

C32

## Alleviation of MTP inhibitor-induced hepatic steatosis in hyperlipidemic *fa/fa* rats by fenofibrate



Boehringer  
Ingelheim

Leo Thomas<sup>1</sup>, Michael Mark<sup>1</sup> and Henning Pripke<sup>2</sup>

Dept. of Metabolic Diseases<sup>1</sup> and Dept. of Chemical Research<sup>2</sup>, Boehringer Ingelheim Pharma GmbH & Co. KG, 88397 Biberach an der Riss, Germany

### INTRODUCTION

The microsomal triglyceride transfer protein (MTP) is a lipid carrier protein of liver and intestine that is required for the intracellular production and secretion of apolipoprotein B-containing lipoproteins [1]. A potential drawback of MTP inhibitors for treatment of hyperlipidemia is the mechanism-related accumulation of lipids in the liver. The aim of the present study was to test in an animal model the hypothesis that this adverse effect can be alleviated by co-administration of a fibrate.

### METHODS

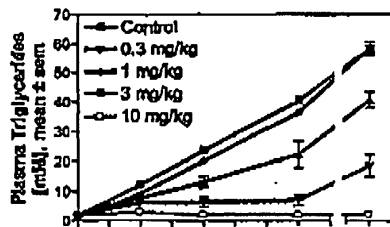
Cell-free MTP activity in rat liver microsomes was determined by measuring the rate of transfer of radiolabeled triglycerides between reconstituted phospholipid vesicles. Apo B secretion from HepG2 cells was measured by a sandwich ELISA. Triglyceride secretion in vivo was determined in fed male Wistar rats (body weight ~ 220 g, n = 5/group) following iv injection of 600 mg/kg Triton WR 1339 30 min after single oral administration of BIBS 2276. Subchronic oral treatment with BIBS 2276 (qd) or fenofibrate (bid) was done for 5 days in fed male *fa/fa* Zucker rats (~ 6 month old, n = 5/group). Data are presented as mean ± sem and statistical analysis was performed using Student's t-test.

### RESULTS

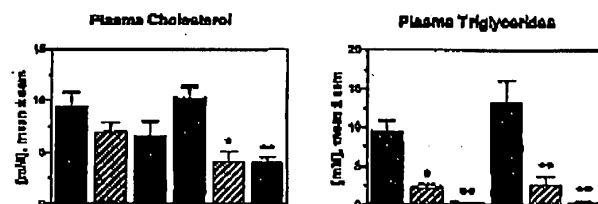
The chemical structure of BIBS 2276, a MTP Inhibitor of the pyrrole carboxamide class, and its in vitro properties are given in the following table.

IC <sub>50</sub> for inhibition of cell-free lipid transfer in rat liver preparations	3 nM
IC <sub>50</sub> for inhibition of apoB secretion in HepG2 cells	1.5 nM

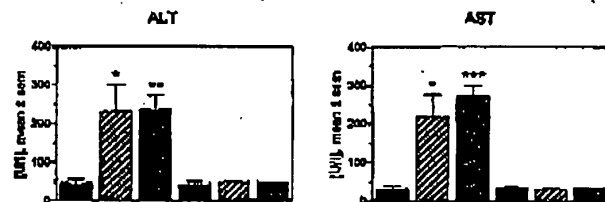
BIBS 2276 leads to an inhibition of triglyceride secretion after single oral administration in Wistar rats (all changes vs. control are significant except for the lowest dose at the 24 h time point).



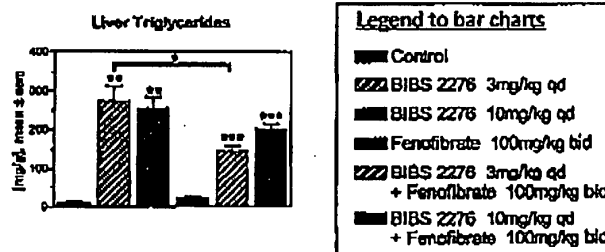
Subchronic treatment with BIBS 2276 lowers plasma lipids in hyperlipidemic *fa/fa* rats.



Subchronic treatment with BIBS 2276 leads to abnormal liver function tests in *fa/fa* rats. This effect is completely reversed by co-administration of fenofibrate.



The MTP inhibitor BIBS 2276 induces hepatic steatosis in *fa/fa* rats. The degree of steatosis caused by the lower dose of BI 2276 is reduced significantly upon co-administration of fenofibrate.



### CONCLUSIONS

- Fenofibrate shows a weak synergistic effect to the plasma cholesterol lowering efficacy of the MTP inhibitor.
- The hepatic steatosis and damage of liver cells induced by a MTP inhibitor can be alleviated by combination with a fibrate, an activator of the transcription factor PPAR $\alpha$ .
- A possible mechanism for the alleviation is the PPAR $\alpha$  mediated stimulation of fatty acid oxidation in the liver.
- Mitochondrial  $\beta$ -oxidation, peroxisomal  $\beta$ -oxidation and microsomal  $\omega$ -oxidation may all contribute to this effect.

#### References:

[1] Waterman, J. P. et al. *Biochim Biophys Acta* (1997) 1245 136-150.