SYNOPSIS

PROTOCOL ID:	ACCOST
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STUDY TITLE:	A PHASE 2, MULTICENTER, RANDOMIZED, DOUBLE- BLIND, PLACEBO-CONTROLLED, PARALLEL- GROUP, EFFICACY STUDY OF APREMILAST (CC-10004) IN SUBJECTS WITH EROSIVE HAND OSTEOARTHRITIS
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INDICATION:	Symptomatic treatment of erosive hand osteoarthritis
PHASE:	II
INVESTIGATOR(S):	
Coordinating principal Investigator	Prof. Dr. Georg Schett Department of Internal Medicine 3 Friedrich-Alexander-University Erlangen-Nuernberg Ulmenweg 18 91054 Erlangen, Germany
Investigators:	The study was conducted at 6 experienced centres in Germany (3 rheumatological departments of university hospitals and 3 practice-based rheumatological specialists)
MATERIAL AND METHODS:	
Study Population:	Subjects, male or female and ≥ 18 years of age must have had a diagnosis of erosive hand osteoarthritis (EHOA), fulfilling the classification criteria of the American College of Rheumatology (ACR) with a disease duration for at least 6 months. Patients must have had active disease and a self assessment of pain at baseline of at least 40 mm on a VAS.

Ethics: This study was performed according to the principles of the current edition of the declaration of Helsinki, according to the German Drug Law (AMG), and according to Good Clinical Practice (GCP), including the archiving of essential documents.

Study Design: This study was designed as phase 2, multicentre, randomised, double-blind, placebo-controlled, parallel-group, efficacy and safety study in 30 patients with erosive osteoarthritis of interphalangeal joints. The study was composed of 4 phases: a pre-randomisation phase for up to 35 days followed by a 91-day randomised, double-blind two arm treatment phase, followed by a 77-day open label treatment phase for all study participants and a 28-day observational follow-up phase. Efficacy of the double blind and open label phase was assessed at study day 84 and 168 after treatment start respectively.

Study Objectives: The primary objective was to evaluate the 84-day efficacy of apremilast 20 mg twice per day [BID], subsequent to a 7-day dose titration, compared with placebo, for the treatment of the symptoms of erosive hand osteoarthritis.

Further objectives were to evaluate the effects on pain, disease activity, structural damage, quality of life, safety and tolerability.

Study Product and Treatment: Apremilast was supplied as 10 mg capsules for oral administration. Identically appearing placebo capsules were provided. After a 7-day titration phase patients received either 20 mg PO BID apremilast (apremilast group), or placebo (placebo group) for 84 days. Afterwards all patients received 20 mg BID apremilast for another 84 days with a 7 day titration phase applying to patients who received placebo during the double blind phase. Batch numbers used: 10F0421, 11F0277, and 12R0015.

Statistical analysis: The primary analysis was done according to the intent-to-treat principle for the full analysis set.

All parameters were planned to be evaluated in an explorative or descriptive manner, P values, if reported, will be presented explicitly without referring to hypotheses or a significance level.

The primary parameter was defined as the response rate based on a $\geq$50% improvement of the AUSCAN Score at day 84 after treatment start compared to baseline. Response rates should be summarised by frequency rates together with exact 95% confidence intervals. Patients with no assessment at day 84 after treatment start will be treated as non-responders in this analysis.

Secondary parameters were patient pain and patient global

assessment assessed on a 100 mm VAS, SACRAH, HAQ-DI and SF-36 scores for patient self assessments, tender and swollen joint count and RAMRIS and HOAMRIS scores for the evaluation of MRI assessments. Secondary target parameters were analysed on available data.

Duration of the Study: First Patient First Visit (FPFV): 29-Nov-2010

Last Patient Last Visit (LPLV): 19-Jul-2013

Number of Patients:
Planned: 30
Screened: 43
Randomised: 34
Treatment started (ITT and safety population): 30
(apremilast group: N=20, placebo group: N=10)
Per protocol population: 21
(apremilast group: N=14, placebo group: N=7)

RESULTS:

Study Population: 30 patients were randomised as planned to start treatment with apremilast or placebo in a 2:1 ratio. The patients were 63.1 years (Range: 47-75) in the apremilast and 58.4 years of age (Range: 45-72) in the placebo group. 12 patients (60%) in the apremilast and 8 (80%) in the placebo group were female and all patients were caucasian. The body mass index was 26.2 ± 3.7 in the apremilast and 23.8 ± 3.8 (Mean ± standard deviation) in the placebo group. Time from initial diagnosis was 7.9 ± 6.8 in the apremilast and 8.9 ± 7.2 years (Mean ± STD) in the placebo group. Patient global assessment of pain at baseline was 62.5 ± 18.8 mm and 57.6 ± 17.0 mm in the apremilast and placebo group respectively (Mean ±STD) on a 100 mm VAS. Patient global assessment of disease activity at baseline on a 100 mm VAS was 62.3 ± 21.8 mm and 60.2 ± 13.8 mm (Mean ± STD) in the apremilast and the placebo group.

AUSCAN sum scores were nearly identical at baseline (Mean ± STD: apremilast: 17.27 ± 4.00, placebo: 17.79 ± 3.94).

All patients had concomitant diseases ongoing at the time of randomisation. The most frequently reported were essential (primary) hypertension in 9 patients (45%) in the apremilast and 5 (50%) patients in the placebo group, followed by disorders of lipoprotein metabolism and other lipidemias in 7 patients (35%) in the apremilast group, whereas no such disease was reported in the placebo group. An equal frequent disease was hypothyreoidism in 4 patients (20%) in the apremilast and in 3 patients (30%) in the placebo group.

Primary Endpoint: Regarding the primary endpoint which is response defined by a ≥ 50% improve in AUSCAN score at day 84 after treatment start compared to baseline two responders were detected, one in the

apremilast group and one in the placebo group accounting for a response rate of 5% rsp. 10%. The risk difference (apremilast – placebo) was calculated to –5% with exact confidence intervals between –43% to +34% (Santner & Snell) or –39% to +19% (Chan & Zhang). As both confidence intervals include null there is no evidence of a treatment effect measured by AUSCAN-50 response after the double blind treatment phase.

Secondary Efficacy Endpoints:

The result of the primary endpoint is confirmed in the per protocol population which contains one AUSCAN-50 responder in the apremilast and none in the placebo group (Risk difference: 7.14%, 95% CI: -40% to +52% or –34% to 34%).

Secondary endpoints included patient self assessments as well as MRI assessments of the dominant hand. The following results in table E1 were obtained for the response rates bases on a ≥50% improvement of the score during the double blind treatment phase.

Tab. E1: Response defined as ≥50% improvement after double blind treatment *)

Response ≥50% improvement	Apremilast N: n(%)	Placebo N: n(%)	Risk Diff [Trt-Ctr] (95% CI) **)
VAS PAIN	19: 6 (31.58)	9: 2 (22.22)	9.36 (-29.82; 47.19)
VAS PGA	19: 4 (21.05)	9: 2 (22.22)	-1.17 (-39.13; 37.71)
Joint Pain	19: 8 (42.11)	9: 3 (33.33)	8.77 (-31.59; 47.19)
Joint Swelling	18: 10 (55.56)	9: 5 (55.56)	0.00 (-40.92; 40.92)
Morning Stiffness	19: 14 (73.68)	8: 6 (75.00)	-1.32 (-41.69; 39.46)
SACRAH	19: 4 (21.05)	9: 1 (11.11)	9.94 (-27.89; 47.19)
SF-36 PCS	18: 0 (0.00)	9: 0 (0.00)	-
SF-36 MCS	18: 0 (0.00)	9: 0 (0.00)	-
HAQ-DI	18: 0 (0.00)	9: 0 (0.00)	-
RAMRIS	14: 6 (42.86)	7: 2 (28.57)	14.29 (-33.56; 58.11)

*) Based on available data **) risk difference (apremilast – placebo) with exact confidence intervals (Santner & Snell).

Evaluation of responders defined as a ≥20% improvement during the double blind treatment phase did also not provide evidence for a treatment effect of apremilast, nor did the analysis of the open label treatment phase.

All analysis criteria were more or less improved during the study period. Comparing the differences in change from baseline values by use of 95% confidence intervals again provided no hint for group differences.

Originally RAMRIS was chosen for the evaluation of MRI assessments but when HOAMRIS was published during the study period this score was chosen for the assessment of MRIs. Scoring was done by a single experienced reader who was blinded for the identity of the patients as well as time sequence and clinical findings. The results do not show evidence for a treatment effect in any of the domains (table E2). The study was not able to show a difference in structural damage in hand or

finger joints when comparing apremilast to placebo treatment.

Tab. E2: HOAMRIS Change from Baseline During Double Blind Treatment [*)]

Change from Baseline	Apremilast N: Mean ± Std	Placebo N: Mean ± Std	DMC from baseline mean (95% CI) [**)]
Synovitis	15: -0.47 ± 3.52	7: -2.00 ± 3.37	1.53 (-1.79; 4.85)
Erosive damage	13: 0.08 ± 1.71	5: 0.00 ± 0.71	0.08 (-1.62; 1.77)
Cysts	14: -0.14 ± 0.86	8: -0.25 ± 0.46	0.11 (-0.59; 0.80)
Osteophytes	13: -0.23 ± 3.72	6: -0.67 ± 1.86	0.44 (-2.99; 3.86)
Cartilage space loss	13: -0.46 ± 2.54	7: 1.00 ± 1.83	-1.46 (-3.75; 0.83)
Malalignment	15: 0.07 ± 1.16	8: 0.13 ± 1.13	-0-06 (-1.11; 0.99)
Bone marrow lesions	15: 0.40 ± 2.67	8: -0.86 ± 2.67	1.26 (-1.29; 3.81)

[*)] Based on available data [**)] DMC: difference in mean change (apremilast – placebo) [mean (95% CI)]; <0 is in favour of apremilast

Safety Results:

The study treatment was well tolerated during the study. During the mean 158 days trial period (apremilast 160 days, placebo 154 days) a total of 154 adverse events (AE) were reported. Most of the reported events were mild to moderate and only 8 AE were severe (apremilast 6, placebo 2) according to CTCAE V3.0. 10 AE were classified as related to the study drug (apremilsat 7, placebo 3) and 44 were classified with unknown relationship (apremilast 31, placebo 13) which were considered possibly related for this analysis.

Two patients discontinued the study therapy during the double blind treatment phase due to adverse events (gastrointestinal symptoms in the apremilast group and ongoing pain in the placebo group) and one patients stopped study treatment due to worsening of arthritis two weeks after entering the open label phase (patient in the apremilast group).

During the whole study period 90% of the patients reported at least one adverse event in both study groups. During the double blind treatment phase AEs were reported by 87% of the patients (apremilast 85%, placebo 90%) and during the following open label phase 63% of the patients reported at least one adverse event (60% in the initial apremilast and 70% in the initial placebo group). The following table S1 shows the most frequent adverse events defined as events occuring in at least 10% of the patients in either the apremilast or the placebo group.

Most frequent events were found in the PAIN-Domain occurring in 63% of the patients (65% in the apremilast and 60% in the placebo group) with headache being the dominant event (apremilast 40%, placebo 50%), followed by gastrointestinal complaints in 47% of the patients (apremilast 55%, placebo 30%) with diarrhea in 27% of the patients (apremilast 30%, placebo 20%) and nausea in 20% of the patients (apremilast 30%, placebo 0%). Nausea is the only event which was clearly more frequent in the apremilast group.

Tab. S1: Most Frequent Adverse Events				
	Double Blind Study		Open Label Phase	
	Apremilast (N=20)	Placebo (N=10)	Apremilast (N=20)	Placebo (N=10)
Any AE	17 (85%)	9 (90%)	12 (60%)	7 (70%)
CARDI	4 (20%)	0 (0%)	1 (5%)	1 (10%)
Hypertension	2 (10%)	0 (0%)	1 (5%)	0 (0%)
CONST	3 (15%)	2 (20%)	0 (0%)	0 (0%)
Fatigue	3 (15%)	1 (10%)	0 (0%)	0 (0%)
GASTR	7 (35%)	2 (20%)	4 (20%)	1 (10%)
Diarrhea	3 (15%)	1 (10%)	3 (15%)	1 (10%)
Enteritis	3 (15%)	0 (0%)	0 (0%)	0 (0%)
Nausea	4 (20%)	0 (0%)	2 (10%)	0 (0%)
INFEC	3 (15%)	3 (30%)	4 (20%)	2 (20%)
Upper airway Infection	1 (5%)	1 (10%)	3 (15%)	0 (0%)
MUSCU	3 (15%)	1 (10%)	2 (10%)	3 (30%)
NEURO	3 (15%)	0 (0%)	0 (0%)	0 (0%)
PAIN	7 (35%)	4 (40%)	6 (30%)	2 (20%)
Head/headache	6 (30%)	3 (30%)	2 (10%)	2 (20%)
Bone pain	2 (10%)	0 (0%)	2 (10%)	1 (10%)
SYNDR	1 (5%)	1 (10%)	2 (10%)	1 (10%)
Flu-like syndrome	1 (5%)	1 (10%)	2 (10%)	1 (10%)

The evaluation of vital signs and physical examination revealed nothing unusual. The evaluation of laboratory values also did not show conspicious findings.

No serious adverse events and no deaths were reported during the study period and the four weeks follow up.

The safety profile was found to be consistent with the expectations for this substance and does not provide evidence for additional safety risks of apremilast.

DISCUSSION:

The large in-patient variability of used outcome measures can be addressed as one difficulty in this study on the treatment of erosive osteoarthritis of the hand. Patient self assessments are influenced by many environmental factors and by concomitant diseases and medications and show a large variability over time. The study was designed to detect only a considerable large treatment effect and found no evidence for superiority of apremilast over placebo in the treatment of erosive hand osteoarthritis.

RAMRIS/HOAMRIS scoring was affected by a substantial amount of unevaluable joints due to different MRI quality of local radiologists. HOAMRIS could be a reliable measure, but efforts should be made for best possible image quality and scoring by two independent assessors is recommended for further studies.

CONCLUSION:

The study could not demonstrate evidence for a relevant treatment effect of apremilast in patients with erosive hand osteoarthritis.

Safey data confirmed the known safety profile of apremilast and did not indicate additional safety risks.