CLINICAL TRIAL REPORT SYNOPSIS

EudraCT No.:	2011-002986-39
Study code:	DXM/AMT
Investigational Product(s):	Dextromethorphan, Amantadine
Title:	A phase IIa, double-blind, placebo-controlled, randomised, fourfold cross-over study to investigate the glucose lowering effects of dextromethorphan and amantadine in subjects with type 2 diabetes mellitus (T2DM) after an oral glucose tolerance test
Clinical Phase:	Phase IIa
Sponsor:	Profil Institut für Stoffwechselforschung GmbH Hellersbergstr. 9 41460 Neuss, Germany Phone: +49 (0) 2131 4018-157 Fax: +49 (0) 2131 4018-557

Investigators

There was 1 principal investigator for this trial: Alin Stirban, M.D.: Profil Institut für Stoffwechselforschung GmbH, Hellersbergstrasse 9, D-41460 Neuss, Germany. Dr Stirban was also the signatory investigator for this trial.

Trial sites

This trial was conducted at one site in Germany: Profil Institut für Stoffwechselforschung GmbH, Hellersbergstrasse 9, D-41460 Neuss, Germany.

Trial Period

Initiation date: 22 September 2011

Completion date: 23 May 2012

Publications:

No publications were prepared at the time of finalisation of this report.

CLINICAL STUDY PROTOCOL SYNOPSIS

Aim and Objectives:

Primary objective:

To demonstrate that dextromethorphan (DXM) and amantadine compared to placebo exert blood glucose (BG) lowering effects following an oral glucose tolerance test (OGTT) in male subjects with type 2 diabetes mellitus (T2DM)

Secondary objectives:

- To compare other pharmacodynamic (PD) properties (based on glucose, insulin, C-peptide and catecholamine measurements) of oral DXM and amantadine (termed: Investigational Medicinal Product – IMP) before and during an OGTT
- For dextromethorphan: to assess whether a dose-dependency of PD exists
- To compare the pharmacokinetic (PK) exposure to DXM and metabolites following an oral DXM dose for 5h post-dosing
- To assess the PK/PD relationship (based on AUC_{DXM} and $AUC_{glucose}$)
- To assess the safety after single oral dosing

Study design:

The study had a randomised, double-blind, double placebo-controlled, fourfold cross-over design. Males with T2DM on a stable metformin monotherapy were screened for participation in the study. Eligible subjects were randomised to receive DXM 60mg, DXM 270mg, amantadine (AMT) 100mg or placebo during four treatment days. An OGTT was started 1 hour after study drug administration and blood glucose was measured over the next 4 hours. There was a 7 to 14-day washout period between doses.

Number of subjects:

The total of 20 subjects were planned to be started on trial product. A total of 56 subjects were screened, of which 20 were randomised and exposed to trial product. A total of 20 subjects completed the trial. All 20 randomised subjects were included in the full analysis set (FAS) and safety analysis set (SAS).

Main eligibility criteria:

Male with T2DM on a stable regimen of metformin monotherapy, between 45 and 70 years of age, with a BMI between 25 and 35 kg/m^2, HbA_{1c} $\geq$6.5 and <7.5%. Key exclusion criteria included type 1 diabetes mellitus, maturity onset diabetes of the young (MODY) or secondary forms of diabetes such as due to pancreatitis; current or previous treatment with insulin therapy; and treatment with any hypoglycaemic medication other than metformin within the three months prior to screening.

Investigational medicinal products (IMPs), dose and mode of administration

Orally administered dextromethorphan 60 mg/dose, dextromethorphan 270 mg/dose, amantadine 100 mg/dose, and placebo for dextromethorphan and for amantadine.

Duration of the treatment:

Four single doses of the IMPs administered on 4 different days with a wash-out of 7-14 days between.

Reference treatment, dose and mode of administration

Treatment with IMPs was compared to placebo (see above)

Criteria for evaluation – Efficacy

Primary pharmacodynamic variable:

Area under the blood glucose (BG) concentration-time profile from 1-3 hours post-dose ($AUC_{BG(1-3)}$ i.e. from 0-2 hours after an oral glucose tolerance test (OGTT))

Pharmacokinetic variables:

Area under the concentration-time profile 0-1 and 1-5 hours postdose for plasma DXM (dextromethorphan), plasma HM (3-Hydroxy-Morphinan), plasma MM (3-Methoxy-Morphinan) and plasma DX (Dextrorphan).

Criteria for evaluation – Safety

Adverse events, laboratory safety variables, physical examination, vital signs, electrocardiogram (ECG), hypoglycaemic episodes

Statistical Methods

The PK analyses were based on the FAS, which included all randomised subjects. The safety analyses were based on the SAS, which included all subjects who had received at least one dose of IMP.

The null hypothesis was that there is no difference between Placebo and each IMP. The alternative hypothesis was that there is a difference between Placebo and IMP. The null hypothesis was tested for each dose.

For the primary (PD) endpoint the primary hypothesis of interest was:

• AUCBG(1-3h) is lower after administration of IMP than after administration of Placebo

The primary hypothesis was tested for each dose of IMP.

All parameters and variables were analysed descriptively for each treatment group, and missing data were not imputed.

Statistical analysis of primary endpoint were done based on log-transformed data using a linear mixed model with sequence, treatment and baseline as fixed factors and subject within sequence as a random factor.

A Sensitivity Analysis was performed excluding subject 114 and 115 because of high insulin concentrations. In addition a second Sensitivity Analysis was performed excluding subject 101 and 105 as they were non-responder.

Statistical analysis of secondary endpoints and other pharmacokinetic parameters (except time parameters) were done as described for the primary endpoint. Time parameters were analysed using the Wilcoxon Signed Rank test based on a two sided alpha of 5%. Hodges and Lehmann estimates and

corresponding non-parametric confidence intervals were also calculated.

Statistical analysis of safety endpoints were done by means of descriptive statistics.

Demography of trial population

All of the subjects were male Caucasians. The mean age and body mass index (BMI) were 58.9 years and 29.2 kg/m^2, respectively.

Efficacy results and conclusions

Pharmacodynamic endpoints (data presented as geometric least-square mean)

- the area under the blood glucose (BG) concentration-time profile from 1-3 hours post-dose ($AUC_{BG(1-3)}$ i.e. from 0-2 hours after an oral glucose tolerance test (OGTT)) was significantly lower following DXM 270mg (396.79) compared to placebo (444.26, $p<0.001$), but not following DXM 60mg (450.76) or AMT 100mg (455.49).
- the area under the blood glucose (BG) concentration-time profile from 1-5 hours post-dose ($AUC_{BG(1-5)}$ i.e. from 0-4 hours after an oral glucose tolerance test (OGTT)) was significantly lower following DXM 270mg (754.85) compared to placebo (831.27, $p<0.01$), but not following DXM 60mg (807.47) or AMT 100mg (830.53).
- the area under the insulin (INS) concentration-time profile from 1-3 hours post-dose ($AUC_{INS(1-3)}$ i.e. from 0-2 hours after an oral glucose tolerance test (OGTT)) was significantly higher following DXM 60mg (94.85) compared to placebo (76.78, $p<0.01$), but not following DXM 270mg (83.67) or AMT 100mg (79.66).
- the area under the insulin (INS) concentration-time profile from 1-5 hours post-dose ($AUC_{INS(1-5)}$ i.e. from 0-4 hours after an oral glucose tolerance test (OGTT)) was significantly higher following DXM 60mg (179.42) compared to placebo (152.53, $p<0.01$), but not following DXM 270mg (164.89) or AMT 100mg (154.41).

Pharmacokinetic profile

- As expected, there was a dose-dependent increase in circulating concentrations of DXM and metabolites

SAFETY RESULTS

- A total of 44 adverse events were reported for 15 subjects during the trial. All of these events were either of mild (30 events) or moderate (14 events) severity. One event was considered by the investigator *not to be* related, 37 events to be *possibly* related and 6 events to be *probably* related to trial product. All subjects recovered from their events. There were more events on days of dextromethorphan treatment.
- The most frequently reported events of mild or moderate severity were “dizziness” (8 events) followed by “headache” (7 events) and fatigue (5 events).
- No serious adverse events or severe adverse events were reported.
- No clinically significant abnormal findings in laboratory parameters, vital signs, physical examination or electrocardiogram were reported.

Overall conclusions

The conclusions of this single-centre, randomised, double-blind, placebo-controlled, cross-over-trial in male subjects with type 2 diabetes mellitus is that:

- Dextromethorphan 270mg as single dose compared to placebo significantly improves glucose profiles following an OGTT
- Neither dextromethorphan 60mg, nor amantadine 100mg had significant effects on glucose profiles.
- Therefore, for dextromethorphan a dose-dependency of PD exists.
- Interestingly dextromethorphan 60mg and not 270mg as single dose induced a significantly higher insulin secretion following the OGTT expressed as area under the insulin concentration-time profile from 1-3 and 1-5 hours post-dose.
- Dextromethorphan at all dosages and amantadine were well tolerated and no safety issues were identified in this trial.

The trial was conducted in accordance with the Declaration of Helsinki (2008) and ICH Good Clinical Practice (1996).
The results presented reflect the data available in the clinical database as of 28.May.2013