



Institute for Quality and Efficiency in Health Care

Inhaled Insulin (Exubera®)* **- Rapid Report -**

[Assignment No. A05-22]

8 May 2006

*Translation of the German Rapid Report “Inhalatives Insulin (Exubera®)”, Version 1.0 of 2 April 2006. Please note: The translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Theme: Evaluation of the Therapeutic Benefits and Harms of Inhaled Insulin in the Treatment of Diabetes Mellitus – Rapid Report

Contracting agency: Federal Joint Committee

Date of the Commission: 17 November 2005

Internal Assignment Number: A05-22

External Expert:

Bernd Richter, MD, Private Lecturer, Cochrane Metabolic and Endocrine Disorders Review Group, Faculty of Medicine, Heinrich Heine University, Düsseldorf

External Review:

Hans Liedholm, MD, PhD, Associate Professor, Drug and Therapeutics Committee, Malmö University Hospital, Sweden

Contact:

Institute for Quality and Efficiency in Health Care
Dillenburger Str. 27
51105 Köln
Internet: www.iqwig.de

Tel: 0221/35685-0

Fax: 0221/35685-1

Email: A05-22@iqwig.de

In the following text, the male form is used exclusively to designate individuals. This is solely to improve readability. The term “diabetes” is always used as an abbreviation of “diabetes mellitus”.

The date of access is always given for documents taken from the Internet and cited. If these documents can no longer be found at the Internet address given, they can be inspected at the Institute for Quality and Efficiency in Health Care (IQWiG).

The present report should be cited as follows:

IQWiG. Inhalatives Insulin (Exubera®). Rapid Report 01. Köln: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG). April 2006.

[IQWiG. Inhaled Insulin (Exubera®). Rapid Report 01. Cologne: Institute for Quality and Efficiency in Health Care (IQWiG). April 2006].

Core Statements

Exubera® is the first inhaled insulin approved for diabetes treatment. The product consists of a special preparation of insulin (dry powder based on human insulin) and a special device for use in inhalation. Treatment with Exubera® has only been approved for adults, not children or adolescents.

The pharmacokinetics and pharmacodynamics of Exubera® are similar to those found with short-acting subcutaneous human insulin or insulin analogues. The duration of action is about the same as that of short-acting human insulin. The time to onset of action is about the same as with short-acting insulin analogues (also referred to as rapid-acting insulin analogues). It is thus possible to use Exubera® as a substitute for short-acting human insulin or a short-acting insulin analogue.

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.” (Summary of Product Characteristics). There are no available studies in which Exubera® is compared with subcutaneous short-acting human insulin or short-acting insulin analogues in patients with type 2 diabetes, within an identical therapeutic regime (e.g. intensified insulin therapy).

Potential risks - including pulmonary risks - linked to long-term use cannot be excluded. The published data do not provide any basis for the conclusion that Exubera® is a safe alternative to subcutaneous insulin for patients with type 2 diabetes.

Exubera® is “also indicated for the treatment of adult patients with type 1 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.” (Summary of Product Characteristics). There are two available studies in which Exubera® was compared with subcutaneous short-acting human insulin, within an identical therapeutic regime (intensified insulin therapy). Although the efficacy (based on reductions in blood sugar) was comparable, the incidence of severe hypoglycaemia was greater with Exubera® than with human insulin. From this point of view and according to current knowledge, Exubera® is not a safe alternative to subcutaneous insulin for patients with type 1 diabetes mellitus. There are no reliable comparative studies available with short-acting insulin analogues.

In the available intervention studies to compare Exubera® with subcutaneous insulin, it appears that most of the patients did not administer the subcutaneous insulin with pens, but used syringes to take up the insulin, to mix it and then to administer it. This type of treatment is only of secondary importance in Germany. Studies of this sort therefore cannot be used as a basis for statements about the satisfaction with the therapy, the convenience of the therapy or the quality of life for patients in Germany.

Although it is possible to reduce the number of subcutaneous injections with Exubera®, they cannot be totally avoided, if the additional administration of basal insulin is necessary. Moreover, self-measurement of blood sugar is still necessary if inhaled insulin is used. This qualifies the potential advantage of Exubera® for patients who do not want to perform insulin therapy, because of an “aversion to injections”.

The patients were specifically trained in the use of Exubera®. In addition, at least in some studies, not only printed material, but also videos and oral instruction were employed. The exact manner and intensity of the training is unclear. It is not clear whether training programmes will be used during the market launch which have been demonstrated to be suitable for guaranteeing the safe use of Exubera® and of fulfilling the specific requirements of the European registration agency.

The incidence of severe hypoglycaemia is increased with Exubera®, presumably particularly during the early morning. This was also found in studies in which the type and quantity of basal insulin were comparable in the treatment groups (Exubera® on the one hand and normal insulin on the other). The reason for this is unclear, although the formation of insulin antibodies was increased under Exubera®. On the basis of currently available information, the possibility cannot be excluded that this is the cause of the increased incidence of nocturnal hypoglycaemia with Exubera®, which is sometimes severe.

Exubera® can have a negative effect on pulmonary function. The relevance of these findings for the long-term use of Exubera® is unclear. There has been no demonstration of safety for patients with lung diseases. Exubera® is contraindicated for patients with severe bronchial asthma and severe chronic obstructive lung disease.

Treatment with Exubera® is contraindicated for smokers. Exubera® is also contraindicated for ex-smokers who have smoked within the preceding 6 months. Smoking modifies the pharmacokinetics of Exubera®, not only chronically, but also acutely, so that there is the danger of severe hypoglycaemia if the patients starts or resumes smoking.

Table of contents

Core Statements.....	4
Table of contents	6
List of abbreviations.....	7
1. Background	8
2. Objectives of the Rapid Report	11
3. Methods.....	12
3.1 Criteria for study inclusion.....	12
3.1.1 Population.....	12
3.1.2 Intervention and Comparator Treatment	12
3.1.3 Outcome Parameters	13
3.1.4 Study Types.....	13
3.1.5 Duration of the Studies.....	13
3.1.6 Other Inclusion and Exclusion Criteria	14
3.2 Acquisition of Information.....	14
3.2.1 Literature Search	14
3.2.2 Search for Registration Documents and Study Reports	15
3.2.3 Questions to the Firm of Pfizer	15
3.3 Study Evaluation	15
3.4 Study Synthesis and Analysis	16
3.4.1 Meta-Analysis	16
3.4.2 Sensitivity Analysis.....	16
3.4.3 Subgroup Analysis	17
4. Results	18
4.1 Results of the Information Acquisition	18
4.1.1 Literature Search	18
4.1.2 Documents of the Registration Agencies	20
4.1.3 Study Register	20
4.1.4 Information Provided by the Firm of Pfizer.....	20
4.1.5 Resulting Study Pool.....	22
4.2 Characteristics of the Studies Included in the Evaluation.....	23
4.2.1 Study Design and Population	23
4.2.2 Study and Publication Quality.....	32
4.3 Results on Therapeutic Objectives.....	35
4.3.1 Hypoglycaemia and Blood Sugar Control	35
4.3.2 Quality of Life and Treatment and Patient Satisfaction	41
4.3.3 Other Adverse Events.....	44
4.3.4 Secondary Complications, Mortality, Admissions to Hospital	46
4.3.5 Hyperglycaemia	46
4.4 Subgroup Analyses.....	46
4.4.1 Gender	46
4.4.2 Age	46
4.4.3 Concomitant Diseases, Presence of Late Complications	47
4.5 Aspects of Implementation in Normal Daily Health Care	47
5. Discussion	49
6. Reference list.....	52
Appendix A.1: Irrelevant Phase 3 / Phase 2 Studies	56
Appendix A.2: Irrelevant Publications Viewed in Full Text	63
Appendix A.3: Reviews, HTA Reports, Rapid Reports.....	67
Appendix B: Search Strategies.....	69

List of abbreviations

Abbreviation	Meaning
--------------	---------

BIOSIS	BioScience Information Service
BMI	Body Mass Index
CINAHL	Cumulative Index to Nursing & Allied Health Literature
Embase	Excerpta Medica Database
EMA	European Medicines Agency
FDA	United States Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss [Federal Joint Committee]
HbA _{1c}	Subfraction c of glycosylated haemoglobin
HTA	Health Technology Assessment
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care]
IPA	International Pharmaceutical Abstracts
ISSHP	Index to Social Sciences and Humanities Proceedings
ISTP	Index to Scientific and Technical Proceedings
ISTPB	Index to Scientific and Technical Proceedings and Books.
ITT	Intention-To-Treat
Medline	Medical Literature Analysis and Retrieval System Online
NPH	Neutral Protamine Hagedorn
OAD	Oral Antidiabetics
PhRMA	Pharmaceutical Research and Manufacturers of America
RCT	Randomised Controlled Trial
SEM	Standard Error of the Mean
T1DM	Type 1 Diabetes mellitus
T2DM	Type 2 Diabetes mellitus
UL	Ultralente
USA	United States of America
WHO	World Health Organization

1. Background

The Federal Joint Committee wrote to the Institute for Quality and Efficiency in Health Care on 17.11.2005 to commission a rapid report to evaluate the therapeutic use of inhaled insulin in the treatment of diabetes mellitus. More details of the commission were decided during the meeting of the Subcommittee on Medicines on 6.12.2005. This rapid report has been prepared in accordance with the Institute's current methods for preparing rapid reports, Methods Version 1.0, Section 4.6.

The Disease Diabetes Mellitus

Diabetes mellitus is a chronic disease, characterised by increased blood sugar, and which can lead to late complications, such as renal failure and blindness. There are two main types of diabetes mellitus, type 1 and type 2 diabetes. Whereas type 1 diabetes mostly occurs in children, adolescents or young adults, type 2 diabetes normally first occurs in adults aged over 40 years [1].

In **type 1 diabetes**, there is an absolute deficiency of insulin, so that lifelong insulin substitution is needed for survival. The objective of insulin substitution is to achieve blood sugar values which are as near normal as possible, as this decreases the risk of secondary complications [2]. The gold standard is intensified insulin therapy [3]. In intensified insulin therapy, insulin substitution consists of a combination of once or twice daily administration of long- or intermediate-acting basal insulin, together with a short-acting insulin, depending on meal times. Although intensified insulin therapy reduces blood sugar to nearly normal levels, there remains the risk of severe hypoglycaemia [2]. This risk can be greatly reduced by participation in a structured training and treatment programme [4, 5]. It is an essential component of intensified insulin therapy that the patient who has taken part in a training programme should be able to adapt his dose individually, after measuring his own blood sugar several times daily [4]. Independently of the treatment used to reduce blood sugar, this self measurement of blood sugar is currently mostly performed in an invasive manner, by taking a drop of blood. Conventional insulin therapy involves twice daily treatment of a mixture of long- and short-acting insulins and is only of secondary importance in the treatment of type 1 diabetes in Germany.

In **type 2 diabetes**, the body still produces insulin, but the activity of this is decreased. Graduated treatment usually starts with non-medical approaches, such as diet and exercise, if necessary, with the intention of losing weight [6]. The second step is treatment with oral antidiabetic drugs. The use of insulin is then only the third step. Patients with type 2 diabetes are often given a fixed combination of short-acting normal insulin and longer-acting insulin, which is mostly injected in the morning and evening (conventional insulin therapy). It is also recommended that blood sugar should be measured less often in conventional therapy (e.g.

two to three times daily) [7]. In contrast to type 1 diabetes, only a comparatively small proportion of type 2 diabetes patients are given intensified insulin therapy.

Treatment with Insulin

Treatment with insulin is currently performed with subcutaneous injections of short-acting and/or basal insulin several times daily. It has been reported that fear of injections may be an obstacle to the treatment of some patients with type 2 diabetes [8]. Thus, an alternative route of administration which avoided injections might improve the quality of treatment of these patients. However, there are only a few cases in which fear of injections really conflicts with insulin therapy [9]. Thanks to the availability of the insulin pen, pain on injection is evidently less important than pain during the self-measurement of blood sugar [9]. Moreover, other factors play a role in the avoidance of insulin treatment, e.g. fear of the side effects of the therapy [9]. What is more, experience in the treatment of patients with bronchial asthma has shown that there can also be problems in the administration of drugs by inhalation, including compliance [10]. It is thus by no means an inevitable conclusion that the possibility of administration of insulin by inhalation is an inherent advantage in diabetes treatment. This must be investigated in specific studies.

The Technology of Exubera®

Exubera® was approved in January 2006, as the first inhaled insulin for the treatment of diabetes mellitus. The product Exubera® consists of a specific insulin preparation (dry powder based on human insulin) and a special device for administration by inhalation [11]. The inhalation device consists of a lower section with a holder, into which the insulin powder is inserted as a blister, and an inhalation chamber. If the chamber is pulled out, the device is about 20 cm long [12]. The chamber can be pushed over the lower section for transport.

The pharmacokinetics and pharmacodynamics of Exubera® are similar to those of subcutaneous normal insulin or short-acting insulin analogues [11]. The duration of action is about the same as that of normal insulin (up to about 8 hours). The time to onset of action is about the same as with the short-acting insulin analogues (about 10 to 15 min). It would thus be conceivable to use Exubera® as a substitute for normal insulin or for a short-acting insulin analogue. The insulin powder is available in two blisters at two different dosages (1 mg and 3 mg). 1 mg then corresponds to about 3 injection units of subcutaneous insulin. 3 mg correspond to about 8 injection units [13]. This implies that a 3 mg blister is not equivalent to three 1 mg blisters.

The insulin powder developed for Exubera® is based on a specially developed recombinant human insulin. In the early development phase, the firm of Lilly collaborated with the firm of Pfizer in the product development and was responsible for the production of the insulin in powder form [14]. The early phase 2 studies were performed with a 20% concentration of this insulin [14]. At the end of the 1990s, the firm of Aventis replaced Lilly as development

partner and took over the task of preparing the insulin. All phase 3 studies were performed with a 60% concentration of the recombinant human insulin “HMR4006” [14]. In addition, the version of the inhalation device was changed, from version number P2 to version P3 [14]. At the time of approval, device P3 was used with recombinant human insulin HMR4006 [14]. Only those studies are relevant for the present rapid report in which Exubera® was used in this version.

Approval in the USA (FDA) and in Europe (EMA) was in parallel and almost simultaneous. Approval in Europe is limited to the following areas of use [13]:

For type 2 diabetes mellitus:

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.” (Summary of Product Characteristics).

For type 1 diabetes mellitus:

Exubera® is “also indicated for the treatment of adult patients with type 1 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.” (Summary of Product Characteristics).

The approval therefore lays down the following restrictions and criteria for the treatment of type 2 diabetes:

1. Adult patients;
2. Prior treatment with oral antidiabetic drugs. This gave inadequate stabilisation of blood sugar, so that insulin had to be administered. Possibly also patients for whom treatment with all antidiabetic drugs was either impossible or contraindicated;
3. No restriction as regards combination with other antidiabetics (e.g. combination with OAD or basal insulin, Exubera® monotherapy is also possible).

There are the following restrictions for type 1 diabetes mellitus:

1. Adult patients;
2. Combination treatment with Exubera® in addition to basal insulin.

The present Rapid Report is restricted to the possible treatments with Exubera® as laid down in the approval.

2. Objectives of the Rapid Report

The following question is to be answered in this Rapid Report:

Does treatment with the short-acting inhaled insulin Exubera® lead to additional benefits in the treatment of patients with type 1 diabetes mellitus and/or patients with type 2 diabetes mellitus, in comparison to treatment with short-acting subcutaneously injected insulin (human insulin or insulin analogues)?

There is additional benefit, if comparison and consideration of the desired and adverse effects on therapeutic goals relevant to the patient (risk-benefit assessment) is favourable for Exubera®. This evaluation of benefits and harms is restricted to the treatment situation laid down in the approval text (adult patients who require insulin treatment).

The conditions for the use of Exubera® in normal health care practice will also be discussed. In particular, the type and intensity of training of the patients in the different studies will be described.

3. Methods

The present evaluation of benefits and harms is based on the systematic research and analysis of published scientific studies on Exubera®. In the following sections, the inclusion criteria for these studies will be described, together with the methods of the literature search and evaluation.

3.1 Criteria for study inclusion

3.1.1 Population

Studies were included with adult patients (aged at least 18 years) with type 1 or type 2 diabetes mellitus according to the study, e.g. according to the WHO definition [5]. Studies which included patients under 18 years were also included, if the majority of the patients were 18 or older.

3.1.2 Intervention and Comparator Treatment

Studies were regarded as being of **primary relevance** if they corresponded to the approval status described in Section 1 and in which Exubera® was compared with subcutaneous insulin, using an identical treatment regime in both therapy groups (e.g. intensified insulin treatment). In particular, the therapeutic regime included the frequency of administration of short-acting insulin and of basal insulin, the type of basal insulin used, the intensity of patient training, instructions on self-measurement of blood sugar and other interventions to reduce blood sugar.

Studies were regarded as being of **secondary relevance** if they corresponded to the approval status described in Section 1 and in which Exubera® was compared with subcutaneous insulin, but in which the therapeutic regime was different in the two treatment groups (e.g. intensified vs. conventional insulin therapy).

Irrelevant phase 2 and phase 3 studies: Studies were excluded from this evaluation, but were listed in a separate table, if they included a comparison between Exubera® and other interventions to reduce blood sugar (e.g. oral antidiabetic drugs) or in which Exubera® was used with an insulin formulation which was other than that approved, but which corresponded to the other inclusion and exclusion criteria (see following sections).

3.1.3 Outcome Parameters

The following parameters were used. These allow evaluation of the therapeutic goals relevant to the patients:

- Reduction in overall mortality
- Reduction in cardiac morbidity and mortality
- Reduction in cerebral morbidity and mortality
- Reduction in non-cardiac and non-cerebral vascular morbidity and mortality
- Reduction in the rate of blindness, delay of deterioration in vision
- Reduction in the rate of terminal renal failure with necessity of dialysis
- Reduction in the rate of amputation (minor and major amputations)
- Reduction in the rate of admission to hospital for any reason
- Reduction in the rate of hyperosmolar or ketoacidotic coma
- Reduction in the rate of symptoms from chronic hyperglycaemia
- Reduction in the rate of hypoglycaemia (in particular, severe hypoglycaemia)
- Reduction in the rate of other adverse events (in particular, serious adverse events, discontinuation of the study because of adverse events, adverse pulmonary events)
- Maintenance or improvement in the disease-associated quality of life (including ability to work and other everyday activities)
- Maintenance or improvement in patient or therapy satisfaction.

In addition, the effect on the HbA_{1c} value (glycosylated haemoglobin A_{1c}) will be described, as a measure of the reduction in blood sugar.

3.1.4 Study Types

If the methods are adequate and the design appropriate, randomised clinical trials (RCTs) provide the most reliable results for the evaluation of a medical intervention, as they minimise the uncertainty of the results. Evaluation in RCTs is both possible and practicable for all the therapeutic objectives given in section 3.1.3 and all the interventions given in section 3.1.2.

The present Rapid Report therefore exclusively included RCTs as relevant scientific literature for this evaluation.

3.1.5 Duration of the Studies

Studies were considered which lasted at least 12 weeks, to allow reliable evaluation of the reduction in blood sugar, on the basis of HbA_{1c} measurements. An initial inspection showed

that the duration of all potentially relevant studies phase 2 and phase 3 studies was at least 12 weeks [14].

3.1.6 Other Inclusion and Exclusion Criteria

All studies were considered for which one or more full text publications were available. Studies which were only available as abstracts are also mentioned as references for additional and potentially relevant information, but their results were not incorporated in this evaluation. There were no restrictions on the language of the publication.

3.2 Acquisition of Information

3.2.1 Literature Search

The following sources were searched for relevant studies (including congress abstracts on these studies):

- Bibliographic data banks: Medline, Embase, Embase Alert, BIOSIS, CINAHL, Cochrane Library, Adis Newsletters, Derwent Drug File, International Pharmaceutical Abstracts (IPA), ISTP/ISSHP + ISTEPB, SciSearch
- The publishers' data banks of Karger, Kluwer, Springer, Thieme
- Literature lists of relevant secondary publications (HTA reports, including Rapid Reports, systematic surveys, reviews)

All search strategies are listed in Appendix B. The search was performed on 31.1.2006.

The relevance of the citations was independently assessed by two reviewers on the basis of the titles and, if present, also of the abstracts. Publications which were considered by both reviewers to be relevant (possibly after discussion) were submitted to a final assessment of their relevance on the basis of the full text - once again by two reviewers.

Search in literature lists in secondary publications

The literature lists in relevant secondary publications were searched for relevant potentially relevant primary publications. The search for relevant secondary publications was performed in the above named data banks in parallel to the search for relevant primary literature. In addition, Google Internet searches were repeatedly performed for published Rapid Reports on Exubera® (<http://www.google.de>).

Search in congress volumes

The congress volumes of the European and American Diabetes Societies were searched between 2000 and 2005 for potentially relevant abstracts.

3.2.2 Search for Registration Documents and Study Reports

Publicly accessible documents on Exubera® which might indicate relevant studies were sought on the Internet sites of the European and American registration agencies (<http://pharmacos.eudra.org/F2/home.htm>, <http://www.emea.eu.int> and <http://www.fda.gov>). In addition, study reports of completed studies were sought in the study result register of the USA Association of the Pharmaceutical Industry (Pharmaceutical Research and Manufacturers of America, PhRMA, <http://www.clinicalstudyresults.org>).

3.2.3 Questions to the Firm of Pfizer

An agreement for the confidential transmission of information relevant to Exubera® was concluded with the firm of Pfizer on 20.1.2006. This included the confidential transmission of the form but not the content of all studies performed with Exubera® and additional information on these studies which was relevant to this evaluation. In the course of the preparation of this Rapid Report, the firm of Pfizer was repeatedly requested for relevant information. The questions and the corresponding answers are documented in Section 4.1.4.

3.3 Study Evaluation

The studies were evaluated on the basis of the available information, so that the evaluation is heavily dependent on the quality of the primary publications.

The evaluation took place in two steps:

1. Data extraction,
2. Evaluation of the study and publication quality, including testing the consistency of the data within the publication and with information in congress abstracts (if these were available).

Data extraction

The extraction of the data from the primary publications was performed independently by two reviewers, using standardised data extraction sheets. On the basis of these extraction sheets, both reviewers then prepared the evidence tables for the present Rapid Report. If there were

discrepancies in the first step of the evaluation, these were resolved in advance by discussion between the reviewers.

Study and Publication Quality

Data on aspects of study quality were systematically extracted. These included the randomisation process (generation of the randomisation list, concealment of allocation), type of blinding, procedure for protocol violators and for patients who left the study and/or the treatment prematurely, the adequacy of the statistical analyses, sample size planning and the consistency of the information. The quality of the study and publication were evaluated on the basis of these criteria. In addition, information on the performance of training, comparability of the therapeutic regimes, reports of comedication and comorbidity, etc., were extracted and presented.

3.4 Study Synthesis and Analysis

Aspects of the study design, the study quality and the results of the individual studies were summarised and presented for the whole study pool.

3.4.1 Meta-Analysis

A meta-analytical summary in accordance with the methods of the Institute was planned in advance for those parameters for which this appeared both sensible and possible, both from the content and the methods, after inspection of the studies. However, this was not possible for any of the parameters investigated, as the studies were too heterogenous.

3.4.2 Sensitivity Analysis

Sensitivity analyses were planned in advance for

- Parameters of study or publication quality

- In so far as possible, for the per-protocol evaluations described in the publications versus ITT evaluations and a (statistical) model with fixed effects (versus a model with random effects), if a meta-analysis was undertaken.

3.4.3 Subgroup Analysis

Subgroup analysis was undertaken for the following characteristics, in so far as this was possible and sensible:

-Gender

-Age

-Concomitant diseases

-Possibly, different definitions of diabetes

-Additional therapy to reduce blood sugar

-Duration of diabetes

-Presence of late complications at the start of the study

-If a meta-analysis established that there was substantial heterogeneity between the studies, the characteristics responsible for this heterogeneity, in so far as these could be identified.

4. Results

The results of the information acquisition will be presented first. This is followed by the presentation of the relevant studies. This is then followed by a discussion as to whether specific statements can be made for definite subgroups, on the basis of the available information. Finally, aspects on the implementation in normal daily health care will be presented, as derived from an evaluation of the relevant studies.

4.1 Results of the Information Acquisition

4.1.1 Literature Search

The search in the bibliographic data banks was performed on 31.1.2006. All search strategies are listed in Appendix B.

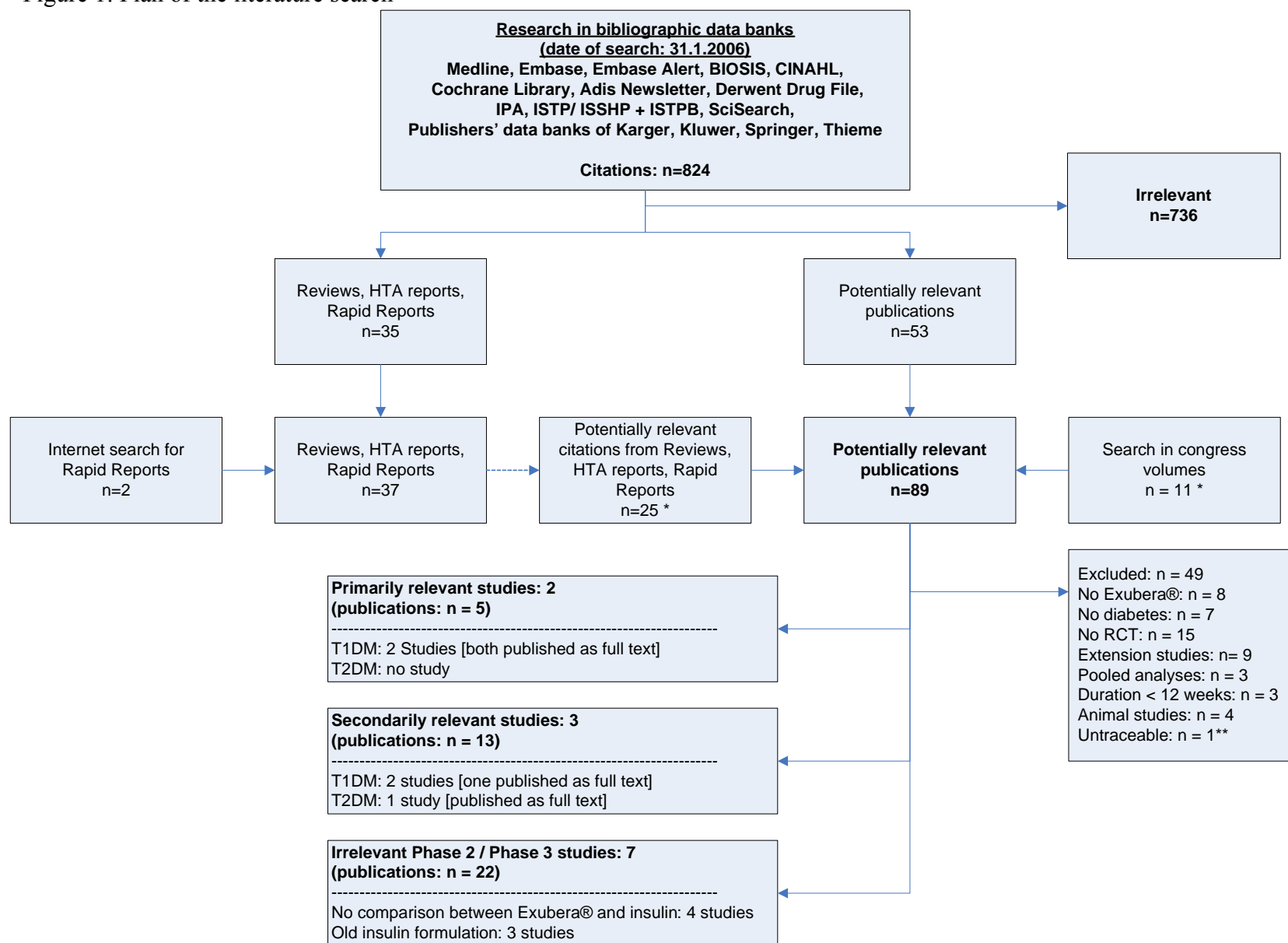
After removal of the duplicates, 824 hits were initially identified. Both reviewers agreed that 736 of these had to be rated as irrelevant. Of the remaining 88 publications, 53 were rated as publications on potentially relevant studies and 35 classified as relevant reviews. The Internet research identified two additional Rapid Reports. 25 additional publications on potentially relevant studies were identified from the literature lists of the total of 37 Reviews / Rapid Reports and a further 11 in the congress volumes. This then gave a total of 89 publications on potentially relevant studies. Of these,

- 5 were publications on 2 studies of primary relevance
- 13 were publications on 3 studies of secondary relevance
- 22 were publications on 7 irrelevant phase 2 or phase 3 studies and
- 49 were irrelevant publications (including 1 congress poster which could not be traced).

Appendix A.1 includes the list of the 22 publications on the irrelevant phase 2 or phase 3 studies. Appendix A.2 gives the list of the remaining 49 irrelevant publications viewed in full text. Appendix A.3 contains the list of the reviews and rapid reports.

Figure 1 depicts the plan of the literature search.

Figure 1: Plan of the literature search



*excluding duplicates. **: Congress poster of Hollander 2001 untraceable, perhaps a withdrawn contribution (according to information in congress volume)
T1DM: Type 1 diabetes mellitus. T2DM: Type 2 diabetes mellitus.

4.1.2 Documents of the Registration Agencies

Aside from the Summary of Product Characteristics [11, 13], no relevant publication and accordingly no relevant reference to additional relevant studies was found in the Internet page of the European registration agency.

The following relevant documents were found under <http://www.fda.gov>:

- “Initial Clinical Review” of 5.8.2005 [15]

- “Statistical Review and Evaluation” of unknown date [16]

No reference to additional relevant studies was found in either of these documents.

4.1.3 Study Register

No reference to studies on Exubera® was found under <http://www.clinicalstudyresults.org>.

4.1.4 Information Provided by the Firm of Pfizer

As agreed, parts of the registration dossier for Exubera® were made available by the firm of Pfizer on 30.1.2006. These provided no evidence for additional relevant studies. In addition, a variety of questions were put on various aspects of individual studies. Table 1 summarises the questions and the answers from Pfizer.

Table 1: Questions to Pfizer

Date of Question	Content of Question	Answer from Pfizer
9.1.2006	Request to send parts of the registration dossier and possibly separate list to identify individual studies	30.1.2006: Documents provided
3.2.2006	Request to send training material used in relevant studies, including audiovisual material	10.2.2006: Instructions for use for patients and doctors/pharmacists provided (version of November 2005, i.e. not the version used in the studies).
15.2.2006	Repeat of request to send the training material used in the relevant studies	Not answered
20.2.2006	Questions on the type of insulin administration in the relevant studies (pen system or syringes)	27.2.2006: Only answered indirectly: Quote: "The aim of the studies you refer to was to investigate glycaemic metabolic control under the individual treatment regimens. It was not possible in these studies to distinguish between patient preference (PRO) for inhaled insulin on the one hand and insulin administered by pen or syringe on the other. This was not an objective either."
27.2.2006	Repeat of the request made on 20.2. to send training material.	6.3.2006: Request for explanation why this information was regarded as necessary.
15.3.2006	Explanation of the relevance of the information; Reference to the passage in the confidentiality agreement covering transfer of information. Repeat of request to transmit information.	As yet, no answer

4.1.5 Resulting Study Pool

Table 2 shows the pool of studies of established or potential relevance arising from the different steps of the literature search. All studies of primary or secondary relevance were included in the study for which a full text publication was available.

Table 2: Pool of Relevant Studies

Diabetes Type Study Number ^a	Primary/ Secondary relevance ^b	Full text publication available	Congress abstract available	Inclusion in the evaluation
Type 2 Diabetes mellitus				
108	secondary	yes: Hollander 2004 [17]	yes, 2: [18,19]	yes
Type 1 Diabetes mellitus				
107	primary	yes: Skyler 2005 [20]	yes, 2: [21,22]	yes
1026	primary	yes: Heise 2005 [23]	yes, 1: [24]	yes
106	secondary	yes: Quattrin 2004 [25]	yes, 4: [26-29]	yes
1027	secondary	no	yes, 5: [30-34]	no ^c
a: Study number from [14]				
b: Primarily relevant: identical therapeutic regime in the treatment groups; secondarily relevant: different therapeutic regimes in the treatment groups; see too section 3.1.2.				
c: As no full text publication available.				

There was no study of primary relevance on the treatment of type 2 diabetes mellitus, although one study of secondary relevance was identified (Hollander 2004, Study 108).

Two studies of primary relevance were found for the treatment of type 1 diabetes mellitus (Skyler 2005, Study 107, and Heise 2005, Study 1026; therapeutic regime: intensified insulin therapy). Two studies of secondary relevance were found (Quattrin 2004, Study 106, and Study 1027). No full text was identified for study 1027, so that this could not be included in this evaluation.

The list of the irrelevant phase 2 and phase 3 studies is included in Appendix A.1. The essential design characteristics of these studies are tabulated there.

4.2 Characteristics of the Studies Included in the Evaluation

4.2.1 Study Design and Population

Tables 3 to 8 provide information on the design of the 4 published studies included in this Rapid Report and on the groups of patients enrolled in each.

General Design

All 4 studies employed a randomised, controlled and open parallel group design. A 4-week run-in phase was used in all studies, in which the subsequent control treatment (subcutaneous insulin therapy) was administered to all patients. The subsequent duration of therapy after randomisation was 24 weeks in all cases, plus the run-in phase of 4 weeks.

The only study on type 2 diabetes compared intensified insulin therapy with Exubera® and conventional insulin therapy with subcutaneous human insulin. Of the three studies on type 1 diabetes, two compared Exubera® with subcutaneous human insulin in the context of intensified insulin therapy (Skyler 2005 und Heise 2005), whereas Quattrin (2004) compared intensified insulin therapy with Exubera® with conventional insulin therapy with subcutaneous human insulin.

Three of the four studies (Skyler 2005, Hollander 2004, Quattrin 2004) were performed in multiple centres in the USA and Canada. The fourth study was performed in a single centre in Germany (Heise 2005). The patients in all studies were outpatients.

The primary outcome parameter in three of the four studies was the change in HbA_{1c} and in one study the maximal postprandial glucose concentration (Heise 2005). The three studies in which the change in HbA_{1c} was the primary outcome parameter were non-inferiority studies, with a planned and predefined inferiority limit of 0.5% (group difference of the HbA_{1c} change). The hypothesis for inferiority/non-inferiority is not clear in Heise's publication (2005). In all studies, data on the rates of hypoglycaemia and other adverse events were collected. Data on quality of life and patient and therapeutic satisfaction were only collected in the two studies of secondary relevance (Hollander 2004 and Quattrin 2004).

Intervention to Reduce Blood Sugar

The defined target values for blood sugar were identical in the two studies of primary relevance and also identical in the two studies of secondary relevance. The values were 80-120 mg/dl fasting and 100-140 mg/dl at night (primarily relevant studies) and 80-140 mg/dl fasting and 100-160 mg/dl at night (secondarily relevant studies). As a potentially additive

intervention to stabilise or reduce blood sugar, three of the four studies include instruction or a diet and moderate physical exercise (Skyler 2005, Hollander 2004, Quattrin 2004).

In all studies, Exubera® was to be inhaled within 10 minutes or immediately before meals. For subcutaneous insulin, the preprandial injection-to-meal interval was given as follows: in Skyler (2005) 30 minutes, in Heise (2005) 15 minutes (during the inpatient evaluation phase). For the studies of secondary relevance, no information was provided on the injection-to-meal interval of subcutaneous insulin.

The information provided on the type and extent of general and Exubera®-specific training was generally inadequate. In Skyler (2005) and Hollander (2004), training with the Exubera® inhalation device was mentioned, although this was not specified more closely. In Quattrin (2004), it is stated that this training was oral and was performed with the help of a video cassette. There was no information on Exubera®-specific training in Heise (2005). No information on the patients' general training status could be gathered from the publications - either for the intervention or for the control groups. In other words, it is unclear whether the participants were given training on intensified or conventional insulin therapy and, if so, of what sort this was and whether there were relevant differences between the treatment groups.

All patients in both the intervention and control groups were intended to perform self-measurements of blood sugar. The frequency of these measurements was only specified in two of the four studies - as four times daily (Hollander 2004) or at least five times daily (Skyler 2005). All studies include insulin dose adjustment on the basis of blood sugar target values, although the patient is only given as the active agent in this respect in a single publication (Hollander 2004).

Study Population

For **type 2 diabetes**, the data base is limited to 149 patients treated with Exubera® and 150 patients treated with subcutaneous insulin in a study of secondary relevance (Hollander 2004, intensified insulin therapy with Exubera® vs. conventional insulin therapy with human insulin). The mean age in this study was about 58 years. The mean duration of diabetes was about 13 years. About two thirds of the enrolled patients were men.

The data base of the two studies of primary relevance (intensified insulin therapy in both groups) on **type 1 diabetes** included a total of 187 randomised patients on Exubera® and 188 randomised patients on subcutaneous human insulin. About 32% of the patients in both groups were aged under 18 years [14]. A further 170 patients (Exubera®) and 165 patients (subcutaneous insulin) were enrolled in the study of secondary relevance (Quattrin 2004), of whom 19% and 18%, respectively, were aged under 18 years. No specific data on the patients aged under 18 years were given in the publications, so that their possible influence on the overall result cannot be evaluated. Overall, the data basis for type 1 diabetes is restricted to 264 adult patients treated with Exubera® and 264 adult patients treated with subcutaneous

human insulin. The mean age in the studies on type 1 diabetes was between 29 and 38 years. The overall balance of the genders was about equal. The mean duration of diabetes was between 13 and 18 years.

Essential **exclusion criteria** in all studies included clinically important lung diseases (e.g. asthma or COPD), smoking, hospital treatment for poor metabolic control and repeated severe hypoglycaemia within the six months before the start of the study. It was striking that only the monocentre study in Germany apparently complied with the defined criteria for inclusion and exclusion. All the publications on the North American studies exhibited discrepancies in these criteria (some of which are essential for diagnosis) and in the reported baseline characteristics.

Table 3: Included Studies - Overview

Diabetes Type, Study (Study Number)	Study design	Study duration	Number of randomised patients	Site and period of the study	Relevant target criteria ^a
Type 2 Diabetes mellitus					
Hollander 2004 (108)	RCT, parallel, open	24 weeks (+ 4 week run-in phase)	Exubera®: 149 Control: 150	USA, Canada Period unclear	Primary outcome parameter: change in the HbA _{1c} (non-inferiority study) Relevant: hypoglycaemia rates (overall and severe), adverse events, quality of life, therapy satisfaction
Type 1 Diabetes mellitus					
Skyler 2005 (107)	RCT, parallel, Open	24 weeks (+ 4 week run-in phase)	Exubera®: 163 ^b Control: 165 ^b	USA, Canada Period unclear	Primary outcome parameter: change in HbA _{1c} (non-inferiority study) Relevant: hypoglycaemia rates (overall and severe), adverse events
Heise 2005 (1026)	RCT, parallel, Open	24 weeks (+ 4 week run-in phase)	Exubera®: 24 Control: 23	Germany Period unclear	Primary outcome parameter: not given (sample size planning: C _{max} of the postprandial glucose concentration [measurements on the first day of the time in hospital after a standardised meal]) Relevant: change in HbA _{1c} , hypoglycaemia rates (overall and severe) adverse events
Quattrin 2004 (106)	RCT, parallel, open	24 weeks (+ 4 week run-in phase)	Exubera®: 170 ^c Control: 165 ^c	USA, Canada Period unclear	Primary outcome parameter: Change in the HbA _{1c} (non-inferiority study) Relevant: hypoglycaemia rates (overall and severe) undesired adverse events, quality of life, therapy satisfaction
^a : Statement of the applicable primary outcome parameter and its endpoints, which provide information on the patient-relevant therapeutic objectives given in section 3.1.3. ^b : ca. 36% < 18 years old (inclusion criterion: 12-65 years). ^c : ca. 18% (Exubera®) and 19% (control) < 18 years old (inclusion criterion: 12-65 years) BMI: body mass index. C _{max} : time to the maximal blood concentration. HbA _{1c} : glycosylated haemoglobin A _{1c} . RCT: randomised controlled trial					

Table 4: Diabetes-Related Inclusion and Exclusion Criteria – Study on Type 2 Diabetes mellitus

Study (Study number)	Diabetes Diagnosis	Inclusion and Exclusion Criteria
Hollander 2004 (108)	NG	<p>I: Type 2 diabetes mellitus, for at least one year; age 35-80 years; stable insulin treatment (2-3 injections insulin for the last two months); no oral antidiabetic drugs; screening-und prerandomisation HbA_{1c} 6-11%; Fasting plasma C-peptide > 0.2 pmol/ml); BMI ≤ 35 kg/m²; compliance for the blood sugar self-measurement and for the study protocol; written declaration of consent.</p> <p>E: poorly controlled bronchial asthma, COPD or other significant respiratory disease; smoking within the previous six months; significant abnormalities in a screening chest X-ray; abnormal lung function test on screening; disease of a major organ system; predisposition for severe hypoglycaemia (two or more severe events of severe hypoglycaemia within the previous six months); admission to hospital or emergency treatment for poor metabolic control within the previous six months; insulin pump therapy two months before screening</p>
BMI: body mass index. E: Exclusion criteria. I: Inclusion criteria. HbA _{1c} : glycosylated haemoglobin A _{1c} . NG.: Not given		

Table 5: Diabetes-Related Inclusion and Exclusion Criteria – Studies on Type 1 Diabetes mellitus

Study (Study Number)	Diabetes Diagnosis	Inclusion and Exclusion Criteria
Skyler 2005 (107)	according to ADA 1998	I: Type 1 diabetes mellitus; age 12-65 years; stable insulin treatment (≥ 2 injections/day for the last two months); HbA _{1c} 6-11%; BMI ≤ 30 kg/m ² ; readiness to self-measurement of blood sugar; written declaration of consent E: Poorly controlled bronchial asthma; significant respiratory, hepatic or cardiac disease; smoking within the previous six months; repeated severe hypoglycaemia; treatment with oral antidiabetic drugs or insulin pump therapy within two months of screening; admission to hospital or emergency treatment for poor metabolic control within the previous six months
Heise 2005 (1026)	NG	I: Type 1 diabetes mellitus; age 18-50 years; HbA _{1c} 5.0-9.0%; baseline insulin antibodies ≤ 20 μ U/ml; fasting C-peptide ≤ 0.3 pmol/ml E: Smokers; patients with lung diseases, reference to additional exclusion criteria as in Quattrin (2004)
Quattrin 2004 (106)	NG	I: Type 1 diabetes mellitus, for at least one year and fasting plasma C-peptide ≤ 0.2 pmol/ml ^a ; age 12-65 years; stable insulin treatment (≥ 2 injections insulin or insulin analogues/day for the last 2 months); HbA _{1c} 6-11%; BMI ≤ 30 kg/m ² ; compliance with self-measurement of blood sugar; written declaration of consent E: Poorly controlled bronchial asthma or clinically significant COPD or significant respiratory disease; smoking within the previous six months; significant abnormalities in a screening chest X-ray; abnormal lung function test on screening; clinically significant disease of a major organ system, with the exception of diabetic microvascular complications; two or more events of severe hypoglycaemia within the previous six months in the history; admission to hospital or emergency treatment for poor metabolic control within the previous six months; insulin pump therapy within two months of screening
^a : In the publication, " ≥ 0.2 pmol/ml" is given, but this is implausible for the inclusion of patients with type 1 diabetes BMI: body mass index. E: Exclusion criteria. I: Inclusion criteria. HbA _{1c} : glycosylated haemoglobin A _{1c} . NG: not given		

Table 6: Target values and therapeutic schemes for reducing blood sugar

Diabetes Type Study (Study Number)	Therapeutic Objective ^a	Time point of Exubera® administration	Time point of Control administration	Other treatment to reduce blood sugar
Type 2 Diabetes mellitus				
Hollander 2004 (108)	Before meals : 80 – 140 mg/dl (4.4 – 7.8 mmol/L) For the night: 100 – 160 mg/dl (5.6 – 8.9 mmol/L)	IIT: within 10 min. of start of meal ^b + UL for the night	CIT: mixed NPH + N, always before breakfast and evening meal No information on injection-to-meal interval.	Instruction on diet three weeks before randomisation (emphasised at run-in and at every study visit); participants should take moderate physical exercise for 30 min at least three days per week (emphasised at run-in and at every study visit).
Type 1 Diabetes mellitus				
Skyler 2005 (107)	before meals: 80 – 120 mg/dl (4.4 – 6.7 mmol/L) for the night: 100 – 140 mg/dl (5.6 – 7.8 mmol/L)	IIT: Within 10 min before meals + NPH before breakfast and for the night	IIT: N ca. 30 min preprandial + NPH 2x/day (total of four injections/day)	Diet instructions during the run-in + in week 12; Participants were advised to take moderate physical exercise for 30 min for at least three days per week
Heise 2005 (1026)	Before breakfast: 80 – 120 mg/dl ^c (4.4 – 6.6 mmol/L) for the night: 100 – 140 mg/dl ^c (5.5 – 7.7 mmol/L)	IIT: Immediately before meals (inpatients: 5 min. before) + NPH before breakfast and for the night	IIT: N before meals (inpatients: 15 min. before) + NPH before breakfast and for the night	NG
Quattrin 2004 (106)	fasting and before meals: 80 – 140 mg/dl (4.4 – 7.8 mmol/L) for the night: 100 – 160 mg/dl (5.6 – 8.9 mmol/L)	IIT: Within 10 min before meals + UL for the night	CIT: NPH + N before breakfast + N before evening meal + NPH either before evening meal or for the night No information on injection-to-meal interval.	Diet instructions during the run-in and in week 12 (meal plan) + emphasised at each study visit; participants were advised to take 30 min moderate exercise at least 3 days per week (run-in + emphasised at each study visit)
^a : Information on blood glucose concentrations ^b : According to [14], within 10 min <i>before</i> meals ^c : Data not given in mg/dl in the publication. Recalculated and rounded to facilitate comparison. CIT: conventional insulin therapy. IIT: Intensified insulin therapy. NG: not given N: Normal insulin. NPH: Neutral Protamine Hagedorn. UL: Ultralente.				

Table 7: Blood Sugar Self-Measurement, Dose Adjustment and Patient Training

Diabetes Type, Study (Study Number)	Blood Sugar Self-Measurement	Insulin Dose Adjustment	Training Programme
Type 2 Diabetes mellitus			
Hollander 2004 (108)	Run-in: All patients were given instructions on blood sugar measurement. These were to be performed 4 times daily (before breakfast, lunch, evening meal and for the night)	Weekly by the investigator + also possible by patient	Before randomisation, all patients (including the control group) were given instructions on operating the Exubera® inhalation device; no information on general training
Type 1 Diabetes mellitus			
Skyler 2005 (107)	The patients were instructed about blood sugar measurement and were told to test at least 5 times daily (before meals, 2 h after meals, for the night)	The blood sugar values were checked at each visit and the means calculated; Blood sugar target values adjusted after considering several factors (size of meals, composition of meals, blood sugar before meal, recent or anticipated physical exertion).	Exubera®: Before the intervention, patients given training on inhalation technique. Control: NG No information on general training
Heise 2005 (1026)	Blood sugar measurements at home were used to adjust the insulin doses to the target blood sugar values.	Blood sugar measurements at home were used to adjust the insulin dose for the target. The dosages were fixed weekly on the basis of the mean blood sugar values from the previous week.	NG
Quattrin 2004 (106)	The self-measurements of blood sugar were discussed on the phone in the first five study days and then adjusted at each follow-up visit	The insulin doses were adjusted to the blood sugar target values.	Exubera®: oral and video training on inhalation technique. No information on general training. Control: NG
NG: not given			

Assignment No. A05-22: Inhaled Insulin (Exubera®) - Rapid Report

Table 8: Demographic and Baseline Data Related to Diabetes

Diabetes Type Study (Study Number)	n	Age [years] ^a	Gender f[%]	Gender m[%]	Duration of Diabetes [years] ^a	HbA _{1c} [%] ^a	BMI [kg/m ²] ^a
Type 2 Diabetes mellitus							
Hollander 2004 ^b (108)							
Exubera®:	149	59 (10)	34	66	14 (0.4–59)	8.5 (1.2)	m: 30 (4) f: 32 (5)
Control:	149	56 (11)	34	66	13 (1–43)	8.5 (1.2)	m: 30 (4) f: 31 (4)
Type 1 Diabetes mellitus							
Skyler 2005 (107)							
Exubera®:	162	29 (15) [<18 years: 36% ^c]	48	52	13 (1-50)	8.2 (1.1)	24 (3)
Control:	165	30 (15) [<18 years: 36% ^c]	46	54	15 (1-49)	8.2 (1.2)	24 (4)
Heise 2005 ^b (1026)							
Exubera®:	24	38	26	74	17	7.0	25
Control:	23	36	45	55	18	7.4	25
Quattrin 2004 (106)							
Exubera®:	170	m: 34 (12–63) f: 33 (11-63) [<18 years: 19%]	48	52	16 (1-41)	8.3 (6.0-11.1)	m: 26 (17-36) f: 25 (18-34)
Control:	164	m: 34 (11-61) f: 34 (12-64) [<18 years: 18%]	45	55	17 (1-49)	8.3 (6.0-10.8)	m: 25 (18-32) f: 25 (18-33)
^a : Means, rounded as necessary, with standard deviations or range in brackets, as available ^b : Data from screening time point ^c : Data from [14]. BMI: body mass index. NG: not given. m: male. f: female.							

4.2.2 Study and Publication Quality

The criteria for study and publication quality are summarised in Table 10 and in Figure 2.

Additional details on the randomisation process for two of the four studies were contained in the corresponding publications (Hollander 2004, Heise 2005). Only one publication provided information on the concealment of allocation (Hollander 2004). All studies were open in principle, so that the lack of clarity as regards the concealment of allocation in the other three studies must be seen as a serious deficiency. No publication stated whether the recording of the endpoints was blinded. Sample size planning was described in two studies (Heise 2005, Skyler 2005).

The drop-out rate for the Exubera® arm varied between 6% and 11% for the individual studies. The drop-out rate for the control arm with subcutaneous insulin administration varied between 7% and 22%. The reasons for the drop-outs were given in all publications.

Figure 2 illustrates important methodological parameters for study and publication quality, together with essential clinical parameters. It can be seen from this that less than half of the criteria were fulfilled. It could be said that the studies and publications, taken together, exhibit major deficiencies.

Table 9: Study and Publication Quality

Diabetes Type Study (Study Number)	Randomisation Process/ Concealment of Allocation	Blinding: Patient	Blinding: Physician	Blinding: Recording of Endpoint	Sample Size Planning	Study Drop-outs	ITT Analysis of the Primary Endpoints	Consistency of the Information within the Publication ^a
Type 2 Diabetes mellitus								
Hollander 2004 (108)	described / described	no	no	NG	NG	E: 17/149 (11%) C: 10/150 (7%) Reasons given	Not reported ^b	yes
Type 1 Diabetes mellitus								
Skyler 2005 (107)	NG/NG	no	no	NG	described	E: 9/163 (6%) C: 13/165 (8%) Reasons given	Not reported ^b	yes
Heise 2005 (1026)	Described/NG	no	no	NG	described	E: 2/24 (8%) C: 5/23 (22%) Reasons given	Not reported	yes
Quattrin 2004 (106)	NG/NG	no	no	NG	NG	E: 18/170 (11%) C: 14/165 (8%) Reasons given	Not reported ^b	yes
^a : With reference to the primary publication. If there are any inconsistencies with respect to the congress abstracts, they are discussed individually in the later sections. ^b : Non-inferiority study; according to [14,15], ITT analysis planned and carried out. E: Exubera®. ITT: Intention-to-Treat. C: Control. NG: not given								

Figure 2: Illustration of important methodological and objective study parameters

Study (Study number)	Identical regimens for treatment with insulin	Injection-to-meal interval of subcutaneous insulin described in detail	Use of pen or insulin syringes described in detail	Training with the inhalation device described in detail	Inclusion and exclusion criteria complied with	Randomisation described in detail	Allocation concealment described in detail	Blinded recording of endpoint	Primary outcome parameter given unambiguously ^a	Sample size planning, power given	Intention-to-treat analysis reported	Sensitivity analysis (Per Protocol / Intention-To-Treat)	Consistency of the information within the primary publication	Patient Flow Chart	Comparability of the groups given ^b	Comorbidities and comedication given	Adverse effects described in detail
Hollander 2004 (108)	0	0	0	0	0	X	X	0	X	0	0	0	X	0	X	0	X
Skyler 2005 (107)	X	X	0	0	0	0	0	0	X	X	0	0	X	X	X	0	X
Heise 2005 (1026)	X	0	0	0	X	X	0	0	0	X	0	0	X	0	0	0	X
Quattrin 2004 (106)	0	0	0	0	0	0	0	0	X	0	0	0	X	0	X	0	X

Criterion fulfilled: X; criterion not fulfilled: 0.

^a: Primary outcome parameter in the Heise publication (2005) can be indirectly deduced from the information in the sample size planning: C_{\max} of the postprandial glucose concentration (measured on day 1 of the periods in hospital after a standardised meal); according to the answer of Heise et al. to a reader's letter from Chantelau et al. [35], "postprandial glucose" was designated directly as the primary endpoint.

^b: The comparability of the groups can only be evaluated with respect to the characteristics given in the publication.

4.3 Results on Therapeutic Objectives

4.3.1 Hypoglycaemia and Blood Sugar Control

Extent of Blood Sugar Reduction

Controlled studies comparing insulin-based therapies leading to more or less intensive reduction of blood sugar have repeatedly shown that therapies leading to intense reduction in blood sugar are accompanied by greater risk of hypoglycaemia [2,36]. If there is apparently a lower rate of hypoglycaemia in one of the treatment groups of an intervention study, the sole reason might be that the intensity of the reduction in blood sugar was less, without there necessarily being any substance specific effect. Therefore, if the observed hypoglycaemia rates in a controlled study comparing different active substances to reduce blood sugar are to be compared, it is absolutely essential to know the extent of the reduction of blood sugar in the different treatment groups. Table 10 summarises the relevant information in the publications.

The information on the extent of blood sugar reduction (based on the HbA_{1c} value) over the 24-week period of observation was provided clearly enough in all studies, with the proviso that this was only for the subgroup designated as “evaluable” or “assessable” in the non-inferiority studies and in the Heise study (2005). These analyses should be seen as per-protocol analyses, which can be regarded as an adequate method of analysis for the non-inferiority studies. Although intention-to-treat analyses were also planned and performed for the non-inferiority studies [14,15], the results of these analyses are not included in the publications.

Overall, there were no statistically significant or clinically relevant differences between the treatment groups in any study. For all three of the studies planned to be non-inferiority studies (Hollander 2004, Skyler 2005, Quattrin 2004), the differences in the mean HbA_{1c} changes between the Exubera® intervention group and the control group (subcutaneous insulin) fulfilled the previously fixed criterion for the non-inferiority of Exubera® (difference in change < 0.5% HbA_{1c}). In the four relevant studies, it can be assumed that the reduction in blood sugar over the period of the study is comparable in the treatment groups.

Table 10: HbA_{1c} (%) during the Study

Diabetes Type Study (Study Number)	Start ^a	Week 12 ^a	Endpoint ^{a,b}	Difference Endpoint - Start	Change Endpoint - Start (Group Difference E-C) ^{a,c}
Type 2 Diabetes mellitus					
Hollander 2004 (108)	E: 8.1 C: 8.2	NG	E: 7.4 C: 7.6	E: -0.7 C: -0.6	-0.1 (95% CI -0.3 to 0.2); Non-inferiority demonstrated
Type 1 Diabetes mellitus					
Skyler 2005 (107)	E: 8.0 (1.0) C: 7.9 (1.0)	NG	E: 7.7 (1.0) C: 7.8 (1.2)	E: -0.3 C: -0.1 ^c	-0.2 (95% CI -0.3 to 0.0) Non-inferiority demonstrated
Heise 2005 (1026)	E: 6.8 (0.7) C: 7.1 (0.6)	E: 6.6 (0.8) C: 7.2 (0.9)	E: 6.7 (0.9) C: 7.1 (1.0)	E: -0.1 ^c C: -0.1 ^c	NG
Quattrin 2004 (106)	E: 8.1 (1.0) C: 8.1 (1.0)	NG	E: 7.9 (1.1) C: 7.7 (0.9)	E: -0.2 C: -0.4	0.2 (95% CI 0.0 to 0.3) Non-inferiority demonstrated
^a : Means, rounded as necessary, with standard deviations in brackets, if available. ^b : Value at time point of last observation (24 weeks or last-observation-carried-forward). ^c : According to data in abstract E: Exubera®. C: Control. NG = not given CI: confidence interval					

Definition of “Hypoglycaemia” including “Severe Hypoglycaemia”

Neither the patient nor the physician was blinded to the treatment reducing blood sugar in any study. The reliability of the results determined is highly dependent on whether the definition of the event “hypoglycaemia” allows more or less scope for conscious or unconscious subjective influence. A possible way to minimise bias by deliberate influence would, for example, be to have an independent person to record the endpoints in a blinded manner. This is particularly the case as the symptoms are non-specific and hypoglycaemia is not so serious that specific treatment from third parties is essential. In the present studies, hypoglycaemia which was not classified as severe was generally identified on the basis of the patient’s self-measurement of blood sugar. As blood sugar self-measurements are not regularly performed at night, this procedure cannot provide an unbiased measure of the hypoglycaemia rate over 24 hours. An overall evaluation of the non-severe hypoglycaemia in these studies is therefore virtually impossible.

The criterion “necessity for external help” in the history as a definition for severe hypoglycaemia may also be susceptible to subjective influence, as this could, for instance, be understood as administration of glucose by third parties for non-specific symptoms. The definition “intravenous administration of glucose or administration of glucagon and/or coma and/or death with measurement of blood sugar under 50 mg/dl”, for example, permits much less scope for subjective interpretation. Table 11 summarises the definitions of a hypoglycaemic event used in the studies.

It is not evident in any study that there was an effort to minimise systematic bias in the results, for example, by independent validation of the events. For this reason, all the studies were susceptible to bias in the rates of hypoglycaemia.

Severe and non-severe hypoglycaemic events

The results on the outcome parameter “severe hypoglycaemia” are individually listed in Table 12, together with the data on total hypoglycaemic events (including the non-serious events) for comparison.

There is no evidence that independent and treatment-blinded validation of the results was performed in any study. In particular, as discussed above, the rate of non-severe hypoglycaemic events, for which the criterion “necessity for external help” must not be fulfilled, is unreliable. For the reasons discussed above, the results for severe hypoglycaemia are also of limited reliability. In the Hollander (2004) and Skyler (2005) studies, per-protocol analyses were performed and there were no data on the intent-to-treat population. For Quattrin (2004) and Heise (2005), the type of analysis is unclear.

Under Exubera®, the rate of severe hypoglycaemia in all studies was either numerically greater or statistically significantly greater than in the control group with subcutaneously administered insulin, leading to an increased risk of severe hypoglycaemic events with Exubera®. In the largest study of primary relevance (Skyler 2005), there was a statistically significant increased risk of severe hypoglycaemia with Exubera® in comparison to subcutaneous insulin, with intensified insulin therapy in type 1 diabetics. In the Quattrin study (2004) - of secondary relevance - a higher blood sugar target was given and the observed difference was not statistically significant. In Heise (2005) only a few patients were investigated, so that only a few events of severe hypoglycaemia occurred. In the only available study on type 2 diabetes, comparatively few events of severe hypoglycaemia occurred. However, the rates were compatible with those found with type 1 diabetes, in that there were more events with Exubera®.

Hypoglycaemia not classified as severe was frequent in all studies: in more than 70% of the patients in Hollander (2004), in more than 99% in Skyler (2005), in ca. 90% in Quattrin (2004) (reference population unclear). Heise (2005) contains no data on the number of patients who suffered at least one hypoglycaemic event. In all studies, there were fewer episodes of hypoglycaemia not classified as severe with Exubera® than with subcutaneous insulin treatment. For the reasons discussed above, these results are unreliable.

Table 11: Definition of the event “severe hypoglycaemia” in the individual studies

Diabetes Type, Study (Study Number)	Definition
Type 2 Diabetes mellitus	
Hollander 2004 (108)	1) Patients were incapable of treating themselves, 2) exhibited neurological symptoms (loss of memory, confusion, uncontrollable or irrational behaviour, difficulties in waking up, seizures or coma) and had 3) measured blood sugar of <49 mg/dl ^a (<2.7 mmol/L) or – if there was no measurement - the condition was reversible by administration of oral carbohydrates, subcutaneous glucagon or intravenous glucose.
Type 1 Diabetes mellitus	
Skyler 2005 (107)	1) External help 2) Neurological symptoms (e.g. loss of memory, confusion, irrational behaviour, unusual difficulties in waking up, seizure, loss of consciousness) and 3) Association with a blood sugar self-measurement of <2.8 mmol/L (<50 mg/dl), or – if there was no measurement - the condition was reversible by administration of oral carbohydrates, subcutaneous glucagon or intravenous glucose.
Heise 2005 (1026)	Hypoglycaemic event in which the patient could not treat himself, exhibited at least one neurological symptom and either had blood sugar of <49 mg/dl (<2.7 mmol/L) or the symptoms improved after administration of glucose or glucagon.
Quattrin 2004 (106)	Patients were not capable of treating themselves, exhibited neurological symptoms and had a blood sugar value of <50 mg/dl (<2.8 mmol/L) or – if there was no measurement - the condition was reversible by administration of oral carbohydrates, subcutaneous glucagon or intravenous glucose.
^a : Calculated value, not contained in the publication	

Table 12: Severe and non-severe hypoglycaemia events

Diabetes Type, Study (Study Number), Type of Treatment	Patients with severe hypoglycaemia [n (%)]	Total number of events of severe hypoglycaemia [n]	Rate of severe hypoglycaemia [per 100 patient months]	Relative Risk^a (95% CI)	Patients with at least one event of hypoglycaemia [n (%)]	Total number of events of hypoglycaemia [n]	Overall rate of hypoglycaemia [per patient month]	Relative Risk^a (95% CI)
Type 2 Diabetes mellitus								
Hollander 2004 (108) IIT [E] vs. CIT [C]	NG	E: 4 C: 1	E: 0.5 C: 0.1	5.00 ^{b,c}	E: 109 (76) C: 104 (72)	E: 1104 C: 1278	E: 1.4 C: 1.6	0.89 (0.82 to 0.97)
Type 1 Diabetes mellitus								
Skyler 2005 (107) IIT [E] vs. IIT [C]	E: 25 (16) C: 22 (14)	E: 58 C: 29	E: 6.5 C: 3.3	2.00 (1.28 to 3.12)	E: 158 (99) C: 158 (99)	E: 8348 C: 8832	E: 9.3 C: 9.9	0.94 (0.91 to 0.97)
Heise 2005 (1026) IIT [E] vs. IIT [C]	E: 3 (NG) ^d C: 2 (NG) ^d	E: 4 C: 2	E: 3.2 ^b C: 1.8 ^b	1.78 ^b	NG	E: 985 C: 1041	E: 7.8 C: 9.4	0.83 ^b
Quattrin 2004 (106) IIT [E] vs. CIT [C]	E: 29 (NG) ^d C: 21 (NG) ^d	E: 48 C: 41	E: 5.5 C: 4.7	1.16 (0.76 to 1.76)	E: 155 (NG) ^d C: 155 (NG) ^d	E: 7536 C: 7806	E: 8.6 C: 9.0	0.96 (0.93 to 0.99)
^a : Ratio of rate of events per patient time for Exubera® to control, rounded as necessary ^b : Calculated value, not contained in publication ^c : According to the abstract “no significant difference in severe events” ^d : Unclear whether per-protocol or intention-to-treat analysis CIT: conventional insulin therapy. E: Exubera®. IIT: intensified insulin therapy. C: control. NG: not given CI: confidence interval.								

4.3.2 Quality of Life and Treatment and Patient Satisfaction

Only Hollander (2004) and Quattrin (2004) - the two studies of secondary relevance - contained information on quality of life and treatment and patient satisfaction. With different scales of measurement, statistically significant improvements were reported with Exubera® in comparison with subcutaneously administered insulin (Table 13). Quantitative data on these two studies are only given in the congress abstracts for these two studies. However, these do not fulfil the criteria for detailed evaluation, as the presentation is not transparent enough. There were also no quantitative data in the congress abstract for the Skyler study (2005), which was of primary relevance.

The two studies employed different insulin treatment regimens in the two treatment groups. Exact information is missing on the injection-to-meal interval for the patients treated with subcutaneous insulin. Moreover, at least in Hollander (2004), even the patients in the control group had to measure their blood sugar four times daily, even though they only administered insulin twice daily. In Hollander (2004), patients who had previously injected insulin three times daily were also included and adjusted to twice daily injections. Finally, it is not evident in the publications which administration aids were used for the subcutaneous insulin (pens or syringes). It is stated in a Rapid Report published in 2005 that Pfizer had announced that it had repeatedly used syringes for the patient to fill in studies with Exubera® and that pens had only been used comparatively rarely [37]. This is also supported by the locations of the Hollander (2004), Skyler (2005) and Quattrin (2004) studies (North America), as insulin treatment there (e.g. in 2002) was performed much more often with syringes than with the pen system, whereas the pen system is used in up to 90% of cases in other countries [38]. It is also noted in Skyler (2005) that the twice daily administration of NPH insulin plus the three times daily administration of normal insulin led to a total of four daily injections, allowing the conclusion that in the morning NPH insulin was taken up in a syringe with normal insulin and mixed. Pfizer was asked by the Institute about the site of administration of subcutaneous insulin. Although their answer was evasive, it contained the comment that “It was not possible in these studies to distinguish between patient preference (PRO) for inhaled insulin on the one hand and insulin administered by pen or syringe on the other. This was not an objective either.” Moreover, the possibility cannot be excluded that not only the treatment satisfaction, but also the quality of life, are influenced by the manner of administration of subcutaneous insulin, the necessary effort and the intensity of the pain on injection.

It is striking that there are no results on quality of life and treatment and patient satisfaction in the publication of the largest study of primary relevance (Skyler 2005), even though these parameters were recorded [14]. Only the corresponding congress abstracts report that there was statistically significant improvement in treatment satisfaction in comparison to subcutaneous insulin [21,22].

Assignment No. A05-22: Inhaled Insulin (Exubera®) - Rapid Report

In summary, the available information does not allow the deduction that Exubera® provides any benefit with respect to the quality of life and/or patient satisfaction in comparison to subcutaneously administered insulin.

Table 13: Quality of life and treatment satisfaction

Diabetes Type, Study (Study Number)	Quality of Life	Treatment Satisfaction
Type 2 Diabetes mellitus		
Hollander 2004 (108)	The “quality-of-life scale” and subscales of the “health perception, symptom interference” gave greater improvements for Exubera® in comparison to subcutaneous insulin ($p < 0.05$) ^a	Significant ($p < 0.0001$) improvement in “overall satisfaction score” for Exubera® and slight deterioration in the control. All “satisfaction subscales (advocacy, burden, convenience, efficacy, flexibility, general satisfaction, hassle, interference, pain, preference, side effects, and social)” gave similar favourable effects for Exubera® (all $p < 0.0001$). ^a
Type 1 Diabetes mellitus		
Skyler 2005 (107)	NG	NG ^b
Heise 2005 (1026)	NG	NG
Quattrin 2004 (106)	The “overall quality-of-life scale” and subscales of “health perception, symptom interference, depression, positive affect, life satisfaction, psychological well-being, and cognitive function” gave more marked improvements for Exubera® in comparison to subcutaneous insulin ($p < 0.05$). ^c	Significant ($p < 0.001$) improvement in “overall satisfaction summary score” for Exubera® and significant deterioration ($p < 0.05$) for the control. All “satisfaction subscales (advocacy, burden, convenience, efficacy, flexibility, general satisfaction, hassle, interference, pain, preference, side effects, and social)” gave similar favourable effects for Exubera® (all $p < 0.0001$). ^c
^a : In the publication, reference to “Editor’s note”: Quality of life and patient satisfaction have been published as a congress abstract [19] – “an additional publication is planned”. No quantitative data on health related quality of life and treatment satisfaction were presented in the publication. ^b : According to congress abstracts [21,22], patients under Exubera® exhibited more marked improvements than with subcutaneously administered insulin ($p < 0.0001$). ^c : Reference [26] is referred to in the publication. No quantitative data on health related quality of life and treatment satisfaction were presented in the publication. E: Exubera®. C: Control. NG: Not Given		

4.3.3 Other Adverse Events

None of the studies was primarily planned to investigate safety aspects of inhaled Exubera® insulin. To assist in a comparative evaluation of the safety, Table 14 gives the results on the following target criteria: rate of therapy drop-outs because of adverse events; rate of serious adverse events; total number of patients with adverse events; specific and frequently reported adverse events, such as cough, increase in insulin antibodies and changes in lung function parameters.

The therapy drop-outs because of adverse events were between 0% and 3% with Exubera® and between 0% and 1% with subcutaneous insulin. The number of serious and general unexpected events was roughly comparable in the two groups. Two deaths were reported with Exubera® therapy. (One patient died of oesophageal carcinoma and one from oesophageal bleeding). No patient died under subcutaneous insulin.

In Hollander (2004), there was a mean increase in weight of 1.4 kg (from 89.2 kg to 90.6 kg), in the subcutaneous insulin group, while the weight in the Exubera® group remained stable at 90.5 kg. The difference was statistically significant. Skyler (2005) found no significant difference between the groups with respect to weight change. There was no corresponding information in Heise (2005) and Quattrin (2004).

After administration of inhaled insulin, there was a marked and statistically significant increase in insulin antibodies in all studies. The clinical relevance of this cannot be assessed on the basis of published information. In particular, it is unclear whether this is linked to the higher rate of severe hypoglycaemia. About a quarter of the patients reported cough after insulin inhalation. The only change in the lung function tests was a reduction in the pulmonary diffusion capacity in two of three studies after administration of Exubera®. It was striking that the primary publications consistently contained different results on diffusion capacity to those in the congress abstracts and that the primary publications were always more in favour of Exubera®. According to [18], in study 108 (Hollander 2004) too, the diffusion capacity under Exubera® after 24 weeks was also decreased to a greater extent (both numerically and statistically) than with subcutaneous insulin. It is unclear whether this discrepancy is due to different methods of evaluation (e.g. adjusted vs. non-adjusted differences in means).

Continuous peak flow measurements and tests of bronchial reactivity were not performed in the studies included.

Table 14: Other Adverse Events

Diabetes Type Study (Study Number)	Therapy Drop-outs because of Adverse Events [n (%)]	Patients with Severe Adverse Events [n (%)]	Patients with Unexpected Events [n (%)]	Cough [%]	Weight increase during the Study ^a [kg]	Insulin Antibodies [%]	Lung Function ^b [ml * min ⁻¹ * mm Hg- 1]
Type 2 Diabetes mellitus							
Hollander 2004 (108)	E: 4/149 (3) C: 2/150 (1)	E: 6/149 (4) ^c C: 1/149 (1)	E: 126/149 (85) C: 118/149 (79)	E: 21 C: 2 ^h	-1.3 (95% CI -2.0 to - 0.6)	E: 5 ^d C: 2 ^d	-0.4 (95% CI -1.2 to 0.4) ⁱ
Type 1 Diabetes mellitus							
Skyler 2005 (107)	E: 2/163 (1) C: 1/165 (1)	NG	NG	E: 25 C: 7	-0.2 (95% CI -0.9 to 0.5)	E: 28 ^{d,g} C: 4 ^{d,g}	-0.8 (95% CI -1.5 to -0.1) ^k
Heise 2005 (1026)	E: 0/24 (0) C: 0/23 (0)	E: 3/24 (13) C: 0/23 (0)	NG	NG	NG	E: 53 ^f C: 0 ^f	NG
Quattrin 2004 (106)	E: 3/170 (2) C: 0/165 (0)	E: 6/170 (4) C: 11/165 (7)	E: NG (99) C: NG (99)	E: 27 C: 5	NG ^e	E: 29 ^d C: 3 ^d	-1.2 (95% CI -2.0 to -0.5) ^j
^a : Adjusted mean group difference (rounded if necessary) of the change in weight from baseline Exubera® – control. ^b : Adjusted mean group difference (rounded if necessary) of the group difference (Exubera® – control) of the diffusion capacity DL _{CO} . (There were no statistically significant differences in other lung function parameters). ^c : Also two deaths (1x oesophageal carcinoma, 1x oesophageal bleeding). ^d : Median percentage binding. ^e : Exubera® +0.9 kg, control +1.5 kg (increase relative to baseline at week 24). Difference not statistically significant ^f : Difference of the medians between baseline and week 24 in µU/ml – calculated value, not given in the publication ^g : Mean change (standard deviation) from baseline in % insulin-antibody binding: Exubera® 23 (16), control 1 (4). ^h : Difference to abstract data: cough in the control group 3%. ⁱ : Difference publication to abstract data: publication -0.403 (95% CI -1.166 to 0.360), abstract -0.808 (95% CI -1.574 to -0.043). ^j : Difference publication to abstract data: publication -1.218 (95% CI -1.950 to -0.485), abstract -1.303 (95% CI -2.030 to -0.577). ^k : Difference publication to abstract data: publication -0.791 (95% CI -1.466 to -0.117), abstract -0.819 (95% CI -1.491 to -0.147). E: Exubera®. C: control. NG.: not given. CI: Confidence interval.							

4.3.4 Secondary Complications, Mortality, Admissions to Hospital

None of the included studies was planned in design or duration to investigate the benefits and harms of inhaled Exubera® in comparison with subcutaneous insulin administration, with respect to the prevention of microvascular and macrovascular secondary complications, including cardiac, cerebral and other vascular disease, loss of sight, terminal renal failure requiring dialysis and amputations (both minor and major).

It therefore remains unclear whether Exubera® is favourable, unfavourable or neutral in comparison with subcutaneously administered insulin in this respect. The same applies to overall mortality. Deaths only occurred in study 108 (Hollander 2004) (see too Table 14). None of the studies was planned or suitable to investigate the effect of treatment with Exubera® on the total mortality, in comparison with subcutaneously administered insulin. The mortality rates observed in the studies do not permit the conclusion that these two treatments are equivalent, or that either is superior.

None of the publications contained information on the necessity of admission to hospital for reasons connected with diabetes, or for any other reason. In this respect too, the benefit of Exubera® is unclear.

4.3.5 Hyperglycaemia

There was no information in the publications on hyperosmolar or ketoacidotic coma.

4.4 Subgroup Analyses

4.4.1 Gender

No gender-specific statements can be made on the basis of the available data. In the only relevant study on type 2 diabetes mellitus, more men than women were investigated (ratio about 2:1), whereas the gender distribution was roughly balanced in the studies on type 1 diabetes. There was no evidence that the results reported for men and women have to be seen as different.

4.4.2 Age

No age-specific statements can be made on the basis of the available data. In all studies on type 1 diabetes mellitus, the mean age was between 29 and 38 years. The mean age in the

study on type 2 diabetes mellitus lay between 56 and 59 years. There were no studies which were deliberately performed in specific age groups (e.g. geriatric patients).

Exubera® has not been approved for children and adolescents. Children and adolescents from age 12 were included in the Skyler (2005) and Quattrin (2004) studies. No separate subgroup evaluation is available. It is unclear whether the patients aged under 18 years had a relevant influence on the results of these studies.

4.4.3 Concomitant Diseases, Presence of Late Complications

The available data do not permit specific statements on patients with or without a disease or diseases which accompany type 1 or type 2 diabetes mellitus. The available data also do not permit specific statements on patients with or without late complications from diabetes or patients whose diabetes has been diagnosed for longer or shorter periods. No statement of any sort can be made about patients with (severe) lung diseases, as these patients were specifically excluded.

“Injection phobia” was not a specific inclusion criterion in any of the studies. It follows, that the available information does not permit any statement as to whether there is any relevant benefit from treatment with Exubera® for this specific group of patients.

4.5 Aspects of Implementation in Normal Daily Health Care

Training Programmes

Implementation of the novel Exubera® inhalation system requires not only structured training on all aspects of intensified and conventional insulin therapy (which are still necessary), but also additional structured training measures for patients, their relatives and medical personnel (doctors and assistants) on the use of the new insulin inhalation device. These requirements are also a component of the registration modalities in Europe [39]. It is unclear whether these requirements were fulfilled in the relevant clinical studies with Exubera®. In spite of repeated enquiries, Pfizer did not disclose the training material. According to the EMEA requirements, training programmes should contain the following points [39]:

1. The necessity of a uniform standard inhalation procedure with the goal of optimal and steady release of substance.
2. The careful use of the insulin inhalation device.
3. Hypoglycaemia.
4. The lack of equivalence of the 1 mg and 3 mg doses.
5. The size of the titration steps and the corresponding precautions.
6. The changes in lung function and the necessity of monitoring lung function.

7. The influence of smoking on pharmacokinetics.
8. Rare pulmonary events.
9. Increases in insulin antibodies.
10. Recommendations for specific patient groups: current lung diseases - such as asthma and COPD, heart failure, pregnancy, children and adolescents.

The Patient Handbook submitted by Pfizer (dated: November 2005) does not completely fulfil these requirements. For example, there is no comment that insulin antibodies are often formed during Exubera® treatment. Moreover, there is no titration table to support the independent dose titration. It can be assumed that it will often be necessary to refer to tables of this sort during dose titration, as the 1 mg and 3 mg blisters are not equivalent. There is also no reference to rare pulmonary events. Finally, it is unclear from the available information whether, in the event of introduction to the market, training programmes will be available for patients and medical personnel, to support the adequate daily use of this device. Just like subcutaneous insulin therapy, inhaled insulin therapy is intended to be an integral component of the management of type 1 and type 2 diabetes. It follows that these questions must be answered by adequate studies, planned to evaluate these complex interventions in the context of primary medical care. Studies of this sort were not identified by our literature research.

Specific Patient Groups

For the introduction of the novel Exubera® inhalation system, it appears to be essential to examine the available data critically, in particular, for the risk groups of patients with lung diseases and smokers. Moreover, the available relevant studies generally excluded these patients. It follows, for example, that it is currently impossible to assess the effects of long-term therapy with inhaled insulin on patients with bronchial asthma, COPD or a hypersensitive bronchial system. There are currently no available data on long-term results on possible adverse effects (particularly pulmonary effects) from randomised controlled studies. In addition, short-term negative effects in these patient groups cannot be excluded. For example, the use of rapid-acting β -sympathomimetics may influence the pharmacokinetics of Exubera® [11]. The possibility cannot be excluded that using Exubera® could be a major risk for smokers, as smoking has a marked effect on the pharmacokinetics, with the danger of severe hypoglycaemia [11].

Use in children and adolescents has generally not been approved.

5. Discussion

This systematic evaluation of the relevant studies performed with Exubera® demonstrates that the available data, taken together, are inadequate.

There is not a single study on type 2 diabetes in which Exubera® was compared with subcutaneous insulin, with identical therapeutic regimes. Only a single study compared Exubera® with subcutaneous insulin at all and even in this case the treatment regimes were different (intensified vs. conventional insulin therapy). Nevertheless, more serious episodes of hypoglycaemia were recorded under Exubera® than under subcutaneous insulin, even though the reductions in blood sugar were comparable. It cannot be inferred from this study that Exubera® is an equivalent and - importantly - safe alternative to subcutaneous insulin for patients with type 2 diabetes, if identical therapy regimes are used. On the one hand, the increase in weight over 24 weeks was less with Exubera®, with a mean value of 1.3 kg. On the other hand, cough and formation of insulin antibodies were frequent adverse events with Exubera®. Moreover, the published data do not demonstrate the long-term pulmonary safety of Exubera®. In contrast, the published results of instrumental measurements are somewhat inconsistent and indicate that there may be a potential pulmonary risk. This is also reflected in the Summary of Product Characteristics provided by the EMEA and the requirements for training programmes discussed above [13].

There were only two studies on patients with type 1 diabetes mellitus in which Exubera® was compared with subcutaneous insulin, using intensified insulin therapy. The larger of these included almost 40% children and adolescents - for whom Exubera® has not been approved - without the results for adults being separately reported. It remains unclear whether the Exubera® results from this study for adults would be more or less favourable. Currently published studies show that severe hypoglycaemia occurs statistically significantly more often with Exubera® than with subcutaneous insulin, using intensified insulin therapy and with comparable reductions in blood sugar. On the basis of currently published studies on the treatment of type 1 diabetes mellitus using intensified insulin therapy, there is no evidence that Exubera® provides any additional benefit in comparison with subcutaneous human insulin - although there is evidence for more potential damage. Moreover, the above comments on the questionable long-term pulmonary safety apply to type 1 diabetes too [13]. The approval text for type 1 diabetes particularly emphasises the importance of carefully considering benefits and risks [13]. Bearing this in mind, the published data do not permit the identification of any group of type 1 diabetes patients for whom this consideration would yield a favourable result. In this context, the only plausible reason for treatment with Exubera® would be if the patient totally rejects subcutaneous injections, thus putting his life at risk.

Practically all relevant questions on essential aspects of the implementation in normal daily health care are still open. Thus it is unclear how intensively the patients in the studies were trained, either in general aspects of insulin treatment, or in specific aspects of using the inhalation device. Questions about this were not properly answered by Pfizer. The handbooks provided cannot fully correspond to the materials used in the studies, as these also employed oral instruction and audiovisual material. Moreover, they do not fully cover the training content suggested by the EMEA. It is unclear whether the present version of the handbook would be used after the introduction of Exubera®. It is also unclear that, at the time of market launch, there will be a training and treatment programme, evaluated to guarantee adequate handling of the device, including insulin dosage etc., so that safe use in the target population can be assumed. If this is not the case, this can be regarded as an additional and essential uncertainty for the safe use of Exubera®.

There has been no conclusive answer to the question as to whether or to what extent syringes for self-filling or pen systems were used in the studies. There are however several indications that pen systems were used relatively rarely, at least in the studies performed in North America. The transferability of the results of these studies thus appears to be generally questionable. In this context, Pfizer's statement that "It was not possible in these studies to distinguish between patient preference (PRO) for inhaled insulin on the one hand and insulin administered by pen or syringe on the other. This was not an objective either," appears to be relevant. With this, Pfizer contradicts the views of many specialists on Exubera® as expressed in reviews (see too Appendix A.3). However, this statement appears plausible, as judged by the general design of the studies - with their emphasis on efficacy parameters, lack of blinding, high frequency of self-measurement of blood sugar in the subcutaneous insulin patients (often without therapeutic justification), etc..

Before Exubera® is widely prescribed in Germany, it must be demanded that an adequate randomised intervention study should be performed, which should address the open questions on the implementation in normal daily health care. This could be guaranteed by a "simple real world RCT" with random allocation to two treatment groups (Exubera® vs. subcutaneous insulin therapy), under the conditions in Germany, including the performance of evaluated training programmes, the usual type of administration of subcutaneous insulin, etc.. A randomised "real world" study - primarily designed to answer health economic questions - is now being planned and can in principle serve as an example [40].

It should finally be mentioned that the present Rapid Report is exclusively based on published information on Exubera®. Study reports of studies which have not yet been completely published were not requested from Pfizer and this was indeed not planned during writing. The documents provided to the public by the American registration agency (FDA) [15,16,41] raise many relevant questions about Exubera® and these can only be answered, if at all, by extensive study reports on the studies with Exubera® which have not yet been published. These include questions about pulmonary safety (e.g. results from study 1027), the clinical relevance of the formation of insulin antibodies, differences in the safety and efficacy

between adults and children or adolescents etc.. Essential aspects of the evaluation of the relevant studies might also change if the study reports are assessed. Thus, it is pointed out in the document “Initial clinical review for inclusion in advisory committee briefing” [15] that the number of drop-outs because of adverse events under Exubera® is presumably greater than published, as the author states that there were many misclassifications, particularly in favour of Exubera®. On the other hand, the “preliminary model” of the FDA questions the statistical significance of the severe hypoglycaemia in study 107. It is also pointed out in this document that the severe episodes of hypoglycaemia observed in these studies occurred most frequently in the early morning hours and that the blood sugar values were often clearly below the given target range. These data indicate that the risk of nocturnal hypoglycaemia may be raised under Exubera®, although they do not permit any firm conclusions. Finally, it is evident from the documents that, aside from the published per-protocol analyses, intention-to-treat analyses were planned and performed. It is currently unclear to what extent this additional and as yet unpublished information would modify the evaluation of the study results.

In summary, it is recommended that in the short-term additional evaluation of Exubera® should be performed on the basis of unpublished data, in so far as Pfizer provides this information.

6. Reference list

1. World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications. Geneva: WHO/NCD/NCS/99.2; 1999.
2. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329(14): 977-986.
3. Dreyer M, Berger M, Kiess W, Lüdecke HJ, Redaelli M, Schatz H, et al. Evidenzbasierte Leitlinie der Deutschen Diabetes Gesellschaft - Therapie des Diabetes mellitus Typ 1. Scherbaum WA, Landgraf R., ed.. http://www.deutsche-diabetes-gesellschaft.de/redaktion/mitteilungen/leitlinien/therapie_typ1.pdf; Zugriff am 15.3.2006.
4. Mühlhauser I, Berger M. Patient education - evaluation of a complex intervention. Diabetologia 2002; 45(12): 1723-1733.
5. Sämann A, Mühlhauser I, Bender R, Kloos C, Müller UA. Glycaemic control and severe hypoglycaemia following training in flexible, intensive insulin therapy to enable dietary freedom in people with type 1 diabetes: a prospective implementation study. Diabetologia 2005; 48(10): 1965-1970.
6. Nationales Programm für Versorgungs-Leitlinien bei der Bundesärztekammer. Nationale Versorgungsleitlinie Diabetes mellitus Typ 2. 1. Auflage, 2002. Korrigierte Version vom 01.04.2003. <http://www.versorgungsleitlinien.de/themen/pdf/nvldiabetes.pdf>; Zugriff am 15.3.2006.
7. Jörgens V, Grüßer M. Behandlungs- und Schulungsprogramm für Typ-2-Diabetiker, die Insulin spritzen. Curriculum. Deutscher Ärzteverlag, Köln. 2004.
8. Hunt LM, Valenzuela MA, Pugh JA. NIDDM patients' fears and hopes about insulin therapy. The basis of patient reluctance. Diabetes Care 1997; 20(3): 292-298.
9. Scholze A. Angst vor Insulintherapie bei Typ-2-Diabetikern. Dissertation. Erlangen: Otto-Friedrich-Universität Bamberg; 2005.
10. Rau JL. Determinants of patient adherence to an aerosol regimen. Respir Care 2005; 50(10): 1346-1356.
11. EMEA. Summary of product characteristics for "Exubera". 2006. http://pharmacos.eudra.org/F2/register/2006/2006012410856/annexes_exubera_aut_special_mah_en.pdf; Zugriff am 14.2.2006.
12. Quattrin T. Inhaled insulin: recent advances in the therapy of Type 1 and 2 diabetes. Expert Opin Pharmacother 2004; 5(12): 2597-2604.

13. EMEA. Zusammenfassung der Merkmale des Arzneimittels "Exubera". 2006. http://pharmacos.eudra.org/F2/register/2006/2006012410856/annexes_exubera_aut_special_mah_de.pdf; Zugriff am 14.2.2006.
14. Pfizer. Exubera®: Advisory Committee Briefing Document. 8. September 2005. http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4169B1_01_01-Pfizer-Exubera.pdf; Zugriff am 15.1.2006.
15. Mahoney KM. Initial clinical review for inclusion in advisory committee briefing content. NDA 21868 N 000. Exubera® (inhaled human insulin). Food and Drug Administration (FDA). http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4169B1_02_07-FDA-Clin-Efficacy.pdf; Zugriff am 2.2.2006
16. Mele J. Statistical review and evaluation – clinical studies. NDA 21-868. Exubera® (insulin [rDNA origin] powder for oral inhalation). Food and Drug Administration (FDA). http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4169B1_02_05-FDA-Clin-Stats-Efficacy.pdf; Zugriff am 2.2.2006.
17. Hollander PA, Blonde L, Rowe R, Mehta AE, Milburn JL, Hershon KS, et al. Efficacy and safety of inhaled insulin (exubera) compared with subcutaneous insulin therapy in patients with type 2 diabetes: results of a 6-month, randomized, comparative trial. Diabetes Care 2004; 27(10): 2356-2362.
18. Belanger, A. for the Exubera Phase III Study Group. Efficacy and safety of inhaled insulin (Exubera) compared to subcutaneous insulin therapy in patients with type 2 diabetes: results of a 6-month, randomized, comparative trial: P-808. Diabetologia 2002; 45(Suppl 2): A260-A261.
19. Testa MA, Turner RR, Hayes JF, Simonson DC. Patient satisfaction with insulin therapy in type 2 diabetes: a randomized trial of injectable vs. inhaled insulin: P544. Diabetes 2002; 51(Suppl 2): A135.
20. Skyler JS, Weinstock RS, Raskin P, Yale JF, Barrett E, Gerich JE, et al. Use of inhaled insulin in a basal/bolus insulin regimen in type 1 diabetic subjects: a 6-month, randomized, comparative trial. Diabetes Care 2005; 28(7): 1630-1635.
21. Skyler JS for the Exubera Phase III Study Group. Efficacy and safety of inhaled insulin (Exubera) compared to subcutaneous insulin therapy in an intensive insulin regimen in patients with type 1 diabetes: results of a 6-month, randomized, comparative trial: P540. Diabetes 2002; 51(Suppl 2): A134.
22. Skyler, J.S. for the Exubera Phase III Study Group. Efficacy and safety of inhaled insulin (Exubera) compared to subcutaneous insulin therapy in an intensive insulin regimen in patients with type 1 diabetes: results of a 6-month, randomized, comparative trial: P45. Diabetologia 2002; 45(Suppl 2): A17.
23. Heise T, Bott S, Tusek C, Stephan J-, Kawabata T, Finco-Kent D, et al. The effect of insulin antibodies on the metabolic action of inhaled and subcutaneous insulin: A

- prospective randomized pharmacodynamic study. *Diabetes Care* 2005; 28(9): 2161-2169.
24. Heise T, Tusek C, Stephan JA, Krasner A, Landschulz WH, Sha S, et al. Insulin antibodies with inhaled insulin (Exubera): no evidence for impact on postprandial glucose control: P463. *Diabetes* 2004; 53(Suppl 2): A109.
 25. Quattrin T, Belanger A, Bohannon NJ, Schwartz SL, Exubera Phase III Study Group. Efficacy and safety of inhaled insulin (Exubera) compared with subcutaneous insulin therapy in patients with type 1 diabetes: results of a 6-month, randomized, comparative trial. *Diabetes Care* 2004; 27(11): 2622-2627.
 26. Testa MA. Patient satisfaction and quality of life in type 1 diabetes: a randomized trial of injectable vs. inhaled insulin. *Diabetes* 2001; 50(Suppl 2): A45.
 27. Quattrin T. Efficacy and safety of inhaled insulin (Exubera) compared to conventional subcutaneous insulin therapy in patients with Type 1 diabetes: results of a 6-month, randomised, comparative trial: P809. *Diabetologia* 2002; 45(Suppl 2): A261.
 28. Turner RR, Testa MA. Using structural equation models (SEM) to interpret treatment satisfaction and quality of life data: the case for inhaled insulin. *Qual Life Res* 2001; 10: 222.
 29. Su M, Testa MA, Turner RR, Simonson DC. The relationship between regimen burden and psychological well being in persons with type 1 diabetes: inhaled vs. injectable insulin: P1843. *Diabetes* 2002; 51(Suppl 2): A448-A449.
 30. Dumas R, England RD, Riese, R.J., Teeter, J.G. for the Exubera Phase 3 Study Group. Exubera is well tolerated and achieves tight glycemic control in patients with type 1 diabetes: P355-OR. *Diabetes* 2005; 54(Suppl 1): A87.
 31. Dumas R, Krasner AS, England RD, Riese RJ, Teeter, J.G. for the Exubera Phase III Study Group. Immunologic response to exubera in patients with Type 1 Diabetes is not associated with functional evidence of airway sensitization: P437. *Diabetes* 2005; 54(Suppl 1): A108.
 32. Krasner A, Teeter JG. Time-course of development of insulin antibodies does not correlate with changes in pulmonary function tests observed during inhaled insulin therapy. American Thoracic Society 2005 International Conference; May 20-25; San Diego, California 2005: B68.
 33. Norwood P, Dumas R, England D, Riese RJ, Teeter, J.G. on behalf of the Exubera Phase III Study Group. Inhaled insulin (Exubera) achieves tight glycemic control and is well tolerated in patients with type 1 diabetes: P-73. *Diabetologia* 2005; 48(Suppl 1): A30.
 34. Teeter JG. Chronically inhaled insulin treatment of patients with diabetes is not associated with functional evidence of airway sensitization. American Thoracic Society 2005 International Conference; May 20-25; San Diego, California 2005: B68.

35. Heise T, Bott S, Tusek C, Stephan J, Kawabata T, Finco-Kent D, et al. The effect of insulin antibodies on the metabolic action of inhaled and subcutaneous insulin: Response to Chantelau et al. *Diabetes Care* 2006; 29(2): 477-478.
36. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; 352(9131): 837-853.
37. National Prescribing Centre and Wessex Drug and Medicines Information Centre. Inhaled insulin (Exubera) for type 1 and type 2 diabetes. 2005. <http://www.ukmi.nhs.uk/NewMaterial/Secure/Inhaled%20Insulin.pdf>; Zugriff am 17.2.2006.
38. Mehta M, Vincze G, Lopez DA. Emerging technologies in diabetes care. *US Pharmacist* 2002; 27(11). <http://www.uspharmacist.com/index.asp?show=article&page=8:995.htm>; Zugriff am 20.2.2006.
39. EMEA. Bedingungen oder Einschränkungen hinsichtlich der sicheren und wirksamen Anwendung des Arzneimittels zur Umsetzung durch die Mitgliedsstaaten. http://pharmacos.eudra.org/F2/register/2006/2006012410857/annex_exubera_aut_spec_ial_ms_de.pdf; Zugriff am 14.2.2006.
40. Freemantle N, Blonde L, Bolinder B, et al. Real-world trials to answer real-world questions. *Pharmacoeconomics* 2005; 23(8): 747-754.
41. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research. Endocrinologic and Metabolic Drugs Advisory Committee. Volume I. Advisory Panel Meeting – Transcript. Thursday, September 8, 2005. Silver Spring, Maryland. <http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4169T1.pdf>; Zugriff am 1.2.2006.

Appendix A.1: Irrelevant Phase 3 / Phase 2 Studies

Tables A.1-1 and A.1-2 lists Phase 2 and Phase 3 studies with Exubera® which were performed with adult patients, but which did not fulfil the inclusion criteria for intervention and control. The citations on the publications on these studies are also listed, including congress abstracts.

Table A.1-1: Irrelevant Phase 3 Studies - Listing

Publication (Study Number)	Study Design	Diabetes Type	Treatment Groups	Outcome Parameter	Reason for Exclusion
Rosenstock 2005 (109)	RCT, parallel, open	Type 2, inadequate stabilisation with OAD	1. Exubera® monotherapy 2. Exubera® + OAD from pretreatment 3. OAD from pretreatment	Change in HbA _{1c}	Comparison not relevant (Exubera® versus OAD)
De Fronzo 2005 (110)	RCT, parallel, open	Type 2, inadequate stabilisation under diet and exercise	1. Exubera® monotherapy 2. OAD (Rosiglitazone)	Proportion of patients with HbA _{1c} < 8%	Comparison not relevant (Exubera® versus OAD); no “OAD failures”
No full text publication (1001)	RCT, parallel, open	Type 2, inadequate stabilisation with sulfonylurea	1. Exubera® + OAD (sulfonyurea) 2. OAD (Metformin + sulfonylurea)	Change in HbA _{1c} / Tolerance	Comparison not relevant (Exubera® versus OAD)
No full text publication (1002)	RCT, parallel, open	Type 2, inadequate stabilisation with metformin	1. Exubera® + OAD (metformin) 2. OAD (glibenclamide + metformin)	Change in HbA _{1c} / tolerance	Comparison not relevant (Exubera® versus OAD)
HbA _{1c} = glycosylated haemoglobin. OAD = oral antidiabetics. RCT = randomised controlled trial					

Table A.1-2: Irrelevant Phase 2 Studies - Listing

Study (Study Number)	Study Design	Diabetes Type	Treatment Groups	Outcome Parameter	Reason for Exclusion
Skyler 2001 (102)	RCT, parallel, open	Type 1	1. Exubera® + UL (intensified insulin therapy) 2. subcutaneous insulin from the previous treatment (variety of therapy regimes)	change in HbA _{1c}	old insulin formulation
Cefalu 2001 (103)	RCT, parallel, open	Type 2 under insulin therapy	1. Exubera® + UL (intensified insulin therapy) 2. subcutaneous insulin from the pretreatment (variety of therapy regimes)	Change in the HbA _{1c}	old insulin formulation
Weiss 2003 (104)	RCT, parallel, open	Type 2, inadequate stabilisation under OAD	1. Exubera® + OAD from the pretreatment 2. OAD from the pretreatment (sulfonylurea and/or metformin)	reduction of HbA _{1c} > 1%	old insulin formulation; no insulin comparison
BMI: body mass index. HbA _{1c} : glycosylated haemoglobin A _{1c} . OAD: oral antidiabetics. RCT: randomised controlled trial. UL: Ultralente.					

Irrelevant Phase 3-Studies:

Study 109, Rosenstock 2005

Full text

Rosenstock J, Zinman B, Murphy LJ, Clement SC, Moore P, Bowering CK, et al. Inhaled insulin improves glycemic control when substituted for or added to oral combination therapy in type 2 diabetes: a randomized, controlled trial. *Ann Intern Med* 2005; 143(8): 549-558.

Abstract

Cefalu, W.T. for the Exubera Phase 3 Study Group. Mealtime rapid-acting inhaled insulin (Exubera) improves glycaemic control in patients with type 2 diabetes failing combination oral agents: a 3 month, randomized, comparative trial: P807. *Diabetologia* 2002; 45(Suppl 2): A260.

Rosenstock, J. for the Exubera Phase 3 Study Group. Mealtime rapid-acting inhaled insulin (Exubera) improves glycemic control in patients with type 2 diabetes failing combination oral agents: a 3-month, randomized, comparative trial: P535. *Diabetes* 2002; 51(Suppl 2): A132-A133.

Simonson DC. Treatment satisfaction and preferences in type 2 diabetes: a randomized controlled trial of oral agents versus inhaled insulin. *Diabetes* 2001; 50 (Suppl 2): A131.

Study 110, De Fronzo 2005

Full text

DeFronzo RA, Bergenstal RM, Cefalu WT, Pullman J, Lerman S, Bode BW, et al. Efficacy of inhaled insulin in patients with type 2 diabetes not controlled with diet and exercise - A 12-week, randomized, comparative trial. *Diabetes Care* 2005; 28(N8): 1922-1928.

Abstract

Bergenstal, R.M. for the Exubera Phase 3 Study Group. Efficacy and safety of inhaled insulin (Exubera) compared with rosiglitazone in type 2 diabetes patients not optimally controlled on diet and exercise; results of a 3-month, randomized, comparative trial: P801. *Diabetologia* 2003; 46(Suppl 2).

DeFronzo, R.A. for the Exubera Phase 3 Study Group. Efficacy and safety of inhaled insulin (Exubera) compared with rosiglitazone in type 2 diabetes patients not optimally controlled on

diet and exercise: results of a 3-month, randomized, comparative trial: P162-OR. Diabetes 2003; 52(Suppl 1): A38.

Study 1001 (no full text publication)

Abstract

Testa MA, Turner RR, Hayes JF, Scranton RE, Simoson DC. Satisfaction and quality of life with sulfonylurea plus either Metformin or Exubera: an international randomized phase 3 trial: P487. Diabetes 2004; 53(Suppl 2): A115.

Testa MA, Turner RR, Hayes JF, Scranton RE, Simoson DC. An international trial of sulfonylurea plus either Metformin or Exubera: impact on quality of life and treatment satisfaction: P9. Diabetologia 2004; 47(Suppl 1).

1002 (no full text publication)

Abstract

Simonson DC, Turner RR, Hayes JF, Scranton RE, Testa MA. Improving quality of life in type 2 diabetes when Exubera is added after failure on Metformin: a multicenter, international trial: P865. Diabetologia 2004; 47(Suppl 1).

Testa MA, Hayes JF, Turner RR, Simoson DC. Quality of life improvements in type 2 diabetes when Exubera is added after failure on Metformin monotherapy: an international randomized phase 3 trial: P1831. Diabetes 2004; 53(Suppl 2): A437.

Irrelevant Phase 2 Studies:

Study 102, Skyler 2001

Full text

Gerber RA, Cappelleri JC, Kourides IA, Gelfand RA. Treatment Satisfaction with Inhaled Insulin in patients with Type 1 Diabetes. A randomized controlled trial. Diabetes Care 2001;24(9):1556-1559.

Skyler JS, Cefalu WT, Kourides IA, Landschulz WH, Balagtas CC, Cheng SL, et al. Efficacy of inhaled human insulin in type 1 diabetes mellitus: a randomised proof-of-concept study. Lancet 2001; 357(9253): 331-335.

Additional publications

Gale EAM. Two cheers for inhaled insulin. Lancet 2001; 357(9253): 324-325.

Nagaoka T, Miyakoshi H. Inhaled insulin in type 1 diabetes. Lancet 2001; 357(9272): 1979.

Study 103, Cefalu 2001

Full text

Cappelleri JC, Cefalu WT, Rosenstock J, Kourides IA, Gerber RA. Treatment Satisfaction in Type 2 Diabetes: A Comparison Between an INhaled Insulin Regimen and a Subcutaneous Insulin Regimen. Clinical Therapeutics 2002;24(4):552-564. Cefalu WT, Skyler JS, Kourides IA, Landschulz WH, Balagtas CC, Cheng S, et al. Inhaled human insulin treatment in patients with type 2 diabetes mellitus. Ann Intern Med 2001;134(3): 203-207.

Cefalu WT, Skyler JS, Kourides IA, Landschulz WH, Balagtas CC, Cheng S, et al. Inhaled human insulin treatment in patients with type 2 diabetes mellitus. Ann Intern Med 2001; 134(3): 203-207.

Additional publications

Cefalu WT. Inhaled insulin: a proof-of-concept study. Ann Intern Med 2001;134(9 Pt 1): 795.

Nathan DM. Inhaled Insulin for Type 2 Diabetes: solution or Distraction? Ann Intern Med 2001; 134(3): 242-244.

Study 104, Weiss 2003

Full text

Weiss SR, Cheng SL, Kourides IA, Gelfand RA, Landschulz WH, Inhaled Insulin Phase 2 Study Group. Inhaled insulin provides improved glycemic control in patients with type 2 diabetes mellitus inadequately controlled with oral agents: a randomized controlled trial. Arch Intern Med 2003; 163(19): 2277-2282.

Overlapping studies 102 and 103:

Full text

Rosenstock J, Cappelleri JC, Bolinder B, Gerber RA. Patient satisfaction and glycemic control after 1 year with inhaled insulin (Exubera) in patients with type 1 or type 2 diabetes. Diabetes Care 2004 27(6): 1318-1323.

Abstract

Gerber RA et al. Balancing compliance, patient satisfaction and improved glycaemic control in patients with type 1 and type 2 diabetes: long-term studies with inhaled insulin (Exubera): P751. Diabetologia 2002; 45(Suppl 2):A240.

Appendix A.2: Irrelevant Publications Viewed in Full Text

Not Exubera

1. Elliott RB, Edgar BW, Pilcher CC, Quested C, McMaster J. Parenteral absorption of insulin from the lung in diabetic children. *Aust Paediatr J* 1987; 23(5): 293-297.
2. Laube BL, Georgopoulos A, Adams GK, III. Preliminary study of the efficacy of insulin aerosol delivered by oral inhalation in diabetic patients. *JAMA* 1993; 269(16): 2106-2109.
3. Wigley FW, Londono JH, Wood SH, Shipp JC, Waldman RH. Insulin across respiratory mucosae by aerosol delivery. *Diabetes* 1971; 20(8): 552-556.
4. Laube BL, Benedict GW, Dobs AS. Time to peak insulin level, relative bioavailability, and effect of site of deposition of nebulized insulin in patients with noninsulin-dependent diabetes mellitus. *J Aerosol Med* 1998; 11(3): 153-173.
5. Himmelmann A, Jendle J, Mellen A, Petersen AH, Dahl UL, Wollmer P. The impact of smoking on inhaled insulin. *Diabetes Care* 2003; 26(3): 677-682.
6. Raman PG, Prasad RS. Preliminary study of aerosol delivered insulin by oral inhalation in NIDDM. *J Assoc Physicians India* 2000; 48(2): 264-265.
7. Inoue K, Yoshioka K. Pulmonary administration of insulin as an aerosol. *Chest* 1999; 116(2): 581-582.
8. Mecikalski M. Insulin by inhalation? *Chest* 1999; 116(2): 581.

Not Diabetes Mellitus

1. Heinemann L, Traut T, Heise T. Time-action profile of inhaled insulin. *Diabet Med* 1997; 14(1): 63-72.
2. Heise T, Rave K, Bott S, Sha S, Willawize SA, Carroll RS, et al. Time action profile of an inhaled insulin preparation in comparison to insulin lispro and regular insulin (P39-OR). *Diabetes* 2000; 49(Suppl 1): A10.
3. Wise SD et al. Smoking increases the bioavailability of inhaled insulin but relative insulin resistance ameliorates differences in action: P12. *Diabetologia* 2001; 44(Suppl 1): A5.
4. Sha S, Becker RH, Willawize SA, Schumacher DA, Lee JD, Carroll RS, et al. The effect of smoking cessation on the absorption of inhaled insulin (Exubera): P538. *Diabetes* 2002; 51(Suppl 2): A133.
5. Becker RHA, Sha S, Frick AD, Piechatzek R. The effect of smoking cessation and subsequent resumption on absorption of inhaled insulin (Exubera): P160-OR. *Diabetes* 2003; 52(Suppl 1).
6. Becker RHA, Sha S, Frick AD, Piechatzek R. The effect of smoking cessation and subsequent resumption on absorption of inhaled insulin (Exubera): P803. *Diabetologia* 2003; 46(Suppl 2).

7. Heinemann L, Klappoth W, Rave K, Hompesch B, Linkeschowa R, Heise T. Intra-individual variability of the metabolic effect of inhaled insulin together with an absorption enhancer. *Diabetes Care* 2000; 23(9): 1343-1347.

Not RCT

1. Klonoff DC. Inhaled insulin. *Diabetes Technol Ther* 1999; 1(3): 307-313.
2. Heinemann L, Pflutzner A, Heise T. Alternative routes of administration as an approach to improve insulin therapy: update on dermal, oral, nasal and pulmonary insulin delivery. *Curr Pharm Des* 2001; 7(14): 1327-1351.
3. Bindra S, Rosenstock J, Cefalu WT. Inhaled insulin: a novel route for insulin delivery. *Expert Opin Investig Drugs* 2002; 11(5): 687-691.
4. Patton JS. Deep-lung delivery of therapeutic proteins. *Chemtech* 1997; 27: 34-38.
5. Freemantle N, Blonde L, Bolinder B, Hompesch M, Duhot D, Eggertsen, R. et al. Inhaled Insulin (Exubera) leads to a greater potential acceptance of insulin therapy in patients with uncontrolled type 2 diabetes: P1950-PO. *Diabetes* 2004; 53(Suppl 2).
6. Cappelleri JC, Gerber RA, Kourides IA, Gelfand RA. Development and factor analysis of a questionnaire to measure patient satisfaction with injected and inhaled insulin for type 1 diabetes. *Diabetes Care* 2000; 23(12): 1799-1803.
7. Bilous R. Overall satisfaction increased more with inhaled insulin than with subcutaneous insulin in type 1 diabetes. *ACP J Club* 2002; 136(3): 101.
8. Freemantle N, Blonde L, Duhot D, Hompesch M, Eggertsen R, Hobbs FDR, et al. Availability of inhaled insulin promotes greater perceived acceptance of insulin therapy in patients with type 2 diabetes. *Diabetes Care* 2005; 28(2): 427-428.
9. Göke B. Vorstellung der Reale-Welt-Studien für inhalatives Insulin [Inhalative insulin in the real world]. *Dtsch Med Wochenschr* 2005; 130(Suppl 2): S91-S94.
10. Hollis S, Mansell P. Inhaled human insulin. *Diabetic Med* 2001; 18(Suppl 4): 8-10.
11. Mansell P. Inhaled human insulin. *Diabet Med* 2001; 18(Suppl 4): 8-10.
12. Sadri H, Mackeigan LD, Leiter LA, Einarson TR. Willingness to pay for inhaled insulin: a contingent valuation approach. *Pharmacoeconomics* 2005; 23(12): 1215-1227.
13. Zambanini A, Newson RB, Maisey M, Feher MD. Injection related anxiety in insulin-treated diabetes. *Diabetes Res Clin Pract* 1999; 46(3): 239-246.
14. Hsia CC, Raskin P. The diabetic lung: relevance of alveolar microangiopathy for the use of inhaled insulin. *Am J Med* 2005; 118(3): 205-211.
15. Summers KH, Szeinbach SL, Lenox SM. Preference for insulin delivery systems among current insulin users and nonusers. *Clin Ther* 2004; 26(9): 1498-1505.

Extension Studies

1. Barnett, A.H. for the Exubera Study Group. Efficacy and one-year pulmonary safety of inhaled insulin (Exubera) as adjunctive therapy with metformin or glibenclamide in type 2 diabetes patients poorly controlled on oral agent monotherapy: P454. *Diabetes* 2004; 53(Suppl 2): A107.

2. Skyler, J.S. for the Exubera Phase 2 Study Group. Sustained long-term efficacy and safety of inhaled insulin during 4 years continuous therapy: P486. Diabetes 2004; 53(Suppl 2): A115.
3. Fineberg SE, Schatz D, Krasner A. Results of insulin antibody monitoring during phase 2 and phase 3 clinical studies of inhaled insulin (Exubera) in patients with type 1 or type 2 diabetes: P46. Diabetologia 2002; 45(Suppl 2): A17.
4. Cefalu WT, Sercarevic-Pehar, M. for the Exubera Phase 3 Study Group. Long-term use of Exubera in Type 2 Diabetes: observations on glycemic control, pulmonary function and antibody formation: P356OR. Diabetes 2005; 54(Suppl 1): A88.
5. Teeter JG, the E, Pfizer-Global-Research-and-Development-GCU. One-year pulmonary safety and efficacy of inhaled insulin as adjunctive therapy in type 2 diabetes patients poorly controlled on oral agent monotherapy: P3773. Eur Respir J 2004; 24(Suppl 48): 618.
6. Cefalu WT. Sustained long-term efficacy and pulmonary safety of inhaled dry-powder insulin. Am J Respir Crit Care Med 2001; 163: A163.
7. Cefalu WT. Sustained efficacy and pulmonary safety of inhaled insulin during 2 years of outpatient therapy. Diabetologia 2000; 43 Suppl 1: A47.
8. Gerber RA. Improved patient satisfaction with inhaled insulin in subjects with type 1 diabetes mellitus after one year: Results from a multicenter extension trial. Diabetes 2000; 49(Suppl 1): A436.
9. Dreyer M. Efficacy and two-year pulmonary safety of inhaled insulin as adjunctive therapy with metformin or glibenclamide in Type 2 diabetes patients poorly controlled with oral monotherapy. Diabetologia 2004; 47(Suppl. 1): A44-A45.

Pooled Analyses

1. Fineberg SE, Kawabata T, Finco-Kent D, Liu C, Krasner A. Antibody response to inhaled insulin in patients with type 1 or type 2 diabetes. An analysis of initial phase 2 and III inhaled insulin (Exubera) trials and a two-year extension trial. J Clin Endocrinol Metab 2005; 90(6): 3287-3294.
2. Bergenstal RM. Achieving target HbA1C in studies with inhaled insulin in type 2 diabetes. Diabetologia 2004; 47(Suppl. 1): A312.

Study Duration < 12 Weeks

1. Gelfand RA, Schwartz SL, Horton M, Law CG, Pun EF. Pharmacological reproducibility of inhaled human insulin dosed pre-meal in patients with type 2 diabetes mellitus: P773. Diabetes 2002; 51(Suppl 2): A202.
2. Henry R, Mudaliar S, Fryburg DA, Becker RHA, Willavize SA, Fisher JM, et al. Within-subject variability of inhaled insulin (Exubera) versus subcutaneous regular insulin in elderly obese patients with type 2 diabetes mellitus: P448. Diabetes 2003; 52(Suppl 1): A105.
3. Mudaliar S, Henry RR, Fryburg DA, Becker RHA, Willavize SA, Fisher JM, et al. Within-subject variability of inhaled insulin (Exubera(R)) versus subcutaneous regular insulin in elderly obese patients with type 2 diabetes mellitus. Diabetologia 2003; 46(Suppl 2).

Animal Studies

1. Hu P, Zhang D, Swenson L, Chakrabarti G, Abel ED, Litwin SE. Impaired cardiac insulin signaling leads to early cardiac failure in response to pressure overload hypertrophy: P1355. Diabetes 2003; 52(Suppl 1).
2. Edgerton DS, Cherrington AD, Neal DW, Scott M, Glass D, Bowen LE, et al. Inhalation of Insulin (Exubera) compared to matched intravenous infusion: hepatic glucose balance post intraportal glucose infusion in dogs: P459. Diabetes 2004; 53(Suppl 2).
3. Edgerton DS, Neal D, Scott M, Bowen LE, Wilson W, Hobbs CH. Inhalation of insulin (Exubera) augments the efficiency of muscle glucose uptake in vivo: P435. Diabetes 2005; 54(Suppl 1): A107.
4. Labiris R, Garofalo R, Kawabata T, Sadrzadeh N, Guenther T, Valliant J. Validation of radiolabeled insulin powder for Exubera studies: P433. Diabetes 2005; 54(Suppl 1): A107.

Untraceable

1. Hollander, P. for the Exubera Phase 3 Study Group. Efficacy and safety of inhaled insulin (Exubera) compared to subcutaneous insulin therapy in patients with type 2 diabetes: results of a 6-month, randomized, comparative trial: P34. Diabetes 2001; 50(Suppl 2).

Appendix A.3: Reviews, HTA Reports, Rapid Reports

1. Insulin inhalation--Pfizer/Nektar Therapeutics: HMR 4006, inhaled PEG-insulin--Nektar, PEGylated insulin--Nektar. *Drugs R D* 2004; 5(3): 166-170.
2. Agencia de Evaluación de Tecnologías Sanitarias de Andalucía (Gesundheitsministerium der Region Andalusien). Eficacia y seguridad de la insulina inhalada en el tratamiento de la diabetes mellitus [Wirksamkeit und Sicherheit von inhalativem Insulin bei der Behandlung des Diabetes mellitus] [online]. 2005.
http://www.juntadeandalucia.es/salud/contenidos/aetsa/pdf/2005_F5_insulina_inhalada_def.pdf; Accessed on 15.2.2006.
3. Barnett AH. Exubera inhaled insulin: A review. *Int J Clin Pract* 2004; 58(4): 394-401.
4. Belmin J, Valensi P. Novel drug delivery systems for insulin: clinical potential for use in the elderly. *Drugs Aging* 2003; 20(4): 303-312.
5. Brain JD. Unlocking the opportunity of tight glycaemic control. Inhaled insulin: safety. *Diabetes Obes Metab* 2005; 7(Suppl 1): S14-S18.
6. Cefalu WT. Concept, strategies, and feasibility of noninvasive insulin delivery. *Diabetes Care* 2004; 27(1): 239-246.
7. Cefalu WT. Evolving strategies for insulin delivery and therapy. *Drugs* 2004; 64(11): 1149-1161.
8. Cefalu WT. Novel routes of insulin delivery for patients with type 1 or type 2 diabetes. *Ann Med* 2001; 33(9): 579-586.
9. Cox SL. Exubera: Treatment of type 1 and type 2 diabetes. *Drugs Future* 2004; 29(12): 1206-1210.
10. DeVries JH. Mealtime inhaled insulin lowers fasting glucose: A look at possible explanations [1]. *Diabetologia* 2005; 48(12): 2682-2683.
11. Heine RJ. Unlocking the opportunity of tight glycaemic control. Promise ahead: the role of inhaled insulin in clinical practice. *Diabetes Obes Metab* 2005; 7 Suppl 1(Suppl 1): S19-S23.
12. Heinemann L. Alternative delivery routes: inhaled insulin. *Diabetes Nutr Metab* 2002; 15(6): 417-422.
13. Heinemann L, Heise T. Current status of the development of inhaled insulin. *British Journal of Diabetes & Vascular Disease* 2004; 4(5): 295-301.
14. Lin CR, Gokhale R, Trivedi JS, Ranada V. Recent strategies and methods for improving insulin delivery. *Drug Dev Res* 2004; 63(N4): 151-160.
15. Mandal TK. Inhaled insulin for diabetes mellitus. *Am J Health Syst Pharm* 2005; 62(N13): 1359-1364.
16. Matthews J, Rozenfeld V. Non-invasive insulin-delivery system: pulmonary inhaler. *P and T (USA)* 2001; 26(11): 581-583, 594.
17. McAuley L. Inhaled insulin for the treatment of diabetes mellitus. *Issues Emerg Health Technol* 2001(18): 1-4.

18. National Prescribing Centre and Wessex Drug and Medicines Information Centre. Inhaled insulin (Exubera) for type 1 and type 2 diabetes. 2005.
<http://www.ukmi.nhs.uk/NewMaterial/Secure/Inhaled%20Insulin.pdf>; Accessed on 17.2.2006.
19. Odegard PS, Capoccia KL. Inhaled insulin: Exubera. *Ann Pharmacother* 2005; 39(5): 843-853.
20. Owens DR, Zinman B, Bolli G. Alternative routes of insulin delivery. *Diabet Med* 2003; 20(11): 886-898.
21. Patel AA, White CM, Coleman CI. Exubera - An orally inhaled insulin. *Formulary* 2005; 40(N12): 429.
22. Patton JS. Unlocking the opportunity of tight glycaemic control. Innovative delivery of insulin via the lung. *Diabetes Obes Metab* 2005; 7(Suppl 1): S5-8.
23. Patton JS, Bukar J, Nagarajan S. Inhaled insulin. *Adv Drug Deliv Rev* 1999; 35(2-3): 235-247.
24. Patton JS, Bukar JG, Eldon MA. Clinical pharmacokinetics and pharmacodynamics of inhaled insulin. *Clin Pharmacokinet* 2004; 43(12): 781-801.
25. Quattrin T. Inhaled insulin: recent advances in the therapy of Type 1 and 2 diabetes. *Expert Opin Pharmacother* 2004; 5(12): 2597-2604.
26. Radermecker RP, Selam JL. [Inhaled insulin, new perspective for insulin therapy]. *Rev Med Liege* 2005; 60(5-6): 355-360.
27. Royle P, Waugh N, McAuley L, McIntyre L, Thomas S. Inhaled insulin in diabetes mellitus. *Cochrane Database Syst Rev* 2004(3): CD003890.
28. Scherbaum WA. Unlocking the opportunity of tight glycaemic control. Inhaled insulin: clinical efficacy. *Diabetes Obes Metab* 2005; 7(Suppl 1): S9-13.
29. Selam JL. Inhaled insulin for the treatment of diabetes: projects and devices. *Expert Opin Pharmacother* 2003; 4(8): 1373-1377.
30. Selam JL. [Inhaled insulin: clinical results in type 2 diabetic patients]. *Diabetes Metab* 2001; 27(5 Pt 3): 5S28-5S32.
31. Skyler JS. Pulmonary insulin update. *Diabetes Technol Ther* 2005; 7(5): 834-839.
32. Stoever JA, Palmer JP. Inhaled insulin and insulin antibodies: a new twist to an old debate. *Diabetes Technol Ther* 2002; 4(2): 157-161.
33. Teeter J, Becker R. The clinical relevance of inhaled insulin in the diabetic lung. *Am J Med* 2006; 119(2): 184-185.
34. Trubo R. Interest in Inhaled Insulin Grows. *JAMA* 2005; 294(10): 1195-1196.
35. Valente AX, Langer R, Stone HA, Edwards DA. Recent advances in the development of an inhaled insulin product. *BioDrugs* 2003; 17(1): 9-17.
36. White JR, Jr, Campbell RK. Inhaled insulin: an overview. *Clin Diabetes* 2001; 19(1): 13-16.
37. White S, Bennett DB, Cheu S, Conley PW, Guzek DB, Gray S, et al. EXUBERA(R): Pharmaceutical Development of a Novel Product for Pulmonary Delivery of Insulin. *Diabetes Technol Ther* 2005; 7(6): 896-906.

Appendix B: Search Strategies

In all the following data bank searches, the publication period was restricted to 1996-2006.

Medline (PubMed)

Search Step	Search Formulation
#23	#7 OR #9 OR #11 OR #12 OR #16 OR #17 OR #18 OR #21 OR #22
#22	inhal* insulin* AND diabet*
#21	powder* inhaler* AND insulin*
#18	powder* insulin* Limits: Humans
#17	insulin* [ti] AND powder* [ti] Limits: Humans
#16	pulmonar* insulin* AND diabet* Field: All Fields, Limits: Humans
#12	pulmonar* [ti] AND insulin* [ti]
#11	inhal* [ti] AND insulin* [ti]
#9	Exubera
#7	"Exubera"[Substance Name]

Embase, CINAHL (OVID)

Search Step	Search Formulation
1	exubera.af.
2	inhal\$ insulin\$.ec,hw,fs.
3	(inhal\$ and insulin\$).ti.
4	powder-inhaler.sh,ec,hw,fs. and insulin\$.mp. [mp=ti, hw, ab, it, sh, tn, ot, dm, mf]
5	(pulmonar\$ and insulin\$).ti.
6	(powder\$ and insulin\$).ti.
7	1 or 2 or 3 or 4 or 5 or 6
8	remove duplicates from 7

The Cochrane Library (Wiley)

Search Step	Search Formulation
#1	exubera in All Fields
#2	inhaled insulin* in All Fields
#3	inhal* AND insulin* in Record Title
#4	pulmonar* insulin* in All Fields
#5	pulmonar* AND insulin* in Record Title
#6	insulin* powder in All Fields
#7	insulin* AND powder* in Record Title
#8	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)

Adis Newsletters, BIOSIS, Embase Alert, Derwent Drug File, International Pharmaceutical Abstracts (IPA), ISTP/ISSHP + ISTPB, SciSearch, publishers' databanks from Karger, Kluwer, Springer, Thieme (DIMDI grips)

Search Step	Search Formulation
1	exubera