Clinical Study Report Synopsis

LEO 29102 Cream in the Treatment of Atopic Dermatitis

A Phase 2, proof of concept and dose finding study, investigating treatment efficacy of LEO 29102 cream (2.5 mg/g, 1.0 mg/g, 0.3 mg/g, 0.1 mg/g, 0.03 mg/g), LEO 29102 cream vehicle, and Elidel® (pimecrolimus) cream 10 mg/g, after cutaneous administration twice daily for 4 weeks

An international, multi-centre, prospective, randomised, double-blind, 7-arm, vehicle-controlled, parallel group study

LEO Pharmaceutical Products Ltd. A/S
(LEO Pharma A/S)
Clinical Development

LEO 29102-C21
31-MAR-2011
EudraCT Number 2009-013792-22

CLINICAL STUDY REPORT SYNOPSIS APPROVAL

APPROVAL STATEMENT

On behalf of LEO, only the Vice President, International Clinical Development and the Head of Biostatistics, LEO HQ are authorised to approve the Clinical Study Report Synopsis.

All LEO approvers will be identified on a signature page of the pdf-file of the final Clinical Study Report Synopsis when the last LEO approval is obtained. The time and date of their e-signatures are likewise presented on the approval page.

The following persons have approved this Clinical Study Report Synopsis using electronic signatures:

[redacted] Biostatistics, LEO HQ

[redacted], International Clinical Development

APPROVAL STATEMENT INVESTIGATORS

The International Co-ordinating Investigator approves the Clinical Study Report Synopsis by manually signing the International Co-ordinating Investigator Clinical Study Report Approval Form, which is a separate document adjoined to this report.

The following person has approved this Clinical Study Report Synopsis

Professor [redacted]
International Co-ordinating Investigator

SYNOPSIS

Name of Sponsor/Company: LEO Pharma A/S	Individual Trial Table Referring to Part of the Dossier	
Name of Finished Product: To be decided.	Volume:	
Name of Active Ingredient: LEO 29102 (2-{6-[2-(3,5-dichloro-pyridin-4-yl)-acetyl]-2,3-dimethoxy-phenoxy}-N-propyl-acetamide)	Page:	

Title of trial: LEO 29102 cream in the treatment of atopic dermatitis.

Investigators:
International Co-ordinating Investigator: Prof. [redacted]
National Co-ordinating Investigators: Dr [redacted] (Canada), Prof. [redacted] (Finland), Prof. [redacted] (Germany) and Dr. [redacted] (New Zealand).

Trial centres: Canada; Fourteen centres initiated, thirteen centres recruited patients. Germany; Fifteen centres initiated, thirteen centres recruited patients. Finland; Four centres initiated, four centres recruited patients. (No trial activities were initiated in New Zealand.)

Publication (reference): Not applicable.

Trial period:	Phase of development:
Date of first enrolment: 18-Dec-2009 Date of last completed: 06-Jul-2010	Phase 2

Objectives:
The primary objective of the study was to identify the optimal strength with respect to efficacy of five different strengths of LEO 29102 cream in the topical treatment of patients with atopic dermatitis (AD), when applied twice daily for up to 4 weeks.

The secondary objectives were to compare and describe the efficacy of each of the five dose strengths of LEO 29102 cream, LEO 29102 cream vehicle and Elidel® 10 mg/g cream (pimecrolimus) with regards to:

- EASI (Eczema Area and Severity Index)
- Investigator's Global Assessment (IGA) of disease severity
- symptom-free responders
- pruritus
- erythema
- oedema/induration/papulation
- excoriation
- lichenification
- time to permanent response
- subject overall assessment of disease severity

and to compare and describe the safety and local tolerance profile.

Number of subjects:

	LEO 29102 cream vehicle	LEO 29102 0.03 mg/g cream	LEO 29102 0.1 mg/g cream	LEO 29102 0.3 mg/g cream	LEO 29102 1.0 mg/g cream	LEO 29102 2.5 mg/g cream	Elidel® cream 10 mg/g	Total
No. planned	25	25	25	25	25	25	25	175
No. randomised	25	24	25	25	29	30	25	183
No. analysed (primary	25	24	25	25	29	30	25	183

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efficacy variable)								

Diagnosis and main criteria for inclusion:

1. Clinical diagnosis of AD defined according to Hanifin and Rajka.
2. IGA assessment scored as mild to moderate AD.
3. Treatment lesions located on the trunk and/or limbs.
4. Treatment lesions involving 3% to 10% of the total body surface area.
5. Subjects of either gender between 18 years and 65 years of age.
6. Use of contraceptives as defined in the study protocol.
7. Following verbal and written information about the trial, the subject had to provide signed and dated informed consent before any study-related activity was carried out, including activities relating to the wash-out period.

Test product, dose and mode of administration, batch number:

Topical administration on AD skin lesions on trunk and limbs twice daily (morning and evening). Maximum daily dose: 8.5 g.

LEO 29102 0.03 mg/g cream. Batch No.: 091617401; LEO 29102 0.1 mg/g cream. Batch No.: 091617501

LEO 29102 0.3 mg/g cream. Batch No.: 091617601; LEO 29102 1.0 mg/g cream. Batch No.: 091617701

LEO 29102 2.5 mg/g cream. Batch No.: 091617801; LEO 29102 cream vehicle. Batch No.: 091617301

Duration of treatment:

Up to 4 weeks treatment. Subjects who were evaluated by the Investigator to be symptom-free (as defined by an IGA of 0 or 1, i.e., clear or almost clear of symptoms) at any of Visits 2-4 could stop treatment at the Investigator's discretion but should remain in the study and attend all visits up to and including Visit 6. The subjects had to have study medication dispensed and should restart treatment if required, based on the subjects own judgement. More than one discontinuation/restart cycle was allowed.

Reference therapy, dose and mode of administration, batch number:

Elidel® cream (pimecrolimus) 10 mg/g. Topical administration on AD skin lesions on trunk and limbs twice daily (morning and evening). Maximum daily dose: 8.5 g. Batch No.: [redacted] and [redacted]

Criteria for evaluation:

Efficacy:

The primary response criterion was the absolute change in EASI (Eczema Area and Severity Index) on trunk and limbs from baseline to the end of treatment (Visit 5). Secondary response criteria included:

- Proportion of subjects with controlled disease ('clear' or 'almost clear' according to IGA)
- IGA of disease severity on the body (trunk and limbs excluding the hands) at Visits 1-5 and change in IGA from baseline to each visit
- Absolute EASI score on trunk and limbs at Visits 1-5 and change in EASI from baseline to each visit
- Each individual element of the EASI score and change in each individual element from baseline
- Patient's overall assessment of disease severity on trunk and limbs (excluding the hands) at Visits 1-5
- Patient's assessment of pruritus on trunk and limbs at Visits 1-5
- Time until permanent response (defined as 'clear' or 'almost clear' according to IGA and no subsequent worsening above 'almost clear' observed).

Safety:

Both systemic, local and laboratory adverse events (AEs) were included to evaluate the safety and local tolerance profile of the various treatments. Additionally, analyses of reproductive hormones were performed.

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Statistical methods:
The primary efficacy criterion was analysed for the full analysis set and the per protocol analysis set. The analysis based on the full analysis set is considered as primary.

The absolute change in EASI on trunk and limbs from baseline to end of treatment was analysed in a linear model with treatment group and pooled country (Canada, German + Finland) as factors. Least Square (LS)-mean absolute change in each treatment group including 95% confidence intervals (CIs) were calculated. Each of the active LEO 29102 treatment groups was compared to both the vehicle group and the Elidel® group, with respect to difference in LS-means including 95% CI and p-value for each comparison.

The secondary efficacy criteria were only analysed for the full analysis set. The proportion of symptom-free responders ('clear' or 'almost clear' according to IGA) at end of treatment were calculated by treatment group with exact 95% CIs. The treatment effect of LEO 29102 was evaluated in a logistic regression model with concentrations 0 (vehicle), 1 (LEO 29102 0.03 mg/g), 2 (LEO 29102 0.1 mg/g), 3 (LEO 29102 0.3 mg/g), 4 (LEO 29102 1.0 mg/g), 5 (LEO 29102 2.5 mg/g) as a covariate and pooled country (Canada, German + Finland) as a factor.

Patient's assessment of pruritus on trunk and limbs and patient's overall assessment of disease severity were tabulated at end of treatment by treatment. The effect of treatment with LEO 29102 was evaluated in a proportional odds model with concentrations (see paragraph above) as a covariate and pooled country as a factor.

The analysis of safety was based on the safety analysis set. Adverse events were coded during the trial in accordance with the current version of the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The AEs are presented by preferred terms and primary system organ class (SOC). The causal relationship to trial medication for each type of AE (according to the coding system) was tabulated by treatment group. The number of subjects experiencing each type of adverse drug reaction (ADR) was tabulated by treatment group by the same principles as described for adverse events. The intensity for each type of ADR was tabulated by treatment group.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:
The mean EASI score at baseline was low, ranging from 4.6 to 6.4. Although none of the differences between vehicle and the five LEO 29102 groups in LS-mean absolute change in EASI from baseline to end of treatment were statistically significant, they all represented a numerically better effect compared to the vehicle, Table 1. The estimated difference between the vehicle and the comparator, Elidel® 10 mg/g, with regard to LS-mean absolute change in EASI on trunk and limbs from baseline to end of treatment in the full analysis set was statistically significant, Table 1. The estimated mean differences between Elidel® 10 mg/g and each of the five LEO 29102 groups were all in favour of Elidel® 10 mg/g but none of these differences were statistically significant, Table 1.

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Table 1: Absolute and percentage change in EASI from baseline to end of treatment: full analysis set

	LEO 29102 vehicle (N=25)	LEO 29102 0.03 mg/g (N=24)	LEO 29102 0.1 mg/g (N=25)	LEO 29102 0.3 mg/g (N=25)	LEO 29102 1.0 mg/g (N=29)	LEO 29102 2.5 mg/g (N=30)	Elidel 10 mg/g (N=25)
LS-mean absolute change (mean percentage change)[1]	-0.85 (-19.95%)	-2.13 (-28.53%)	-1.09 (-17.04%)	-2.86 (-37.76%)	-2.41 (-47.36%)	-2.50 (-39.40%)	-3.30 (-53.12%)
Difference in absolute change[1] (active treatment minus vehicle)		-1.29	-0.25	-2.01	-1.56	-1.65	-2.46
95% CI		-3.60 to 1.03	-2.53 to 2.04	-4.30 to 0.28	-3.77 to 0.65	-3.84 to 0.54	-4.74 to -0.17
p-value		0.27	0.83	0.08	0.16	0.14	0.04
Difference in absolute change[1] (active treatment minus comparator)	2.46	1.17	2.21	0.45	0.90	0.81	
95% CI	0.17 to 4.74	-1.14 to 3.48	-0.08 to 4.50	-1.84 to 2.73	-1.31 to 3.10	-1.38 to 3.00	
p-value	0.04	0.32	0.06	0.70	0.42	0.47	

[1] Adjusted for the effect of (pooled) country.

To account for the differences in baseline EASI between the treatment groups, a post-hoc analysis was performed with baseline EASI as an additional covariate. In this model, the estimated mean difference between vehicle and the five LEO 29102 groups were in favour of LEO 29102 but none of the differences were statistically significant. The test for a dose-response relationship (test for linear trend in EASI change with increasing LEO 29102 dose group, adjusted for baseline EASI score) resulted in a p-value of 0.06.

The percentages of responders (IGA classified as “clear” or “almost clear”) at end of treatment were 24.0% (vehicle), 8.3% (LEO 29102 0.03 mg/g), 20.0% (LEO 29102 0.1 mg/g), 36.0% (LEO 29102 0.3 mg/g), 34.5% (LEO 29102 1.0 mg/g), 43.3% (LEO 29102 2.5 mg/g) and 48.0% (Elidel® 10 mg/g). The logistic regression analysis showed a statistically significant effect of LEO 29102 (odds ratio [OR]: 1.3; 95% CI: 1.1-1.6; p=0.01).

The percentage of subjects reporting no pruritus at end of treatment ranged from 4.2% (LEO 29102 0.03 mg/g) to 28.0% (LEO 29102 0.3 mg/g) and the percentage of subjects reporting severe pruritus at end of treatment ranged from 0.0% (LEO 29102 0.3 mg/g) to 29.2% (LEO 29102 0.03 mg/g). The analysis (proportional odds model) of the patient’s assessment of pruritus showed a dose-dependent statistically significant effect of LEO 29102 (OR: 1.2; 95% CI: 1.0-1.5; p=0.01).

Similar results were observed for patient’s overall assessment of disease severity. The percentage of subjects assessing the severity as “cleared” at end of treatment ranged from 3.3% (LEO 29102 2.5 mg/g) to 13.8% (LEO 29102 1.0 mg/g) and the percentage of subjects reporting severe disease at end of treatment ranged from 0.0% (LEO 29102 1.0 mg/g) to 16.0% (vehicle). The analysis (proportional odds model) showed a dose-dependent statistically significant effect of LEO 29102 (OR: 1.2; 95% CI: 1.0-1.4; p=0.03).

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In summary, with regard to the primary efficacy variable, the LS-mean absolute changes in EASI on trunk and limbs from baseline to end of treatment in the full analysis set, all five LEO 29102 groups showed a numerically better effect than the vehicle but the differences were not statistically significant. However, the logistic regression analysis of percentages of responders (IGA classified as "clear" or "almost clear") at end of treatment showed a statistically significant effect of LEO 29102 (OR: 1.3; 95% CI: 1.1-1.6; p=0.01). Moreover, analyses showed a dose-dependent statistically significant effect of LEO 29102 on the patient's assessment of pruritus (OR: 1.2; 95% CI: 1.0-1.5; p=0.01) and patient's overall assessment of disease severity (OR: 1.2; 95% CI: 1.0-1.4; p=0.03). From the efficacy data in this study it was not possible to identify one optimal strength with respect to efficacy but the data clearly indicated that the three highest strengths (LEO 29102 0.3 mg/g, LEO 29102 1.0 mg/g and LEO 29102 2.5 mg/g) were more efficacious than the lower ones.

SAFETY RESULTS:

The frequency of AEs was highest in the vehicle group (13 subjects [52.0%] reporting 16 AEs) in the treatment phase. Among the LEO 29102 dose groups, the frequency of AEs was higher in the lowest LEO 29102 dose group (11 subjects [45.8%] reporting 12 AEs) than in the other treatment groups. The lowest frequency of AEs was observed in the highest dose group (8 subjects [26.7%] reporting 10 AEs). Eight subjects (32.0%) in the Elidel® 10 mg/g group reported a total of 12 AEs during the treatment phase.

The SOC with the highest number of AEs was "infections and infestations", affecting 24 subjects with the highest numbers in the vehicle and Elidel® groups (5 subjects each) and the lowest in the LEO 29102 2.5 mg/g group (1 subject). The SOC "skin and subcutaneous tissue disorders" was the next most commonly reported and affected 19 subjects with the highest number in the vehicle group (7 subjects) and the lowest in the LEO 29102 0.3 mg/g group (0 subjects).

Six preferred terms were reported by more than one subject within a treatment group in the treatment phase. These were: atopic dermatitits (12 subjects with the highest frequency [13.3%] in the LEO 29102 2.5 mg/g group), nasopharyngitis (11 subjects with the highest frequency [12.0%] in the Elidel® 10 mg/g group), application site pain (reported by 5 subjects with the highest frequency [8.3%] in the LEO 29102 0.03 mg/g group), headache (5 subjects with the highest frequency [7.1%] in the LEO 29102 1.0 mg/g group), rhinitis (2 subjects [8.0%] in the LEO 29102 0.3 mg/g group) and pruritus (2 subjects [8.0%] in the Elidel® 10 mg/g group).

Thirty-two lesional/perilesional AEs were reported by 27 subjects in the treatment phase. Atopic dermatitis was the most common lesional/perilesional AE and was reported with a frequency ranging from 0.0% in the LEO 29102 0.3 mg/g group and the Elidel® 10 mg/g group to 13.3% in the LEO 29102 2.5 mg/g group. Nine lesional/perilesional AEs were of severe intensity: 4 in the vehicle group, 3 in the LEO 29102 2.5 mg/g group and 2 in the LEO 29102 0.1 mg/g group. The highest frequency of lesional/perilesional AEs was observed within the category of AEs with onset on Days 1-6.

Thirty-four subjects reported 42 ADRs in the treatment phase. The frequency of ADRs ranged from 4.0% in the LEO 29102 0.3 mg/g group to 29.2% in the LEO 29102 0.03 mg/g group. Atopic dermatitis was the most commonly reported preferred term among ADRs and the frequency ranged from 0% in the LEO 29102 0.3 mg/g group and the Elidel® 10 mg/g group to 13.3% in the LEO 29102 2.5 mg/g group. Nine ADRs were of severe intensity: 4 in the vehicle group (one case each of application site pruritus, atopic dermatitis, erythema and generalized pruritus), 3 cases of atopic dermatitis in the LEO 29102 2.5 mg/g group and 2 cases of atopic dermatitis in the LEO 29102 0.1 mg/g group.

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Ten AEs were of severe intensity (4 in the vehicle group, 3 in the LEO 29102 2.5 mg/g group, 2 in the LEO 29102 0.1 mg/g group and 1 in the LEO 29102 0.03 mg/g group). The only preferred term with more than one AE of severe intensity in the treatment phase was atopic dermatitis (3 in the LEO 29102 2.5 mg/g group, 2 in the LEO 29102 0.1 mg/g group and 1 in the vehicle group). Forty AEs were of moderate intensity and 38 were of mild intensity.

The highest frequency of AEs was observed within the category of AEs with onset on Days 1-6. A trend of decreasing frequency of AEs with increasing dose was observed among the AEs with onset on Days 1-6.

No deaths or SAEs were reported in the study. Nine subjects discontinued the treatment phase due to any AE(s): 4 (16%) in the vehicle group, 2 (6.7%) in the LEO 29102 2.5 mg/g group and one subject in each of the LEO 29102 0.03 mg/g, 0.1 mg/g and 1.0 mg/g groups. The 10 AEs leading to discontinuation were atopic dermatitis (7 subjects), erythema (1 subject), generalised pruritus (1 subject) and swelling of the face (1 subject).

No trends were observed in any treatment group with regard to mean changes in haematology, clinical chemistry or urinalysis variables from baseline to the subsequent visits. A few females (one subject in each of the LEO 29102 0.1 mg/g, 1.0 mg/g and 2.5 mg/g groups and one subject in the Elidel® 10 mg/g group) had lower FSH values at end of treatment than at baseline. However, the trial was neither designed nor powered to assess whether this was due to biological variation or could possibly be a drug effect.

No trends were observed in any treatment group with regard to mean changes in blood pressure, heart rate, respiration rate or body temperature from baseline to the subsequent visits.

CONCLUSION:
All five LEO 29102 treatment groups showed a numerically better effect on the EASI score from baseline to end of treatment than the vehicle but the differences were not statistically significant. However, testing for a linear trend in change of EASI score with increasing LEO 29102 dose group) resulted in a p-value of 0.06 when using baseline EASI as an additional covariate. The logistic regression analysis of percentages responders (IGA classified as “clear” and “almost clear”) at end of treatment showed a statistically significant effect of LEO 29102 (OR: 1.3; 95% CI: 1.1-1.6; p=0.01). Moreover, analyses showed a dose-dependent statistically significant effect of LEO 29102 on the patient’s assessment of pruritus and patient’s overall assessment of disease severity. In summary, it was not possible to identify one optimal strength with respect to efficacy but the data clearly indicated that the three highest strengths (LEO 29102 0.3 mg/g, LEO 29102 1.0 mg/g and LEO 29102 2.5 mg/g) were more efficacious than the lower ones.

Date of the Report:

SCHEDULE/CHART OF TRIAL PROCEDURES

Visit	**0 Screen-ing** [a)]	**1 Randomi-sation (baseline)** [b)]	**2**	**3**	**4**	**5**	**6**	**End of treatment** [c)]
Day	**-28 to 0**	**0**	**7**	**14**	**21**	**28**	**56**	**-**
Visit window (days)			**±1**	**±2**	**±2**	**±3**	**±4**	
Informed consent	X	(X)						
Subject demographics (including height and weight)	X	(X)						
In/exclusion criteria	X	X						
Pregnancy test	X	X				X		X
Concomitant treatment	X	X	X	X	X	X	X	X
Concomitant illnesses	X	X						
Medical history	X	(X)						
Atopic dermatitis history	X	(X)						
Dermatological examination		X						
Vital signs [d)]		X	X			X		X
ECG [m)]	X	(X)						
Blood sample (clinical chemistry, haematology) [e)]		X	X			X	X	X
Blood sample (serology) [f)]		X						
Blood sample (hormone screen) [g)]		X	X	X		X	X	X
Urine sample [h)]		X	X			X	X	X
Randomisation		X						
Adverse event(s)		X[i)]	X	X	X	X	X	X
EASI assessment		X[j)]	X	X	X	X		X
Assessment of other symptoms of AD		X				X		X
IGA assessment		X	X	X	X	X		X
Patient's overall assessment		X	X	X	X	X		X
Patient's assessment of pruritus		X	X	X	X	X		X
Dispensing of investigational product		X	X	X	X			
Dispensing of other treatment [k)]	X	(X)	X	X	X			
Compliance			X	X	X	X		X
Return of used/unused investigational product			X	X	X	X		X
End of Trial Form [l)]		X	X	X	X	X	X	X

a) The screening period was defined as the time between Visit 0 and Visit 1. The screening period included any wash-out period. This period varied between 0 to 28 days depending on whether the subject was using a treatment for AD.

b) Procedures indicated with an X within brackets did not have to be repeated for subjects who had been on wash-out. All procedures at baseline had to be performed for subjects not requiring wash-out.

c) End of Treatment (including those within brackets) was applicable for all randomised subjects. If a subject was prematurely withdrawn from the trial due to an AE classified as possibly or probably related to the investigational product or not assessable in relation to the investigational product an End of Treatment procedure was to be completed.

d) Vital signs including blood pressure, pulse rate, body temperature (oral or ear) and respiration rate

e) Clinical chemistry including total bilirubin, bilirubin, alkaline phosphatase, gamma glutamyl transferase (γ-GT),

aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), lactate dehydrogenase (LDH), creatinine kinase (CK), CK myocardial band (CK MB) isoenzyme, creatinine, urea, uric acid, cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, total protein, albumin, globulin, glucose, bicarbonate, inorganic phosphate, Na^+, K^+, Ca^{2+}, Cl^-, Mg^{2+}, high sensitivity C-reactive protein (CRP).
Haematology including: leucocytes, erythrocytes, haemoglobin, haematocrit, thrombocytes, partial automated differentiation: lymphocytes, monocytes, eosinophils, basophils, neutrophils and mean corpuscular volume (MCV).

f) Serology including: hepatitis B, hepatitis C and human immunodeficiency virus (HIV)
g) Hormone screen including: inhibin B, anti-Mullerian hormone (AMH), follicle stimulating hormone (FSH), luteinising hormone (LH). Oestrogen and progesterone (females only) and testosterone (males only)
h) Urinalysis including blood, ketones, glucose, protein, pH, nitrites, leucocytes, microscopy if results were positive for blood or protein
i) Only for subjects who underwent wash-out
j) Including the head/neck area.
k) Other trial medication: hydrocortisone 1% cream, Locobase® fatty cream and Essex® cream. Other trial medication was dispensed on an individual basis per subject as needed.
l) If a subject was not randomised or when a subject was ending the trial, the End of Trial Form was to be completed.
m) Applicable for subjects in Canada only.

LEO 29102-C21 Clinical Study Report Synopsis - English

ELECTRONIC SIGNATURES

Electronic signature made within eDoc LEO by LEO Pharma A/S employees or employees of any LEO Pharma A/S affiliate located anywhere in the world, are to be considered to be legally binding equivalent of traditional handwritten signatures.

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
[redacted]	[redacted], International Clinical Development Approval	05-apr-2011 20:23 GMT+02
[redacted]	[redacted] Biostatistics Approval	06-apr-2011 08:38 GMT+02