Report Synopsis of Study

Name of Sponsor/Company: Julius-Maximilians-Universität Würzburg	Individual Study Table Referring to Part of the Dossier: not applicable Volume: not applicable Page: not applicable	*(For National Authority Use only)*
Name of Finished Product: *Zemplar*		
Name of Active Substance: *Paricalcitol*		

Title of Study:

The Effects of Paricalcitol capsules on Inflammation (CRP levels) and Calcification regulation (fetuin-A levels) in CKD stage 5D patients [EPIC-CKD].

Investigators:

LKP: Prof. Dr. Christoph Wanner, Universitätsklinik Würzburg

PI: Prof. Dr. Markus Ketteler, Klinikum Coburg

Study centre(s):

Center 1:	Universitätsklinik Würzburg, Germany
Center 2:	Klinikum Coburg, Germany
Center 3:	KfH-Nierenzentrum Coburg, Germany
Center 4:	KfH-Nierenzentrum Lichtenfels, Germany
Center 5:	KfH-Nierenzentrum Haßfurt, Germany
Center 6:	KfH-Nierenzentrum Sonneberg, Germany
Center 7:	KfH Nierenzentrum Bamberg, Germany
Center 8:	KfH-Nierenzentrum Kronach, Germany
Center 9:	Dialysepraxis Meiningen, Germany
Center 10:	KfH-Nierenzentrum Fürth, Germany
Center 11:	KfH-Nierenzentrum Kulmbach, Germany

Publication (reference):

not applicable

Studied period (years): *Date of first enrolment: 27. Jan 2009* *Date of last completed: 28. Mrz 2011*	**Phase of development:** Prospective, randomised, placebo-controlled, crossover study (phase III)

Objectives:

Primary Objectives:

30 % decrease of serum hsCRP and 20 % increase of serum fetuin-A (Nephelometrie; Dade Behring)

Secondary Objectives:

ucMGP und GlaMGP (Sandwich ELISA; Dr. L. Schurgers, Maastricht)

Osteoprotegerin (BioVendor, Heidelberg, Germany)

uc- und Gesamt-Osteocalcin (Immulite)
IL-1-beta, TNF-alpha, IL-6, IL-10 (Immulite / Agilent microbeads)

Methodology:

According to the study protocol (page 23) the statistical analysis is based on the per-protocol population, that means for the respective endpoint all patients with complete measurements for both periods.

The cross-over study design was chosen to investigate the effects of Paricalcitol as well on inflammation (hsCRP) and calcification regulation (Fetuin-A) as on the secondary endpoints ucMPG, iron, TSAT, ferritin and hepcidin. We analyzed the parameter FGF-23, precisely the log-transformed parameter LN(FGF-23), as further primary endpoint. According to the cross-over design we followed within the statistical analysis the 3-step-procedure of Tudor & Koch (1994). This strategy is based on the Grizzle-model for 2x2 cross-over-studies. But the 3-step-procedure of Tudor & Koch is a modification of the 2-step pretest-strategy originally proposed by Grizzly because of whose possibly considerable inflation of type I error rate and other drawbacks. Furthermore according to Hill & Armitage (1979) we include additionally baseline values for period 1 and period 2 in the model to increase the power. For the primary endpoints we provided graphical representations of the results from the crossover trial, as well treatment-summarizing descriptive plots not reflecting statistical comparisons, as analytic plots, that means confidence limit plots for treatment effects. According to chapter 6.1.3 of the study protocol we analyzed descriptively all safety variables and provided a line listing of all serious adverse events (SAEs), including all suspected unexpected serious adverse reactions (SUSARs) occurring in the concerned trial.

Number of patients (planned and analyzed):

Number of planned patients n = 50, 25 patients finished the protocol with full data sets available: 14 had followed treatment sequence A (paricalcitol→placebo), and 11 had followed treatment sequence B (placebo→paricalcitol)

Diagnosis and main criteria for inclusion:

hemodialysis patients (≥ 18 years)

hemodialysis treatment for ≥ 6 month and ≤ 5 years

no previous treatment with active vitamine D-analoga or withdrawal prior to study participation for at least 1 month (washout)

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

Paricalcitol Capsules, maximum dose 2µg per day, oral use

Duration of treatment:

8 month

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

Placebo Capsules, one per day, oral use

Criteria for evaluation:

Efficacy:

The aim of the study was to show or exclude a regulatory impact of paricalcitol on hsCRP and fetuin-A (analysed in week 0-12).

Safety:

Serum levels of calcium, phosphate and intact parathyroid hormone (iPTH) served as safety parameters and for guidance of therapy (calcium and phosphate analysed in week 0-12, intact parathyroid hormone (iPTH) in week 0, 6 and 12).

Statistical methods:

According to the study protocol (page 23) the statistical analysis is based on the per-protocol population, that means for the respective endpoint all patients with complete measurements for both periods.

The cross-over study design was chosen to investigate the effects of Paricalcitol as well on inflammation (hsCRP) and calcification regulation (Fetuin-A) as on the secondary endpoints ucMPG, iron, TSAT, ferritin and hepcidin. We analyzed the parameter FGF-23, precisely the log-transformed parameter LN(FGF-23), as further primary endpoint. The statistical analysis for this study design includes some additional steps compared to the analysis of data from a simple parallel design. Firstly we have to investigate possible different carry-over effects. Furthermore we have to investigate whether there are time effects not based on any effects from the treatments compared. This strategy for the statistical analysis is formalized by the 3-step-procedure of Tudor & Koch (1994). The approach is based on the Grizzle-model for 2x2 cross-over-studies. But the 3-step-procedure of Tudor

& Koch is a modification of the 2-step pretest-strategy originally proposed by Grizzly because of its possibly considerable inflation of type I error rate and other drawbacks. Furthermore according to Hill & Armitage (1979) we include additionally baseline values for period 1 and period 2 in the model to increase the power. By means of the Tudor & Koch 3-step strategy we can establish a direct treatment effect of Paricalcitol compared to placebo within a cross-over study in two situations: Firstly by evidence for an overall significant effect of Paricalcitol over both periods together with not significantly different carry-over effects (not different between Paricalcitol and placebo) from period 1 to period 2. Secondly by evidence for an overall significant effect of Paricalcitol over both periods together with significantly different carry-over effects from period 1 to period 2 and significant non-zero direct treatment effect given these different carry-over effects. For detailed explanation concerning the rationale of the analysis strategy, concerning the probabilistic foundation and concerning the inclusion of baseline values we want to refer to Tudor & Koch (1994) and Hills & Armitage (1979). For the understanding of the statements in the results-section we introduce some notations. We use the letter T as subscript to denote the study treatment, here Paricalcitol, and the letter C to denote placebo. Furthermore by TC we denote the patient group resp. sequence which comprehends the patients randomized to the treatment sequence Paricalcitol- placebo, and by CT the patient group resp. sequence which comprehends the patients randomized to the treatment sequence placebo-Paricalcitol. We consider the following model for the population means of the observed measurement variables at baseline, at the end of period 1, at the end of washout (that means begin of period 2), and at the end of period 2:

Sequenz TC:

Baseline $\mu + \pi(0)$

Periode 1 $\mu + \pi(1) + \tau(T)$

Washout $\mu + \pi(W) + \eta(T)$

Periode 2 $\mu + \pi(2) + \tau(C) + \lambda(T)$

Sequenz CT:

Baseline $\mu + \pi(0)$

Periode 1 $\mu + \pi(1) + \tau(C)$

Washout $\mu + \pi(W) + \eta(C)$

Periode 2 $\mu + \pi(2) + \tau(T) + \lambda(C)$

At this we denote by $\tau(\bullet)$ the direct treatment effects, by $\pi(\bullet)$ period effects, by $\lambda(\bullet)$ possible carry-over effects, which act from period 1 to period 2, and by $\eta(\bullet)$ possible carry-over effects, which are effective from period 1 to the begin of period 2, that means, directly at the end of the „washout"-period. With this, $2(\tau(T) - \tau(C)) – (\lambda(T) - \lambda(C))$ is the sum of the differences between the treatment effects for Paricalcitol and placebo across the two periods. The 3-step-strategy for the analysis of 2x2 cross-over studies with baseline values is based on sequential testing of three null-hypotheses formulated in terms of the parameters above.

Grafic procedures (Q-Q plots, histograms, Box-plots) indicate that generally endpoint data are not well compatible with the assumption of normal distribution. Therefore we primarily used nonparametric methods of data analysis and the respective parametric methods only for comparison. Furthermore we created graphical representations of results from the crossover trial analyzing the effect of Paricalcitol compared with placebo on hsCRP-levels, Fetuin-A serum values and FGF23 serum values including measurements at baseline, after 6 weeks and after 12 weeks for both periods:

1) Treatment-summarizing descriptive plots not reflecting statistical comparisons

2) Analytic plots: confidence limit plots

For details concerning the corresponding the procedure we refer to Senn & Auclair 1990.

G. Tudor, G.G. Koch

Review of nonparametric methods for the analysis of crossover studies

Statistical Methods in Medical Research 1994; 3: 345-381

M. Hills P. Armitage

The two-period cross-over clinical trial

B. J. Pharmac. 1979; 8: 7-20

S.J. Senn, P. Auclair

The graphical representation of clinical trials with particular reference to measurements over time, Statistics in Medicine 1990; 9: 1287-1302

Summary – Conclusions

Efficacy results:

Generally we have to note, that there is a serious problem because of the small sample size. Analysis based on the per-protocol population and missing values complicates this situation additionally.

Primary endpoints:

Primary endpoint hsCRP-Level

The null-hypothesis H0 : {2(τ(T) - τ(C)) – (λ(T) - λ(C)) = 0} couldn't be rejected at significance level 0.05 . That means there is no significant difference between the treatment effect of Paricalcitol compared with placebo across the two periods. Descriptively we observed in the Paricalcitol-placebo sequence a relative decrease in mean hsCRP-values of 36.7% during the 12 weeks. But primarily a single outlyer value (67 mg/L) accounts for this effect. All nonparametric and parametric 95% confidence intervals for the parameters 2(τ(T) - τ(C)) – (λ(T) - λ(C)), λ(T) - λ(C), τ(T) - τ(C) , π(1) - λ - π(2) and η(T) - η(C) include the zero- value.

Generally there is a tendency for lower hsCRP-values after treatment with Paricalcitol compared with placebo, but the effects are clearly to small in order to achieve significance.

Primary endpoint Fetuin-A

The difference between the treatment effect of Paricalcitol compared with placebo across the two periods is nearly zero. Descriptively we didn't observe in the Paricalcitol-placebo sequence any change in the mean Fetuin-A values during the 12 weeks. Concerning the confidence intervals for all parameters the same is valid as for hsCRP.

Endpoint LOG FGF 23

The original FGF 23 values show deviations in order of magnitude. Therefore according to the usual procedure for analyzing FGF 23 values we used log-transformed data (natural logarithm).

We observed in the Paricalcitol- placebo sequence an absolute increase in mean LOG FGF 23-values of 0.581 during the 12 weeks with corresponding 95% CI (0.245 , 0.918). That means there is a significant increase in mean LOG FGF 23 values in the sequence TC for the first period. Testing the null-hypothesis H0 :

{2(τ(T) - τ(C)) – (λ(T) - λ(C)) = 0} results in a classical "borderline"-effect (p-value for the Mann-Whitney test 0.05). The value of the Hodges-Lehman estimator for the shift in location is 0.599 with exact 95% CI (0.064 , 1.173). This result shouldn't be ignored. According to the 3-step procedure of Tudor & Koch we tested the null-hypothesis H0λ : λ(T) = λ(C) with non-significant result (p-value for the Mann-Whitney test 0.467), that means this null- hypothesis was not rejected. These results suggest that there is a true positive effect of Paricalcitol compared with placebo with respect to the endpoint LOG FGF 23. The value of the Hodges-Lehman estimator for the shift in location for the difference in direct treatment effects, τ(T) - τ(C), is 0.61 with exact 95% CI (-0.06 , +1.20). There is a clear tendency to higher mean and median LOG FGF 23 values after treatment with Paricalcitol compared with placebo.

Secondary endpoints:

Endpoint ucMPG

For this endpoint we observed a large effect, which is hardly to interprete. In period 1 there are nearly zero changes in mean and median in both sequence groups during the 12 weeks. But in period 2 we observed a considerable increase in mean and median during the 12 weeks in both sequence groups, that means as well under Paricalcitol as under placebo. That means the mean and median measurement differences (end of period 2) – (begin of period 2) are positive and large as well under Paricalcitol as under placebo. There is an excessive total period effect π(2) + λ - π(1), that means by far larger mean and median ucMPG values in period 2 compared with period 1. The value of the Hodges-Lehman estimator for the shift in location is 1102.5 with exact 95% CI (691.0 , 1594.0).

Ferritin, hepcidin:

Overall, across the two periods there is a moderate (ferritin) resp. small (hepcidin) tendency to higher responses under treatment with Paricalcitol compared with placebo. But the corresponding effects are not significant.

Iron:

For the difference of the direct treatment effects, τ(T) - τ(C), we observed a tendency to posive values, that means larger mean and median values for paricalcitol compared with placebo.

TSAT:

Not interpretable tendencies at all.

Safety results:

As prespecified, serum levels of calcium, phosphate and intact parathyroid hormone (iPTH) served as safety parameters and for guidance of therapy. As expected, PTH was significantly lowered by paricalcitol treatment.

There was also a trend for higher serum calcium levels in association with paricalcitol therapy. This trend reached statistical significance during weeks 4, 8, 10, and 12. Serum phosphate levels were not significantly different between treatment phases and treatment groups. There were no relevant therapeutic adaptations (phosphate binders) explaining this neutral effect.

In total, 52 adverse events (AE) were observed in 43 patients, out of which 20 were considered serious (SAE). With regard to treatment phases 24 (46.2%) AE occurred in the paricalcitol arm and 19 (36.5%) AE occurred in the placebo arm; 9 (17.3%) AE were observed during washout.

Concerning the 25 patients available for full data set analysis, 13 (52%) experienced anAE, and 4 (16%) experienced a SAE.There were no differences in the frequency of both AE and SAE between paricalcitol and placebo groups.

In only2 patients, the investigators considered a potential causal relationship between AE and study drug. One AE was hypercalcemia, the other was gastrointestinal reflux. Both events occurred in the paricalcitol group.
2 patients were withdrawn from the study due to a SAE. One patient experienced upper gastrointestinal bleeding, the other patient from terminal congestive heart failure (this patient subsequently died from his/her condition).

Conclusion:

In this prospective, regional, multicenter trial, 43 patients on hemodialysis were included and randomized to 2 treatment sequences (paricalcitol→placebo, placebo→paricalcitol) in a crossover fashion. Twenty-five patients completed the study with full data sets, so unfortunately insufficient power is a limitation in analyzing the study results. The aim of the study was to investigate a possible regulatory impact of Paricalcitol on hsCRP and fetuin-A. With regard to hsCRP, there was a trend towards lower mean and median serum levels under Paricalcitol compared with placebo, but this effect was not statistically significant. For Fetuin-A we couldn't observe any treatment effect at all. For ucMPG

we couldn't detect any tendency to a stable treatment effect for Paricalcitol . As an additional surrogate parameter, log- transformed FGF23 was also investigated showing borderline significance with higher mean and median levels under Paricalcitol treatment. These results were unfortunately hampered by the relatively small sample size. Our observations concerning hsCRP levels suggest that Paricalcitol may have some anti-inflammatory potential, however, that there may be therapeutic responders and non-responders.