SCIENTIFIC DISCUSSION

1. Introduction

Aventis/ Pfizer EEIG has applied for marketing authorisation through the centralised procedure for the product EXUBERA, insulin inhalation powder.

Exubera consists of two components: the drug product, a spray dried insulin powder in unit dose blisters and a pulmonary inhaler, a medical device.

The insulin spray dried powder contains recombinant human insulin, sodium citrate, sodium hydroxide, mannitol and glycine.

The intended pulmonary inhaler is a reusable, manually operated, pneumatically powered, dried powder delivery system for unit dose blisters containing insulin spray dried powder.

Diabetes mellitus (DM) is a chronic illness characterized by elevated blood glucose levels that leads secondarily to long-term microvascular and macrovascular complications such as neuropathy, retinopathy, foot ulceration, heart disease and renal failure.

Insulin therapy is an absolute requirement for the treatment of type 1 DM and is indicated for the treatment of type 2 DM when oral agents fail to provide adequate glycaemic control. Subcutaneously injected insulin has been used to treat (DM) since the 1920s.

Although the long-term benefit of tight glycaemic control in patients with DM has been demonstrated in the DCCT and UKPDS studies, the inconvenience of insulin injection therapy, especially a multiple-times daily regimen, represents a hurdle in achieving good glycaemic control.

The pulmonary route was considered because the alveoli features include a large absorptive area, adequate permeability to macromolecules, extensive vascularisation, minimal mucociliary clearance mechanisms and low chemical and enzymatic degradation (compared to the gastrointestinal system). Therefore, inhaled insulin is expected to allow a fast absorption of insulin resulting in rapid onset.

INH is administered before each meal as part of an individualised DM control regimen that may include other subcutaneous insulin formulations or oral hypoglycaemic agents.

The drug substance is a recombinant human insulin (referred to as rhu-insulin). Rhu-insulin has an amino acid sequence identical to endogenous human insulin, and is therefore not an insulin analogue. The drug product is produced with a newly developed spray drying process and pre-dispensed in 1mg and 3 mg blisters. The bioavailability of Exubera is approximately 10%. One 1mg and one 3 mg blisters are equivalent to approximately 3 IU and approximately 8 IU subcutaneously administered insulin.

The applicant submitted a risk management plan in its marketing authorisation application.

2. Quality aspects

Introduction

Insulin (Human) will be provided as insulin spray-dried powder, comprised of recombinant human insulin, sodium citrate, mannitol and glycine; and is presented in pre-dispensed 1 and 3 mg unit dose blisters.

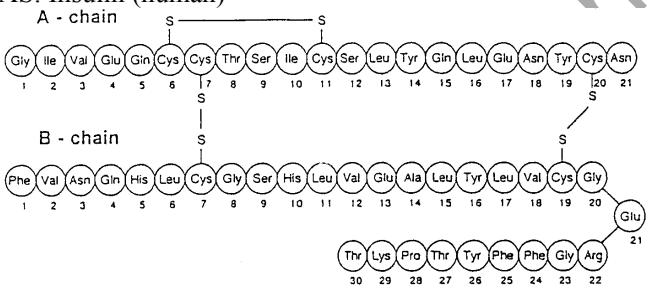
For pulmonary drug delivery, a reusable manually operated dry powder inhaler is used. Key functions of the pulmonary inhaler are the dispersion of powder to form an aerosol cloud (inspiratory

independent) into a holding chamber and the delivery of the aerosolized powder to the patient. The insulin pulmonary inhaler is CE certified.

Drug Substance

Introduction
The recombinant human insulin used for the commercial manufacture of insulin inhalation powder is sourced from Diabel, Germany.

General Information

Generic Name(s)	INN: Insulin Human
Chemical Name	CAS: Insulin (human)
Chemical Structure:	

Insulin human is a 51 amino acid polypeptide consisting of two polypeptide chains. The A and B chain, consisting of 21 and 30 amino acid residues, respectively, are linked by 2 disulfide bridges. The A chain contains one intra-chain disulfide bridge.

Molecular Formula	$C_{257}H_{383}N_{65}O_{77}S_6$
Molecular Weight	5808

- Manufacture

The recombinant humin insulin (HMR4006) is manufactured from a fusion protein produced by *Escherichia coli* using recombinant DNA technology.

Development genetics
The rationale for the construction of the vector/host system has been given and the preparation of the production strain (*E. coli*) has been sufficiently described.

Cell bank

For the production of HMR4006, starting from the production strain, a two tiered cell bank system of master and working cell banks was established. The cell banks are tested for microbiological purity, identity, viability, plasmid retention and plasmid copy number. In addition, the ability to express the fusion protein was verified on the basis of test fermentation runs. The stability of the cell banks was confirmed during storage and fermentation. The results of these studies confirm the genetic and physiological stability of the production strain.

Description of the manufacturing process
The manufacturing process has been sufficiently described and a flow chart has been provided. The process consists of 16 steps divided into three major parts: namely fermentation and harvesting and downstream processing and final purification.

Batch definition
Adequate information on batch definition and sub-batching is provided. A single ampoule is processed to give one harvest of cells with fusion protein. For the subsequent downstream and purification

process the batch system is adequately described; in defined cases due to the capacity of the equipment of some stages sub-batches are produced.

Fermentation
After inoculation with one ampoule of working seed, the bacteria of the production cells are cultivated in a three-step procedure.

Modification and Purification
The inactivated cells are separated by centrifugation and disrupted by pressure-expansion treatment to obtain the fusion protein that is enriched by on-line washing and centrifugation steps. The downstream processing of the fusion protein to human insulin is a sequence of modification and purification steps. Sub-batches are mixed to obtain the final drug substance and stored at -20°C ± 5°C.

In-process controls
The fermentation process, the downstream processing and purification of the expression product are sufficiently controlled by appropriate in-process controls and acceptance criteria. The efficiency of the concentration and purification steps is monitored by HPLC analysis. The structure of most by-products has been elucidated and their removal is either demonstrated by validation data and/or limits are set for in-process control testing at the respective purification stages.

Development of the Manufacturing Process of the Active Substance
During the early development phase of insulin inhalation powder, pre-dispensed, different recombinant human insulin sources deriving from modified manufacturing processes were used for clinical (Phase 3) and development batches. Information demonstrating the equivalence between these sources was provided. Scale up activities at different stages of the purification process and the introduction of a new drying pocess were carried out to produce the required amount of HMR4006 insulin, the commercial source for drug product. No changes occurred in fermentation and down stream processing. The overview of differences between the processes for the different sources of human insulin is clearly and in sufficient detail presented .

Process validation
Adequate validation data were provided covering the complete drug substance manufacturing process. With the reported batches the acceptance limits for validation parameter and specifications for purity and impurities, respectively, were consistently met. The submitted data confirm that the applied procedures are adequately designed and controlled to yield a consistent quality of the drug substance.

Detailed justification as well as the criteria for the handling of non-conformity intermediates were given for reprocessing at defined manufacturing steps.

Lifetime of column resins / column resin reuse
The lifetime of the chromatography resins is validated ongoing by monitoring column performance on full-scale production equipment over the course of commercial production. Data presented on the monitoring of all columns of selected runs show no decrease in column performance.

Characterisation
Characterization studies were performed for the different recombinant insulin sources comparing each other. The complete study reports were provided showing that HMR 4006 was adequately characterised. In addition, analytical comparability between the different sources of insulin was demonstrated by Edman degradation, CD spectroscopy, NMR spectroscopy, X-ray diffraction and comparison of impurities profiles.

Impurities
Impurities are extensively addressed. Full details on the potential impurities, the methods, in-process controls and batch results were provided. Removal studies were included as part of the process validation.

Product related impurities were also addressed in detail as well as potential insulin related substances arising as the result of incomplete cleavage or cleavage at a non-desired site. These potential product-related impurities are removed by the manufacturing process and are controlled by appropriate in-process controls and by the final drug substance specification. Release limits for total insulin related substances, and for A21-desamidoinsulin were set.

- Specification

Appropriate specifications for the drug substance were set and justified. Full analytical methodology is provided including the validation of the test procedures and batch results. The specification for insulin human HMR4006 covers release and shelf-life limits.

Batch results were provided for 9 batches of insulin human HMR4006. All batches met the specifications and showed consistency. The choice of test parameters and acceptance criteria are justified by these batch data. Analytical methods for assay, purity, microbiological and biological properties are described in sufficient detail and were validated in accordance with ICH standards.

- Reference Standards

The choice and control of the reference substance are considered acceptable. The procedure for qualification of secondary reference standards was described. The certificate of analysis of the current secondary standard was submitted. Calibration against the Ph.Eur. CRS was performed.

- Container Closure System

Insulin drug substance is packaged into stainless steel lidded drums for storage and transport to the drug product manufacturing facility. The containers are specific to HMR4006. Specifications and quality control documentation are submitted. The container closure system is considered acceptable.

- Stability

The applicant provided real time stability data for the storage of the drug substance at -20 ± 5°C. Data from three production scale batches of human insulin stored in glass ampoules (60 months) and from three production scale batches of human insulin HMR4006 stored in steel drums (24 months) were submitted. In addition data were provided from which it can be concluded that the stability behaviour of the drug substance is similar in glass ampoules and steel drums.

Real time data for HMR4006 covering 24 months stored both in stainless steel and in glass ampoules are well within the shelf life specifications and no significant changes in product stability are observed after 24 months.
A shelf life for the drug substance HMR4006 of 48 months under the recommended conditions of -20°C ±5° can be granted under the condition that the applicant committed to submit the 36 months and 48 months stability data for drug substance HMR4006 in steel drums (and in glass ampoules) at -20 ± 5°C on an ongoing basis.

Drug Product

- Pharmaceutical Development

Introduction

The applicant performed an extensive pharmaceutical development program.

A dry powder insulin formulation was developed in view of the physicochemical stability of insulin and to allow storage at room temperature. A novel spray drying process was developed to produce primary particle size distributions in the desired range for delivery to the deep lung (mean

aerodynamic particle diameters ~3µm). The spray-dried powder is filled into unit dose blisters. The blister provides the means to insert insulin inhalation powder into the pulmonary inhaler for aerosolisation before dosing.

Key functions of the pulmonary inhaler are the dispersion of powder to form an aerosol cloud that contains drug particles for alveolar deposition in a holding chamber and the delivery of the aerosolised powder to the patient. Patient inspiratory effort is independent from the generation process of the aerosolised cloud.

Summary of Pharmaceutical Development (selected points)

During the development and clinical trials, different insulin sources, pulmonary inhalers and different drug product formulations were used.

Excipients
Selection criteria for excipients were suitability (safety) for inhalation use, acceptable long-term stability, aerosol delivery performance with the pulmonary inhaler and appropriate aqueous solubility to facilitate rapid absorption. Mannitol was chosen as stabilising/bulking agent, glycine as buffering agent and sodium citrate as buffering/stabilising agent.

Drug substance
The drug substance used came from two suppliers. In the development, toxicology studies, and Phase I, IIa and IIb trials the earlier insulin supplier was used while the later supplier was used for pivotal Phase III and stability studies. To demonstrate comparability of the insulins from the two suppliers, a series of characterisation analyses were performed on the insulin drug substance and the corresponding spray dried powders. Comparability of the insulin spray dried powders manufactured from drug substance of both suppliers was demonstrated.

Developmental stability studies
Developmental stability studies showed that moisture content is a critical parameter impacting chemical stability. Measures were implemented, including blister design and development, to maintain the product moisture content and minimize moisture uptake. In addition, moisture protection was optimized during the product shelf life, and protective secondary packaging, consisting of a sealed foil laminate overwrap and desiccant, was developed.

Aerosol Product Performance
Key aerosol performance attributes of the powder-filled blister, when actuated with the pulmonary inhaler, include aerodynamic particle size distribution (PSD), fine particle dose (FPD) and to a lesser extent total emitted dose (ED). Among these aerosol metrics, FPD was found to be most predictive of systemic exposure, although a precise quantitative correlation could not be concluded.

Lack of dose equivalence between 1 mg and 3 mg blister strengths
Subsequent to the initiation of the Phase 3 clinical trial program a confirmatory dose equivalence study with the 60% insulin formulation was conducted, demonstrating that the two strengths are not dose-equivalent: Three 1 mg blisters are not bioequivalent to one 3 mg blister. In conclusion, 1 mg and 3mg blisters are not interchangeable. AUC and Cmax values of 3x1 mg inhaled insulin are approximately 40% and 30% greater, respectively, than 1x3 mg inhaled insulin. This finding is qualitatively supported by in – vitro data for the FPD. The FPD of 3x1mg blister is 20% higher than the FPD for 1x3 mg blister. The applicant explained that the performance difference was fully characterised, and shown to be inherent in the drug product system.

The lack of dose equivalence between the two proposed blister strengths was considered as a major concern during the review of the application. It was extensively discussed under pharmaceutical aspects and concerning its clinical implications, as patients cannot rely on the same efficacy of both dose strengths when the same nominal amount of drug substance is administered. In clinical trials dose titration and approximal dose proportionality over the range of 1mg to 6 mg were achievable with both strengths. No safety and efficacy concerns arose from the lack of interchangeability of both blisters in

these trials. Therefore, it was concluded that the lack of dose equivalence between the two blister strengths could sufficiently be addressed by a clear and strong warning in the SPC/ PIL and on the outer package and on the foil overwrap.

Clinical product performance
In clinical product performance studies, the sensitivity of the aerosol performance to environmental humidity conditions during use was discovered. In insulin release unit (IRU) use-life studies a linear relationship between emitted dose and humidity was evident. The emitted dose varied not more than 10% over 14 days of continuous exposure to relative humidities up to 65%, supporting a two-week replacement interval for the IRU.

This issue is sufficiently addressed by instructions for use included in the SPC and the PIL concerning inadvertent exposure to high environmental humidity. The risk of patient non-compliance with the replacement interval of 14 days for the insulin release unit, is minimized by the increase of the package sizes for the insulin release unit (6-unit package plus one spare unit) and proposed reminder stickers on the IRU folding carton.

Bioequivalence
Particle size distribution between clinical-scale and commercial-scale insulin dried powder is not identical, which is in line with the observed differences in aerodynamic particle size distribution between clinical-scale and commercial-scale batches of drug product. Therefore, bioequivalence studies were performed to show comparability of clinical-scale and commercial-scale batches.

Product performance
During evaluation of product performance, information on product behaviour (blister + pulmonary inhaler) emerged that led to several inhaler instructions for use.

- Manufacture of the Drug Product

Manufacturers
Information on the different manufacturing sites and their responsibilities was provided.

Batch Formula
The batch size and batch formula for the production of commercial scale batches of the drug product were defined.

Description of the Manufacturing Process
The manufacturing process of the drug product consists of three steps: (1) The solution preparation and (2) the spray drying process for the manufacture of the insulin spray dried powder and 3) filling and packaging. Insulin spray dried powder is an intermediate in the manufacturing process of the drug product. The powder is stored in steel containers and shipped to the blister-filling site, where it is filled in 1mg and 3mg blisters.

Descriptions of the commercial scale solution preparation, spray drying process and the filling process were provided along with flowcharts including in - process controls. The target spray dryer parameters were based on development and scale-up studies. Adequate in-process controls with suitable acceptance criteria were set. Critical steps were identified and are sufficiently controlled. Analytical methods were described and validated where appropriate.

Control of intermediates
Insulin spray dried powder is considered as intermediate in the manufacture of the drug product. The selected tests and acceptance criteria for the spray dried powder are adequate to routinely determine identity, purity and content of insulin. The analytical methods were described. Acceptance criteria for the intermediate were set and sufficiently justified.
All proposed acceptance criteria are supported by results of 168 batches of intermediate product.

Process validation

Data from several qualification batches were submitted. Qualification lots were produced under GMP conditions. These data demonstrate the validity of the manufacturing process.

Control of excipients
Mannitol, glycine, sodium citrate (dihydrate), sodium hydroxide and water for injections used in the manufacture of insulin inhalation powder, pre-dispensed meet their respective monographs. Ph. Eur. Certifications from suppliers were provided. All excipients have been certified as not of human or animal origin.

Since Exubera is an inhalation product, additional tests for microbiological evaluation and stricter acceptance criteria for microbiological tests were implemented in the control of excipients.

- Product Specification

Regarding the choice of test procedures the applicant employed methods or criteria for human insulin and injectable insulin preparations published in the Ph. Eur. and other tests, which are specific for this entirely new product. The methods for release testing of the drug product were sufficiently described and validated following ICH guidelines.

Release and end of shelf – life specifications were submitted for the 1-mg and 3-mg packaged strengths. The acceptance criteria were sufficiently justified based on relevant clinical batch results. The acceptance criteria for the aerosol performance parameter were tightened based on batch release results from batches used in phase 3 (pivotal) Type 1 diabetes clinical trials, stability data from batches used in Type 1 diabetes clinical trials and data from production scale batches. However, further reconsidering based on commercial production experience is expected as a follow up – measure.

The release and end of shelf life specifications were revised with regard to impurities. Two of them should be further reconsidered as follow-up measure.

- Batch analysis data

Batch release data were presented from a total of over 150 batches; over 15 were production scale batches.

- Characterisation of impurities

Potential impurities deriving from the human insulin recombinant process, the drug product manufacturing process or originating from the degradation of insulin and insulin inhalation powder were characterised and are qdequately controlled by the introduction of acceptance criteria in the release and end of shelf life specifications.

- Reference standards or materials

Sufficient information on the chemical reference standards or reference materials for human insulin was provided.

Control inhalers and insulin release unit assemblies to test the drug product meet commercial specifications. They were also used for the testing of clinical batches.

- Container closure system

Insulin inhalation powder, pre-dispensed utilizes two container closure systems: a container system for transport and further processing of the insulin spray dried powder into unit dose blisters and a unit

dose blister system. The primary packaging materials from these container closure systems was sufficiently described. Primary packaging material is either tested according to Ph.Eur. or certified by the supplier in compliance with relevant EU and US requirements.

- Stability of the Drug Product

Intermediate
The stability data support the proposed shelf life of 12 months for the insulin spray dried powder.

Finished Product
In general, stability data support the shelf life and storage conditions as defined in the SPC.

According to the ICH Guideline, stability data over 36 months from clinical-scale batches of both strengths were provided to support the proposed shelf life of 2 years. Additionally, 6-months stability data stored at 25°C/75% RH after removal of the protective foil pouch showed acceptable quality through the proposed additional 3-month "in-use period".

Because of the changed spray drying process during scale-up, the investigated batches are not considered to be fully representative of the commercial manufacturing process. A stability program for commercial scale material has been started; an interim stability report was provided consistent with release testing and ICH stability testing results. A commitment has been given to finish the stability program on an ongoing basis according to the provided stability protocols.

- Facilities and Equipment

Flow charts of the manufacturing process were provided together with appropriate details of the equipment and facilities.

- Adventitious Agents Safety Evaluation

No excipients of human or animal origin are used in the product manufacture and therefore there is no risk of contamination with viral or TSE agents by these ingredients. No animal ingredients are used for the preparation of the cell banks or in the fermentation process. During down stream processing, trypsin and carboxypeptidase B are used, which are derived from porcine pancreas. Viral validation studies were carried out demonstrating that the possibility of viral contamination with the use of porcine enzymes in the production process is considered negligible.

- Medical Device

The pulmonary inhaler and associated accessories (insulin release unit assembly and chamber) are the subjects of the Nektar Therapeutics and Pfizer technical files. EC certificates were awarded for both technical files. The stability of base/ chamber and insulin release unit was demonstrated to be 2 years. The proposed use life of 1 year for the base and chamber and the use life of 14 days for the insulin release unit is supported by the clinical experience program. Since environmental moisture from 65% RH has been identified to be a critical parameter during use additional instructions are included in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

In general, the different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The information provided in the application showed a consistent batch-to-batch production of Exubera achieving an acceptable quality for the drug substance and drug product. The fermentation, basic down-stream processing and purification of the drug substance, human recombinant insulin, are adequately controlled and validated. Appropriate drug substance specifications are set. The drug substance was well-characterized using state-of the-art methods with regard to its physicochemical characteristics. During the extensive pharmaceutical development program the lack of dosage form equivalence between the 1mg and 3mg blister strengths was revealed

which has been addressed taking its clinical implications into account (see clinical part of this report). The manufacturing process of the drug product was described and validated in sufficient detail. The quality of the drug product is controlled by adequate test methods and specifications. No excipients of human or animal origin are used in the product manufacture and therefore there is no risk of contamination with viral or TSE agents by these ingredients. No animal ingredients are used for the cell culture process, the basic down stream processing and purification with the exception of porcine trypsin and porcine carboxypeptidase B. Sufficient virus validation data were provided for the manufacturing processes of both porcine enzymes and, as well, for the manufacturing process of recombinant human insulin to consider that Exubera is virologically safe. The applicant will address a number of quality points as follow-up measures post opinion.

3. Non-clinical aspects

Introduction

Exubera is an insulin formulation suitable for administration with a pulmonary delivery device. The drug substance is a recombinant human insulin.

Two inhalation powder formulations, each containing one of two marketed insulin preparations for subcutaneous injection, were used in both the nonclinical and clinical development programs.

Due to the fact that the systemic safety profile of marketed recombinant human insulin is well described both non-clinically and clinically, the respiratory system was the primary focus of the toxicology studies for the insulin inhalation powder, and the excipient powder (mannitol, glycine and sodium citrate excipients).

All pivotal toxicological studies were stated to be carried out according to GLP Principles.

Toxicology data from an earlier supplier and Aventis rhu-insulins administered subcutaneously were also used to support the inhalation program.

Pharmacology

- Primary pharmacodynamics (*in vitro/in vivo*)

The pharmacology of recombinant human insulin is well known. A set of pharmacology studies, which demonstrated the feasibility of inhaling various dry powder insulin formulations in rats, monkeys and dogs, was submitted.

Different insulin strengths and excipients were employed in the pulmonary dosing formulations, and, with the exception of the dog study, they varied from the current clinical formulation (I-016). In addition, the methods of lung exposure to insulin powder in the nonclinical studies were different from those employed in clinical studies, in which inhalation from a pulmonary delivery system was employed. Nevertheless, like in humans, insulin inhalation powder administered by the pulmonary route to rats, monkeys and dogs, was absorbed into the bloodstream in a dose-dependent manner and produced the expected pharmacodynamic response of decreasing glucose concentrations.

- Secondary pharmacodynamics, Safety pharmacology, Pharmacodynamic drug interactions

A cardiovascular study was conducted in anaesthetised dogs where the rhu-insulin used in the current formulation was compared with a corresponding marketed rhu-insulin, Humulin, following intravenous injection. Both formulations produced a slight increase in heart contractility and heart rate, a well-known effect of human insulin.

No specific secondary pharmacology, additional safety pharmacology or pharmacodynamic drug interaction studies were conducted and, in consideration of the nature of recombinant human insulin to the endogenous hormone, comparable pharmacology would be expected.

Pharmacokinetics

No definitive nonclinical pharmacokinetic studies were conducted. Nonclinical pharmacokinetics in rats, dogs and monkeys was determined in several pharmacology studies and in 2 pilot nonclinical safety studies using non-validated radioimmuno-assays. In the nonclinical studies, different insulin concentrations and excipients were employed in the pulmonary dosing formulations. The method of formulation delivery was a pulmonary delivery system, which is different than the method of delivery in humans.

- Absorption- Bioavailability

The apparent systemic bioavailability is relatively low and variable. Inter-animal variability appears to be even higher than in clinical studies at least in part due to the difficulty in delivering precise doses of insulin to the airways. In the preclinical studies conducted, the range of bioavailability relative to a subcutaneous dose ranged from 10% to 93%. The range of bioavailability observed was due to the differences in doses administered across the studies and methods by which the pulmonary dose was determined. However, independent of the species, formulation and route of administration, the time of the observed maximal systemic concentrations of insulin was generally right after the administration of dose, suggesting that insulin was rapidly absorbed from the lung.

The mechanism of insulin absorption is described in the scientific literature; it is believed to occur via paracellular transport, which primarily involves passive diffusion of insulin across the alveolar epithelium through extracellular tight junctions.

- Distribution, Metabolism, Excretion

No pharmacokinetic studies on distribution, metabolism or excretion were performed on account of the identity of recombinant human insulin to the endogenous hormone.

In the inhalation toxicology studies in rats and monkeys for up to 6-months there was no evidence for an accumulation of particles in the lung.

An assessment of the respiratory tract deposition and clearance of insulin inhalation powder was also based on literature. Prior to deposition in the deep lung following inhalation, there are several sites at which insulin inhalation powder is eliminated, including residual retention in the blister/device, and deposition in the oropharynx and conducting airways. Once deposited in alveolar spaces, a portion of the inhaled bolus is absorbed into systemic circulation, while the remaining material is likely removed by a combination of mechanisms, including mucociliary clearance, phagocytosis and destruction by alveolar macrophages, insulin-specific and non-specific enzymatic degradation, and lymphatic drainage.

Also, regarding the excipients in Exubera, mannitol, glycine and sodium citrate, there are no data on their clearance on long-term administration. From literature there is no indication for an accumulation in the lung. Mannitol, as a relatively small molecule, is presumed to clear rapidly from airspaces. Available literature data suggest that clearance half-times for mannitol delivered to respiratory tract via inhalation may be of the order of approximately one hour. Glycine is a naturally occurring amino acid, with relatively low molecular weight and is present in biological fluids. The relatively small amounts of glycine delivered in insulin inhalation powder are not judged likely to accumulate in the lung. Sodium citrate is also a naturally occurring substance and present in biological fluids. Sodium citrate and citric acid are inactive ingredients contained in an approved suspension for inhalation.

Toxicology

A toxicology program was conducted to evaluate the toxicity of insulin inhalation powder and excipients to the respiratory tract. The program consisted of pivotal 1- and 6-month inhalation studies in the rat and monkey using the earlier supplier of rhu-insulin. A pivotal 1-month rat inhalation study was done with Aventis rhu-insulin to confirm the toxicological equivalence of the two formulations. In addition, lung cell proliferation indices and anti-insulin antibody titers were measured.

- Single dose toxicity

The single dose inhalation studies in rat and monkey were exploratory studies mainly to validate inhalation exposure system, define an upper limit of insulin powder exposure and estimate the bioavailability of inhaled insulin relative to SC injection.

- Repeat dose toxicity (with toxicokinetics)

The main characteristics of the pivotal repeated-dose toxicity studies (Inhalation) are given in the table below.

Study Type	Species/ Strain	No./ Sex/ Group	Target Doses (mg/kg/day)	Achieved Doses (mg/kg/day)
1 month	Rat/Sprague-Dawley	10	0, 1, 3, 6	0, 1.1, 3.2, 6.0
1 month	Rat/Sprague-Dawley	10	0, 0, 1, 3, 6	0, 0, 1, 3.2, 5.9
6 month	Rat/Sprague-Dawley	10	0, 0, 1, 3, 6	0, 0, 0.9, 2.7, 5.8
1 month	Monkey/ Cynomolgus	4	0, 0.15, 0.6	0, 0.14, 0.58
6 month	Monkey/ Cynomolgus	4	0, 0, 0.2, 0.6	0, 0, 0.29, 0.64

The high doses were defined in exploratory studies and are at the same time the MTDs that induce hypoglycaemia.

The high doses for rat and monkey were approximately 40x and 4x the human clinical starting dose based on mg/kg/day.

The pivotal studies have been conducted at an experienced inhalation contract laboratory (nose-only system for rats; individual head domes for monkeys). The exposures were well controlled and doses were approximately as targeted. The particle sizes were appropriate for the species used and allowed for exposure of the entire respiratory tract.

A dose-dependent systemic exposure to insulin was confirmed by increased insulin and decreased glucose concentrations.

From the standard toxicology endpoints (mortality, body weights, clinical observations, clinical pathology, ECG in monkeys) no special hazard was identified; the studies showed the expected hypoglycaemia responses from the exaggerated insulin doses. There was no mortality in monkeys. In rats a few deaths from hypoglycaemia (medium and high doses) and a few other deaths from incidental causes occurred. There were neither body weight or opthalmological changes, nor ECG effects in monkeys.
Anti-insulin antibodies were evaluated in serum from rats and monkeys or in lavage fluid from monkeys. There was no antibody response in monkeys and a weak antibody response in rats, which is consistent with subcutaneous data and literature data.

Pulmonary function assessments have been conducted on anaesthetised, spontaneously breathing animals. There were no exposure related effects on respiratory rate, tidal and minute volumes, peak inspiratory and expiratory flow rates, resistance and compliance.
Following section there were no gross findings. Occasional significant differences from control for several organ weights, including the lung, have been seen. There was a trend to slightly increased absolute lung weights, mainly in females. However, the effect was neither dose-related nor duration-related.

The histopathological evaluation of the respiratory tract was done by standard hematoxylin and eosin staining on nasal turbinates, larynx, trachea and lungs with bronchi and bronchial lymph nodes. The most frequently observed changes in the lungs of rats were random, focal infiltrates of either interstitial mononuclear cells or clusters of inflammatory cells within alveolar spaces and, focal or multifocal aggregates of alveolar histiocytes within alveolar spaces in monkeys. The findings were morphologically similar, minimal to mild in severity and were observed in all dose groups, including air and excipients controls. There was no evidence of permanent anatomic or physiological changes.

- Genotoxicity

There is no evidence of a genotoxic effect of rhu-insulin.

Rhu-insulin in Exubera is a biotechnologically produced homologue of human insulin. Therefore genetic toxicology testing is not required (according to Guideline ICH S6). Nevertheless, some tests (e.g. AMES test) were performed with either Aventis rhu-insulin or rhu-insulin Humulin ; these tests were negative.

- Carcinogenicity

No carcinogenicity studies have been performed, mainly based on the following arguments:

- According to ICH S6 guidelines on the Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals, standard carcinogenicity bioassays are generally inappropriate for biotechnology-derived pharmaceuticals.

- No insulin or excipient powder-related histopathological changes were observed in the respiratory tract of rats and monkeys in the 1- or 6-month inhalation toxicology studies.

- A previous supplier and Aventis rhu-insulins are identical in amino acid sequence to the endogenous human hormone, and thus are not insulin analogues.

- There is no evidence for a genotoxic effect.

- There is no epidemiological evidence that injected animal or rhu-insulin is associated with tumour formation in humans at either local or distal sites based on approximately 80 years of clinical experience.

Cell proliferation studies:
It is generally accepted that insulin acts through the insulin receptor (IR) to initiate its metabolic signalling pathway while insulin-like growth factor-1 (IGF-1) acts through the IGF-1 receptor (IGF-1R) to initiate a mitogenic signalling pathway.

The cellular proliferation indices in formalin-fixed lung tissue from the 6-month inhalation studies in rats and monkeys via the PCNA and Ki-67 immunhistochemistry procedures were determined retrospectively. The examined tissue samples consisted of alveolar and bronchiolar epithelium, the most relevant anatomic location in the lung for tumorgenesis. There were no statistically significant differences in proliferation indices for air control, excipient control, or high dose insulin inhalation

powder groups either in rats or monkeys. However, in the rat the mean proliferation indices in the high dose insulin groups were approximately 2 fold compared to the mean proliferation indices in the air control or excipients control groups. Since a doubling of the proliferation index could be of biological relevance, the applicant has been requested to provide additional data on carcinogenic potential

In conclusion, non-clinical data on insulin inhalation powder did not show a tumorigenic risk for the lung relevant to human therapeutic use.

- Reproductive and developmental studies

No studies on reproductive and developmental toxicity have been conducted with Exubera. Taking into account the data existing on human insulin given subcutaneously, the omission of such studies performed via the inhalatory route of administration can be accepted.

Administration of insulins at high doses to non-diabetic animals during pregnancy caused a teratogenic response. However, it is unlikely that insulin has direct teratogenic effects. Rhu-insulin, insulin from other mammals, and oral antidiabetic agents are known to induce in experimental animals birth defects probably secondary to maternal hypoglycemia.

From epidemiological data in diabetic women treated with human insulin, it is well known that the increased mortality and morbidity of their offspring can be significantly reduced by careful control of the maternal glucose level.

The anti-insulin antibody response observed after Exubera treatment was questioned as a potential hazard for the foetus. Although insulin does not cross the placenta, theoretically insulin-specific antibodies may cross the placenta alone or in complex with insulin leading to metabolic aberrations in the foetus. Based on the literature submitted, no association between increased insulin antibody levels and major neonatal morbidities in pregnancies with good glycaemic control was suggested, although an increased risk of neonatal hypoglycaemia could not be fully excluded. Results from clinical studies did not indicate that insulin antibodies associated with Exubera treatment affect dosing of either short-acting or basal insulin, fasting plasma glucose levels, or the incidence or timing of hypoglycaemic events. Although based on these findings, the increase in insulin antibodies was considered to be a low risk, a hypothetical risk for prenatal development cannot be excluded. The applicant has committed to monitor antibody levels in ongoing clinical trials to increase understanding of insulin antibody production and define its potential consequences.

Furthermore, in the "Comparative Discontinuation Phase of Study 111" it was shown that among subjects with type 1 DM, mean insulin antibody level fell by approximately 50% within the initial 3 months after inhaled insulin discontinuation. Among subjects with type 2 DM, mean insulin antibody level also fell after discontinuation, but the decline was slightly less and more protracted than in type 1 patients. When an Exubera treated patient becomes pregnant, appropriate subcutaneous insulin should be substituted for Exubera. Therefore, maternal IAB levels are expected to be much lower when maternofetal IgG transfer begins early in the second trimester.

As a consequence, the following is stated in the SPC:

"There is no clinical experience with Exubera use in pregnancy. Exubera frequently induces insulin antibodies, the risk of which to the foetus is not known. Therefore, Exubera should not be used during pregnancy. When an Exubera treated patient becomes pregnant, appropriate subcutaneous insulin should be substituted for Exubera."

- Local tolerance

No specific local tolerance studies were done in support of the inhalation program. However, local tolerance was assessed for the respiratory system in repeat dose 1- and 6-month inhalation studies. No adverse effects related to local tolerance were observed.

- Other toxicity studies

Excipients

The safety of the excipients has been demonstrated in the inhalation toxicology studies in rats at levels of up to approximately 100-300 times the human level and in monkeys of up to approximately 10-30 times the human level. The safety is also supported by a literature review on the respiratory tract deposition and clearance of insulin inhalation dry powder. The excipients are therefore considered safe for the intended use.

Ecotoxicity/environmental risk assessment

Considering the nature of the insulin inhalation powder, its degradation to amino acids, the very low amount of urinary excretion, its potential for biodegradation and hydrolysis during and after sewage treatment plant, as well as inactivation after oral uptake, Exubera is of low environmental risk.

Discussion on the non-clinical aspects

Pharmacology studies showed that insulin inhalation powder administered by pulmonary route to rats, monkeys and dogs, was absorbed into the bloodstream in a dose-dependent manner and produced the expected pharmacodynamic response of decreasing glucose concentrations. No definitive nonclinical pharmacokinetic studies were conducted. The apparent systemic bioavailability was relatively low and variable.

According to limited non-clinical study and the applicant's literature review, chronic administration of Exubera is not likely to result in accumulation in the lung.

Due to insulin's affinity for insulin-like growth factor-1 (IGF-1) receptors, the tumorigenic risk for the lung was questioned. The applicant provided estimation of local insulin concentrations and information on IGF-1 receptors and insulin receptors in lung. Based on these data and considering that Aventis recombinant human insulin has a low affinity for IGF-1 receptors (compared to IGF-1 itself), it is concluded that insulin inhalation powder is unlikely to stimulate mitogenesis via the IGF-1 receptor.

The potential for insulin to act as a growth promoter in humans who might have pre-existing, undetected tumors or pre-neoplastic changes in the lung, was also questioned. In response the applicant provided data regarding characterization of growth factors and their receptors in normal tissue and human tumor tissues, a discussion on growth factor/growth factor receptors in various tumor-derived cultured cell models that are used as model systems for human lung tumors and for in vitro mitogenicity assays, as well as literature data.

In conclusion, non-clinical data on insulin inhalation powder did not show a tumorigenic risk for the lung nor suggest that insulin inhalation powder may promote pre-existing preneoplastic/neoplastic

changes in the lung. Further non-clinical experimentation would be of limited relevance for human risk assessment. See also clinical safety section.

The potential hazard for the foetus of the frequently induced insulin antibody is unknown therefore Exubera should not be used during pregnancy.

4. Clinical aspects

Introduction

Exubera consists of a dry powder formulation of regular insulin (in unit dose blisters) to be inhaled through a manually operated, pneumatically powered delivery system. The product was designed to optimise alveolar deposition of powder while minimizing deposition in upper airways through the use of a holding chamber that encourages a slow deep inspiration of an aerosol cloud that contains drug particles.

Four different insulin spray dried powder formulations which contained different amounts of insulin and excipients were used in the development and clinical program. The active substance used came from two suppliers. The drug substance supplied by the earlier supplier was used for development, toxicology studies, and Phase I, IIa and IIb trials. Commercial source of insulin was used for pivotal Phase III and stability studies.

The proposed commercial inhaler and its constituents were used in the Phase 3 clinical trials and further modified considering clinical experiences.

The clinical development program is extensive and consists of 32 single-dose pharmacological studies, 1 multi-dose (6-month) exploratory clinical pharmacology study (study 1026) and more than 20 Phase 2/3 studies.

Eight controlled Phase 3 studies (106, 107, 108, 109, 110, 1001, 1002 and 1009), and three controlled supportive Phase 2 studies (102, 103, 104) had been completed at the time of the marketing authorisation application and represent the core of the INH Phase 2/3 clinical development program. During the procedure, results on additional comparative phase 3 studies (1022, 1027, 1029, preliminary results on studies 1028 and 1030) were submitted.

Overall, 821 subjects were exposed to INH during the 32 single-dose pharmacological studies and more than 1975 patients have received INH for more than 6 months.

Because there are insufficient long-term safety data in children, the applicant did not seek a paediatric indication at the present time. Its use is therefore not recommended in patients under 18 years of age.

The applicant stated that all clinical studies conformed to ICH good clinical practice standards and were conducted according to the principles of the Declaration of Helsinki.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

The Applicant has conducted a comprehensive clinical pharmacology program including 32 single-dose studies and one 6-month chronic-dose study. These studies were conducted in healthy volunteers, in patients with type 1 or type 2 DM or in special populations such as children, elderly, obese, smokers and subjects with underlying lung disease (asthma, COPD).

Seventeen of the 32 pharmacological studies were conducted during early development stage and used early powder formulations and inhaler versions. Most of these early studies were performed to

characterise and optimise the INH system and to identify variables that may have an effect on the performance of the product and thus direct transferability of the results to the final formulation was not intended. A number of these studies investigated important issues such as INH deposition, effect of particle size, changes in breathing maneuver, and effect of mild asthma on bioavailability of INH. The combination of the final inhaler version and the clinical trial formulation produced slightly higher total exposure and peak serum insulin concentrations than the combination of earlier inhaler and powder formulation. Therefore, results from early studies are only of limited applicability to the final formulation. However, it can be expected that some main conclusions still apply, e.g. that lack of breath hold after inhalation does not have a major effect on exposure or that exposure may decrease with increasing airway resistance (asthma).

Comparability of the clinical (phase 3) and commercial formulation of INH was formally demonstrated for the 3 mg blister. Although equivalence could not formally be demonstrated for the 1 mg blister, the deviation from the lower limit of the pre-defined acceptance range was minimal and considered clinically not relevant.

- Absorption

Following oral inhalation of a single dose of human insulin approximately 60% of the emitted dose (about 40% of the blister content) reaches the lung while 30% is deposited in the oropharynx and 10% in the conducting airways. Insulin is a peptide drug with negligible gastrointestinal absorption. Consequently, the amount of drug deposited in the oropharynx or swallowed is not expected to affect blood PK profiles.

Inhaled human insulin is absorbed as rapidly as the ultrarapid acting insulin analogue lispro and more rapidly than SC soluble human insulin in healthy subjects and in subjects with type 1 or type 2 diabetes. The time to peak insulin concentration (Tmax) is about 45 min and is generally half of that for SC soluble human insulin. Peak insulin concentration (Cmax) and total exposure (AUC) of INH are generally comparable to those of SC soluble human insulin. At 400 min post-INH dose, insulin levels returned close to baseline.

Bioavailability
In diabetic subjects, the bioavailability of INH relative to SC regular insulin ranged from 8% to 11% (mean about 10%).

Particle size was shown to significantly influence the bioavailability of INH. The optimal diameter for pulmonary penetration is 2 to 3 μm, and, the degree of monodispersion of the aerosol is critical to avoid impaction in larger airways and the oropharynx. The final inhaler device delivers particles with a mean mass aerodynamic diameter (MMAD) that approximate the optimal diameter for pulmonary penetration outlined above.
The effect of the inhalation procedure/manoeuvres on bioavailability of INH was studied with early INH formulations and inhaler. Slow deep inspiration of INH with a subsequent 5 to 7 seconds breath hold appears to provide highest bioavailability although failure to hold breath did not have a major effect. Based upon modeled inhaled particle deposition predictions, certain conclusions about the effect of peak inspiratory flow rate from the early studies using earlier INH formulation and inhaler types are expected to also apply to the final formulation and inhaler.
A consistent and standard inhalation procedure is important to ensure both optimal and consistent drug delivery. Detailed guidance for the inhalation procedure was successfully provided to the patients in the Phase 3 clinical program. Similar guidance should be given in both the SPC and in the PL.

In case of major changes to the inhalation procedure, an accidental 'increase' in inhalation rate (though unexpected due to the nature of the device and its associated cloud chamber), would potentially result in a lower exposure to insulin and therefore should not be associated with an increased risk of hypoglycaemia. The impact of the opposite case of an accidental and unusually low inhalation rate is considered low for particles of ~3-μm diameter.
In conclusion, patients to be treated with EXUBERA must receive comprehensive instructions in the use of the inhaler, and must know that a consistent and standard inhalation technique should be

employed to ensure optimal and consistent drug delivery. Adequate wording detailing the appropriate inhalation procedure in conjunction with a precautionary statement on the potential to alter insulin exposure in case of major deviations should be included in the SPC and PL.

- Distribution and elimination

The metabolism of human insulin is well known. Human insulin circulates in blood as the free monomer with a volume of distribution that approximates the volume of extracellular fluid. The degradation of insulin by peripheral tissues, including lung, is well established. The metabolites are inactive. Thus, no investigations on distribution and elimination of INH or in subpopulations with renal or hepatic impairment were performed and no such investigations are required. In patients with hepatic or renal impairment, insulin requirements may be reduced.

- Dose proportionality and dose equivalence

Dose proportionality of INH has been assessed in a number of studies. Although mean insulin exposure (AUC) and Cmax increased approximately linearly with INH doses from 1 to 6 mg (using both 1 and 3 mg blister strengths), dose proportionality could not formally be established in any of these studies. The lack of dose proportionality is not surprising given the fact that the 1 and 3 mg blisters are not dose equivalent.

A dose-equivalence study in healthy volunteers has shown that three 1-mg blisters are not equivalent to one 3-mg blister; consecutive inhalations of three 1 mg blisters resulted in approximately 40% higher exposure than inhalation of one 3 mg blister. See discussion on clinical efficacy.

- Variability

Since insulin is titrated individually, the intra-subject variability rather than the between-subject variability is the primary concern because high within-variability could increase the risk for impaired glycaemic control and/or hypoglycaemia. In patients with type 1 DM, the within-subject variability in AUC was similar for INH (clinical formulation) and SC regular insulin, but the variability in Cmax was greater for INH. In subjects with type 2 DM, the within-subject variability of PK parameters was similar or lower for INH than SC regular insulin. In multiple-period, single dose studies, an apparent trend toward a lower variability in later treatment periods was observed for both the INH AUC and Cmax values consistent with increased familiarity with the inhalation procedure. Therefore, patients started on EXUBERA must receive comprehensive instructions on the use of the inhaler.

The between-subject variability in AUC for INH (clinical formulation) appears to be comparable to that of SC regular insulin, but the between-subject variability in Cmax and Tmax was found to be higher for INH than for SC regular insulin in subjects with Type 1 DM.

- Special populations

No difference in pharmacokinetic profile was observed in relation to gender, age or Japanese ethnicity.

Effect of smoking
The effect of smoking and/or smoking cessation for up to 13 weeks has been investigated in 4 studies. All studies clearly demonstrated that active smoking significantly increases the rate and extent of absorption of INH compared to non-smokers (Tmax about 20-30 minutes earlier, Cmax about 3 to 5 times and AUC about 2 to 3 times higher). Smoking cessation resulted in quick changes including an initial transient increase (over the first day) followed by a decrease in bioavailability with a concomitant delay in absorption. These changes occurred early during the period of smoking cessation. However, data from week 3 to week 13 of smoking cessation showed that bioavailability of INH continued to be increased compared to matched non-smokers, suggesting that 'normalisation' of INH absorption may not be achieved for a long time. Resumption of smoking promptly increased absorption of INH to pre-cessation levels. In summary, smoking may make INH absorption

unpredictable and could result in poor glycaemic control and hypoglycaemia. Accordingly, use in smokers and smoking should be contraindicated. See also discussion on clinical efficacy.
In addition, the Applicant has provided the results of a study requested to evaluate the effect of passive smoking (environmental tobacco smoke) on bioavailability. Acute passive exposure to tobacco smoke, as opposed to active cigarette smoking, decreased bioavailability of inhaled insulin (AUC and Cmax were reduced by 17% and 29%, respectively). The study results are included in the SPC.

Pulmonary and airway disorders
The effects of mild asthma or cold ('rhinoviral challenge') have been investigated in two studies using early INH formulations and inhaler. In subjects with mild asthma not using bronchodilators, absorption of INH was slightly but consistently less than in healthy subjects. In contrast, no difference in pharmacokinetics of INH was found between subjects with and without cold but the results from this study are questionable due to the low number of study subjects and the high variability in PK parameters.

In subjects with COPD (chronic bronchitis or emphysema), absorption of INH was increased by approximately 2 fold compared to healthy controls.

The reason for this increased absorption (as opposed to the decreased absorption in patients with asthma) is unclear. Overall, the timing of bronchodilator administration (30 min prior vs. 30 min after INH administration) did not affect INH bioavailability. In a small subset (n=5) of subjects with COPD who were retrospectively determined to be bronchodilator responsive, absorption of INH increased when INH was administered 30 minutes after bronchodilator administration. However, it is difficult to draw valid conclusions from this study because of differences in dosing conditions, small sample size and large between-subject variability. Differences in bioavailability of SC insulin in patients with chronic bronchitis compared to patients with emphysema are unexplained and complicate the interpretation of study results. See also clinical safety section.

Obese patients
Pharmacokinetics of INH was not different in obese versus normal-weight healthy subjects. In obese type 2 subjects, INH resulted in higher Cmax than SC soluble human insulin. In addition, relative bioavailability of INH was higher than in non-obese type 1 diabetic patients. These findings are most likely due to the delayed and decreased absorption of SC insulin in obese patients.

Children
The PK profile of INH was found to be similar in adult and paediatric patients with diabetes.

- Pharmacokinetic interaction studies

Upon CHMP request, formal interaction studies were performed to investigate the effect of bronchodilators and respiratory steroids on bioavailability of inhaled insulin. The results demonstrate that the use of a short-acting bronchodilator (salbutamol, 30 min prior to inhalation of Exubera) in asthmatic patients enhances the bioavailability of inhaled insulin. In contrast, inhalation of fluticasone (10 min prior to inhalation of Exubera) does not appear to affect the bioavailability of Exubera. Exubera itself does not change the bronchodilatory response tosalbutamol. These study results are reported in the SPC in section 4.5 and not in section 4.2, as initially claimed by the applicant, since the use of Exubera is currently not recommended in patients with underlying lung disease such as asthma or COPD, and actually contraindicated in patients with poorly controlled, unstable, or severe asthma and in patients with severe (GOLD stage III or IV) COPD.
Since the effect of mucolytics is difficult to evaluate in interaction studies, the Applicant will address this issue as part of a study in COPD patients (study 1030).

Pharmacodynamics

- Mechanism of action

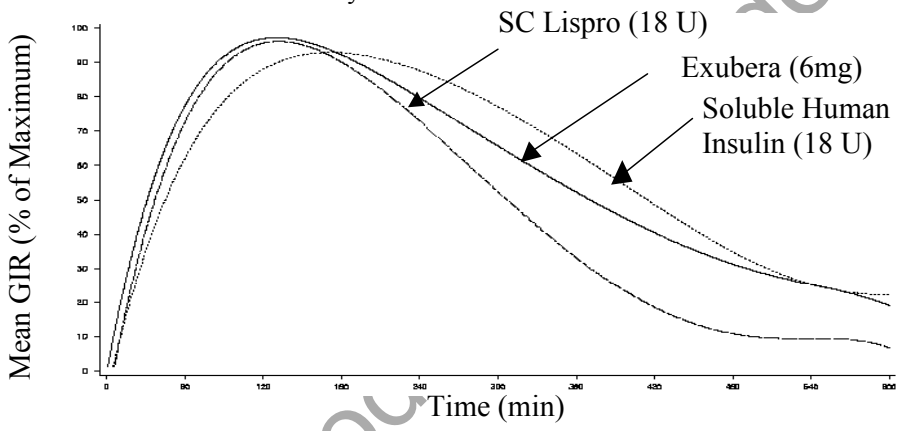
The mechanism of action and the metabolic effects of insulin are well known; human insulin lowers blood glucose and promotes anabolic effects, decreases catabolic effects, and increases the transport of glucose into cells as well as the formation of glycogen in the muscles and the liver.

- Primary and Secondary pharmacology

The pharmacodynamics of inhaled insulin has been evaluated in three types of studies:
- by measuring glucose levels after insulin administration in fasting subjects with type 2 DM.
- in euglycemic clamp studies in healthy subjects and subjects with type 2 DM. In these studies, the glucose level was maintained to a pre-defined level by varying the glucose infusion rate (GIR). The insulin action profile was evaluated by the glucose infusion rate.
- by measuring postprandial glucose levels after insulin administration in meal studies in subjects with type 1 DM.

Glucodynamic responses in the pharmacology studies following administration of INH or SC insulin generally reflected the changes in insulin concentrations.

In healthy subjects, onset of action of INH was shown to be as fast as that of SC ultrarapid-acting insulin analogue lispro, and more rapid than that of SC soluble human insulin. The duration of action was longer for INH than for SC insulin lispro and comparable to SC soluble human insulin. The following figure shows the mean Glucose Infusion Rate (GIR) normalised to GIRmax for each subject treatment versus time in Healthy Volunteers.



Similar results were observed in subjects with diabetes where INH was compared with SC regular insulin

The onset of glucose lowering activity of INH is within 10 to 20 minutes, the maximum effect is observed approximately 2 hours after inhalation and the duration of action was determined at approximately 6 hours.

The within-subject variability of inhaled INH in glucose-lowering activity was generally comparable to that of SC regular insulin in subjects with type 1 and type 2 DM.

In a chronic-dose study (1026), the effect of INH on postprandial glucose seemed well conserved after 24 weeks, similar to that of SC soluble human insulin. Although insulin antibody (IAB) levels increased markedly during the study period, this did not influence glucose pharmacodynamics of inhaled insulin.

Clinical efficacy

The applicant has conducted an extensive phase 2/3 clinical program to investigate efficacy and safety of INH in patients with either type 1 or type 2 DM.

No classic dose response studies were performed; INH doses chosen in the phase 2/3 trials were based on results from PK/PD studies, which is acceptable since the dose response relationship of the active substance is well known.

The following tables present an overview of the main phase 2-3 trials.

Phase 2/3 Trials with available efficacy and safety data

Study	Duration	Subjects (INH):	Treatment Arms	Objective
Studies in type 1 diabetic subjects using SC insulin Note: both treatment groups used a SC long-acting insulin				
102 – Phase 2	3 months	72 (35)	INH vs. SC insulin	Non-inferiority, supportive
106 – Phase 3	6 months	335 (170)	INH vs. SC insulin	Non-inferiority
107 – Phase 3	6 months	328 (163)	INH vs. SC insulin	Non-inferiority
1009 – Phase 3	3 months	121 (61)	INH vs. SC insulin	Exploratory
Studies in type 2 diabetic subjects using SC insulin at study entry Note: both treatment groups used a SC long-acting insulin				
103 – Phase 2	3 months	56 (28)	INH vs. SC insulin	Non-inferiority, supportive
108 – Phase 3	6 months	299 (149)	INH vs. SC insulin	Non-inferiority
Studies in type 2 diabetic subjects not using SC insulin at study entry				
104 - Phase 2	3 months	69 (33)	INH plus OA including sulfonylurea and/or metformin vs. OA alone	Superiority, supportive
109 - Phase 3	3 months	309 (207)	INH monotherapy vs. INH + OA including: sulfonylurea or repaglinide plus a glitazone or metformin vs. Pre-study combination oral agents	Superiority
110 - Phase 3	3 months	145 (76)	INH monotherapy vs. Rosiglitazone	Superiority
1001- Phase 3	6 months	427 (222)	INH + sulfonylurea vs. metformin + sulfonylurea	Superiority/Non-inferiority*
1002–Phase 3	6 months	470 (239)	INH + metformin vs. glibenclamide + metformin	Superiority/Non-inferiority*
Other studies				
1022	2 years	Type 1 diabetes (290)	INH vs. SC insulin	Annualized rates of change in FEV1 and Dlco
1029	2 years (12- month interim report)	Type 2 diabetes (311)	INH vs. SC insulin	Annualized rates of change in FEV1 and Dlco
1027	24 weeks	Type 1 diabetes	INH vs. SC insulin	FEV1 (or DLco) response status

* Superiority was hypothesised for the high HbA_{1c} stratum; non-inferiority the combined HbA_{1c} strata.

Study 1009 included paediatric patients only. Results on paediatric patients are described and discussed in section 'Clinical studies in Special populations'. The applicant did not pursue a paediatric indication in the initial application.

- Main studies

METHODS

All Phase 2-3 controlled, completed studies used a randomised, multi-centre, active-controlled, open-label, parallel-group design.

Study Participants

Inclusion and exclusion criteria

a) Studies in patients with type 1 DM

Main inclusion criteria:

- Age 18-55 years (phase 2 study 102), age 12-65 years (phase 3 studies 106 and 107)
- Type 1 diabetes mellitus (for more than one year in studies 106 and 107).
- Screening and pre-randomisation HbA1c 7.0%-11.9% (study 102), 6.0%-11% (studies 106 and 107).
- Fasting plasma C-peptide ≤ 0.2 pmol/ml.
- Stable insulin administration schedule (for at least 2 months) involving at least 2 injections daily of insulin or an insulin analogue
- Body weight between 80 and 130% of ideal (Metropolitan Life Insurance Tables) (study 102), BMI ≤30 kg/m^2 (studies 106 and 107).

Main exclusion criteria:

- Major organ system disease, except for well-controlled, stable disorders, such as essential hypertension and complications directly related to diabetes. Significant laboratory abnormalities. Abnormal screening ECG.
- "Brittle" diabetes or predisposition to severe hypoglycaemia.
- Subjects requiring more than 150 units of insulin daily.
- Clinically significant abnormalities on chest X-ray, frankly abnormal pulmonary function test and/or significant respiratory disease (e.g. poorly-controlled asthma).
- Smokers (any smoking within past 6 months). Smoking was not permitted at any time during the study.
- Pregnant or nursing females.

b) Studies in patients with type 2 DM

Main inclusion criteria:

- Age 35-65 years (phase 2 studies), 35-80 years (phase 3 studies).
- Type 2 diabetes mellitus, diagnosed at least one year (study 109), 2 months (study 110), 6 months (studies 1001 and 1002) prior to screening.
- Screening and pre-randomisation HbA1c 7.0%-11.9% (study 103), 8.1%-11.9% (study 104), 8.0-11.0% (study 109), 6.0-11.0% (study 110), 8%-12% (studies 1001 and 1002).
- Fasting plasma C-peptide ≥ 0.2 pmol/ml.
- Body weight between 100 and 175% of ideal (Metropolitan Life Insurance Tables) (studies 103 and 104), body mass index ≤ 35 kg/m2 (studies 108, 109), ≤ 40 kg/m2 (study 110).

In addition:

- Patients using insulin at baseline: Stable insulin administration schedule for at least 1 month (study 103) or 2 months (study 108) involving at least 2 prescribed injections daily.

- Patients not using insulin at baseline:

Study 104: stable dose of sulfonylurea and/or metformin, for at least 1 month.
Study 109: stable OA combination regimen for at least 2 months involving 1) an insulin secretagogue (either sulfonylurea or repaglinide) and 2) either a glitazone or metformin.
Study 110: stable diet and exercise regimen for at least 2 months and DM no pharmacologic therapies.
Study 1001: treatment with sulphonylurea alone for at least 2 months.
Study 1002: treatment with only metformin ≥1.5 g/day for at least two months.

Main exclusion criteria:

Same as in type 1 DM. In addition:

- Autonomic neuropathy.
- Significant history of atopy or allergic drug reactions, including local insulin allergy.
- Positive urinary cotinine test (studies 1001 and 1002).

- Concomitant therapy with sulfonylureas, metformin, or acarbose within 1 month (study 103), any oral hypoglycaemic agents within 2 months (study 108), insulin, acarbose, or troglitazone within 1 month (study 104) prior to screening. Any therapy with hypoglycaemic agents except sulfonylureas (study 1001) or metformin (study 1002).

Withdrawal: Subjects with significant deterioration in glycaemic control (e.g. >1.5%) could be and subjects with repeated HbA1c >12% had to be withdrawn from the study.

Treatments

All comparative studies were preceded by a 4-week lead-in period during which eligible patients received the control SC insulin or OA regimen and were instructed in the use of the inhaler device. At the week 0 visit, subjects were randomised to the treatment groups.

The control treatment was principally the treatment given during lead-in (except for studies 1001 and 1002). Doses of oral OA medication given during lead-in (background treatment) were to remain fixed throughout the study period. Add-on OAs, however, were titrated according to a pre-specified schedule up to week 18 (study 1001) or week 24 (study 1002), if necessary (see schedule below).

Initial dosing of INH:
The initially prescribed pre-meal doses were based on the patient's weight and previous response to insulin. INH was administered immediately prior to meals (within 10 min).

Dose titration of insulin:
INH dosing or insulin injections always had to be preceded by blood glucose checks. Patients on OAs only had to perform 2-times daily home glucose monitoring (prior to breakfast and supper). Dose adjustments for insulin were made according to a pre-defined schedule to reach the following blood glucose levels:
- Phase 2 studies: pre-meal blood glucose of 100-160 mg/dl.
- Phase 3 studies: blood glucose of 80-140 mg/dl before meals and 100-160 mg/dl at bedtime – except in study 107, in which an intensive regimen was used, the goal was to reach 80-120 mg/dl before meals, < 180 mg/dl post-prandially, and 100-140 mg/dl at bedtime.

The recommended dose of short-acting insulin was to be used for pre-meal glucose values in the range of 80-180 mg/dl (80-200 mg/dL in phase 2 studies). For higher (lower) values a dose increase (decrease) by 1mg for INH or 2-4 U for SC regular insulin was recommended. In addition to pre-meal dosing, INH could be administered on an as required basis, e.g. an additional bedtime dose of 1-2 mg for INH or 2-6 U for regular insulin could be given in case bedtime glucose exceeded 180 mg/dl. Insulin dose was adjusted at weekly intervals, as necessary.
Patients on INH were allowed to switch to SC or IV insulin during study-emergent intercurrent illness or surgery.

Dose titration of add-on OAs:

- In study 1001, patients randomised to adjunctive metformin underwent a period of dose titration during which the dose of metformin was increased in 500 mg steps up to maximally 2.5 g/day.

- In study 1002, patients randomised to adjunctive glibenclamide underwent dose titration during which the dose of glibenclamide was increased at from 2.5 mg once daily to maximally 15 mg daily.

Objectives

In studies in diabetic (type 1 or type 2) subjects using SC insulin at study entry, the objective was to determine whether glycaemic control could be achieved at least as effectively with an insulin regimen involving pre-meal (TID) INH plus SC basal insulin (Conventional insulin regimen except in study 107 where it consisted in an intensive regimen – see above "Dose titration of insulin").

In studies in type 2 diabetic patients not using SC insulin at study entry, the objective was to determine whether:

- INH, either alone (Studies 109 and 110) or in addition to OA treatment (Studies 104, 109, and the high HBA1c strata of Studies 1001 and 1002) was superior to an exclusively OA therapeutic regimen in providing glycaemic control,
- INH in addition to OA treatment (low HbA1c strata of Studies 1001 and 1002) was non-inferior to combined OA treatment.

Other objectives in all studies were the local tolerance and safety of INH therapy and its effects on measures of pulmonary function.

Outcome/endpoints

The primary endpoint was the Mean change in HbA1c from baseline to end of study (except for study 110). The primary endpoint in study 110 was the proportion of subjects reaching the end of study goal of $HbA_{1c} < 8.0$ %.

The main secondary endpoints were: change in HbA1c from baseline to week 12 (study 110 only), proportion of patients with acceptable (HbA1c < 8%) or good (HbA1c <7%) glycaemic control at end of treatment (phase 3 studies), change in fasting glucose and meal glucose response, incidence and severity of hypoglycaemic episodes, body weight, mean daily insulin doses, QOL and treatment satisfaction (self-administered questionnaire).

Definitions of hypoglycaemia:

- Mild-moderate: Typical symptoms without glucose measurement; Typical symptoms with glucose measurement < 60 mg/dl; or Any glucose measurement < 50 mg/dl. Prompt resolution of symptoms with food intake.
- Severe: (1) the subject was unable to treat him/herself; and (2) the subject exhibited symptoms of central nervous system impairment; and (3) either blood glucose was <50 mg/dL or, if not measured, hypoglycaemic symptoms were reversed by a glucose source. This prospective definition in phase 3 studies was retroactively applied to phase 2 studies (where initially the definition of severe hypoglaemia was: subject requires the assistance of another person; coma and/or seizures) for consistency.

A pre-specified 16-item questionnaire was used to assess satisfaction with insulin treatment during the study. Questions related to advocacy, burden, convenience, efficacy, flexibility, general satisfaction, hassle, interference, pain, preference, side effects, social aspects.

The Diabetes Quality of Life and Treatment Satisfaction Questionnaire (Phase V Outcomes System) was used to assess satisfaction with diabetes treatment, quality of life and preferences during the study. Satisfaction scales measured advocacy, burden, convenience, efficacy, flexibility, general satisfaction, hassle, interference, pain, preference, side effects, and social aspects. Quality of life scales measured perceived health, diabetes symptoms interference, sleep, vitality, sexual satisfaction, anxiety, affect, behaviour/emotional control, psychological well-being, life satisfaction, mental health, cognitive performance, and symptom distress.

Sample size

In non-inferiority studies, sample size was estimated to provide 80% power to ensure that the upper limit of the 2-sided 95% CI (97.5% CI for combined strata in studies 1001 and 1002) of the difference between groups in change from baseline HbA1c did not exceed 1.0% (absolute units) in phase 2 studies or 0.5% in phase 3 studies.

In superiority studies, sample size was estimated to provide 80% power to detect a difference between the groups in HbA1c of 1.0% in phase 2 studies or 0.7% in phase 3 studies.

In Study 110, a sample size was estimated to provide 80% power to detect a difference between groups of at least 20% in response rates, using a 2-sided 5% level of significance, and assuming a 35% response rate in the rosiglitazone group. The number of patients was later increased to 150 per group to accommodate the required power for patient satisfaction and QOL assessments.

Randomisation

Patients were randomised 1:1 to the two treatment groups or 1:1:1 to the 3 treatment groups (Study 109). In the phase 2 studies, randomisation was stratified according to the patients' week –1 HbA1c (> 8.5% or ≤ 8.5% in studies 102 and 103, > 10.0% or ≤ 10.0% in study 104). In studies 1001 and 1002 subjects were stratified according to their HbA1c at week-1; low stratum (HbA1c ≥8% to ≤ 9.5%) and high stratum (HbA1c ≥9.5% to ≤ 12.0%).

Statistical methods

ITT population was defined as all randomised patients with a baseline value and at least one post-baseline measurement. It was the primary analysis population in superiority trials.

PP population was defined as subset of the ITT population without major protocol violations, randomised into the correct stratum, have received at least half the protocol required duration of treatment as assigned by the randomisation scheme, baseline and at least one evaluable HbA1c assessment (defined as having been preceded by a treatment duration of 75% or more of the elapsed time since the previous assessment). It was the primary analysis population in non-inferiority trials.

Analysis for the primary endpoint and for hypoglycaemia was performed for both the ITT and PP population. For other secondary efficacy endpoints analysis was performed for the primary analysis population only.

Last observation carried over (LOCF) method was used.

Most studies in the phase II / phase III programme used end of study change from baseline in HbA1c as the primary endpoint and an ANCOVA-model including baseline HbA1c as a continuous covariate and centre and treatment group as categorical variables.

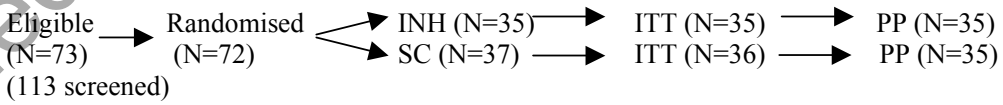
Non-inferiority margins were set to 0.5% deterioration with respect to change from baseline in HbA1c in phase III studies (and to 1% in phase II studies).

In superiority trials (except for study 110) relevance margins were set at 1.0 % for phase 2 studies and 0.7 % for Phase 3 studies. The relevance margin used in study 110 was 20%.

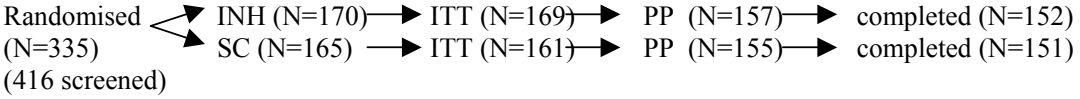
RESULTS OF PHASE 2/3 STUDIES IN TYPE 1 DM

Participant flow

Study 102 (Phase II – 3 months duration)



Study 106 (Phase III – 6 months duration – conventional regimen)



Of the 170 patients randomised to INH, 137 were ≥18 years of age, of whom 120 completed. Of the 165 patients randomised to SC insulin 136 were ≥18 year of age, of whom 123 completed.

Study 107 (Phase III – 3 months duration – intensive regimen)

Randomised (N=328) → INH (N=163) → ITT (N=162) → PP (N=159) → completed (N=154)
Randomised (N=328) → SC (N=165) → ITT (N=162) → PP (N=159) → completed (N=152)
(419 screened)

Of the 163 patients randomised to INH 103 were ≥18 year of age, of whom 97 completed. Of the 165 patients randomised to SC insulin 105 were ≥18 year of age, of whom 96 completed.

Baseline data

There were no notable imbalance across treatment groups in demographic or clinical characteristics, past or present medical history, or concomitant medication. Study subjects were predominantly Caucasian.

Demographics of Clinical Trial Subjects ≥ 18 Years of Age

Study 102	**INH**		**SC Insulin**	
Total Subjects	35		37	
Age (yrs.)	35.4 [9.0]		39.7 [8.6]	
Gender M/F (%)	M: 19 (54.3%)	F: 16 (45.7%)	M: 19 (51.4%)	F: 18 (48.6%)
BMI (kg/m^2)	M: 25.1 [21-31]	F: 24.4 [20-28]	M: 26.0 [22-31]	F: 24.6 [19-31]
HbA_{1c} (%)	8.89 [6.8 - 11.4]		8.95 [6.7 - 11.9]	
Study 106				
Total Subjects (%)	137		135	
Age (yrs.)	38.2 [10.3]		38.2 [10.5]	
Gender M/F (%)	M: 70 (51.1%)	F: 67 (48.9%)	M: 71 (52.6%)	F: 64 (47.4%)
BMI (kg/m^2)	M: 26.4 [21-36]	F: 25.1 [19-34]	M: 25.8 [19-32]	F: 25.2 [18-33]
HbA_{1c} (%)	8.23 [6.0 - 11.0]		8.24 [6.00 - 10.80]	
Study 107				
Total Subjects (%)	103		105	
Age (yrs.)	38.1 [10.6]		38.6 [11.0]	
Gender M/F (%)	M: 54 (52.4%)	F: 49 (47.6%)	M: 59 (56.2%)	F: 46 (43.8%)
BMI (kg/m^2)	M: 26.1 [19-32]	F: 24.7 [18-32]	M: 26.3 [20-35]	F: 24.9 [17-31]
HbA_{1c} (%)	8.12 [6.40 - 10.90]		8.16 [6.00 - 11.50]	

Data are presented as mean [SD] for age; mean [range] for body weight, BMI and HbA1c, M/F = Male/Female.

Outcome

Primary endpoint: Based on the pre-specified non-inferiority margins all three studies showed non-inferiority of an insulin regimen involving INH to SC insulin regimens.

Change from Baseline in HbA_{1c}, (%) in Subjects ≥ 18 Years of Age – PP population

		Unadjusted Mean [SD]			Adjusted Difference (95% CI)*
Study	**N**	**Baseline**	**End of Study**	**Change**	
102					
INH	35	8.5 [1.1]	7.9 [1.0]	-0.6 [1.0]	0.16 (-0.20, 0.51)
SC insulin	35	8.5 [1.1]	7.7 [0.9]	-0.8 [0.9]	
106					
INH	125	7.9 [0.9]	7.7 [1.0]	-0.2 [0.8]	0.15 (-0.02, 0.33)
SC insulin	126	8.0 [1.0]	7.6 [0.9]	-0.4 [0.7]	
107					
INH	100	7.8 [0.9]	7.5 [0.9]	-0.3 [0.8]	-0.10 (-0.30, 0.09)
SC insulin	100	7.8 [1.0]	7.5 [1.0]	-0.2 [0.8]	

*Adjusted mean difference between groups (INH – SC) in change from baseline and 95% CI were based on the primary model with terms for baseline, treatment, and centre.

Secondary endpoints

- The proportion of subjects in each treatment group achieving good (HbA1c <7%) or acceptable (HbA1c <8%) glycaemic control did not differ between treatment groups.

Subjects ≥ 18 Years of Age Achieving End-of Study HbA_{1c} < 8% or <7% - PP population

Study	INH N (%)	SC insulin N (%)
106	N = 125	N = 126
<8%	81 (64.8%)	87 (69.0%)
<7%	21 (16.8%)	23 (18.3%)
107	N = 100	N = 100
<8%	75 (75.0%)	68 (68.0%)
<7%	29 (29.0%)	31 (31.0%)

- In studies 106 and 107 INH patients had a significant decline in fasting glucose compared to SC insulin patients. Mean difference in change (95% CI) was –29mg/dL (-49, -9) for study 106 and –37mg/dL (-60, -14) for study 107. In study 102 the decline in fasting glucose was not different between groups.

- In studies 106 and 102, the change in the postprandial glucose increment was comparable between treatment groups. However, in Study 107, the change in glucose increment was statistically different between the two groups with INH subjects exhibiting an increase in glucose increment insulin compared to SC subjects.

- *Daily insulin dose:* In all 3 studies, baseline short and long-acting insulin doses were similar across treatment groups. During the treatment period, a shift from long-acting to short-acting insulin occurred in the INH group but not in the SC group. At the end of study, the short-acting insulin doses in the INH group were approximately 2.3, 2.2 and 1.3 fold higher in studies 102, 106 and 107, respectively, than those in the SC insulin groups (calculation based on the assumption that 1 mg INH corresponds to approximately 3 U of SC regular insulin) but total daily insulin doses remained similar.

- *Hypoglycaemia:* The percentage of patients who experienced a hypoglycaemic event and the respective event rates were similar in the INH and SC insulin groups. In study 107, event rates for severe hypoglycaemia was higher in patients using INH. See clinical safety section.

Overall Hypoglycaemic Events in Subjects ≥ 18 Years of Age – PP population

Study	N	N (%) with Event	Total Events	Total Subject-Months	Event Rate*
102					
INH	35	33 (94.3)	558	99.5	5.6
SC insulin	35	29 (82.9)	536	101.6	5.3
106					
INH	125	123 (98.4)	6109	696.1	8.8
SC insulin	126	126 (100.0)	6380	709.3	9.0
107					
INH	100	99 (99.0)	5285	563.5	9.4
SC insulin	100	100 (100.0)	5909	558.8	10.6

*Number of events/subject-month.

Severe Hypoglycaemic Event Rates in Subjects ≥ 18 Years of Age

Study	N	N (%) with Event	Total Events	Total Subject-Months	Event Rate*
102-PP					
INH	35	4 (11.4)	7	99.47	7.0
SC insulin	35	4 (11.4)	8	101.58	7.9
106- PP					
INH	125	22 (17.6)	39	696.1	5.6
SC insulin	126	17 (13.5)	31	709.3	4.4
107- PP					
INH	100	17 (17.0)	42	563.5	7.5
SC Insulin	100	13 (13.0)	19	558.8	3.4

*Number of events/100 subject-months.

- In all 3 studies, body weight increased slightly by the end of study for subjects in both treatment groups. Weight changes were not different between treatment groups.

- *Treatment satisfaction and QoL:* Results were favouring INH. Nevertheless, due the open-label design of the studies, results should be interpreted with caution. Despite the overall preference of INH, only 38% and 32% of patients in studies 106 and 107, respectively, found it easier to adjust the dose with the inhaler than SC insulin.

RESULTS OF PHASE 2/3 STUDIES IN PATIENTS WITH TYPE 2 DM USING INSULIN AT BASELINE

Participant flow

Study 103 (3-month phase II trial)

Randomised (N=56) (112 screened) → INH (N=28) → ITT (N=28) → PP (N=26) → completed (N=25)
SC (N=28) → ITT (N=27) → PP (N=25) → completed (N=26)

Study 108 (6-month phase III trial)

Randomised (N=299) (520 screened) → INH (N=149) → ITT (N=146) → PP (N=143) → completed (N=132)
SC (N=150) → ITT (N=149) → PP (N=145) → completed (N=140)

Baseline data

Treatment groups were generally balanced for demographic characteristics and medical profile except for slightly higher HbA_{1c} and insulin doses in the INH-treated group of study 103. Study subjects were almost exclusively Caucasian.

Baseline Characteristics

Study 103	**INH (N=28)**		**SC Insulin (N=28)**	
Age (yrs.)	51.8 [8.5]		52.5 [7.5]	
Gender – M/F (%)	M: 18 (64.3%)	F: 10 (35.7%)	M: 15 (53.6%)	F: 13 (46.4%)
BMI (kg/m^2)	M: 29.8 [23-37]	F: 33.1 [26-41]	M: 28.3 [23-35]	F: 33.4 [25-40]
HbA_{1c} (%)	9.21 [7.0 - 12.9]		8.25 [7.0 - 11.3]	
Study 108	**INH (N=149)**		**SC Insulin (N=149)**	
Age (yrs.)	58.7 [9.5]		56.2 [11.1]	
Gender – M/F (%)	M: 99 (66.4%)	F: 50 (33.6%)	M: 99 (66.4%)	F: 50 (33.6%)
BMI (kg/m^2)	M: 29.9 [21-38]	F: 31.7 [22-51]	M: 29.5 [21-38]	F: 31.1 [22-38]
HbA_{1c} (%)	8.48 [6.5 - 11.9]		8.47 [5.80 - 11.60]	

M/F = Male/Female; Data are presented as mean [SD] for age; mean [range] for body weight, BMI and HbA1c

Outcome

Primary endpoint: In both studies, a similar change from baseline was observed across treatment groups. Based on the 95% confidence intervals for the adjusted treatment differences and the predefined non-inferiority margins, INH was non-inferior to treatment with SC insulin. Results were similar for ITT analysis.

Change from Baseline in Glycosylated Hemoglobin (HbA_{1c}, %) – PP population

PP analysis		**Unadjusted Mean [SD]**			**Adjusted Difference (95% CI)***
Study	**N**	**Baseline**	**End of Study**	**Change**	
103			Week 12		
INH	26	8.7 [1.4]	8.0 [1.4]	-0.7 [0.7]	0.18 (-0.21, 0.58)
SC insulin	25	7.9 [0.9]	7.1 [0.9]	-0.7 [0.7]	
108			Week 24		
INH	143	8.1 [1.1]	7.4 [1.5]	-0.7 [1.2]	-0.07 (-0.32, 0.17)
SC insulin	145	8.2 [1.1]	7.6 [1.1]	-0.6 [1.1]	

*Adjusted mean difference between groups (INH – SC) in change from baseline and 95% CI were based on the primary model with terms for baseline, treatment, and centre.

Secondary endpoints

- INH was comparable to SC insulin in enabling subjects to achieve HbA_{1c}<8% and superior to SC insulin in enabling subjects to achieve HbA_{1c}<7%.

Number (Percentage) of Subjects Achieving End-of-Study HbA_{1c} <8% or <7% - PP analysis

Study	**INH n (%)**	**SC insulin n (%)**
108	N=143	N=145
<8%	109 (76.2)	100 (69.0)
<7%	67 (46.9)	46 (31.7)

- In Study 108, the decrease in fasting glucose levels was significantly greater in INH than in SC insulin patients (mean difference in change –16 mg/dL, 95% CI: -27, -5). In study 103, the change was not different.

- In both studies, postprandial glucose increment results were not different across treatment groups.

- *Daily insulin dose:* At baseline, mean daily insulin doses were similar across treatment groups for both short and long-acting insulin. During the 24-week treatment period, a shift from long-acting to short-acting insulin occurred in the INH group but not in the SC group. At 24 weeks the amount of daily short-acting insulin used in the INH group was about 1.9 fold of that used in the SC insulin group but total daily insulin doses remained similar. There was a slight and similar increase in total insulin dose over time in both groups.

- *Hypoglycaemia:* The risk of experiencing hypoglycaemic events was similar in both treatment groups.

Overall Hypoglycaemic Events in Subjects with Type 2 Diabetes Using Insulin at Study Entry

Study	N	N (%) with Event	Total Events	Total Subject-Months	Event Rate*
103 – PP					
INH	26	18 (69.2)	61	73.3	0.8
SC	25	18 (72.0)	77	72.0	1.1
108 – PP					
INH	143	109 (76.2)	1104	787.5	1.4
SC	145	104 (71.7)	1278	814.8	1.6

*Number of events/subject-month.

Severe Hypoglycaemic Event Rates

Study	N	N (%) with Event	Total Events	Total Subject- months	Crude Event Rate*
108 - PP					
INH	143	3 (2.1)	4	787.5	0.5
SC insulin	145	1 (0.7)	1	814.8	0.1

*Number of events/100 subject-months.

- In study 108, patients receiving SC insulin gained significantly more weight over the 24-week study than did subjects treated with INH (mean difference –1.3 kg, 95% CI: -2.0, -0.6). A similar trend was observed in study 103 (mean difference –1.3 kg, 95% CI: -2.7, 0.1).

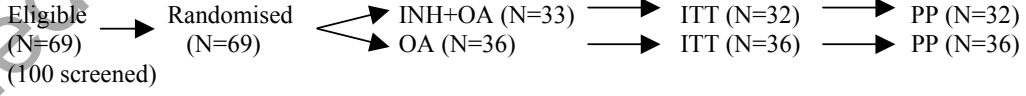
- The Overall Satisfaction Summary score improved significantly for the INH group while it decreased slightly for the SC insulin group.

RESULTS OF PHASE 2/3 STUDIES IN PATIENTS WITH TYPE 2 DM NOT USING INSULIN AT BASELINE

Participant flow

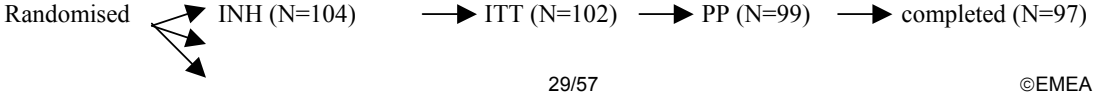
Study 104 (3-month Phase II study).

The OA regimen consisted of sulfonylurea (5 mg or more of glyburide or glipizide daily or 4 mg or more of glimepiride daily) and/or metformin (1.5 g or more daily).



Study 109 (3-month phase III study)

The OA regimen had to consist of 2 antidiabetic medications including a) an insulin secretagogue (either sulfonylurea or repaglinide) and b) either a glitazone or metformin. (Minimum doses had to be: glipizide 10 mg/day, glyburide 10 mg/day, glimepiride 4 mg/day, repaglinide 2 mg TID, metformin 1.7 g/day, troglitazone 400 mg/day, rosiglitazone 4 mg/day, and pioglizatone 30 mg/day.



(N=309) INH+OA (N=103) → ITT (N=100) → PP (N=98) → completed (N=99)
(580 screened) OA (N=102) → ITT (96) → PP (N=93) → completed (N=93)

Study 110 (3-month phase III study in patients failing diet and exercise)

Control regimen consisted of rosiglitazone (4 mg/BID).

Randomised (N=145) (402 screened) → INH (N=76) → ITT (N=75) → PP (N=74) → completed (N=71)
Randomised (N=145) (402 screened) → ROS (N=69) → ITT (N=67) → PP (N=63) → completed (N=63)

Study 1001 (6-month phase III study)

The sulfonylurea regimen consisted of: glibenclamide ≥10 mg/day (standard formulation) or ≥7 mg/day (micronised formulation), gliclazide ≥160 mg/day, glipizide ≥10 mg/day, or glimepiride ≥3 mg/day or equivalent. The metformin regimen was titrated between 500 mg once daily and 1 g twice daily.

Randomised (N=427) (774 screened) → INH+SU (N=225) → ITT (N=214) → PP (N=190) → completed (N=206)
Randomised (N=427) (774 screened) → MET+SU (N=202) → ITT (N=196) → PP (N=171) → completed (N=175)

Study 1002 (6-month phase III study)

Control regimen consisting of glibenclamide (dose titrated between 2.5 mg once daily to 5 mg twice daily) added to metformin 1g BID.

Randomised (N=476) (768 screened) → INH+MET (N=243) → ITT (N=234) → PP (N=215) → completed (N=219)
Randomised (N=476) (768 screened) → GLI+MET (N=233) → ITT (N=222) → PP (N=207) → completed (N=205)

Conduct of the studies

Study 110, which planned to include 150 subjects per group was halted due to enrolment difficulties.

Baseline data

Treatment groups were generally balanced for demographic and medical characteristics. Study subjects were almost exclusively Caucasian.

Baseline characteristics

Study 104	**INH + OA (N=33)**		**OA (N=36)**	
Age (yrs.)	52.7 [7.9]		49.9 [8.2]	
Gender – M/F (%)	M: 19 (57.6%)	F: 14 (42.4%)	M: 26 (72.2%)	F: 10 (27.8%)
BMI (kg/m^2)	M: 30.8 [24-40]	F: 32.1 [23-41]	M: 29.9 [22-40]	F: 33.3 [27-41]
HbA_{1c} (%)	9.90 [8.00 - 12.30]		9.96 [8.00 - 11.90]	

Study 109	**INH (N=105)**		**INH+OA (N=102)**		**OA (N=99)**	
Age (yrs.)	57.4 [9.2]		58.3 [8.6]		56.4 [10.0]	
Gender – M/F (%)	M: 75 (71.4%)	F: 30 (28.6%)	M: 65 (63.7%)	F: 37 (36.3%)	M: 62 (62.6%)	F: 37 (37.4%)
BMI (kg/m^2)	M: 30.5 [22-39]	F: 29.3 [24-39]	M: 29.8 [22-35]	F: 30.0 [18-38]	M: 29.3 [23-38]	F: 31.2 [18-37]
HbA_{1c} (%)	9.58 [8.0 - 11.7]		9.48 [7.0 - 11.7]		9.56 [7.2 - 11.8]	

Study 110	**INH (N=75)**	**Rosiglitazone (N=68)**

Age (yrs.)	53.0 [10.7]		54.4 [11.0]	
Gender –M/F (%)	M: 48 (64.0%)	F: 27 (36.0%)	M: 31 (45.6%)	F: 37 (54.4%)
BMI (kg/m^2)	M: 31.7 [24-43]	F: 32.2 [20-44]	M: 32.6 [24-46]	F: 32.8 [22-48]
HbA_{1c} (%)	9.76 [7.80 - 12.50]		9.64 [7.80 - 13.20]	
Study 1001 – Low	**INH + Sulfonylurea (N=105)**		**Metformin + Sulfonylurea (N=93)**	
Age (yrs.)	60.5 [8.9]		60.2 [10.2]	
Gender – M/F (%)	M: 52 (49.5%)	F: 53 (50.5%)	M: 49 (52.7%)	F: 44 (47.3%)
BMI (kg/m^2)	M: 27.4 [20-34]	F: 29.6 [23-40]	M: 28.6 [21-44]	F: 30.3 [21-42]
HbA_{1c} (%)	9.04 [7.40 - 11.40]		8.95 [7.60 - 11.90]	
Study 1001 – High	**INH + Sulfonylurea (N=117)**		**Metformin + Sulfonylurea (N=108)**	
Age (yrs.)	61.0 [9.0]		59.8 [9.7]	
Gender – M/F (%)	M: 70 (59.8%)	F: 47 (40.2%)	M: 53 (49.1%)	F: 55 (50.9%)
BMI (kg/m^2)	M: 27.9 [22-41]	F: 29.4 [22-48]	M: 28.3 [20-37]	F: 29.3 [21-57]
HbA_{1c} (%)	10.66 [9.20 - 13.70]	10.66 [8.80 - 13.30]		
Study 1002 - Low	**INH + Metformin (N=130)**		**Glibenclamide + Metformin (N=126)**	
Age (yrs.)	56.2 [8.9]		56.3 [8.9]	
Gender – M/F (%)	M: 74 (56.9%)	F: 56 (43.1%)	M: 79 (62.7%)	F: 47 (37.3%)
BMI (kg/m^2)	M: 30.7 [19-51]	F: 33.3 [21-47]	M: 30.7 [24-44]	F: 31.9 [22-45]
HbA_{1c} (%)	8.90 [7.50 - 10.80]		9.00 [7.70 – 11.40]	
Study 1002 - High	**INH + Metformin (N=109)**		**Glibenclamide + Metformin (N=105)**	
Age (yrs.)	54.6 [8.8]		54.4 [8.8]	
Gender – M/F (%)	M: 62 (56.9%)	F: 47(43.1%)	M: 53 (50.5%)	F: 52 (49.5%)
BMI (kg/m^2)	M: 30.9 [22-47]	F: 32.8 [23-43]	M: 30.4 [23-38]	F: 31.9 [22-47]
HbA_{1c} (%)	10.73 [8.80 - 13.60]		10.94 [9.30 - 13.20]	

M/F = Male/Female; Low = low stratum; High = high stratum
Data are presented as mean [SD] for age; mean [range] for body weight, BMI and HbA1c

Outcome

Primary endpoint (except for study 110)

In Studies 104, 109, and 110 and the high strata of studies 1001 and 1002, the use of INH was associated with a significantly greater reduction in mean HbA_{1c} than that in subjects on OA alone.

For subjects into the low strata of studies 1001 or 1002, the decline in HbA1c was similar in the INH+OA and OA groups, and the upper bound of the 95% CI did not exceed 0.5%.

Change from Baseline in HbA_{1c}, (%) – ITT analysis

ITT analysis		Unadjusted Mean [SD]			Adjusted Difference* (95% CI)	P-Value
Study	**N**	**Baseline**	**End of Study**	**Change from Baseline**		
104						
INH + OA	32	9.8 [1.3]	7.5 [1.1]	-2.3 [1.2]	-2.22 (-2.72, -1.73)	<0.0001
OA	36	9.9 [1.3]	9.8 [1.4]	-0.1 [1.2]		
109						
INH	102	9.3 [0.9]	7.9 [1.0]	-1.5 [1.0]	-1.18 (-1.41, - 0.95)[a]	<0.0001[a]
INH + Pre-study OAs	100	9.2 [1.0]	7.3 [0.6]	-1.9 [0.9]	-1.67 (-1.90, -1.44)[b]	<0.0001[b]
Pre-study OAs	96	9.3 [1.0]	9.1 [1.1]	-0.3 [0.9]		
110**						
INH	75	9.5 [1.1]	7.2 [1.0]	-2.3 [1.2]	-0.89 (-1.23, -0.55)	
Rosiglitazone	67	9.4 [0.9]	8.0 [1.3]	-1.4 [1.2]		
1001						
Low Stratum						
INH + SU	101	8.8 [0.5]	7.4 [0.8]	-1.4 [0.8]	-0.07 (-0.33, 0.19)	0.610
Met + SU	93	8.8 [0.5]	7.4 [0.8]	-1.4 [0.9]		
High Stratum						
INH + SU	113	10.5 [0.7]	7.8 [1.0]	-2.7 [1.1]	-0.38 (-0.63, -0.14)	0.002
Met + SU	103	10.6 [0.9]	8.3 [1.2]	-2.4 [1.2]		
1002						
Low Stratum						
INH + Met	125	8.6 [0.5]	7.2 [0.8]	-1.4 [0.8]	0.04 (-0.19, 0.27)	0.733
Glibenclamide + Met	119	8.7 [0.5]	7.1 [0.9]	-1.6 [0.9]		
High Stratum						
INH + Met	109	10.4 [0.7]	7.5 [1.1]	-2.9 [1.2]	-0.37 (-0.62, -0.12)	0.004
Glibenclamide + Met	103	10.6 [0.7]	8.0 [1.2]	-2.6 [1.2]		

[a] Comparison between INH monotherapy to OA; [b] Comparison of INH+OA to OA

*Adjusted mean difference (INH mean minus comparator mean) in change from baseline and 95% CI are based on the primary model , **HbA_{1c} was not the primary efficacy endpoint for Study 110

SU = sulfonylurea; Met = Metformin

Results were similar for the PP analyses.

In Study 110, significantly more INH subjects achieved HbA_{1c} <8% at end of study (primary endpoint) than subjects treated with rosiglitazone (See table below). However, the margin of 20% for achieving HbA_{1c} <8%, which was considered clinically relevant, was not reached.

Secondary endpoints

- Acceptable or good glycaemic control (primary endpoint in study 110; see above):

In Study 109, more subjects in the INH+OA or INH monotherapy group achieved HbA_{1c} <8% or <7% compared to subjects who continued their pre-study OA regimen.

In the low strata of studies 1001 and 1002 and the high stratum of study 1001 the percentage of patients achieving HbA1c <8% or <7% was not different between groups. In the high stratum of study 1002 only, significantly more patients on INH+OA achieved these HbA1c values compared to patients on OA alone.

Number (Percentage) of Subjects Achieving End-of-Study HbA_{1c} <8% or <7% - ITT analysis

Study	N	HbA_{1c} < 8% Subject (%)	P-Value	HbA_{1c} < 7% Subject (%)
109				
INH	102	57 (55.9)		17 (16.7)
INH + Pre-study OAs	100	86 (86)		32 (32.0)
Pre-study OAs	96	18 (18.8)		1 (1.0)
110*				
INH	75	62 (82.7)	0.0003	33 (44.0)
Rosiglitazone	67	39 (58.2)		12 (17.9)
1001				
Low Stratum				
INH + SU	101	82 (81.2)		31 (30.7)
Met + SU	93	68 (73.1)		30 (32.3)
High Stratum				
INH + SU	113	55 (48.7)		23 (20.4)
Met + SU	103	46 (44.7)		15 (14.6)
1002				
Low Stratum				
INH + Met	125	101 (80.8)		50 (40.0)
Glibenclamide + Met	119	103 (86.6)		51 (42.9)
High Stratum				
INH + Met	109	79 (72.5)		37 (33.9)
Glibenclamide + Met	103	58 (56.3)		18 (17.5)

* HbA_{1c} < 8% was the primary efficacy endpoint in Study 110
SU = sulfonylurea; Met = Metformin

Fasting glucose

In Study 109, both the INH monotherapy and INH+OA groups had a significantly greater decrease in fasting plasma glucose than the OA group. Mean difference in change (95% CI) was –24 mg/dl (-36, -11) for the INH monotherapy group and –53 mg/dl (-66, -41) for the INH+OA group compared to the OA group. Results on fasting glucose levels obtained from the phase 2 study 104 (INH+OA vs. OA) support those from study 109 (mean difference in change –61 mg/dL, 95% CI: -81, -41).

In Study 110, the decrease in fasting glucose levels was similar in the two treatment groups.

In both studies 1001 and 1002, the decreases from baseline fasting plasma glucose were similar, and the difference between the two treatment groups was small regardless of treatment received or the stratum into which subjects were placed.

Postprandial glucose increment

In Study 109, both the INH monotherapy and INH+OA groups had a significant decrease in glucose increment compared to subjects who continued their pre-study OA regimen and showed no change. Mean difference in change (95% CI) was –41 mg/dL (-56, -25) for the INH monotherapy group and –22 mg/dL (-38, -7) for the INH+OA group compared to the OA group. Results from phase 2 study 104 (INH+OA vs. OA) showed a trend in the same direction (mean difference –16.4 mg/dL, 95% CI: -34.6, 0.8).
In Study 110, the decrease in glucose increment was similar in both groups.

The decrease in glucose increment was comparable in both the low and high strata for Study 1001 as well as the low stratum for Study 1002. Only the high stratum INH group showed a significantly greater reduction in the glucose increment than did the OA group (mean difference –18 mg/dL, 95% CI: -25, -10).

Daily insulin dose

In all studies, a small increase in mean absolute daily insulin doses was observed over time. This might have been primarily due to the concomitant increase in body weight associated with insulin use since the doses corrected for body weight increased only minimally.

In study 1001, all control patients were taking the protocol specified amounts of metformin of between 500 mg once daily and 1 g twice daily. The doses of the background sulfonylurea were comparable between the INH and metformin groups and remained stable throughout the study.

In study 1002, the mean doses of glibenclamide in the control group at 4 weeks were 4.3 mg in the low stratum and 4.8 mg in the high stratum. The mean doses at 24 weeks were 6.8 mg and 8.5 mg, respectively. All subjects were taking the protocol specified amount of metformin of 2g daily.

Hypoglycaemia

In all studies except for study 1002, INH subjects experienced a significantly greater incidence of hypoglycaemia when compared to subjects receiving OA therapy alone. In Study 1002, subjects in the high stratum who received INH had a hypoglycaemic event rate that was twice that of subjects receiving glibenclamide whereas subjects in the low stratum who received INH had a lower rate of hypoglycaemic events.

Overall Hypoglycaemic Event Rates – ITT analysis

Study	N	N (%) with Event	Total Events	Total Subject-Months	Event Rate*
104					
INH + OA	32	22 (69)	57	89	0.6
OA	36	6 (17)	6	99	0.1
109					
INH	102	68 (67)	365	283	1.3
INH+ Pre-study Oas	100	78 (78)	477	284	1.7
Pre-study Oas	96	8 (8)	14	266	0.1
110					
INH	75	36 (48)	153	215	0.7
Rosiglitazone	67	5 (8)	9	187	0.0
1001					
Low Stratum					
INH + SU	101	51 (51)	168	556	0.3
Met + SU	93	30 (32)	96	506	0.2
High Stratum					
INH + SU	113	61 (54)	206	631	0.3
Met + SU	103	23 (22)	84	555	0.2
1002					
Low Stratum					
INH + Met	125	35 (28)	107	684	0.2
Glibenclamide + Met	119	47 (40)	157	634	0.2
High Stratum					
INH + Met	109	40 (37)	107	580	0.2
Glibenclamide + Met	103	22 (21)	46	557	0.1

*Number of events/subject-month.
[a] for the comparison INH + OA/OA [b] for the comparison INH/OA

No INH subjects in Studies 110 or 1002 and no OA subject in any of the studies experienced a severe hypoglycaemic event. One INH subject in each Studies 104 (INH+OA), 109 (INH), and 1001 (high stratum, INH+SU) experienced a severe hypoglycaemic event.

Body weight

In every study, subjects receiving INH, either alone or in combination with OA therapy, had a 2.2 to 4.5 kg gain in body weight over the course of the study. By comparison, body weight in subjects who continued their pre-study OA therapeutic regimen in Study 109 remained unchanged. Also, sulfonylurea monotherapy failures (Study 1001) experienced no increase in weight when metformin was added to their treatment. Weight gains were statistically different in Study 109 (mean weight gain 3.4 kg, 3.0 kg, and 0.0 kg in the INH monotherapy, INH+OA, and OA groups, respectively) and Study 1001 (mean weight gain: high stratum: 4.5 kg and –0.1 kg in the INH+SUand Met+SU groups, respectively; low stratum: 3.0 kg and –0.3 kg in the INH+SUand Met+SU groups, respectively). However, in Study 1002, subjects who failed on metformin had a similar weight gain when either INH or the insulin secretagogue, glibenclamide, was added to their treatment.

Two-year report on combined studies 1001 /1002

Evaluation Groups:	Inhaled insulin	Oral Agents
Treated	471	441
Entered First Extension (52 weeks)*	336	291
Entered Second Extension (104 weeks + washout)*	173	154
Total Discontinued	71	82
Total 104 weeks Completers cohort	158	146
Total Washout cohort (all subjects who consented to washout phase)	166	154

*Main reason for loss of subjects was regulatory/ethics approval not available at end of previous study period

The protocols were amended to extend the duration from 24 weeks to 104 weeks. Additional therapies, including subcutaneous insulin were allowed in all subjects. The baseline data from the Week 104 cohort were representative of the subjects originally recruited. The demographic characteristics of the Week 104 completers were similar between the INH and oral agents treatment groups and between males and females. The overall rate of hypoglycaemia was similar in both groups. There was one severe hypoglycaemic event in each group.

Efficacy Results:

HbA1c (%) Week 104 Completers: Mean Baseline (BL), Weeks 24 & 104, and Mean Change from Baseline							
Treatment Group	N	BL[a]	Wk 24	Wk 104	Wk 104 Mean change from BL	Wk 104 (LOCF)	Wk 104 (LOCF) Mean change from BL
Inhaled insulin	158	9.6	7.2	7.8	-1.8	7.7	-1.8
Oral agents	146	9.6	7.3	8.1	-1.5	8.1	-1.5

Treatment to goal		N	Number of subjects (%)		Adjusted	95% Confidence
			BL	End of Study	Odds Ratio[b]	Interval for the Ratio
< 8%	Inhaled insulin	158	4 (2.5)	100 (63.3)	1.42	0.88, 2.30
	Oral agents	146	6 (4.1)	80 (54.8)		

[a]Baseline values were the average values of Weeks –1 and 0. End of study was unadjusted Week 104 or Week 104 (LOCF)
[b]Derived based on coefficient of the treatment term in the primary model with terms for baseline HbA1c, treatment, protocol and region

- Clinical studies in special populations

Paediatric population
The applicant does not currently seek an indication for EXUBERA in paediatric patients. Paediatric patients with type 1 DM were treated in studies 106, 107, and 1009. Patients who completed one of these studies were eligible to participate in extension study 111.

Study 1009 was a 3-month study in paediatric patients (Age 6 to 11 years) with type 1 DM. The design, inclusion and exclusion criteria, and endpoints were similar to studies 106 and 107. For inclusion, previous insulin regimen must have included a minimum of 16 U of SC insulin per day

Results are reported for study 1009 and paediatric subpopulations of studies 106 and 107.

Disposition of Subjects < 18 Years of Age with Type 1 Diabetes

	Randomised/Treated		Completed	
	INH	**SC**	**INH**	**SC**
106 (<18 years)	33/33	29/29	32	28
107 (<18 years)	60/59	60/60	57	56
1009	61/61	60/59	59	59

In all three studies, subjects demonstrated a similar change in $HbA_{1c,}$ regardless of treatment group.

Change from Baseline in HbA_{1c}, % - PP analysis

		Mean [SD]			Adjusted Difference (95% CI)*
Study	**N**	**Baseline**	**End of Study**	**Change**	
106					
INH	32	8.6 [1.0]	8.5 [1.2]	-0.1 [1.1]	
SC insulin	29	8.5 [0.8]	8.3 [0.8]	-0.3 [0.7]	0.18 (-0.22, 0.59)
107					
INH	59	8.3 [0.9]	8.1 [1.1]	-0.2 [0.8]	
SC insulin	59	8.3 [0.9]	8.3 [1.4]	0.0 [1.1]	-0.27 (-0.61, 0.08)
1009					
INH	60	8.1 [0.7]	7.8 [0.8]	-0.2 [0.8]	
SC insulin	59	8.1 [0.8]	8.0 [1.0]	-0.1 [0.8]	-0.23 (-0.49, 0.03)

*Adjusted mean difference between groups (INH – SC) in change from baseline and 95% CI were based on the primary model with terms for baseline, treatment, and centre.

Treatment groups were similar with respect to the percentage of subjects achieving HbA_{1c} <8% or <7% in all three studies.

In all 3 studies, baseline daily insulin doses were comparable across treatment groups. During the treatment phase, a shift from long-acting to short-acting insulin occurred in INH-treated patients in studies 106 and 1009 but total insulin doses (adjusted for body weight) increased only slightly (as did total daily insulin doses for the SC groups).

Total and severe hypoglycaemic event rates are presented in the tables below. Overall, total event rates and severe hypoglycaemia event rates were similar between treatment groups.

Total Hypoglycaemic Event Rates – PP analysis

Study	**N**	**N (%) with Event**	**Total Events**	**Total Subject-Months**	**Crude Event Rate***
106					
INH	32	32 (100.0)	1427	181.9	7.8
SC insulin	29	29 (100.0)	1426	162.5	8.8
107					
INH	59	59 (100.0)	3063	335.4	9.1
SC insulin	59	58 (98.3)	2923	333.4	8.8
1009					
INH	60	60 (100.0)	1407	175.9	8.0
SC insulin	59	58 (98.3)	1548	170.7	9.1

*Number of events/subject-month.

Severe Hypoglycaemic Event Rates – PP analysis

Study	N	N (%) with Event	Total Events	Total Subject-Months	Crude Event Rate*
106					
INH	32	7 (21.9)	9	181.9	4.9
SC insulin	29	4 (13.8)	10	162.5	6.2
107					
INH	59	8 (13.6)	16	335.4	4.8
SC insulin	59	9 (15.3)	10	333.4	3.0
1009					
INH	60	9 (15.0)	15	175.9	8.5
SC insulin	59	9 (15.3)	18	170.7	10.5

*Number of events/100 subject-months.

In all studies, both treatment groups showed a similar increase in body weight.

Patients that completed one of the studies 106, 107 or 1009 and entered study 111 were pooled. Although no comparator data is available, the data suggest that HbA_{1c} remained relatively stable throughout the 24-month course of Study 111. Average daily INH insulin dose continued to increase in this paediatric population. On a per kilogram basis, the mean daily INH dose increased only slightly from 0.23 to 0.29 mg/kg during the 2-year observation period. Overall hypoglycaemic event rate was about one third lower during the second than during the first year of treatment. The severe hypoglycaemic event rate was fairly constant during the 2-year observation period.

HbA_{1c} (%) Versus Duration of Inhaled Insulin Treatment in Subjects < 18 Years of Age Who Completed At Least 24 Months of Treatment

	Observed Mean [SD]	Change from Baseline Mean [SD]
Visit		
Baseline*	8.13 [0.74]	
3 Months	7.85 [0.87]	-0.28 [0.89]
6 Months	7.99 [1.01]	-0.14 [0.98]
12 Months	8.18 [1.01]	0.05 [1.00]
18 Months	8.13 [1.08]	0.00 [1.05]
24 Months	8.13 [1.21]	0.00 [1.17]

* Baseline refers to baseline of the parent study

Underlying lung disease, Asthma and COPD

The presence of mild underlying lung disease (e.g. well-controlled mild asthma or COPD) did not influence efficacy in a pooled analysis. However, very preliminary results on studies 1028 ("asthma" study) and study 1030 ("COPD study") showed an increased in the rate of non-severe exacerbations. Therefore, use of Exubera in patients with underlying lung disease such as asthma or COPD is currently not recommended. Respiratory tract infections did not influence glycaemic control or hypoglycaemia rate. There is no experience with Exubera in patients with pneumonia. This is appropriately stated in the SPC.

Elderly

A total of 342 subjects ≥ 65 years of age received INH during the clinical development program, 104 of them in the Completed, Controlled Phase 2/3 Studies. However, only 37 subjects were ≥75 years. Therefore, a statement that experience with INH in patients ≥75 years of age is limited has been included in the SPC. In addition, the Applicant has committed to obtain further data on efficacy and safety of Exubera in the very elderly from a large simple trial ("real world study", see RMP).

Other popuplations

INH was similarly efficacious in young and elderly, and in obese and non-obese diabetic subjects. There were no gender differences that were unique to INH.

- Supportive studies

Study 1022 is a two-year, outpatient, open-label, parallel-group comparative efficacy and safety trial of EXUBERA compared with SC human insulin therapy in adult subjects with type 1 diabetes mellitus. Main inclusion criteria were: age 18 to 65 years, type 1 DM, currently on stable SC insulin regimen, HbA1c between 5.5% and 11%. The primary objective was to establish pulmonary safety of inhaled insulin in patients with type 1 diabetes; change from baseline HbA_{1c} was a secondary endpoint. Nevertheless, results (see below) did not show clinically relevant difference in glycaemic control between the two treatment arms. The treatment group difference at Month 24 (LOCF) of 0.25% (90% CI: 0.134, 0.372) is within the non-inferiority criteria employed in earlier efficacy trials (upper bound of CI ≤ 0.5%).

Study 1022 - Glycosylated Hemoglobin (HbA_{1c}, %) – Observed Value and Change from Baseline in Subjects with Type 1 Diabetes

	INH			SC		
		Observed Value (mean)	Change from Baseline (mean)		Observed Value (mean)	Change from Baseline (mean)
	N			N		
Baseline	288	7.41		286	7.46	
Week 6	269	7.02	-0.40	256	7.03	-0.43
Week 12	276	7.04	-0.37	280	7.04	-0.41
Month 6	261	7.21	-0.21	274	7.10	-0.36
Month 12	238	7.36	-0.05	260	7.13	-0.33
Month 18	230	7.30	-0.10	237	7.15	-0.28
Month 24	209	7.48	0.07	219	7.16	-0.26
Month 24 (LOCF)	288	7.50	0.10	286	7.28	-0.18

Study 1029 is a two-year, outpatient, open-label, parallel-group comparative efficacy and safety trial of EXUBERA compared with SC human insulin therapy in adult subjects with type 2 diabetes mellitus. Main inclusion criteria were: age 35 to 75 years, type 2 DM for more than 1 year, currently on stable SC insulin regimen, HbA1c between 5.5% and 11%. The primary objective was to establish pulmonary safety of inhaled insulin in patients with type 2 diabetes; change from baseline HbA_{1c} was a secondary endpoint. 1-year HbA_{1c} interim analysis data are summarised below. Glycemic control did not differ between treatment groups.

Study 1029 - Summary of mean HbA1c (%)

	Study 1029		
	INH	**SC**	**INH-SC 90% Conf. Interval**
Baseline	N=313 7.66 (1.12)	N=304 7.77 (1.11)	
Week 12 (SD)	N=298 6.86 (0.96)	N=292 7.03 (0.95)	-0.10 (0.06) (-0.20, 0.00)
Month 6 (SD)	N=283 6.99 (1.01)	N=288 7.07 (1.03)	-0.02 (0.06) (0.12, 0.09)
Month 9 (SD)	N=270 7.09 (1.03)	N=280 7.16 (1.04)	0.03 (0.06) (-0.08, 0.13)
Month 12 (SD)	N=232 7.19 (1.15)	N=239 7.21 (1.09)	0.07 (0.07) (-0.04, 0.18)

Hypoglycaemia data in studies 1022 and 1029 were comparable for INH and SC insulin.
Study 1027 was 24-week open-label, randomised, active-controlled, parallel-group design study in type 1 diabetes patients who received either INH or a short-acting SC insulin during a 12-week

'comparative treatment phase' and a short-acting SC insulin during 12-week 'follow up phase'. The primary endpoint was the FEV1 and DLco response status. Efficacy as measured by HbA1c was a secondary endpoint.

There were no clinically relevant group differences in HbA1c decrease at any time. During the comparative phase, the overall risk of a hypoglycaemic event was slightly higher for the INH group relative to the SC group, with a risk ratio of 1.24 (90% CI, 1.17 to 1.31). Event rate tended to decline over time. The risk of a severe hypoglycaemic events phase was lower for the INH group relative to the SC group, with a risk ratio of 0.52 (90 % CI, 0.31 to 0.87).

Studies 102E, 103E, 104E: Subjects who completed the Phase 2 studies (Studies 102, 103, or 104) were eligible to enroll in open-label, extensions of those studies. There were a total of 5 extension periods, spanning a total of 6 years.
Generally, the glycaemic control achieved in the parent studies was maintained throughout the extension studies although sample size was low in these studies.

Study 111: Subjects who completed studies 106, 107, 108, 109, 110, or 1009 were eligible to enter study 111, an open-label, uncontrolled, non-randomised, long-term safety study of up to three years. Most patients completing the parent studies (72 to 95%) entered study 111 (1290 patients (550 type 1, 740 type 2 diabetics)) but discontinuation rates during the following years was high. All subjects in study 111, including those coming from the control arm of a previous study, received INH. Exclusion and withdrawal criteria, INH dosing, titration schedule and home glucose monitoring were the same as in the parent studies.
Generally, the glycaemic control in patients with type 1 or type 2 diabetes achieved in the parent studies was maintained throughout the uncontrolled extension study.

Due to the finding of accelerated decline in lung function, particularly in FEV1, study protocol 111 was amended to include a subsequent controlled part, where patients were randomized to either continue INH for another 6 months or to switch to SC fast-acting insulin. Patients that were switched back to SC insulin showed improved glycaemic control compared to patients that remained on INH

- Discussion on clinical efficacy

The applicant has conducted a comprehensive clinical development programme. All Phase 2/3 controlled, completed studies used a randomised, multi-centre, active-controlled, open-label, parallel-group design.

All subjects with type 1 DM and subjects with type 2 DM using insulin received subcutaneous (SC) basal (intermediate- or long-acting-) insulin in addition to SC short-acting insulin or INH. The most recent clinical trials used predominantly insulin analogues in the comparator arm. Patients with type 2 DM not treated with insulin at baseline received INH either as monotherapy or as add-on to an OA regimen.

Based on the submitted data, both short- and long-term efficacy have been sufficiently demonstrated in patients with type 2 DM. INH was shown to be non-inferior to SC short-acting or rapid-acting insulin and to improve glycaemic control in patients not sufficiently controlled on OAs alone. In patients poorly controlled (HbA1c $\geq$9.5% to $\leq$ 12.0%, high stratum) on OA monotherapy, INH add-on was superior to OA add-on. In patients with HbA1c levels between between 8.0% and 9.5% (low stratum) on OA monotherapy, INH add-on was non-inferior to OA add-on therapy. In addition, in patients failing exercise and diet, INH monotherapy was superior to rosiglitazone. Rosiglitazone, however, is not approved for first-line therapy in this indication. A comparative study with metformin, the current first-line therapy, has not been performed. In patients with type 2 DM, HbA1c values could be maintained in the extension studies for up to 4 years without substantial increase in INH dose.
In patients with type 1 DM, efficacy of INH has been clearly demonstrated for periods up to 6 months. Conclusions on long-term efficacy in this patient population were hampered by the high overall discontinuation rates (50% and more) in the follow-up studies and the discontinuation rate of 6.7% due to 'insufficient treatment response' in study 111. In addition, in the controlled phase of extension

study 111, patients with type 1 or type 2 DM that were switched back to conventional diabetes therapy, showed somewhat improved glycaemic control compared to patients that remained on INH. The explanation for the high discontinuation rates including the high burden of participation in studies of such long duration was accepted. In addition it was shown, that so-called 'insufficient treatment response' was not associated with particularly high HbA1c or insulin antibody levels.
The applicant's arguments that the small improvement in patients switching back from INH to SC insulin observed in study 111 was not a consistent finding in the database and the explanation of stricter self-monitoring and dose adjustment after the switch were accepted.
It was questioned whether in study 1022 in patients with type 1 diabetes, the efficacy of inhaled insulin may be inferior to SC insulin. Considering that the primary objective of this study was to assess pulmonary safety, the difference in HbA1c was not considered clinically relevant between treatment groups.

The pharmacology studies had revealed that one 3 mg blister is not interchangeable with three 1 mg blisters. Consecutive inhalation of three 1 mg doses causes an approximately 40% higher insulin exposure than inhalation of one 3 mg dose. A 1 mg blister of inhaled insulin is approximately equivalent to 3 IU of subcutaneously injected fast-acting human insulin. A 3 mg blister of inhaled insulin is approximately equivalent to 8 IU of subcutaneously injected fast-acting human insulin. The lack of interchangeability raised three related clinical concerns: (1) efficacy and safety of dose titration with the two blister strengths, (2) possible mix-up of 1 mg and 3 mg blisters, (3) hypoglycaemia due to use of three 1 mg instead of one 3 mg blister (e.g. in case the patient runs out of 3 mg blisters). Dose titration with the two blister strengths has been shown to be efficacious, safe and practicable in the extensive clinical trial programme. In addition, confusion of the two blister strengths has not been reported in the clinical trials. Patients with diabetes are accustomed to using different insulins. The CHMP therefore accepted that the risk due to the lack of interchangibility of the two strengths could be solved with appropriate warnings in the SPC, PL and Labelling of the product as well as through educational material to be provided by the marketing authorisation holder. Upon CHMP request, the applicant also committed to improve colour differentiation and to implement additional tactile (e.g. embossed) markings on the protruding end of the blister, which will allow to clearly distinguish the two blister strengths even when the blister is already inserted and in visually impaired patients. 1 mg and 3 mg blisters should not be marketed in a combined package to avoid confusing the blisters with the different dose strengths.

A 1 mg blister of inhaled insulin is approximately equivalent to 3 IU of subcutaneously injected fast-acting human insulin and represents the smallest possible titration step. Therefore, EXUBERA should be used with caution in patients of low body weight. The use of EXUBERA in patients requiring dose titrations of less than 1 mg is not recommended.

Exubera has a faster onset of action than subcutaneously administered soluble human insulin. Therefore, it should be given within 10 minutes before the start of a meal.

Patients must not smoke during therapy due to the risk of hypoglycaemia related to the great increase of absorption of INH.

In trials involving patients with type 2 diabetes, a marked difference was observed between the number of subjects who were screened and who were randomised raising the question whether the study population would be representative of the target population. The main reason for non-eligibility for the clinical trials was found to be abnormal pulmonary function (about 1 in 4 of the screened population). This finding of high prevalence of impaired lung function in patients with diabetes is of concern, particularly with respect to a possible further decline associated with the use of INH. (see safety section)

In all clinical trials, no more than 2 inhalations per dosing session were to be administered initially. In the course of the studies, however, up to 6 (and rarely more) inhalations per dosing session were performed without negative impact on glycaemic control or hypoglycaemia risk.

Overall treatment satisfaction was found to be higher for INH than for SC insulin or OAs and was closely related to perceived improved glycaemic control. However, due to the open-label design of the studies, evaluation of treatment satisfaction may have been subject to bias and should be interpreted with caution.

In summary, sustained efficacy of INH, similar to that of rapid-acting or ultrarapid-acting insulin, has been sufficiently demonstrated in both patients with type 1 or type 2 diabetes. At present, the main added value of INH appears to be the avoidance of SC injections.

Due to the insufficient data from the clinical development programme and very preliminary study results from studies 1028 (asthma) and 1030 (COPD) showing an Exubera-associated increase in the rate of non-severe exacerbations, the use of Exubera in patients with underlying lung disease such as asthma or COPD is not recommended and contraindicated in case of poorly controlled, unstable or severe asthma and severe (Gold stage III or IV) COPD.

EXUBERA has been administered to patients with intercurrent respiratory illness (e.g. bronchitis, upper respiratory tract infections) during clinical trials. Increased risk of hypoglycaemia or poor glycaemic control has not been observed in these trials. During intercurrent respiratory illness close monitoring of blood glucose concentrations is recommended. There is no experience with Exubera in patients with pneumonia and this is stated in the SPC.

The applicant has roughly outlined their intended paediatric development plan. It should take into account that type 1 and type 2 diabetes are distinct entities with different treatment options and possibly different outcome. The applicant committed to provide a paediatric development programme as a follow-up measure.

Clinical safety

- Patient exposure

The initial safety summary presented by the Applicant included safety data from 50 studies in the clinical development program of INH, 31 clinical pharmacology studies, and 19 phase 2/3 studies.

As of June 25, 2004, the Controlled Phase 2/3 protocol set included 1,975 INH treated and 1,837 comparator treated adult diabetic subjects (≥18 years old).
Overall, the safety of Exubera alone, or in combination with subcutaneous insulin or oral agents has been evaluated in clinical studies of more than 2700 patients with type 1 or type 2 diabetes, including more than 1975 adults exposed for greater than 6 months and more than 745 adults for greater than 2 years.

- Adverse events

The most frequently reported all causality and/or treatment-related adverse events (AEs) were hypoglycaemia, respiratory tract infection and cough. Cough, respiratory disorders, rhinitis and pharyngitis were more common in the INH group than in the comparator groups. The cough associated with Exubera occurred usually within seconds to minutes after inhalation and tended to decrease over time. Of those events occurring at less than 5% incidence in any treatment group, chest pain (not of cardiac origin), dry mouth, dyspnoea, epistaxis and increased sputum occurred at greater incidence in the INH than comparator groups. Adverse events were predominantly of mild severity.

As relevant example, the common adverse events in early completed controlled phase 2/3 studies (102, 106, 107, 1009, 103, 104, 108, 109, 110, 1001, 1002) are provided the following tables for the Type 1and Type 2 DM adult patients, respectively.

Adverse Events (≥ 5% incidence in any group):

Adult Subjects with Type 1 diabetes in early Controlled Phase 2/3 Studies

Body system *	Preferred term	Number (%) of Subjects			
		All Causality		Treatment-Related	
		INH N=653	SC N=656	INH N=653	SC N=656
MN	Hypoglycaemia	626 (95.9)	626 (95.4)	618 (94.6)	614 (93.6)
R	Respiratory tract infection	228 (34.9)	222 (33.8)	26 (4.0)	14 (2.1)
R	Cough increased	152 (23.3)	41 (6.3)	110 (16.8)	7 (1.1)
N	Tremor	105 (16.1)	116 (17.7)	96 (14.7)	98 (14.9)
R	Pharyngitis	99 (15.2)	81 (12.3)	34 (5.2)	9 (1.4)
BW	Headache	89 (13.6)	90 (13.7)	30 (4.6)	32 (4.9)
R	Rhinitis	75 (11.5)	52 (7.9)	15 (2.3)	7 (1.1)
BW	Flu syndrome	66 (10.1)	66 (10.1)	1 (0.2)	6 (0.9)
BW	Asthenia	65 (10.0)	70 (10.7)	51 (7.8)	58 (8.8)
BW	Accidental injury	52 (8.0)	57 (8.7)	6 (0.9)	8 (1.2)
N	Dizziness	50 (7.7)	39 (5.9)	45 (6.9)	30 (4.6)
D	Nausea	46 (7.0)	37 (5.6)	13 (2.0)	10 (1.5)
R	Sinusitis	41 (6.3)	37 (5.6)	7 (1.1)	3 (0.5)
D	Diarrhoea	41 (6.3)	27 (4.1)	4 (0.6)	2 (0.3)
SA	Sweating	40 (6.1)	62 (9.5)	36 (5.5)	53 (8.1)
N	Anxiety	33 (5.1)	29 (4.4)	13 (2.0)	15 (2.3)
D	Increased appetite	25 (3.8)	33 (5.0)	24 (3.7)	28 (4.3)

*BW=Body as a Whole; D=Digestive; MN=Metabolic and Nutritional; N=Nervous; R=Respiratory; SA=Skin and Appendages.

Adverse Events (≥ 5% incidence in any group) by Preferred Term:

Adult Subjects with Type 2 diabetes - Early Controlled Phase 2/3 Studies

Body system *	Preferred term	Number (%) of Subjects					
		All-Causality			Treatment-Related		
		INH**	SC	OA	INH	SC	OA
		N=1,145	N=367	N=644	N=1,145	N=367	N=644
MN	Hypoglycaemia	669 (58.4)	250 (68.1)	180 (28.0)	667 (58.3)	249 (67.8)	173 (26.9)
R	Respiratory tract infection	270 (23.6)	85 (23.2)	125 (19.4)	17 (1.5)	2 (0.5)	6 (0.9)
N	Tremor	199 (17.4)	70 (19.1)	57 (8.9)	176 (15.4)	61 (16.6)	29 (4.5)
R	Cough increased	188 (16.4)	18 (4.9)	23 (3.6)	109 (9.5)	4 (1.1)	0
BW	Headache	149 (13.0)	23 (6.3)	67 (10.4)	46 (4.0)	9 (2.5)	8 (1.2)
BW	Asthenia	143 (12.5)	50 (13.6)	59 (9.2)	112 (9.8)	36 (9.8)	19 (3.0)
BW	Flu syndrome	139 (12.1)	27 (7.4)	56 (8.7)	1 (0.1)	2 (0.5)	0
AS	Sweating	136 (11.9)	46 (12.5)	39 (6.1)	116 (10.1)	41 (11.2)	23 (3.6)
N	Dizziness	123 (10.7)	42 (11.4)	37 (5.7)	94 (8.2)	30 (8.2)	18 (2.8)
R	Pharyngitis	97 (8.5)	26 (7.1)	37 (5.7)	23 (2.0)	3 (0.8)	1 (0.2)
BW	Back pain	85 (7.4)	32 (8.7)	40 (6.2)	4 (0.3)	8 (2.2)	2 (0.3)
D	Diarrhoea	77 (6.7)	20 (5.4)	69 (10.7)	7 (0.6)	2 (0.5)	35 (5.4)
R	Rhinitis	76 (6.6)	27 (7.4)	19 (3.0)	14 (1.2)	4 (1.1)	3 (0.5)
CV	Hypertension	74 (6.5)	13 (3.5)	47 (7.3)	17 (1.5)	5 (1.4)	10 (1.6)
BW	Pain	71 (6.2)	18 (4.9)	35 (5.4)	14 (1.2)	4 (1.1)	4 (0.6)
BW	Accidental injury	66 (5.8)	31 (8.4)	41 (6.4)	6 (0.5)	4 (1.1)	0
D	Nausea	66 (5.8)	15 (4.1)	33 (5.1)	23 (2.0)	9 (2.5)	10 (1.6)
M	Arthralgia	65 (5.7)	18 (4.9)	39 (6.1)	7 (0.6)	5 (1.4)	4 (0.6)
R	Respiratory disorder	51 (4.5)	23 (6.3)	11 (1.7)	12 (1.0)	5 (1.4)	0
R	Sinusitis	43 (3.8)	19 (5.2)	15 (2.3)	1 (0.1)	0	0
N	Anxiety	39 (3.4)	20 (5.4)	13 (2.0)	15 (1.3)	9 (2.5)	1 (0.2)
BW	Abdominal pain	36 (3.1)	9 (2.5)	39 (6.1)	6 (0.5)	1 (0.3)	16 (2.5)

*BW = Body as a Whole; D = Digestive; M = Musculoskeletal; MN = Metabolic and Nutritional; N = Nervous; R= Respiratory; SA = Skin and Appendages.

* *The INH group consists of 3 subgroups: INH monotherapy, INH + OA, and INH + SC insulin group

The most common severe AE in patients with type 1 diabetes was hypoglycaemia, which occurred at comparable frequencies in the two treatment groups both on an all-causality and a treatment-related basis. The remaining severe adverse events occurred in ≤ 1.1% of subjects in each group, without a clear imbalance in incidence between treatment groups.

Severe Adverse Events Occurring in ≥ 3 Subjects in Either Group:
Adult Subjects with Type 1 Diabetes in early Controlled Phase 2/3 Studies

		Number (%) of Subjects			
		All Causality		Treatment-Related	
Body system*	Preferred term	INH** N=653	SC N=656	INH N=653	SC N=656
MN	Hypoglycaemia	88 (13.5)	87 (13.3)	86 (13.2)	86 (13.1)
BW	Headache	4 (0.6)	4 (0.6)	2 (0.3)	1 (0.2)
CV	Migraine	4 (0.6)	2 (0.3)	2 (0.3)	0
BW	Accidental injury	3 (0.5)	1 (0.2)	0	0
D	Nausea	3 (0.5)	1 (0.2)	0	0
BW	Flu syndrome	2 (0.3)	7 (1.1)	0	1 (0.2)
BW	Abdominal pain	1 (0.2)	3 (0.5)	0	1 (0.2)
CV	Syncope	1 (0.2)	3 (0.5)	0	0
N	Convulsion	0	3 (0.5)	0	1 (0.2)

*BW=Body as a Whole; CV=Cardiovascular; D=Digestive; MN=Metabolic and Nutritional; N=Nervous.
** The INH group consists of 3 subgroups: INH monotherapy, INH + OA, and INH + SC insulin group

In patients with type 2 diabetes, severe AE incidence was least in the SC group and greatest in the OA group. The most common severe AE among INH-treated type 2 subjects was hypoglycaemia, followed by headache, pain, myocardial infarction, and cough. There were 8 cases of severe cough or bronchitis in the INH group but none in the comparator groups. Four cases of severe cough were considered treatment-related.

Severe Adverse Events Occurring in ≥ 3 Subjects in Any Group by Preferred Term:
Adult Subjects with Type 1 Diabetes in Early Controlled Phase 2/3 Studies

		Number (%) of Subjects					
		All Causality			Treatment-Related		
Body system*	Preferred term	INH** N=1,145	SC N=367	OA N=644	INH N=1,145	SC N=367	OA N=644
MN	Hypoglycaemia	10 (0.9)	7 (1.9)	1 (0.2)	10 (0.9)	7 (1.9)	1 (0.2)
BW	Headache	10 (0.9)	1 (0.3)	6 (0.9)	1 (0.1)	0	0
BW	Pain	6 (0.5)	0	5 (0.8)	1 (0.1)	0	1 (0.2)
CV	Myocardial infarction	5 (0.4)	1 (0.3)	5 (0.8)	0	0	0
R	Cough increased	5 (0.4)	0	0	4 (0.3)	0	0
M	Tenosynovitis	5 (0.4)	0	0	0	0	0
BW	Back pain	4 (0.3)	2 (0.5)	3 (0.5)	0	0	0
D	Diarrhoea	4 (0.3)	0	6 (0.9)	1 (0.1)	0	2 (0.3)
BW	Flu syndrome	4 (0.3)	0	3 (0.5)	0	0	0
BW	Abdominal pain	4 (0.3)	0	3 (0.5)	1 (0.1)	0	0
D	Gastroenteritis	4 (0.3)	0	1 (0.2)	0	0	0
SS	Retinal disorder	4 (0.3)	0	1 (0.2)	1 (0.1)	0	0
M	Myalgia	3 (0.3)	1 (0.3)	1 (0.2)	0	0	1 (0.2)
BW	Asthenia	3 (0.3)	0	1 (0.2)	1 (0.1)	0	0
D	Nausea	3 (0.3)	0	1 (0.2)	0	0	0
N	Depression	3 (0.3)	0	1 (0.2)	0	0	0
N	Dizziness	3 (0.3)	0	1 (0.2)	1 (0.1)	0	0
R	Bronchitis	3 (0.3)	0	0	0	0	0
U	Kidney calculus	3 (0.3)	0	0	0	0	0
D	Vomiting	3 (0.3)	0	0	0	0	0
CV	Angina pectoris	2 (0.2)	0	6 (0.9)	0	0	1 (0.2)
M	Arthralgia	2 (0.2)	0	6 (0.9)	0	0	0
CV	Hypertension	2 (0.2)	0	3 (0.5)	0	0	0
M	Bone fracture	2 (0.2)	1 (0.3)	3 (0.5)	0	0	0
R	Respiratory tract infection	1 (0.1)	1 (0.3)	4 (0.6)	0	0	0
CV	Migraine	1 (0.1)	0	3 (0.5)	0	0	1 (0.2)

*BW=Body as a Whole; CV=Cardiovascular; D=Digestive; M=Musculoskeletal; MN=Metabolic and Nutritional; N=Nervous, R=Respiratory; SS=Special Senses; and U=Urogenital.
* *The INH group consists of 3 subgroups: INH monotherapy, INH + OA, and INH + SC insulin group

Hypoglycaemia

Hypoglycaemia was the most common AE among INH- or SC insulin-treated subjects, occurring in nearly all patients with type 1 DM and the majority of patients with type 2 DM treated with either form of insulin. The majority of events were mild or moderate in severity.

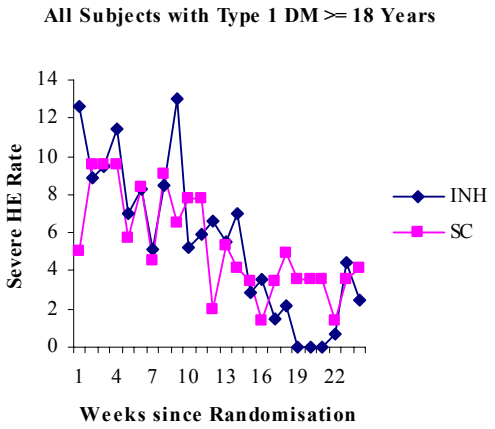
Whereas the proportion of patients experiencing hypoglycaemia and the overall hypoglycaemia event rates were similar or even lower, the rate of severe hypoglycaemic episodes appeared to be higher in INH-treated compared to SC insulin-treated patients with type 1 DM in study 107, in which an intensive insulin regimen was used. These hypoglycaemic events in the INH group occurred primarily at night and during early morning hours. A slight tendency of increased rate of severe hypoglycaemic episodes was also observed in other early studies involving patients with type 1 DM. Therefore, an analysis of severe hypoglycaemia episodes rates was requested for all subjects with type 1 DM, including data from more recent studies (See table below).

Analysis of Protocol-defined Severe Hypoglycemic Events in Subjects with Type 1 DM

Study	N	N (%) with Event	Total Events[a]	Total Subject-Months	Event Rate[b]	Risk Ratio (95% CI)
Subjects with type 1 DM ≥ 18 years of age						
All subjects with type 1 DM ≥ 18 years of age						
INH	691	111 (16.1)	234	4931	4.745	0.91 (0.76, 1.09)
SC insulin	686	123 (17.9)	261	5102	5.115	
All subjects ≥ 18 years of age who received intensive treatment[c]						
INH	520	83 (16.0)	184	4117.6	4.469	0.86 (0.72, 1.02)*
SC Insulin	454	84 (18.5)	192	3906.0	4.915	
102						
INH	35	4 (11.4)	7	99.5	7.0	1.04 (0.39, 2.77)
SC Insulin	36	4 (11.1)	8	105.2	7.6	
106 ≥ 18 years of age						
INH	136	24 (17.6)	43	714.0	6.0	1.23 (0.78, 1.92)
SC Insulin	132	19 (14.4)	35	718.0	4.9	
107 ≥ 18 years of age						
INH	103	18 (17.5)	43	570.0	7.5	2.25 (1.31, 3.87)
SC insulin	103	13 (12.6)	19	562.1	3.4	
107 ≥ 18 years of age – Subject 107 50077988 excluded						
INH	102	17 (16.7)	31	564.5	5.5	1.65 (0.93, 2.91)
SC insulin	103	13 (12.6)	19	562.1	3.4	
1022IA						
INH	288	53 (18.4)	122	3129.8	3.9	0.75 (0.62, 0.92)
SC insulin	286	69 (24.1)	168	3308.1	5.1	
1026						
INH	23	3 (13.0)	4	126.6	3.2	Statistical analysis not performed
SC insulin	21	1 (4.8)	1	111.0	0.9	
1027						
INH	106	9 (8.5)	15	291.2	5.2	0.51 (0.30, 0.86)
SC insulin	108	17 (15.7)	30	297.9	10.1	

*90% CI for All subjects ≥ 18 years of age who received intensive treatment
[a]Severe events [b]Number of events/100 subject-months. [c]Includes Studies 107, 1026, and Studies 1022 IA and 1027 (all INH subjects and SC insulin-treated-subjects who took ≥3 doses of short-acting insulin per day for more than half the study).

Occurrence of Severe Hypoglycaemic Events (Protocol-defined) since Randomisation (Events per 100 Subject-Months) -Adult Subjects with Type 1 DM (FAS)



FAS=Full Analysis Set

The results from this extended database are reassuring. There was no confirmation of the concern, based on data from study 107, that in particular type 1 diabetes patients on intensive insulin regimen may experience severe hypoglycaemia more frequently when using INH compared to SC insulin . The increased rate of severe hypoglycaemic events in study 107 was attributed to a higher number of patients experiencing recurrent events (in particular one patient with 12 severe events, most of which were not verified by blood glucose measurements). In addition, the rate of severe hypoglycemic events decreased over time probably due to increasing familiarity with INH administration and regimen.

High insulin antibody levels were not associated with increased hypoglycaemia risk.

All submitted data demonstrate that INH use is not associated with an increased hypoglycaemia risk in patients with type 2 DM.

- Serious adverse event/deaths/other significant events

As of the 16 September 2003 cut-off for deaths and other serious adverse events, 22 subjects, all adults, in the INH clinical development program had died during or within 30 days following treatment. This total included:
8 (0.4%) of 1,951 subjects who received INH in Controlled Phase 2/3 studies,
3 (0.2%) of 1,815 subjects who received comparator in Controlled Phase 2/3 studies, and
11 (0.8%) of 1,449 subjects who received INH in extension studies.
None of these deaths are judged as being related to study drug. Two deaths of unknown cause occurred during the treatment phase of the studies, one in the INH group and one in a comparator group. No autopsy was performed in either case.

There were no clear differences in event rates for any all-causality serious AE between treatment groups in both patients with type 1 or type 2 DM.

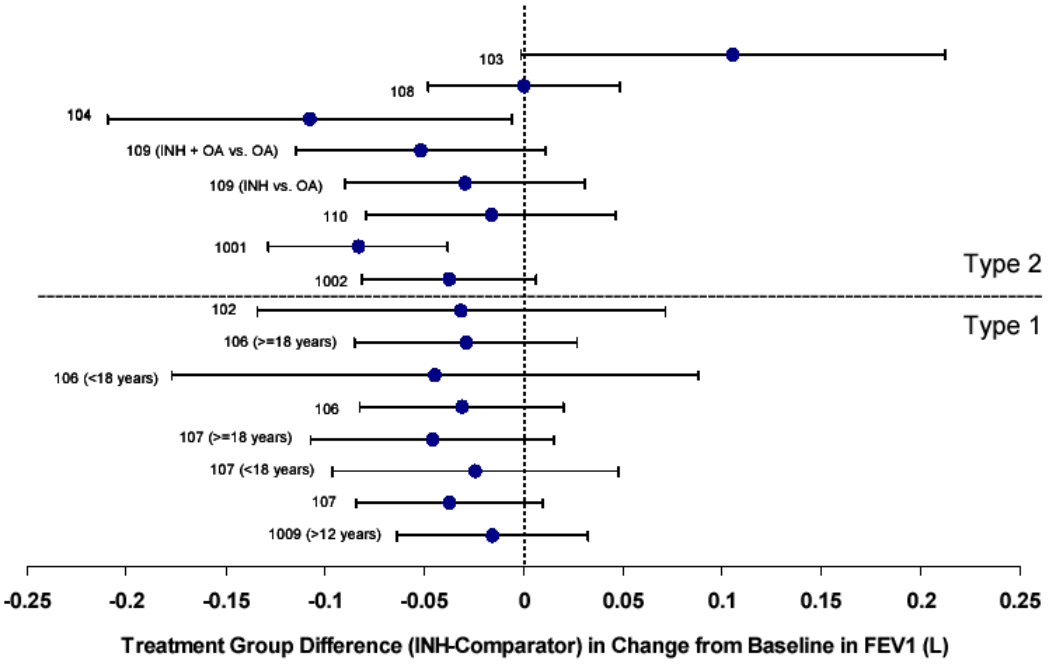
The most common all-causality serious AEs occurring among adult type 1 subjects were hypoglycaemia and loss of consciousness, which occurred at comparable frequencies in both groups.

In the all phase 2/3 protocol set, five patients were diagnosed with lung cancer. Three patients had received INH and two had received SC insulin or OA only. All concerned subjects were former smokers and among subject with type 2 DM.

Pulmonary function

Across studies, INH treated subjects experienced a small but consistent decline in FEV1 (30-40ml on average) and to a lesser extent in DLco compared to their comparator-treated counterparts (see figure below).

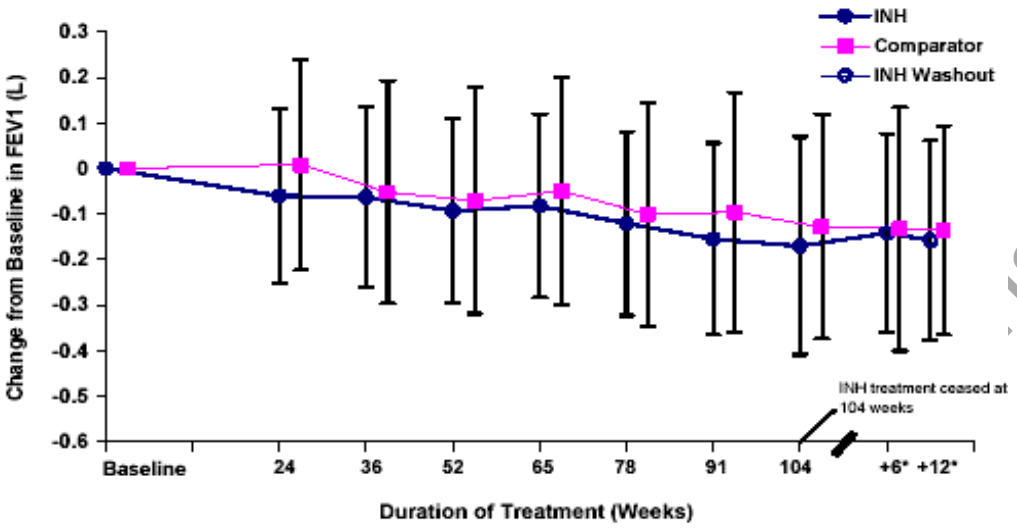
Figure 2. Adjusted Mean Treatment Group Differences and 95% Confidence Intervals for FEV_1 Change from Baseline (L): Completed Controlled Phase 2/3-PFT Studies



The treatment group differences were characterised by shifts in the entire distribution curves for change-from-baseline values, rather than by a small number of subjects with extreme values (outliers). The overall incidence in large declines in FEV1 (>20% from baseline) was small and similar in both groups (2.8% in Exubera-treated and 2.6% in comparator-treated patients). However, it could not be excluded that a subgroup of patients may be more sensitive to the effect of inhaled insulin on the respiratory tract. Therefore and because of the notion that even diabetic patients on standard treatment (oral agents or SC insulin) may exhibit a more rapid decline in FEV1 than the general population, monitoring of lung function was considered necessary to identify such patients and to avoid unacceptably large declines in lung function during treatment with INH. As stated in the SPC, all patients should have baseline evaluation of lung function (FEV1) before starting treatment with Exubera and regular follow-up evaluations thereafter. Exubera should be discontinued if FEV1 declines more than 20% from baseline regardless of a causal relationship..

Decline over time is illustrated in the figure below for studies 1001 / 1002. The accelerated decline was usually limited to the first weeks or months of treatment. The CHMP challenged the Applicant's claim that the decline in FEV1 is non-progressive.

Figure 6. Mean Change from Baseline and Standard Deviation in FEV_1 (L) by Time in Studies 1001 and 1002: 104-Week Cohort



Some analyses provided contrasting results. For example, the reported 'adjusted [for physiological parameters known to affect lung function] difference in change from baseline' was highest after 24 weeks of treatment without further increase up to 104 weeks, but, the mean (unadjusted) decline in FEV1 was 87 ml during the first and 102 ml during the second year of INH treatment and was 63 ml during the first and 55 ml during the second year of comparator treatment. Nevertheless, it appears that the acceleration of the FEV1 decline is largely limited to the first 3 months of treatment. Although the difference in the slope of the FEV1 decline beyond month 3 is not significant, it cannot be excluded be that with a longer duration or a higher power this difference becomes significant. No risk factors could be identified that were associated with a large decline in FEV1. The comparative extension studies 1022 and 1029 as well as the planned large simple study (1069), which are part of the RMP, are expected to provide additional information on long-term pulmonary safety (see RMP).

Reversibility of the initial decline in FEV1 was seen in most patients after treatment with Exubera for up to two years (Studies 1001/1002). Improvement in FEV1 also occurred in most patients with a large decline (>20% from baseline). Discontinuation of INH treatment for 6 months in the controlled part of extension Study 111 (treatment arms: continue vs. discontinue INH) resulted in changes in FEV_1 favouring the group that discontinued INH. This effect was fully manifest within 1 month. The mean treatment effect 6 months after discontinuing INH treatment of –0.042 L was similar in magnitude and opposite in direction to that observed within the first 3-6 months of treatment initiation. Discontinuation of INH treatment also resulted in an increase in DLco at 1 month post-discontinuation. The treatment effect was sustained at 3 months, but diminished at 6 months due to an apparent increase in DLco in the INH group. Studies 1001 / 1002 showed reversibility of PFT decline after long-term treatment of up to 2 years; resolution of treatment group differences in FEV1 following 2 years of continuous INH exposure occurred within 6 weeks of discontinuation of INH.

The study results also revealed a higher than expected FEV1 decline in the comparator groups: a normal FEV1 decline of 30ml / y in healthy adults is reported in the literature but in the control group an adjusted mean annual rate of change of around 70 ml was found. This finding was unexpected and warrants further investigation. Since about 40% of patients in both treatment groups were ex-smokers, a subgroup analysis was requested by the CHMP to investigate whether decline in PFT was dependent on smoking history. The requested analysis suggests that ex-smoking status doesn't affect the decline in lung function in either Exubera or comparator-treated patients. Alternative explanations for the higher than expected FEV1 decline in the comparator groups such as existence of a hypothetical 'diabetes lung' were discussed.

The unexpected finding of high prevalence of impaired pulmonary function in diabetic patients screened for INH trials and the fact that patients with asthma or COPD are often undetected, were additional reasons for CHMP to recommend that all patients should have pulmonary function evaluated before initiating INH, and follow-up examinations.

The mechanism of pulmonary impairment is unclear and should be further investigated. The Applicant has committed to and already started two mechanistic "bronchoalveolar lavage studies", one in patients with type 1 diabetes (Study 1052) and one in patients with type 2 diabetes (Study 1053) (see risk management plan). Since insulin therapy usually is a lifelong therapy, long-term pulmonary safety is of utmost importance.

- Laboratory findings

As expected for a diabetic population, the most commonly reported laboratory abnormality was glycosuria. Otherwise, the rates of laboratory test abnormalities were not clearly different.

Immunological events

Insulin antibodies (IABs) developed more frequently and mean levels of IABs were higher in patients who switched their SC fast-acting insulin to Exubera compared to subjects who remained on SC insulin, particularly in patients with type 1 DM. Additional risk factors appear to be young age and female gender as well as previous insulin exposure in patients with type 2 DM. IAB development usually occurred during the first 6-12 months of INH treatment without further increase thereafter. See table below.

Antibody Levels at Baseline and End of Study: Early Completed Controlled Phase 2/3 Studies

		Serum Antibody Level (% Binding)*(N) [SD]			
		Mean		Median	
Cohort	**Time Point**	**INH**	**Comparator**	**INH**	**Comparator**
Type 1 subjects ≥ 18 years old	Baseline	5.7 (215) [9.8]	6.1 (203) [10.3]	1.5	1.5
	End of study	27.7 [20.7]	7.1 [11.8]	25.0	1.5
	Change	22.0 [17.9]	1.0 [5.3]	20.5	0.0
Type 1 subjects < 18 years old	Baseline	10.4 (138) [11.6]	8.7 (138) [9.3]	6.0	6.0
	End of study	36.1 [19.0]	10.1 [11.3]	32.5	6.0
	Change	25.8 [15.9]	1.4 [4.5]	23.0	0.0
Type 1 subjects < 12 years old	Baseline	13.6 (53) [14.6]	11.1 (55) [11.7]	8.0	9.0
	End of study	36.9 [22.1]	12.9 [13.5]	30.0	10.0
	Change	23.3 [16.2]	1.75 [4.0]	20.0	1.0
Type 1 subjects Female	Baseline	6.2 (104) [10.3]	5.0 (92) [6.5]	1.5	1.5
	End of study	32.6 [22.5]	5.8 [7.6]	31.5	3.0
	Change	26.4 [19.2]	0.8 [3.3]	25.5	0.0
Type 1 subjects Male	Baseline	5.2 (111) [9.4]	7.0 (111) [12.6]	1.5	1.5
	End of study	23.0 [17.8]	8.2 [14.3]	18.0	1.5
	Change	17.9 [15.5]	1.2 [6.5]	14.5	0.0
Type 2 subjects insulin-using at study entry	Baseline	2.7 (134) [4.3]	4.1 (133) [9.3]	1.5	1.5
	End of study	12.8 [18.2]	4.0 [8.0]	5.0	1.5
	Change	10.2 [16.1]	-0.1 [3.3]	3.5	0.0
Type 2 subjects non-insulin-using at study entry	Baseline	1.8 (290)[4.6]	1.5 (181) [0.3]	1.5	1.5
	End of study	6.0 [8.0]	1.5 [0.0]	1.5	1.5
	Change	4.3 [9.2]	0.0 [0.3]	0.0	0.0

*Numbers are rounded to the nearest one tenth of one percent. Values less than the limit of quantitation were imputed as 1.5% binding.
N=number of subjects evaluated for antibody levels at both baseline and end of study, SD=standard deviation

INH associated antibodies are of the IgG class, as are of subcutaneous insulin associated insulin antibodies. In a small exploratory study (study 1026) INH-associated IABs were found to be predominantly low-affinity high-capacity antibodies. High-affinity low-capacity IABs may lead to a clinical picture of insulin resistance whereas high titres of low-affinity high-capacity IABs may act as a reservoir for insulin leading to delayed release and delayed hypoglycaemia.

In patients with type 1 DM, mean IAB levels fell by about 60% relative to end of treatment values within the initial 3 months after discontinuation of INH. Among subjects with type 2 DM, mean IAB level also fell after discontinuation of INH but the decline was slightly smaller and more protracted than in type 1 diabetic patients. The mechanism of increased IAB induction associated with INH is unknown and was unexpected since there was no such indication from animal studies.

Upon CHMP's request, further analyses assessing the clinical significance of IABs were performed. There was no apparent association between INH-associated IABs and adverse clinical outcome (especially glycemic control, hypoglycaemia rate, pulmonary function, other adverse events). Nevertheless, the development of high titres of IABs is still a (at least theoretical) concern. Very rare cases of antibody-related insulin resistance, delayed, prolonged or recurrent hypoglycemia or other adverse events would be unlikely to be detected during clinical trials. Therefore, a well-designed pharmacovigilance programme is important. The Applicant committed to a proactive approach, offering validated measurements of IABs for spontaneous reports of suspected immunologic insulin resistance or repeated unexplained hypoglycaemia using validated assays (see RMP).

An additional concern regarding the development of IABs is the correlation that has been suggested, albeit in a small number of patients, between IAB concentrations measured during pregnancy and foetal morbidity, especially an increased risk for neonatal hypoglycaemia. The CHMP agreed that an appropriate warning in section 4.6 of the SPC is sufficient and that a contraindication would be a too severe measure for a theoretical concern. The SPC recommends that when an Exubera treated patient becomes pregnant, appropriate subcutaneous insulin should be substituted for Exubera.
Recent publications (Kent et al., Nakayama et al., Nature May 2005) suggest that (pro) insulin may play a key role as primary auto-antigen in the development of autoimmune diabetes. Therefore, the question was raised as to whether the marked immunogenic response to Exubera may accelerate β-cell destruction in patients with remaining insulin production. However, non-clinical and clinical studies suggest that oral or intranasal insulin does not accelerate loss of β-cell function but may, to the contrary, induce immune changes consistent with mucosal tolerance to insulin. In response to the theoretical CHMP concern, the Applicant has proposed to study the effect of inhaled insulin on β-cell function in NOD mice, an appropriate animal model of type 1 diabetes. This approach, which is part of the RMP, is generally endorsed (see RMP).

Presently, no validated assay exists to measure insulin specific IgG subclass antibodies. The Applicant has committed to only use fully validated assays for IAB measurements in ongoing or future clinical trials. The Applicant has specified the time frame when the validation of the immunoglobulin class assay and results of the sample analysis will be available, which was agreed upon.

- Safety in special populations

The general pattern of AEs observed in paediatric type 1 diabetic patients appears similar to that in adult type 1 diabetic patients. There were no gender differences that appeared to be genuine to INH. In addition, the data do not indicate an undue risk for INH-treatment of elderly patients. However, the number of patients ≥ 75 years of age included in the clinical trials was small. The latter information has been included in the SPC.

The applicant presented data (subpopulation analysis on pooled data) showing that the use of INH in patients with mild, well-controlled asthma or COPD or during respiratory tract infections was not

associated with increased risk for hypoglycaemia or impaired glycaemic control. The Applicant has later provided preliminary data from studies 1028 and 1030 investigating safety and efficacy of Exubera in patients with mild to moderate asthma and COPD, respectively. These data did not reveal a major safety concern but showed that the rate of non-severe pulmonary exacerbations was increased compared to comparator group. Therefore, it was concluded that Exubera should not be recommended in patients with underlying lung disease such as asthma or COPD. A respective warning has been introduced into the SPC/PL. In addition, it was found necessary to contraindicate the use of Exubera in patients with poorly controlled, unstable or severe asthma and in severe COPD since the risk of both unreliable absorption of inhaled insulin and subsequent hypoglycaemia and/or poor glycaemic control and adverse effects of inhaled insulin on asthma/COPD exacerbations appears high.

In obese patients, dyspnoea was increased with INH use compared to comparator treatment. The applicant explained that the association 'increasing INH dose – increasing incidence of dyspnoea in patients with type 2 diabetes is explained by a common underlying mechanism , i.e. overweight/obesity; this is particularly supported by the fact that this association was not observed in non-obese patients with type 1 diabetes (BMI $\leq$ 30 was inclusion criterion in clinical trials). In addition, results from the newly submitted studies A217-1022 (non-obese type 1 diabetic patients), 1027 (non-obese type 1 diabetic patients), and 1029 (type 2 diabetic patients with an BMI up to 35) prospectively incorporated the Mahler dyspnoea index; such results did not indicate relevant group mean changes in dyspnoea between INH and comparator-treated patients.

- Discontinuation due to adverse events

Overall, only few INH users discontinued for reasons related to study drug. In patients with type 1 DM, overall discontinuation rate was similar in both treatment groups, but more INH than SC insulin subjects discontinued for reasons related to study drug. Cough was the respiratory AE most commonly associated with permanent discontinuation of INH.

In all treatment groups, females were more likely to discontinue than males. Elderly patients were more likely to discontinue INH or OA but not SC insulin than younger patients.

- Post marketing experience

N/A

- Discussion on clinical safety

The Exubera associated mean 30 to 40 ml excess decline in FEV1 initially observed in 3 to 6 months studies was considered a serious safety signal. Nevertheless, the later submitted analyses of the change from baseline over 2 years showed that the initially accelerated decline does not progress beyond the first 3-6 months of treatment in both patients with type 1 and type 2 diabetes, which was considered reassuring. Full reassurance will require a longer controlled follow-up as proposed in the risk management plan with the extension of studies 1022 and 1029. Meanwhile, monitoring of pulmonary function should be performed in patients treated with INH and stopping rules should be implemented, as described in the product information.

It could not be excluded that there might be a subgroup of patients who could be more sensitive to the effects of inhaled insulin on pulmonary function. Nevertheless, this subgroups is not obvious and there are no clear predictive factors.

The applicant has committed to extend the controlled clinical studies 1022 and 1029 to investigate pulmonary safety of Exubera after long-term use (5 years continuous and 7 years cumulative treatment) and to perform a large observational trial to further study the safety of Exubera under "real world" conditions (including adequate representation of very elderly patients). The applicant has to ensure that this study will collect longitudinal pulmonary function data at approximately yearly intervals. A bronchoalveolar lavage study is expected to provide further information on the mechanism of the observed decline in pulmonary function associated with the use of inhaled insulin.

Analyses of FEV1 decline in patients with atopic disease and in different ethnic groups will also be performed post-marketing.

Exubera should not be used in patients with underlying lung disease such as asthma or COPD because there are insufficient data to support the safe use in such patients. In addition, Exubera should be contraindicated in patients with severe, poorly controlled or unstable asthma or COPD since there are no data and will not be generated and the risk of both poor glycemic control and hypoglycemia appears high in such patients.

Concern was expressed that diabetic patients who develop heart failure and subsequent pulmonary edema while being treated with inhaled insulin may experience deterioration of glycemic control due to impaired insulin absorption from the lung. As a consequence, the SPC should state that patient developing dyspnoea with Exubera should be examined for pulmonary or cardiac causes; where pulmonary edema is present, or there is clinically relevant reduction in pulmonary function, Exubera should be discontinued and the patient switched to subcutaneous insulin.

As part of the risk management plan, it was also agreed to obtain further data on cardiovascular risk as well as possible correlation with decline in FEV1.

Due to the observed increase in insulin antibody rate and titre associated with the use of Exubera, the applicant will measure insulin antibodies in case of unusually prolonged or recurrent hypoglycaemia or unexplained lack or loss of efficacy raising the possibility of immunologic insulin resistance.
The risk for occurrence of neoplasias of the respiratory system under long-term treatment with INH needs to be assessed although the Applicant has argued convincingly that the potential cancer risk is low and hypothetical. The arguments are based on the following data: 1) INH has very low IGF-1R affinity (approximately 5,000 times less than IGF-1); 2) nonclinical studies of inhaled INH do not show inflammatory, proliferative, or degenerative effects in the respiratory tract of rats and monkeys; 3) there is no safety signal on lung cancer risk in the INH clinical program; 4) IGF-1 is not associated with increased risk of lung cancer in a recent meta-regression analysis; 5) epidemiologic studies suggest that diabetes mellitus is not associated with increased risk of lung cancer; 6) there is no epidemiologic evidence that insulin use is associated with increased risk for lung cancer and there are no reports of neoplastic transformation in the skin despite very high local concentrations after SC injections.
CHMP agreed that the risk of tumour promoting effects of Exubera within the lung are merely hypothetical at this point. However, it cannot be excluded that INH may accelerate the growth of pre-existing undiagnosed precancerous pulmonary lesions and such an effect could become clinically apparent after a few years of INH-treatment.

The applicant also agreed to perform an epidemiologic study to assess the hypothetical risk of lung cancer associated with inhaled insulin. The use of the Health Improvement Network (THIN) database in the UK appears appropriate for this purpose.

See also section 3.6 Risk management plan.

Description of the Pharmacovigilance system

The applicant has provided documents that set out a detailed description of the system of pharmacovigilance. A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

Risk Management Plan

As part of the Application for Marketing Authorisation the MAH has provided a Risk Management Plan, comprising a Safety Specification and a Pharmacovigilance Plan. In addition, the RMP describes activities to minimize risks.

Safety Specification

In order to specify safety issues, data from the preclinical and clinical development program were considered. With regard to the data from clinical studies the following issues were considered: limitations of the human database; populations not studied in the pre-approval phase; adverse events/adverse drug reactions; identified and potential interactions, including food-drug and drug-drug interactions; Epidemiology, Pharmacological Class Effects.

Analysis of this data allowed identifying real and potential important risks as well as patient populations of which data are lacking:

Important identified risks
- Change in pulmonary function
- Smoking in relation to alterations in pharmacokinetics

Important potential risks
- Dose inequivalence: 1 mg and 3 mg
- Increased insulin antibody levels
- Asthma and COPD
- Rare pulmonary events
- Lung cancer (hypothetical)

Important missing information
- Very elderly subjects (≥ 75 yrs)
- Congestive heart failure
- Pregnancy
- Children and Adolescents

The above listed issues have been considered suitable for specific considerations within the pharmacovigilance plan.

Pharmacovigilance Plan/Risk minimising activities

Within the pharmacovigilance plan routine tools of pharmacovigilance (PSURs, ADR reporting, signal detection tools, etc.) are mentioned which will be used to monitor the postmarketing safety of Exubera. In addition, non-routine measures have been described intended to cover risks as outlined within the safety specification. Information is given on: the objective of proposed actions, the rationale for proposed actions, monitoring safety of proposed actions, and milestones for evaluation and reporting.

The proposed actions comprise the labelling of Exubera-related material (SPC, PL, package, blisters) and measures to teach patients and health care professionnals about the proper use of Exubera; and measures (i.e. preclinical, clinical, epidemiological studies) to assess gathered information on potential/hypothetical risks and areas of missing information.

An overview on relevant clinical trials including information on time-lines is given in the below mentioned table.

Pharmacovigilance Plan; studies					
	Completed	**Ongoing**	**New**	**Start**	**End**
Bronchodilator – Steroid Study (1056)	√				

Passive Smoking Study (1057)	√				
Long-Term PFT Studies (5-Year Extensions 1022/1029)		√			2013
Asthma (1028)		√			2008
COPD (1030)		√			2012
Large Simple Trial (1069); Real World			√	2006	2015
Epidemiologic Lung Cancer Study (1071)			√	2006	2020
Paediatric Studies			√	2006	
PFT Mechanisms – Clinical					
BAL (1052/1053)		√			2007
Proposed Clinical Study			√	2006	2008
Expanded PFT Analysis			√	2005	2006
Insulin Antibodies					
IgG Subclass			√	2005	2006
Ig Class			√	2005	2007
NOD mouse beta cell preservation study			√	2006	2007

Risk minimisation plan

Activities to minimise risks have been specified as follow:

	Activities to Minimise Risk		
	SPC/ PL	Health Care Education/ Customer Care	Blister Package Differentiation
Important Identified Risks			
Change in Pulmonary Function	√	√	
Smoking-induced Alterations in PK	√	√	
Important Potential Risks			
1 and 3 mg Dose Inequivalence	√	√	√
Increased Insulin Antibody Levels	√	√	
Asthma and COPD	√	√	
Rare Pulmonary Events	√	√	
Limited Information			
Congestive Heart Failure	√	√	
Very Elderly Subjects (≥75 yrs)	√	√	
Pregnancy	√	√	
Children and Adolescents	√	√	

In its evaluation of the RMP the Applicant describes that:

- the RMP and its components will be evaluated and modified on an ongoing basis by the Risk Management Committee (RMC), which meets at monthly intervals
- The RMC will pursue a staged approach
  - step 1: safety signal detection and evaluation (routine pharmacovigilance)
  - step 2: additional analyses (use of ongoing studies) and design of new studies (e.g. Large Simple Trial, THIN-database)
  - Step 3: Identify means of prevention and update of communication/education plans

The Risk Management Plan is considered adequate nevertheless it should be considered "living" document, and amendments due to future safety signals are expected.

5. Overall conclusions, benefit/risk assessment and recommendation

Quality

In general, the different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The information provided in the application showed a consistent batch-to-batch production of Exubera achieving an adequate quality for the drug substance and the drug product. The manufacturing processes for the drug substance and the drug product were described and validated in sufficient detail. The quality of the drug substance and drug product is controlled by adequate test methods and specifications. No excipients of human or animal origin are used in the product manufacture and therefore there is no risk of contamination with viral or TSE agents by these ingredients. No animal ingredients are used for the cell culture process, the basic down stream processing and purification with the exception of porcine trypsin and porcine carboxypeptidase B. Sufficient virus validation data were provided for the manufacturing processes of both porcine enzymes and, as well, for the manufacturing process of recombinant human insulin to consider that Exubera is virologically safe. The applicant will address a number of quality points as follow-up measures postopinion. Concerning the lack of dosage form equivalence between the 1 mg and 3 mg blister reference is made to the clinical discussion.

Non-clinical pharmacology and toxicology

Non-clinical pharmacology studies showed that insulin inhalation powder was absorbed into the bloodstream in a dose-dependent manner and produced the expected pharmacodynamic response of decreasing glucose concentrations.

Based on non-clinical data, it is unlikely that chronic administration of Exubera will result in accumulation in the lung or may promote pre-existing preneoplastic/neoplastic changes in the lung.

The potential hazard for the foetus of frequent, induced insulin antibodies is unknown, therefore Exubera should not be used during pregnancy.

Efficacy

In clinical trials in type 1 diabetes, patients using a regimen of EXUBERA and long- or intermediate-acting insulin had similar reductions in HbA1c compared with patients taking subcutaneous insulin alone.

In clinical trials in type 2 diabetes patients using a regimen of EXUBERA and long- or intermediate-acting insulin, had similar changes in HbA1c compared with patients treated with subcutaneous insulin alone.

In clinical trials in type 2 diabetes patients not sufficiently controlled with oral anti-diabetic agents alone, using a regimen of EXUBERA alone or in combination with oral agents, had greater improvements in HbA1c compared with patients treated with oral agents alone.

In patients with type 2 diabetes sufficiently controlled with oral agents, the glycaemic control was not further improved by inhaled insulin.

Safety

The most common adverse reactions were hypoglycaemia and cough. The submitted data demonstrated that INH use is not associated with an increased hypoglycaemia risk in patients with type 1 or type 2 diabetes. Cough was predominantly mild in severity and decreased over time.

The excess of decline in FEV1 is small, does not appear to increase over time and is expected to be reversible.
Exubera should not be used in patients with underlying lung disease such as asthma or COPD because there are insufficient data to support the safe use in such patients. In addition, Exubera is contraindicated in patients with severe, poorly controlled or unstable asthma or COPD since there are

no data (and no data will be generated) and the risk of both poor glycemic control and hypoglycemia appears high in such patients. Smoking/and use in smokers are contraindicated because smoking greatly increases the rate and extent of absorption of inhaled human insulin and therefore could increase the risk of hypoglycaemia.

Other safety concerns include increased frequency and levels of insulin antibodies and potential long term pulmonary or cardiovascular risk.

All safety concerns, identified, potential or hypothetical, have been addressed in the product information and will be part of the educational material. The RMP was found comprehensive and acceptable.

The lack of dose equivalence between the two proposed blister strengths is addressed by a clear and strong warning in the product information and in the educational material. In addition, the Applicant has committed to improving the blister design (colour differentiation and tactile markings on the protruding end of the blisters) to clearly distinguish the two blister strengths.

Risk Management Plan

The company will perform a number of studies to further assess the safety profile of the target population and specific populations potentially at increased risk for adverse effects related to the use of Exubera (e.g. patients with asthma or COPD), set-up an enhanced pharmacovigilance system and ensure the following risk minimisation activites;

- educational material,
- improvement of blister design for improved differentiation of 1 and 3 mg blister strengths.
- differentiation of 1 and 3mg blister strengths.

Benefit/risk assessment

Controlled clinical trials in type 1 or type 2 diabetes have shown that EXUBERA achieves and maintains effective glycaemic control comparable to subcutaneously administered soluble human insulin. Safety concerns have been identified in terms of pulmonary function and smoking-induced alterations in pharmacokinetics. Other risks were potential risks, in particular in relation to the dose inequivalence of the two strengths (e.g. risk of hypoglycaemia), increased insulin antibody levels and rare pulmonary events. Information is insufficient or missing in some special populations (e.g. patients with asthma, COPD or heart failure). The CHMP took into consideration the fact that type 1 diabetes patients are expected to be treated younger when starting treatment and will be treated for a longer period of time. Therefore they may be more at risk of some adverse events (e.g. hypoglycemia due to large titration steps). The CHMP considered the benefit risk balance of Exubera positive provided that a risk management plan is appropriately performed, in the following indication:

> *"Exubera is indicated for the treatment of adult patients with type 2 diabetes mellitus not adequately controlled with oral antidiabetic agents and requiring insulin therapy.*
> *Exubera is also indicated for the treatment of adult patients with Type I diabetes mellitus, in addition to long or intermediate acting subcutaneous insulin, for whom the potential benefits of adding inhaled insulin outweigh the potential safety concerns."*

A minority of the CHMP members did not agree with the approval of Exubera for treatment of type I diabetes, because of long-term safety concerns, including immunogenicity, limited dosing flexibility and the risk for variable/altered absorption in special situations. They were of the view that the use of inhaled insulin should be restricted to the treatment of type II diabetes which population is generally less sensitive to variations in dose, generally older and can be expected to be more compliant to treatment recommendations and the risk management plan.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by majority that the benefit/risk ratio of Exubera in the treatment of above-mentioned indication was favourable and therefore recommended the granting of the marketing authorisation.