2. Synopsis

Name of sponsor: Almirall Hermal GmbH, Scholtzstraße 3, 21465 Reinbek, Germany	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of finished product: Not applicable yet	Volume:	
Name of active ingredient: Isotretinoin Tested in three different doses: 0.1 mg/kg BW 0.3 mg/kg BW 0.5 mg/kg BW	Page:	
Reference to the according CSR: CSR_10033002-0486, Final Version 5-0		

Title of study:

Double-blind, double-dummy, randomised, placebo-controlled, five-armed, multi-centre phase II/III study to evaluate the efficacy and safety of different concentrations of isotretinoin versus doxycycline in the treatment of rosacea, subtype II and III

Study number: 10 0330 02 – 0486 EUDRACT No. 2006-002410-35

Investigators:

Coordinating investigator: [redacted] Otto-von-Guericke-Universität Magdeburg, Universitätsklinik für Dermatologie und Venerologie, 39120 Magdeburg, Germany

In total 35 principal investigators participated in this study – a list of all principal investigators and centres is given in appendix 16.1.4

Study centers:

35 centers in Germany

Publication (reference):

Not applicable to this study

Study period:	**Clinical study phase:**
Date of first patient first visit: 13 February 2007 Date of last patient completed: 08 July 2008	Phase II / III

Objectives:

The objective of this phase II/III study was to assess the efficacy and safety of three different concentrations of isotretinoin compared to doxycycline and placebo in the treatment of rosacea subtypes II and III (according to Wilkin et al, 2002) and to obtain dose-response information for the different isotretinoin concentrations.

The aim of the study was to show that at least one of the chosen concentrations of isotretinoin is non-inferior to doxycycline and superior to placebo.

Primary objective:

As the primary objective the reduction in the total sum of facial papules/noduli and pustules after a 12 weeks treatment was compared between the treatment groups.

Secondary objectives:

To compare the following efficacy variables between the treatment groups:

- changes in the static "Global physician's assessment score – Rosacea"
- changes in the severity scores for erythema, oedema, telangiectasia, seborrhoea, rhinophyma and blepharitis
- investigator's overall improvement rating
- patient's overall improvement rating
- changes in the quality of life measured by patient reported outcomes
- achievement of patient's treatment preferences

To compare the following safety variables between the treatment groups:

- changes in laboratory values
- overall tolerability based on number and severity of study medication-related AEs/SAEs

To compare the following safety variables between the isotretinoin treatment groups:

- changes in the severity scores for mucocutaneous side effects (xerosis cutis, burning and itching, cheilitis, and eye dryness)

Methodology (design if study):

This study was performed as a double-blind, double-dummy, randomised, placebo-controlled, comparator-controlled, five-armed, parallel-group, multi-centre phase II/III study with an adaptive design. Treatment over 12 weeks either with 0.1 mg/kg BW isotretinoin, 0.3 mg/kg BW isotretinoin, 0.5 mg/kg BW isotretinoin, doxycycline or placebo. Regular visits after 2, 4, 8, and 12 weeks of treatment.

Number of patients planned:

Sample size for superiority of isotretinoin to placebo: a total sample size of N=50 (including 20 % drop out) patients was planned to be treated in each treatment group (isotretinoin 0.1 mg/kg, 0.3 mg/kg and 0.5 mg/kg; placebo; doxycycline).

Sample size for non-inferiority of isotretinoin compared to doxycycline: a total sample size of N=140 (including 20 % drop out) patients was planned to be treated in each of the active treatment arms.

Number of patients treated:

In total 573 patients were enrolled into 5 treatment groups and analysed:

- isotretinoin 0.1 mg/kg: 111 patients
- isotretinoin 0.3 mg/kg: 147 patients
- isotretinoin 0.5 mg/kg: 116 patients
- doxycycline: 152 patients
- placebo: 47 patients

Further information on the patients´ validity for analysis sets is given below.

Diagnosis and main criteria for inclusion:

Male or female patients, aged ≥ 18, suffering from rosacea subtype II or III with a minimum grade 4 in the "Global physician's assessment score – Rosacea" and a minimum of 8 inflammatory lesions.

Test products:	isotretinoin (0.1 mg/kg, 0.3 mg/kg and 0.5 mg/kg)
Dose:	once daily; 0.1 mg/kg BW, 0.3 mg/kg BW or 0.5 mg/kg BW
Route of administration:	oral (capsules)
Batch numbers:	520107
Duration of treatment:	12 weeks treatment period
Reference product:	doxycycline (Doxyderma 50®)
Dose:	once daily; 100 mg per day during the first 14 days (2 weeks) and 50 mg per day during the following 70 days (10 weeks);
Route of administration:	oral (tablets)
Batch numbers:	520107
Duration of treatment:	12 weeks treatment period
Control treatment:	placebo
Dose:	once daily;
Route of administration:	oral (tablets / capsules)
Batch numbers:	520107
Duration of treatment:	12 weeks treatment period

Criteria for evaluation:

Efficacy

The following efficacy variables were analysed for comparison of the treatment groups:

- total sum of facial papules/noduli and pustules at each visit counted by the investigator. The reduction in the total sum of facial papules/noduli and pustules was the primary efficacy variable. This reduction was measured as difference in the total sum from baseline to end of treatment after 12 weeks.
- investigator global assessment evaluated using the 9-point static “Global physician’s assessment score – Rosacea”
- severity scores for erythema, oedema, telangiectasia, seborrhoea, rhinophyma and blepharitis assessed at visit 3, visit 4, visit 5 and visit 6 using four point scores (none, mild, moderate, severe)
- dermatology Life Quality Index (DLQI) completed by the patient at visit 2, 4, 5, and 6. Changes in the global score (sum of the single items) of the quality of life questionnaire from visit 2 (baseline visit) to visits 4, 5, and 6 were analysed.
- investigator’s overall improvement rating based on a comparison of the rosacea severity from visit 2 (baseline visit) to each subsequent visit. The rating was performed using a 6 point score reflecting the degree of decrease of disease signs and symptoms (complete remission, marked improvement, moderate improvement, slight improvement, no changes, and deterioration).
- patient’s overall improvement rating based on a comparison of the rosacea severity from visit 2 (baseline visit) to the end of study visit. The rating was performed using a 5 point score reflecting the degree of clearance of disease signs and symptoms (excellent improvement, good improvement, moderate improvement, no changes, deterioration).
- patient’s treatment aims and benefit evaluated at visit 2 and 6.

For these variables the changes from baseline to each visit were analysed.

Safety

The following efficacy variables were analysed for comparison of the treatment groups:

- documentation of adverse events (AEs) during the total study period
- severity and the localization of xerosis cutis as well as the severity of burning and itching, cheilitis, and eye dryness was assessed at each visits (visit 2 to 6) using four point scores (none, mild, moderate, severe).
- laboratory safety evaluations (serum chemistry, haematology) at visits 1, 4, 5 and 6. Changes in laboratory values were analysed.
- vital signs and physical examination at Visit 1 and Visit 6
- documentation of prior- and concomitant medication and medical history

Statistical methods:

The study hypotheses of superiority of isotretinoin concentrations under investigation to placebo (H_1) as stated above was confirmatory tested by a Wilcoxon-Mann-Whitney-test at significance level of α=0.025 for a 1-sided test.

The following hypotheses were tested for superiority:

$H_{0,1|D3}$.: The function of distribution of random variable "change in total sum of facial papules/noduli and pustules" for patients under dosage D3=highest dose of isotretinoin ($X_{SUM\ T}$) is stochastically less or equal compared to the function of distribution under placebo ($X_{SUM\ PL}$).

$H_{0,1|D2:}$ The function of distribution of random variable "change in total sum of facial papules/noduli and pustules" for patients under dosages D2=intermediate dose of isotretinoin ($X_{SUM\ T}$) is stochastically less or equal compared to the function of distribution under placebo ($X_{SUM\ PL}$).

$H_{0,1|D1:}$ The function of distribution of random variable "change in total sum of facial papules/noduli and pustules" for patients under dosages D1=lowest dose of isotretinoin ($X_{SUM\ T}$) is stochastically less or equal compared to the function of distribution under placebo ($X_{SUM\ PL}$).

The error probability for all tests was set to 0.025. According to multiple testing a Bonferroni-Holm adjustment of the error probability was performed.

The following hypothesis was tested for non-inferiority:

$H_{0,2}$: The function of distribution of random variable "change in total sum of facial papules/noduli and pustules" for patients under the most efficient dosage of isotretinoin ($X_{SUM\ T}$) is stochastically smaller than under doxycycline ($X_{SUM\ R}$) minus an accepted margin.

If the null-hypothesis non-inferiority of isotretinoin compared to doxycycline can be rejected, a test for superiority will applied, without change of the error probability.

Secondary efficacy variables were exploratively compared between treatment groups.
Frequencies of patients for secondary target variables were compared between treatment groups by Chi-Square- tests. Scales (severity scores for erythema, oedema, telangiectasia, seborrhoea, and rhinophyma and assessments of global efficacy) were compared by Wilcoxon-Mann-Whitney- tests between treatment groups.

Study population:

A total number of 708 patients was enrolled and screened for the study in 33 study centres. 135 patients were screening failures and not included in the treatment phase. In total 573 patients (81% of all screened patients) entered the treatment phase of the study and received study medication.

The study was performed with an adaptive design; in the first part of the study (1st cohort) patients were assigned randomly into 5 treatment groups: doxycycline (DOXY), isotretinoin 0.5 mg/kg BW (ISO 0.5), isotretinoin 0.3 mg/kg BW (ISO 0.3), isotretinoin 0.1 mg/kg BW (ISO 0.1) and placebo. After inclusion of about 45 patients in each treatment group the placebo treatment group had been closed – from this date

further patients were randomly assigned to the remaining 4 active treatment arms (2nd cohort).

Patients were assigned into the 5 different treatment groups. Patients were valid for the different analysis sets as follows:

Number of patients in		DOXY	ISO 0.5	ISO 0.3	ISO 0.1	Placebo
1st cohort	Safety set	47	40	45	45	47
	Full analysis set	46	39	43	40	46
	Per protocol set	42	36	40	36	39
2nd cohort	Safety set	105	71	102	71	0
	Full analysis set	97	70	99	69	0
	Per protocol set	90	65	89	64	0
Total cohort	Safety set	152	111	147	116	47
	Full analysis set	143	109	142	109	46
	Per protocol set	132	101	129	100	39

Summary of Efficacy:

1. Primary efficacy analyses:

The first study objective was to show the superiority of at least one concentration of isotretinoin (0.1, 0.3 or 0.5 mg/kg BW) to placebo in the treatment of rosacea subtype II and III, measured by the change in total sum of facial papules/noduli and pustules from baseline to end of treatment. This objective was analyzed in the first study cohort and for the Full Analysis Set (FAS).

The decrease the in total number of papules/noduli and pustules was more pronounced in all isotretinoin treatment groups (ISO 0.1: -14; ISO 0.3: -15; ISO 0.5: -13) than in the placebo group (-9).

The isotretinoin dose ISO 0.3 was statistically significant superior to placebo as the 1-sided p-value (p=0.00523) was well below the adjusted limit of p=0.00833. The dosages ISO 0.1 and ISO 0.5 did not reach statistical significance, although they showed a better response than placebo.

The second study objective was to show the non-inferiority of the best isotretinoin group to doxycycline. This objective was analyzed with an adaptive study design combining the first and second study cohort and was performed in the Per Protocol Set (PPS).

In the 1st cohort ISO 0.3 showed a median decrease in the total number of papules/noduli and pustules of 15 compared to 16 in the DOXY group. In the 2nd cohort patients treated with ISO 0.3 showed a better median decrease in the total number of papules/noduli and pustules than patients treated with DOXY (median ISO 0.3: -16, DOXY: -13).

In the first cohort the 97.5%-C.I. of the difference in location reached down to –5, including the accepted difference of –4.8 (30% of the value of patients treated with doxycycline). The p-value for non-inferiority in this cohort is p=0.03776. In the second cohort the 97.5%-C.I. of the difference in location reached down to –1, not including the accepted difference of –3.8. The p-value for non-inferiority in this cohort is p=0.00018. Combining the test results of both cohorts of the study population gave a p-value of 0.00001, which is well below the critical value for the adaptive design of p=0.0038.

Thus the ISO 0.3 dosage was statistically significant non-inferior to the DOXY treatment.

2. Secondary efficacy analyses:

The secondary efficacy variables were analyzed for the first cohort using the FAS comparing all isotretinoin dosages to placebo.

Patients treated with ISO 0.3 showed the best efficacy in reducing the total number of papules/noduli and pustules, followed by ISO 0.1 and ISO 0.5 compared to placebo. Already after 2 weeks of treatment (at V3) a change was documented for all isotretinoin dosages.

In the first cohort the change in severity of erythema, oedema, telangiectasia, seborrhoea and blepharitis was more pronounced in all isotretinoin dosages than under placebo. Only for the symptom "erythema", patients under ISO 0.5 had less improvement than under placebo. For the symptoms seborrhoea and telangiectasia the descriptive p-values for the difference of the active treatments compared to placebo showed a significant advantage of all isotretinoin dosages. Patients receiving ISO 0.3 had significantly more improvements in rhinophyma and patients receiving ISO 0.5 had significantly more improvements in oedema than patients under placebo.

The median scores of the DLQI showed an improvement for all treatment groups The maximal decrease was seen in patients receiving ISO 0.5. No difference of any active treatment compared to placebo could be found.

The median value of the rosacea assessment score was 5 for all treatment groups at baseline (possible range from 0 to 8). It reduced to 2 or less in the active treatment groups and to 3 in the placebo group. Patients receiving ISO 0.1, ISO 0.3 or ISO 0.5 showed an improvement of 3 points compared to 2 points of patients receiving placebo. All active treatment groups showed a significant advantage compared to placebo.
According to the investigator's overall improvement rating at the final visit (V6) the highest rate of "complete remission" was seen in patients receiving ISO 0.3 (27.9%). The rate of "complete remission" was 23.1% for patients receiving ISO 0.1 and 12.5% for patients receiving ISO 0.5. Only 6.5% of the patients under placebo showed a "complete remission". The Cochran-Armitage Test for Trend showed a significant advantage of all active treatment groups compared to placebo

According to the patient's overall improvement rating at the final visit (V6) the highest rate of "excellent improvement" was seen in patients receiving ISO 0.1 and ISO 0.3 (25.6%). The rate of "excellent improvement" was 15.0% of patients receiving ISO 0.5. Only 8.7% of the patients receiving placebo showed an "excellent improvement". The Cochran-Armitage Test for Trend showed a significant advantage of all active treatment groups compared to placebo.

Patients of the active treatment groups showed more benefit in the domains "physical well-being", "psychological well-being" and "quality of life" than patients of the placebo group according to the patient's global assessment of treatment success at the final visit.

The results of the secondary target variables also demonstrate the superiority of ISO 0.3 compared to placebo and substantiate that ISO 0.3 is the most favourable dosage as the higher concentration gains no more therapeutical success.

The secondary efficacy variables were also analysed for the total sample using the PPS to compare the most efficient isotretinoin dosage (ISO 0.3) to doxycycline.

Patients treated with ISO 0.3 showed a better efficacy in reducing the total number of papules/noduli and pustules compared to patients treated with DOXY.

Patients treated with ISO 0.3 showed a higher efficacy in change of the symptoms rhinophyma and blepharitis compared to doxycycline and a lower efficacy in change of the symptoms erythema and oedema. The advantage of ISO 0.3 in improvement of blepharitis compared to DOXY was statistically significant. None of the other differences were statistically significant.

The median score of the DLQI showed a less pronounced improvement in patients treated with ISO 0.3 compared to patients treated with DOXY. This difference is statistically significant.

Patients of both treatment groups showed an improvement in the physician's assessment score throughout the duration of the study. The median change from baseline to the end of study visit was 3 points for both treatment groups. No statistical significance between the treatment groups could be shown.

According to the investigator's overall improvement rating at the final visit a higher rate of "complete remission" was seen in patients receiving ISO 0.3 (24.0%) compared to patients receiving doxycycline (13.6%). The Cochran-Armitage Test for Trend showed a significant advantage of isotretinoin treatment compared to doxycycline.

According to the patient's overall improvement rating at the final visit a higher rate of "excellent improvement" was seen in patients receiving ISO 0.3 (32.6%) compared to patients receiving doxycycline (24.2%). The Cochran-Armitage Test for Trend showed a significant advantage of isotretinoin treatment compared to doxycycline.

Patients treated with ISO 0.3 showed more benefit in all domains of the questionnaire than patients treated with doxycycline according to the patient's global assessment of treatment success.

The results of the secondary target variables verify the finding of non-inferiority of ISO 0.3 compared to doxycycline.

Summary of Safety:

1. Adverse events:

Incidence rates:

The total incidence rate of AEs was highest in patients treated with ISO 0.5 (90%) compared to ISO 0.1 (71 %), ISO 0.3 (68%) and DOXY (52%).

The incidence of drug related AEs was highest on treatment with ISO 0.5 (ISO 0.5 = 45%; ISO 0.3 = 33%; ISO 0.1 and DOXY = 25%) as well as the number of patients with "related" AEs (ISO 0.5 = 29%; ISO 0.3 and ISO 0.1 = 20% and DOXY = 17%). Additionally the incidence of AEs leading to withdrawal of study medication was highest under ISO 0.5 (ISO 0.5 = 12%; ISO 0.3 = 9% and ISO 0.1 = 7% and DOXY = 6%).

Diagnoses of adverse events and respective WHO-System Organ Class:

The most frequent AEs (N=74, 19.3%) were "gastro-intestinal system disorders", with 49 drug-related AEs and the highest incidence rates of drug-related AEs for DOXY and ISO 0.5 (DOXY = 9.9%; ISO 0.5 = 9.5%, ISO 0.1 = 8.1% and ISO 0.3 = 7.5%). The most prominent symptom in this SOC was "diarrhoea".

64 AEs (16.7% of all AEs) were "central and peripheral nervous system disorders", with 33 drug related AEs and the highest incidence rate of drug related AEs under ISO 0.5 (ISO 0.5 = 9.5%; ISO 0.3 = 6.8%; DOXY = 4.6%; ISO 0.1 = 3.6%). The most common AE in this SOC was "headache".

43 AEs (11.2%) were classified as "body as a whole general disorders", with 16 drug related AEs and the highest incidence rate under ISO 0.1 (ISO 0.1 = 5.4%; ISO 0.03 = 2.6%, DOXY = 2.7 %; ISO 0.5 = 1.7%). The most common symptom in this SOC was "pain, leg and back pain".

64 AEs (16.7%) were "respiratory system disorders" with 8 drug related AEs and an incidence rate of drug related AEs of about 2% in ISO 0.5, ISO 0.3 and DOXY. The most common symptoms in this SOC were "Upper Respiratory Tract Infection".

The main number of patients suffering from a "common" AE during the study was treated with ISO 0.5 (ISO 0.5 = 11%, ISO 0.3 = 5%, ISO 0.1 = 8%).

Serious adverse events

In total 8 AEs (2.1% of all AEs) were serious adverse events (SAEs), of which only one SAE was assessed as possible related to study drug. Patient (#303) treated for 12 weeks with ISO 0.5 several

days after scheduled end of study treatment suffered from a cerebral infarction (described as “facial nerve paresis on the right side dysartria”). As there are several case reports documenting vascular events under treatment with isotretinoin the sponsor’s drug safety classified this SAE as possibly related to the study drug isotretinoin (0.5 mg/kg BW).

2. Mucotaneous side effects / concomitant symptoms:

The severity of known mucotaneous adverse reactions of isotretinoin (xerosis cutis, itching or burning, cheilitis, and dry eyes) was evaluated for the different isotretinoin dosages.

All doses of isotretinoin caused a worsening of xerosis cutis in the majority of patients (more than 60%), with an increased severity over the course of treatment period. ISO 0.5 was connected with the highest rate of aggravation (ISO 0.5=68%, ISO 0.3=60%, ISO 0.1=59%, placebo=30%).

Overall burning and itching aggravated less than the other symptoms and was in the range, which also for placebo was observed. ISO 0.5 caused the highest rate of worsening (ISO 0.5=27%, ISO 0.3=16%, ISO 0.1=15%, placebo=20%).

Cheilitis was the most remarkable and common mucotaneous adverse reaction. All doses of isotretinoin caused a rapid increase of the cheilitis´ severity in the majority of patients. Thus 61% of ISO 0.5 patients and 74% of the ISO 0.3 patients showed a change in the symptoms of cheilitis after 2 weeks of treatment. Additionally the severity increased over time of treatment under all isotretinoin doses. ISO 0.3 caused the highest rate of cheilitis´ worsening (ISO 0.5=80%, ISO 0.3=83%, ISO 0.1=69%, placebo=17.5%).

The changes in the symptom “eye dryness” appeared less distinct as a worsening of more than one point was rare. This symptom clearly was dose-dependent as it aggravated strongest in the ISO 0.5 group and appeared already after 2 weeks under treatment. ISO 0.5 caused the highest rate of aggravation (ISO 0.5=38%, ISO 0.3=29%, ISO 0.1=21%, placebo=17.5%).

All concomitant symptoms were well tolerable with use of skin care products. Mild or moderate symptoms, which were treated with skin care products, removed by use of skin care for the most part. The residuary cases were tolerable with use of skin care. Even severe symptoms were assessed as tolerable with use of skin care for the most part, only in a few cases the symptoms were not tolerable and led to the discontinuation of the study medication intake.

3. Safety laboratory parameters:

Concerning the blood values of all safety laboratory parameters the following significant changes were noticed:

An increase over the period of the study was observed for blood values of cholesterol, liver enzymes and triglycerides. Several patients with normal blood test results at baseline (V2) had an increased value during the study (more than 20% above upper limit of normal).

Regarding the liver enzymes (gamma-GT, ASAT, and ALAT) ISO 0.5 caused the main increase of blood values – between 7% and 11% of patients with normal baseline values had an increased value (>20 above upper limit of normal) over the course of the treatment phase. ISO 0.3 treatment was associated with an increase in 2 – 7% of patients, DOXY caused an increase in 4 – 6% of patients.

In contrast cholesterol increased similarly in all isotretinoin dosages, most frequently under treatment with ISO 0.3 (19%) followed by ISO 0.5 (18%), ISO 0.1 (16%) and DOXY (16%).

The most important increase of triglycerides from a normal limit to above upper limit of normal (i.e. from 170 – 204 mg/dl) and/or more than 20 % above upper limit of normal (> 204 mg/dl) was observed for ISO 0.5. 44% of patients on ISO 0.5 experienced any increase of triglycerides above the normal limit during the therapy, but even all other treatments were connected with an increase of triglycerides in several patients (placebo=18%, ISO 0.3=25%, DOXY=19%, ISO 0.1=29%).

Safety conclusions:

Comparing the occurrence of the safety parameters in the different treatment groups lead to the following conclusions regarding the treatments safety profile:

ISO 0.5 caused the highest incidence rates of AEs, related AEs and AEs connected with the stop of study medication. Additionally the most patients suffering from any "common" AE were treated with ISO 0.5. The severity of concomitant symptoms deteriorated strongest under treatment with ISO 0.5; albeit the difference from ISO 0.5 to ISO 0.3 and ISO 0.1 was unspectacular. Regarding the blood values of safety laboratory ISO 0.5 caused the main increase of liver enzymes and triglycerides, with clearly more patients with increased values than in all other treatment groups.

The occurrence of safety parameters was more similar in ISO 0.3 and ISO 0.1, albeit ISO 0.1 had slightly lower incidence rates for AEs, related AEs and AEs connected with the stop of study medication. In both lower dosages of isotretinoin the same AEs commonly occurred than under ISO 0.5, but with a lesser incidence rate.

ISO 0.1 stand out regarding the reasons for a stop of study medication: 3%ISO 0.3 patients withdrew due to a "worsening of rosacea". This may point to a less efficacy of the 0.1 mg/kg BW dosage.

ISO 0.3 more frequently was related to an increase of cholesterol than ISO 0.1 albeit the lowest dosage caused an increase of blood cholesterol in 16% of the patients, too.

Apart from the above named related SAE - a cerebral infarction 5 days after termination of the study medication (isotretinoin 0.5 mg/kg BW) -, for isotretinoin no serious unexpected adverse events with relation to study medication, including concomitant symptoms and laboratory parameters, had been noticed over the whole study. The active comparator – doxycycline – took a middle position concerning the safety characteristics. The occurrence of AEs, and the increase of blood values were lower than under ISO 0.5 treatment but higher or equal to the ISO 0.3 and ISO 0.1. Overall the distribution and frequencies of adverse events had been expected and adverse events that occurred were known side effects of doxycycline.

Overall conclusions:

On the basis of the overall safety profile the dosage of 0.5 mg/kg BW isotretinoin was distinguished as the dose, which caused more adverse events and concomitant symptoms than the lower dosages ISO 0.3 and ISO 0.1. Corresponding, the efficacy results verified the dosage of 0.3 mg/kg BW isotretinoin as superior to placebo and additionally non-inferior to doxycycline in its efficacy against rosacea. Thus ISO 0.3 is the most favourable dosage with the best ratio between benefit and risk.

The dosage of 0.3 mg/kg BW isotretinoin represents an effective and safe treatment option compared to current standard therapy doxycycline for the treatment of rosacea subtype II and III.

Date of report: 09-Dec-2008