A solubilized aqueous budesonide formulation showed higher anti-inflammatory therapeutic efficacy in a murine pulmonary inflammation model compared to marketed products

Sabine Nakowitsch, Marielle Koenig-Schuster, Jan-Marcus Seifert, Elisabeth Foglar, Philipp Graf, Nicole Unger-Manhart, Angelika Bodenteich, Andreas Grassauer, and Eva Prieschl-Grassauer
Marinomed, Biotechnology, Austria

BACKGROUND
Nasally applied corticosteroids are standard therapy for patients suffering from allergic rhinitis. Second generation corticosteroids are highly lipophilic substances that are formulated and applied as suspensions in aqueous solutions. The solid particles have to be dissolved in the nasal fluid before they can permeate into the nasal mucosa. This permeation process needs to occur rapidly after application because the compound is efficiently and rapidly transported into the pharynx due to mucociliary clearance. In contrast, already dissolved drugs permeate faster into the mucosa and are less likely washed out before reaching therapeutic levels than solid dispersed drug particles. Here, we report the results of a novel biocompatible aqueous formulation containing dissolved budesonide with improved efficacy compared to standard budesonide nasal sprays.

MATERIALS & METHODS
Fluorescently labeled estradiol either dissolved using Marinosolv or as suspension was applied onto porcine nasal mucosa and incubated for 60 min. PBS was used as control for auto fluorescence of the tissue. The extent of permeation was determined by light scattering microscopy.

RESULTS
Figure 1: Solubility of budesonide in different formulations.
Analysis of budesonide solubility in Marinosolv, water and the marketed product was done by HPLC after high speed centrifugation of the samples.

Figure 2: Ex-vivo permeation of fluorescently labeled estradiol into porcine nasal mucosa.
We found higher extent of permeated fluorescently labeled estradiol from the Marinosolv formulation compared to the dispersed formulation.

Figure 3: Ex-vivo permeation of budesonide into porcine nasal mucosa.
We found a significantly increased permeation of dissolved budesonide into the nasal mucosa from the much lower concentrated Marinosolv formulation (300 µg/ml) in comparison with the marketed product (1.28 mg/ml) at all time points.

Figure 4: TNFα inhibition in LPS-induced murine acute lung inflammation with treatment 3 hours before LPS challenge.

Figure 5: TNFα inhibition in LPS-induced murine acute lung inflammation with treatment 30 min post LPS challenge.

SUMMARY
For the first time a biocompatible formulation was developed where a 40-fold increase of dissolved budesonide in comparison to established formulations was achieved (800 µg/ml vs 20 µg/ml).

This higher dissolved amount of budesonide present in the Marinosolv formulation not only led to a faster permeation into nasal mucosa tissue but also to higher tissue concentrations compared to the much higher dosed marketed product (1.28 mg/ml).

Remarkably, a higher therapeutic efficacy was achieved with the Marinosolv formulations containing markedly reduced concentration of budesonide (300 µg/ml vs. 1.28 mg/ml, respectively).

Additionally, with the Marinosolv formulations a faster onset of action was observed due to earlier availability of the drug in the tissue.

CONCLUSIONS
With the biocompatible formulation Marinosolv higher amounts of dissolved budesonide can be applied. Therefore the concentration of API in the formulation can be reduced
• with a higher therapeutic efficacy
• resulting in a reduction of the total applied dose
• with an earlier onset of action
• and a faster relief of symptoms

Sterile production is possible and preservatives can be omitted.

Combinations with other APIs are more easy to achieve.

CONTACT INFORMATION
Marinomed Biotechnologie GmbH
Veterinärplatz 1, A-1210 Vienna
T: +43 1 25077 4460
sabine.nakowitsch@marinomed.com
eva.prieschl@marinomed.com