Units: IGSA Score				
arithmetic mean (confidence interval 95%)	2.7 (2.4 to 3.0)	2.8 (2.3 to 3.4)	2.6 (2.3 to 2.9)	2.4 (2.2 to 2.7)

End point values	0.1% Tyrothricin	Clindamycin + BPO	Clindamycin + BPO	BPO 5%
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	11	11	12
Units: IGSA Score				
arithmetic mean (confidence interval 95%)	2.4 (2.1 to 2.7)	2.5 (2.1 to 2.8)	2.3 (1.6 to 2.9)	2.4 (2.1 to 2.7)

End point values	BPO 5%			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: IGSA Score				
arithmetic mean (confidence interval 95%)	2.3 (1.8 to 2.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Sebum content

End point title	Sebum content

End point description:

At the inclusion visit and at each of the following visits the sebum level was determined with a photometric device (Sebumeter®, Courage+Khazaka electronic GmbH). The early, mild non-inflammatory lesions (microcomedones and comedones) are associated with higher sebum amount and higher fluorescence intensity, while the late, severe inflammatory lesions (pustules, papules, nodules and cysts) are associated with lower sebum amount and lower fluorescence intensity. This suggests that the increased sebum secretion and the presence of Propionibacteria are predominantly involved in the initial stages of acne

development. A special opaque plastic tape (64 mm2) was pressed onto the designated skin areas (separately for left and right)25 for 30 seconds with a slight pressure to collect the sebum. The resulting increase in transparency of the tape was be measured. The displayed values corresponded to the sebum amount on the skin surface in micrograms of sebum per square centimeters.

End point type	Secondary

End point timeframe:

Sebum content was measured at the inclusion visit and every subsequent visit (Visit 2-8).

End point values	0.1 % Tyrothricin	Clindamycin + BPO	BPO 5%	0.1% Tyrothricin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	12	12	23
Units: µg/cm^2				
arithmetic mean (confidence interval 95%)				
Forehead	110.7 (65.6 to 155.8)	101.3 (46.2 to 156.4)	128.1 (52.1 to 204)	125.2 (88.4 to 162)
Cheek	130.8 (82.3 to 179.2)	132.3 (75.3 to 189.2)	174.8 (101.6 to 248.0)	151.9 (103.4 to 200.4)

End point values	0.1% Tyrothricin	Clindamycin + BPO	Clindamycin + BPO	BPO 5%
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	11	11	12
Units: µg/cm^2				
arithmetic mean (confidence interval 95%)				
Forehead	211.5 (167.3 to 255.8)	161.4 (80.1 to 242.7)	172.8 (103 to 242.7)	131.3 (87.8 to 175.0)
Cheek	251.1 (196.4 to 305.8)	204.3 (115.2 to 293.4)	203.4 (155.3 to 251.6)	134.4 (73.3 to 195.6)

End point values	BPO 5%			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: µg/cm^2				
arithmetic mean (confidence interval 95%)				
Forehead	320.3 (235.8 to 404.8)			
Cheek	284.5 (192.7 to 376.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Fluorescence Quantity (Visiopor)

End point title	Fluorescence Quantity (Visiopor)

End point description:

At the inclusion visit and at each of the following visits follicular fluorescence was determined by Visiopor® PP34N camera. The camera head was placed on the relevant skin areas.23 Measurements were made separately on the right and left side of the face on four designated areas. The parameters analyzed were the number and the percentage of the area covered by orange-red spots. The orange-red fluorescence shows stronger correlation with the presence of non-inflammatory acne lesions (comedones) and high sebum amount than the presence of inflammatory acne lesions (pustules) and low sebum amount. Yellow color spots in the images were excluded from the analysis. The absolute change in follicular fluorescence was evaluated. The measurement was repeated twice.

End point type	Secondary

End point timeframe:

Visiopor was measured at the inclusion visit as well as all subsequent visits (Visit 2-8).

End point values	0.1 % Tyrothricin	Clindamycin + BPO	BPO 5%	0.1% Tyrothricin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	12	12	23
Units: Quantity				
arithmetic mean (confidence interval 95%)				
Forehead	15.1 (6.3 to 24.0)	5.8 (2.0 to 9.6)	23.3 (5.0 to 41.6)	11.6 (5.6 to 17.5)
Cheek	26.8 (13.4 to 40.1)	19.3 (4.8 to 33.7)	28.4 (9.5 to 47.3)	20.5 (11.8 to 29.3)

End point values	0.1% Tyrothricin	Clindamycin + BPO	Clindamycin + BPO	BPO 5%
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	11	11	12
Units: Quantity				
arithmetic mean (confidence interval 95%)				
Forehead	11.6 (7.0 to 16.1)	3.6 (1.4 to 5.9)	4.9 (2.7 to 7.2)	5.0 (2.2 to 7.7)
Cheek	18.1 (10.3 to 25.8)	7.4 (3.7 to 11.2)	7.7 (2.3 to 13.0)	5.4 (2.1 to 8.7)

End point values	BPO 5%			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Quantity				
arithmetic mean (confidence interval 95%)				

Forehead	4.9 (1.7 to 8.2)			
Cheek	6.0 (2.2 to 9.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Fluoresence size (Visiopor)

End point title	Fluoresence size (Visiopor)

End point description:

At the inclusion visit and at each of the following visits follicular fluorescence was determined by Visiopor® PP34N camera. The camera head was placed on the relevant skin areas.23 Measurements were made separately on the right and left side of the face on four designated areas. The parameters analyzed were the number and the percentage of the area covered by orange-red spots. Yellow color spots in the images were excluded from the analysis. The absolute change in follicular fluorescence was evaluated. The measurement was repeated twice.

End point type	Secondary

End point timeframe:

Fluorensce size (Visipor) was measured at inclusion visit, as well as all subseuqent visits (Visit 2-8).

End point values	0.1 % Tyrothricin	Clindamycin + BPO	BPO 5%	0.1% Tyrothricin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	12	12	23
Units: Size (%)				
arithmetic mean (confidence interval 95%)				
Forehead	1.1 (0.4 to 1.8)	0.3 (0.1 to 0.6)	2.1 (0.4 to 3.9)	0.7 (0.3 to 1.2)
Cheek	1.9 (0.9 to 2.8)	1.0 (0.1 to 2)	2.1 (0.7 to 3.5)	1.5 (0.9 to 2.1)

End point values	0.1% Tyrothricin	Clindamycin + BPO	Clindamycin + BPO	BPO 5%
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	11	11	12
Units: Size (%)				
arithmetic mean (confidence interval 95%)				
Forehead	0.7 (0.3 to 1.1)	0.1 (0.04 to 0.2)	0.1 (0.07 to 0.2)	0.1 (0.04 to 0.2)
Cheek	1.3 (0.7 to 2.0)	0.2 (0.1 to 0.4)	0.3 (0.05 to 0.5)	0.2 (0.1 to 0.3)

End point values	BPO 5%			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Size (%)				
arithmetic mean (confidence interval 95%)				
Forehead	0.2 (0.02 to 0.3)			
Cheek	0.3 (0.08 to 0.6)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs and SAEs were followed throughout the duration of the study. At each subject visit the investigator enquired about any local intolerance or AE using open questions, taking care not to influence the subjects answer.

Adverse event reporting additional description:

At each visit the investigator enquired about any AE by interviewing the subject using an open question, taking care not to influence the subject's answer, and if appropriate a clinical examination. Information regarding AE was immediately recorded in the CRF, and if a concomitant medication was reported an AE and reason for use was documented.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Edema to tyrothricin

Reporting group description: -

Serious adverse events	Edema to tyrothricin		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Edema to tyrothricin		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 24 (8.33%)		
Skin and subcutaneous tissue disorders			
edema			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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 limitations of our proof-of-concept study were the size of the investigational cohort and the short study duration of 25 days. Longer treatment periods are more appropriate to study long-term changes in acne trials.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26458265