2 SYNOPSIS

Name of Sponsor/Company: Ipsen Group	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For national authority use only)*
Name of Finished Product: Taspoglutide		
Name of Active Ingredient(s): BIM 51077		

Title of study: An Interventional, Non-therapeutic Study to Assess Ex Vivo Basophil Activation in Response to Various Preparations of Taspoglutide and Related Items in Blood Samples from Subjects Who Previously Received Taspoglutide and Experienced a Systemic Allergic Reaction.
Study number: 8-55-52133-010

Investigators: There was no principal or co-ordinating investigator assigned to this study. The study was monitored in the United States (US) by the Ipsen US affiliate and in the European Union (EU) by Premier Research Group Ltd, based in the United Kingdom (UK).

Study centre(s): US, Austria, Belgium, Germany, Hungary, Italy, Poland, Spain and the UK.

Publication (reference): Not applicable

Studied period (years):	**Phase of development:**
Date of first enrolment: 03 August 2011 Date of last completed: 21 December 2011	Not applicable

Objectives:
The study objective was to assess the occurrence of a positive reaction (basophil activation signal) to various taspoglutide formulations (including taspoglutide used in Phase III clinical trials, extra pure (EP) and extra-extra pure (XEP) taspoglutide, taspoglutide used in Phase II (active pharmaceutical ingredient (API) from Polypeptide Laboratories, Inc.), synthetic impurities of taspoglutide, placebo and another GLP-1 analogue (liraglutide) in blood samples of subjects who received formulated taspoglutide in the T-Emerge Programme studies and experienced a systemic allergic reaction.

Methodology:
This was a multicentre interventional non-therapeutic ex vivo study conducted in 18 investigational sites in 23 subjects. The study was designed to assess ex vivo basophil activation signal in response to various preparations of taspoglutide and related items in blood samples from subjects who previously received taspoglutide in the T-Emerge Programme studies and experienced a systemic allergic reaction.
Subjects who, during one of the Roche T-Emerge Programme studies, experienced a serious or non-serious adverse event (AE) that was suggestive of a possible systemic

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allergic reaction to the study drug (per the Investigator's assessment) were recalled and asked to consent to one single blood draw (approximately 10 mL) for a basophil activation test (BAT).

A single visit was scheduled to obtain the following:

- Written informed consent from subject.
- Eligibility check (inclusion/exclusion criteria).
- Demographics (sex, date of birth).
- Confirmation of participation in T-Emerge Programme, date of systemic allergic reaction event and date of last taspoglutide administration within the T-Emerge studies based on case report form (CRF) information.

Subjects who met the inclusion criteria and did not meet the exclusion criteria were included in the study and had blood drawn for the BAT. The eligible subjects were identified both with the T-Emerge Programme study protocol and subject number in addition to an Ipsen study protocol and subject number. Subjects completed the study after the BAT blood draw was complete.

Sampling procedures, storage conditions and shipment instructions were detailed in a separate BAT instruction document (Section 16.1.10).

The overall length of this study was 5 months (one day visit and 5 months recruitment).

Stopping rules and discontinuation were not relevant and subjects were able to withdraw from the study at any time.

Full details of the study procedure are provided in the study protocol in Section 16.1.1, and a sample CRF is provided in Section 16.1.2.

Number of patients (planned and analysed):
20 subjects planned, 23 subjects were included in the BAT analysis population.

Diagnosis and criteria for inclusion:
Subjects who, during one of the Roche T-Emerge Programme studies, experienced a serious or non-serious adverse event that was suggestive of a possible systemic allergic reaction to the study drug (per the Investigator's assessment) and the ability and willingness to give written informed consent and provide a blood sample for the BAT.

Test product, dose and mode of administration, batch number:
Not applicable as no study drug was administered in this study.

Duration of treatment:
One study visit where subjects had blood drawn for the BAT.

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Reference therapy, dose and mode of administration, batch number:
Not applicable as no study drug was administered in this study.

Criteria for evaluation:
BAT Analysis:
Subjects had blood drawn for the BAT on Visit 1.
Safety:
Adverse events.

Statistical methods:
The BAT analysis was performed based on the BAT population. The percentage of subjects with positive results with the 95% confidence interval (CI) (calculated using exact binomial test) were summarised by each formulation and impurities but also by combined formulations and impurities according to the combined compounds defined in the BAT instruction document (Section 16.1.10).
Samples were considered positive if the % activated basophils was upper or equal to 5% and the stimulation index (SI) was upper or equal to 2. If it was impossible to calculate the SI (e.g. % activated basophils for the negative control = 0.0 %), then the requirement for SI upper or equal to 2 will not apply and samples will be considered positive solely based on the % activated basophils criteria.

Summary - conclusions:
BAT results:
All 23 subjects who enrolled into the study had a blood sample drawn for the BAT analysis. Five subjects out of 23 (21.7%), experienced a positive result to at least one individual BAT compound. All five subjects experienced a positive response to the combined impurity BAT compounds and three of these subjects experienced a positive response to the Phase III combined compounds while only one subject experienced a positive response to the combined XEP compounds. The combined impurity BAT compounds produced the highest number of positive results (18 positive results in all five subjects). The Victoza and placebo compounds did not produce any positive results. The number of subjects in the per protocol (PP) population experiencing a positive reaction to at least one individual BAT test was identical to that of the BAT analysis population. These data suggest that impurities rather than taspoglutide itself were the root cause of hypersensitivity reactions.

Safety results:
There were no adverse events reported in this study.

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Conclusion:
The study objective was to assess the occurrence of a positive reaction (basophil activation signal) to various taspoglutide formulations (including taspoglutide used in Phase III clinical trials, EP and XEP taspoglutide, taspoglutide used in Phase II (active pharmaceutical ingredient (API) from Polypeptide Laboratories, Inc.), synthetic impurities of taspoglutide, placebo and another GLP-1 analogue (liraglutide) in blood samples of subjects who received formulated taspoglutide in the Roche sponsored T-Emerge Programme studies and experienced a systemic allergic reaction.
All 23 subjects had evaluable data for the BAT analysis. Five subjects out of 23 (21.7%), experienced a positive reaction to individual BAT compounds. Due to the long duration between the hypersensitivity event and blood sample collection, it was expected that a lot of samples would not react positively, since IgE levels may have decreased over time. Therefore only positive results should be taken into account. The combined impurity BAT compounds produced positive results in all five subjects and the highest number of positive results (18 positive results in all five subjects). In addition, the combined Phase III compounds produced three positive results while only one positive result was obtained with the combined XEP compounds. The subject who responded to the XEP compound also responded to several other test compounds, including the combined Phase III and combined impurities compounds. Therefore, the response to XEP can be related to cross-reactivity between the combined impurities and XEP. This could be due to the high amino acid homology between these compounds, i.e., related to previous exposure to the Phase III compound. However, a direct immunogenicity to XEP cannot be ruled out. This is in line and reinforces the conclusion of the BAT study performed by Roche in the T-Emerge programme which suggests that immunogenicity was triggered by multiple impurities rather than taspoglutide itself. The Victoza and placebo compounds did not produce any positive results. One subject ([redacted]) was excluded from the PP population due to a major protocol deviation. This subject did not experience any positive reactions to the BAT tests. The number of subjects in the PP population experiencing a positive reaction to a combined or individual BAT test was identical to that of the BAT analysis population. There were no AEs reported in this study.

Date of report: 08 March 2012