CCL2 Inhibition with Emapticap Pegol (NOX-E36) in Type 2 Diabetic Patients with Albuminuria

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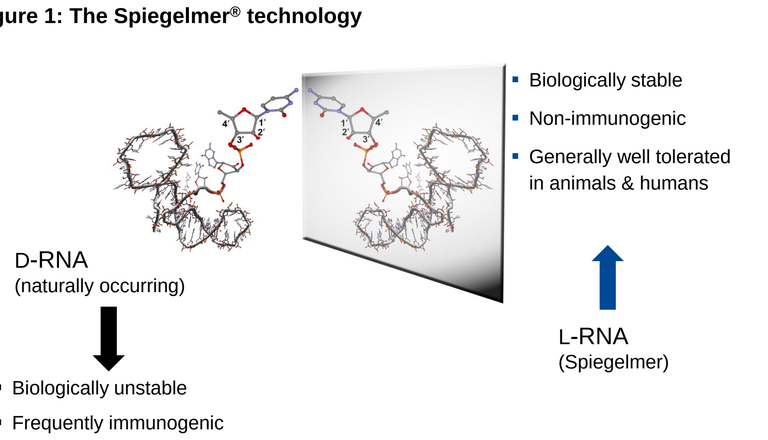
ISN World Congress of Nephrology 2015, Cape Town
Abstract Number: WCN15-0231
Poster Board: SUN-487

Introduction and Aims

Emapticap pegol (NOX-E36) is a Spiegelmer®, i.e. a PEGylated L-RNA oligonucleotide (Figure 1) that specifically binds and inhibits the pro-inflammatory chemokine CCL2 (MCP-1), which plays a major role in monocyte/macrophage infiltration in the kidney and thus in the pathophysiology of diabetic nephropathy. Emapticap was well tolerated in single and repeat dose Phase I studies in healthy volunteers and diabetics and first hints indicating a renoprotective effect were obtained. The objective of this study was to establish the renoprotective and antidiabetic potential of emapticap in type 2 diabetic patients with proteinuria.

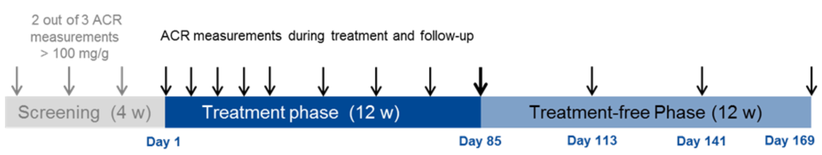
Figure 1: The Spiegelmer® technology



Methods

A randomized, double blind, placebo-controlled multi-site phase IIa POC study in five European countries was initiated in 76 proteinuric type 2 diabetics. Patients in the study had to be on stable antidiabetic therapy and RAS blockade and had to present with an ACR >100 mg/g, an eGFR >25 mL/min × 1.73 m² and an HbA1c from 6.0% to 10.5%. Emapticap was administered SC at 0.5 mg/kg twice weekly for 12 weeks, followed by a treatment-free observation period of 3 months (Figure 2). In addition to analysis of the full patient set (FAS), a *post hoc* analysis was performed for which patients with major protocol violations, treatment with dual RAS blockade and concomitant hematuria and leukocyturia were excluded (primary efficacy analysis set, PEAS).

Figure 2: Study design



Results

Emapticap pegol was generally well tolerated, with few mild local injection site reactions as the only relevant treatment-related AEs. Plasma concentrations reached pharmacologically relevant levels of 355 ± 105 nM (Figure 3) and the expected pharmacodynamic effect was observed, i.e. a decrease in the number of monocytes in peripheral blood which is maintained throughout the whole treatment period and a re-increase back to baseline after stop of dosing. Furthermore, the presence of the CCL2 receptor CCR2 on the monocytes was reduced during treatment with emapticap (Figure 4).

Figure 3: Pharmacokinetics of emapticap pegol

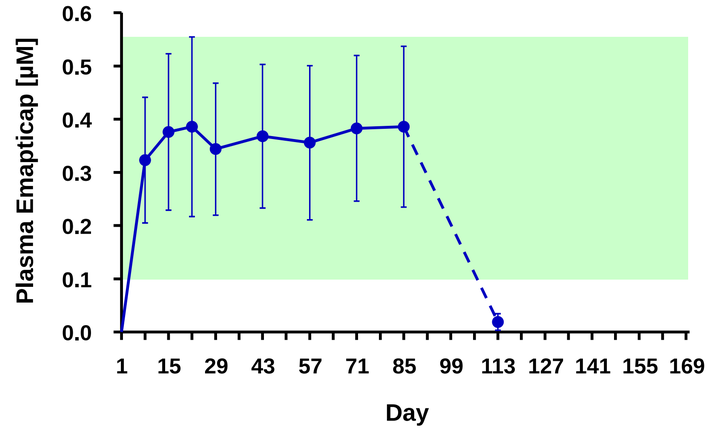
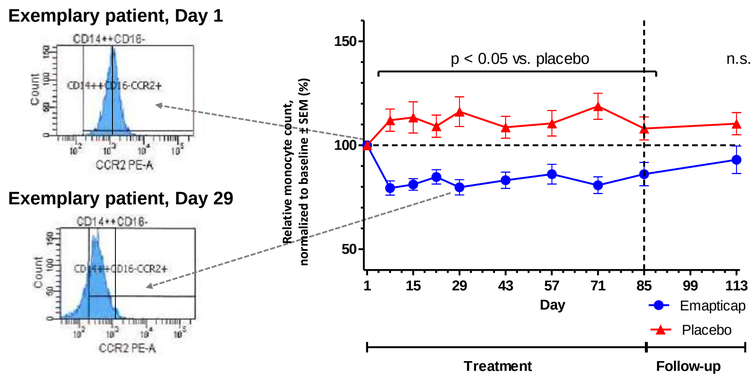


Figure 4: Time course of monocyte count (change from baseline)



At the end of treatment, ACR was reduced significantly in the emapticap group by 29% and 30% vs. baseline in the two analysis sets (Figures 5A and B). Versus placebo, a reduction by 15% (p=0.221) at the end of treatment, and by 26% (p=0.064) eight weeks after end of treatment was observed in FAS (Figures 5A and 7A). The *post hoc* analysis on the PEAS resulted in a 32% (p=0.014) reduction of ACR at the end of treatment and 39% (p=0.010) at 8 weeks of follow-up compared to placebo (Figures 5B and 7B). During follow-up, the therapeutic effect of emapticap was maintained after the cessation of dosing until the end of the three-month observation period. The maximum effect on mean ACR vs. placebo was observed eight weeks after the last dose with 26% (p=0.064) reduction in FAS and 39% (p=0.010) reduction in PEAS.

Figure 5: ACR Change from baseline at end of treatment (Day 85)

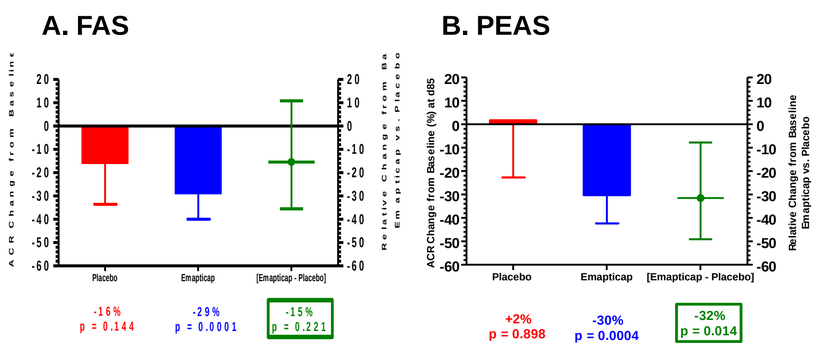


Figure 6: Absolute time course of ACR during and after dosing

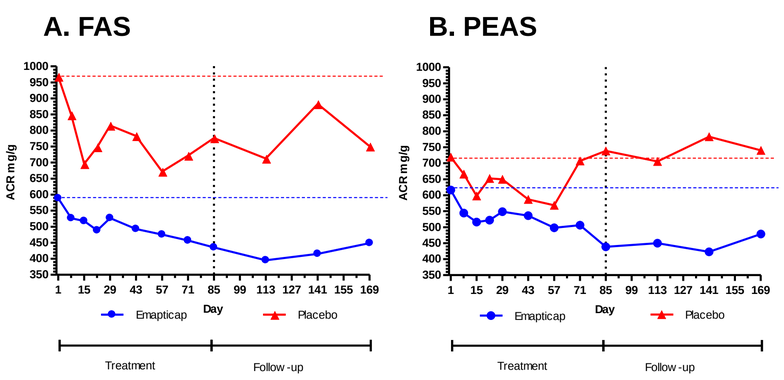
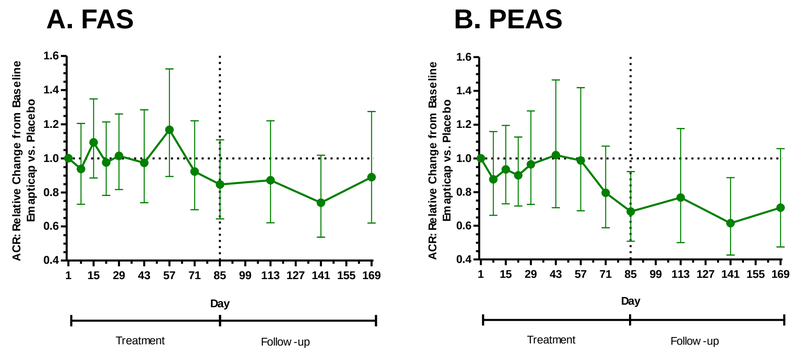


Figure 7: ACR time course versus placebo during and after dosing



No relevant difference in blood pressure or eGFR was seen between the treatment groups throughout the study.

At the end of treatment, HbA1c changed in the emapticap group significantly by -4.0% vs. baseline (absolute change -0.31%, Figures 8A and 9A) and by -3.6% vs. placebo (p=0.146, Figures 8A and 10A). Four weeks after the last dose, HbA1c changed significantly in the emapticap group vs. baseline by -4.8% (absolute change -0.35%, Figure 9A) and by -6.0% vs. placebo (p=0.026, Figure 10A). The absolute difference between emapticap and placebo was -0.48% at the end of treatment and -0.68% four weeks after the last dose.

A *post hoc* analysis of HbA1c on the PEAS came to very similar results as the FAS analysis both qualitatively and quantitatively (Figures 8B-10B).

Figure 8: HbA1c Change from baseline at end of treatment (Day 85)

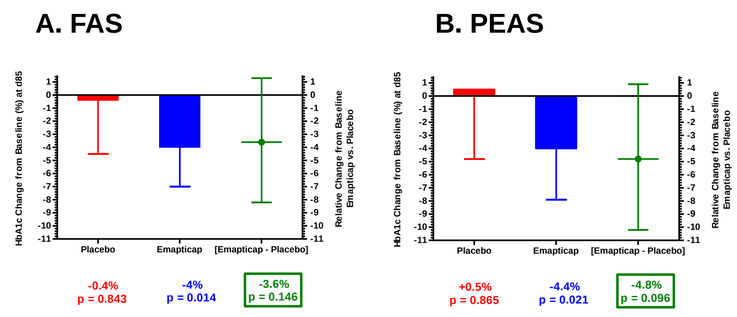


Figure 9: Absolute time course of HbA1c during and after dosing

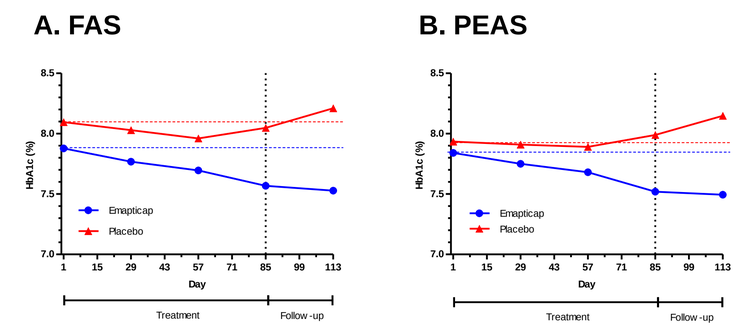
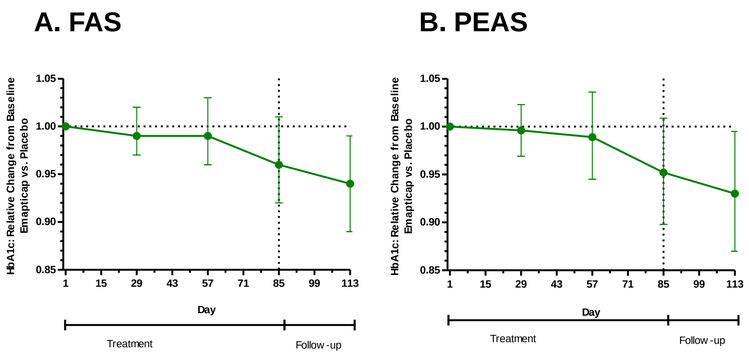


Figure 10: HbA1c time course versus placebo during and after dosing



Conclusions

- Prolonged treatment with emapticap is generally well tolerated, leads to a decrease in the number of monocytes in peripheral blood and their expression of CCR2, and reduces urinary albumin excretion as well as HbA1c in type 2 diabetics with albuminuria.
- The sustained effect on albuminuria even after cessation of treatment indicates that important pathophysiological mechanisms of diabetic nephropathy are influenced. This differentiates emapticap from existing therapeutic strategies and indicates the disease-modifying potential of the drug.
- In contrast to approved drugs and other novel approaches in this indication, emapticap's effect on urinary albumin excretion is not associated with changes of blood pressure or eGFR.
- The results support an important role of CCL2 and inflammatory mechanisms in the pathogenesis of diabetic nephropathy. Further research to prove emapticap's potential for prevention of end stage renal disease and cardiovascular events and to further delineate its anti-inflammatory mode of action in the diabetic milieu is clearly warranted.

Disclosures

H Haller and J Menne were investigators in the emapticap study, supported by NOXXON Pharma AG. D Eulberg is an employee and M Baumann is a board member of NOXXON Pharma AG.

Acknowledgements

We thank the investigators of the Emapticap Study Group: F Saudek, Praha; Z Valkusz, Szeged; D Maděřič, Ostrava; E Öhrig-Pohl, Berlin; J Wachter, Mannheim; E Peterfai, Balatonfüred; T Forst, Mainz; M Dudaś, Gyula; M Nowicki, Łódź; G Klausmann, Aschaffenburg; T Schaefer, Kelkheim; A. Więcek, Katowice; M Gutowska-Jablonska, Warszawa; M Górska, Białystok; G Negrisanu, Timişoara; I Wittmann, Pécs; HJ Hermann, Schwabenheim; L Dohnalová, České Budějovice; Z Kerenyi, Budapest; L Rose, Münster; G Rudowsky, Heidelberg.