Rapid-acting insulin analogues for the treatment of diabetes mellitus type 2*

Final report

[Assignment No. A05-04]

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Topic: Evaluation of the beneficial and harmful effects of rapid-acting insulin analogues for the treatment of diabetes mellitus type 2

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External experts:

Univ. Doz. (University Lecturer) Dr. Andrea Siebenhofer-Kroitzsch, University Clinic Graz, Austria.

Dr. Karl Horvath, University Clinic Graz, Austria.

Dr. Klaus Jeitler, University Clinic Graz, Austria.

External peer reviewer:

Priv. Doz. (Private Lecturer) Dr. med. Bernd Richter, Cochrane Metabolic and Endocrine Disorders Review Group, Medical Facilities of the Heinrich-Heine University, Düsseldorf, Germany.

Contact:

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

Tel: 0221/35685-0
Fax: 0221/35685-1
Email: A05-04@iqwig.de

In this report, the term “diabetes” refers to diabetes mellitus.

For all documents accessed via the Internet, the respective date of access is quoted. If in future these documents are no longer available via the quoted URL address, they may be viewed at the Institute for Quality and Efficiency in Health Care.

List of abbreviations

Abbreviation	Definition
BMI	Body mass index
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CONSORT	Consolidated Standards of Reporting Trials
CSII	Continuous subcutaneous insulin infusion (subcutaneous therapy with an insulin pump)
DARE	Database of Abstracts of Reviews of Effects
DQOL	Diabetes Quality of Life Questionnaire
DTSQ (DTSQc, DTSQs)	Diabetes Treatment Satisfaction Questionnaire (DTSQc: change version; DTSQs: status version)
EMBASE	Excerpta Medica Database
EMEA	European Medicines Agency
FDA	(United States) Food and Drug Administration
GHb	Glycosylated haemoglobin
HbA_{1c}	Glycosylated haemoglobin A_{1c} subfraction
HTA	Health technology assessment
IGF-I	Insulin-like growth factor I
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	Intention-to-treat
Medline	Medical Literature Analysis and Retrieval System Online
NDA	New drug application
NICE	National Institute for Clinical Excellence
NPH	Neutral Protamin Hagedorn
OAD	Oral antidiabetics
PhRMA	Pharmaceutical Research and Manufacturers of America
QoL	Quality of life
RCT	Randomised controlled trial
SEM	Standard error of the mean
UL	Ultralente
WHO	World Health Organization

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1. Background

Insulin and insulin analogues

Insulin therapy is one of the pharmaceutical treatment options used to lower blood glucose levels in patients with diabetes mellitus type 2. Currently, the types of insulin mainly used are structurally unchanged human insulin and insulin analogues. Insulin analogues are insulin-like molecules that were developed based on the molecular structure of primary human insulin by modification of the amino acid sequence. The main aim of such a modification is an alteration of the pharmacokinetic properties of the insulin analogue compared with human insulin, which may result in a more rapid onset of action, a shorter or longer duration of action, and less variability of effective drug concentrations.

The specific property of rapid-acting insulin analogues is that the change in structure leads to a reduction in the self-association tendency of the insulin molecules. Consequently, their absorption after subcutaneous injection is faster, resulting in a more rapid onset of action with an initially increased blood glucose-lowering effect, subsequently lower postprandial blood glucose levels, and an overall shorter duration of action [1,2]. Potential advantages of rapid-acting insulin analogues may be hypothetically derived from their modified pharmacokinetic and pharmacodynamic properties; e.g. a reduction in hypoglycaemia rates and a more stable, i.e. a more constant lowering of blood glucose levels during the course of the day, accompanied by a potential increase in quality of life (QoL) and treatment satisfaction of patients.

Late complications of diabetes type 2

It is unclear whether and to what extent a more intensive or more constant lowering of blood glucose levels prevents serious cardio-, cerebro-, or other vascular events, or other diabetic late complications. Epidemiological studies have demonstrated an association between elevated blood glucose levels, including postprandial elevations, and the development of such complications [3]. However, this does not necessarily mean that the lowering of elevated postprandial blood glucose levels results in a reduced risk of diabetic late complications. In this regard, different intensive blood glucose-lowering strategies with different drugs, mainly targeted at lowering fasting blood glucose levels, but also inevitably lowering postprandial levels, have led to inconsistent results in the past. A reduction in risk for microvascular events has been shown [4]. With regard to macrovascular events, substantial differences in risk reductions between treatment groups have been demonstrated despite similar lowering of

blood glucose levels [5]; an increased numerical risk [6] and even a statistically significantly increased risk [5] for these events have also been reported.

Such inconsistent results for patient-relevant endpoints indicate substance-specific beneficial and harmful effects. A benefit with regard to these endpoints can therefore not be directly inferred from the extent of lowering blood glucose levels (including postprandial levels) alone, but needs to be assessed individually for each drug in respective studies.

Weighing of benefits and harms

In animal and in vitro experiments, an increased mitogenic potency, as well as differences in the insulin- and IGF-receptor binding affinity, have been described for some rapid- and longer-acting insulin analogues compared with regular human insulin (RHI). These properties differ between individual insulin analogues, and the respective relevance for the treatment of patients with diabetes mellitus is unclear [7-12]. For an informed weighing of benefits and harms, it is therefore also necessary to describe the respective long-term effects of treatment with insulin analogues compared with RHI.

2. Aim of the report

The aim of this evaluation is to compare the effects of long-term treatment with rapid-acting insulin analogues vs. short-acting RHI (and also compare the effects of different rapid-acting insulin analogues with each other) with regard to patient-relevant outcomes in patients with type 2 diabetes.

The term “rapid-acting insulin analogues” refers to all currently approved and available preparations of this type in Germany:

- Insulin aspart
- Insulin glulisine
- Insulin lispro

The term “short-acting insulin” refers to RHI; “longer-acting insulin” refers to intermediate-acting (e.g. Neutral Protamin Hagedorn [NPH]) and/or long-acting insulin (e.g. ultralente).

This evaluation was conducted on the basis of the comparison and weighing of desired and undesired effects of the respective drugs (weighing of benefits and harms).

3. Project procedures

The Federal Joint Committee commissioned the Institute for Quality and Efficiency in Health Care to evaluate the effects of rapid-acting insulin analogues in the treatment of diabetes mellitus type 2. This assignment became concrete on 2 February 2005 on the basis of a draft contract; the contract was confirmed on 22 February 2005.

External experts were involved in the project and participated in the production of the report plan, the literature search and evaluation, and in the production of the preliminary report. The report plan (version: 9 June 2005) was published on the Internet on 5 July 2005. The preliminary report (version: 25 July 2005) was published on 1 August 2005 and underwent an external peer review; any interested persons were allowed to make statements. The deadline for statements was 28 August 2005. As the preliminary report for Assignment No. A05-04 was the first publication of the Institute which was open to statements, substantial statements on this report were also considered even if they did not completely fulfil the requirements with regard to form and deadlines. All persons who had made substantial statements and disclosed any potential conflicts of interests (as specified in the Institute's methods) were invited to a scientific hearing on 8 September 2005. In the scientific hearing, the main aspects addressed in the written statements were discussed. This final report was subsequently produced.

4. Methods

The methods for the production of this report were predefined in the report plan dated 9 June 2005. Insofar as any amendments were added during the course of the production of the report, these are described in Section 4.5.

4.1 Criteria for studies included

The criteria which were a prerequisite for the inclusion of a study in this report (inclusion criteria) or led to an exclusion of the study from further evaluation (exclusion criteria) are listed below.

4.1.1 Population

Studies eligible for inclusion were those that had investigated patients with manifest diabetes mellitus type 2 (according to the diabetes definition in the study, e.g. following WHO criteria [13]).

4.1.2 Intervention and comparator treatment

Studies were included that investigated at least one of the three noted rapid-acting insulin analogues, either compared with another insulin of this type or with short-acting RHI. If a combination therapy of an insulin analogue with additional blood glucose-lowering treatment was administered (e.g. insulin aspart combined with NPH insulin), this additional treatment also had to be part of the comparator treatment, as well as approved and available in Germany. The term “blood glucose-lowering therapy” includes all treatment strategies that primarily aim to lower blood glucose levels (including oral antidiabetics [OAD]). Furthermore, studies on premixed formulations of rapid-acting insulin analogues or short-acting RHI combined with longer-acting insulins were only to be included if the respective proportion of components was identical between treatment groups (e.g. 30% rapid-acting insulin analogues or short-acting RHI, 70% longer-acting insulin in both groups).

4.1.3 Endpoints

The endpoints of the evaluation were parameters that enabled an assessment of the following patient-relevant outcomes:

- Reduction of total mortality;
- Reduction of cardiac morbidity and mortality;
- Reduction of cerebral morbidity and mortality;
- Reduction of vascular non-cardiac and non-cerebral morbidity and mortality;
- Reduction of the rate of blinding;
- Reduction of the rate of terminal renal insufficiencies requiring dialysis;
- Reduction of the rate of amputations (major and minor amputations);
- Reduction of the hospitalisation rate (any cause);
- Reduction of the rate of hyperglycaemic or ketoacidotic comas;
- Reduction of the rate of symptoms caused by chronic hyperglycaemia;
- Reduction of the rate of hypoglycaemic episodes, especially severe hypoglycaemic episodes;
- Reduction of the rate of other adverse drug effects;
- Preservation or improvement of disease-related QoL (including capacity to work and other activities of daily life), and treatment satisfaction.

Furthermore, HbA_{1c} levels were recorded as a measure of the long-term lowering of blood glucose levels in order to help interpret outcomes, in particular the occurrence of hypoglycaemic episodes.

4.1.4 Study types

Randomised controlled trials (RCTs) provide the most reliable results for the evaluation of the effects of a medical intervention as, insofar as they have been conducted with appropriate methods and in accordance with the respective research question, they are least prone to produce uncertainty of results.

An evaluation within the framework of RCTs is possible and practically feasible for all outcomes listed in Section 4.1.3 and all interventions listed in Section 4.1.2. Therefore only RCTs were included in this evaluation as relevant scientific literature.

4.1.5 Other study characteristics

This report evaluates the effects of long-term treatment with insulin analogues in comparison with each other and in comparison with RHI. In particular, studies lasting several years should be considered relevant with regard to vascular morbidity and mortality. With regard to the evaluation of the quality of therapy, shorter studies may also possibly be meaningful, as long as the effect on the lowering of blood glucose levels can be adequately evaluated over a period of several months, and can be compared with a possible effect on patient-relevant outcomes (e.g. hypoglycaemia rates). Therefore, only studies with a minimum study period of 24 weeks were included in this evaluation.

4.1.6 Overview of inclusion and exclusion criteria

Studies that fulfilled all of the inclusion criteria and none of the exclusion criteria listed below were included in the evaluation.

Inclusion criteria	
I1	Patients with manifest diabetes mellitus type 2 as defined in Section 4.1.1.
I2	Test intervention: Insulin aspart, insulin glulisine, or insulin lispro (also as premixed formulations consisting of rapid-acting insulin analogues combined with longer-acting insulins, as defined in Section 4.1.2).
I3	Comparator treatment: short-acting RHI or a different insulin analogue from the group of insulin analogues mentioned above (also as premixed formulations consisting of rapid-acting insulin analogues or short-acting RHI combined with longer-acting insulins, as defined in Section 4.1.2).
I4	Endpoints derived from the patient-relevant outcomes formulated in Section 4.1.3.
I5	RCT (blinded or non-blinded).
I6	Treatment period $\geq$ 24 weeks (in cross-over studies: per treatment arm).
I7	Language of publication: German, English, French, Dutch, Portuguese, or Spanish.
I8	Location of administration: subcutaneous tissue.
I9	Options for a combination with other blood glucose-lowering treatments (see also Section 4.1.2): - No additional blood glucose-lowering treatment in either group. - Comparable additional blood glucose-lowering treatment in both groups with drugs approved and available in Germany.

Exclusion criteria	
E1	Animal experimental studies.
E2	Duplicate publications without relevant additional information.
E3	No full-text publication available.[a]
E4	Different mode of administration between test intervention and comparator treatment (e.g. continuous subcutaneous insulin infusion [CSII] vs. multiple subcutaneous injections).
a: In this context, full-text publications also include non-confidential clinical study reports provided to the Institute or other non-confidential reports on a study provided to the Institute that fulfil the CONSORT[†] criteria [14] and enable the evaluation of a study.	

[†] Consolidated Standards of Reporting Trials

4.2 Literature search

The aim of the literature search was to identify full-text published and unpublished clinical studies that provided relevant information on the effects of long-term treatment with rapid-acting insulin analogues.

4.2.1 Literature sources

The following sources were consulted to find relevant full-text published studies:

- Bibliographic databases: Medline,[‡] EMBASE,[§] CENTRAL.[**]
- Reference lists in relevant secondary publications (HTA[††] reports, systematic reviews, meta-analyses).

Search in bibliographical databases

Two reviewers independently assessed the potential relevance of the publications on the basis of their titles and, if available, their abstracts. Publications which both reviewers assessed as potentially relevant were then assessed on the basis of the full text with regard to their relevance. Publications that initially only one reviewer assessed as potentially relevant were then assessed again by both reviewers and subsequently, after discussion, either assessed as irrelevant or were also assessed on the basis of their full-text with regard to their relevance.

The assessment of the relevance of the publications on the basis of the full text was also performed independently by the two reviewers. After this step, publications assessed as relevant for this systematic review were defined as:

- Publications that were assessed as relevant by both reviewers.
- Publications that were initially assessed as relevant by only one reviewer, but after subsequent discussion were assessed as relevant by both reviewers.

Search in reference lists in relevant secondary publications

Reference lists in relevant secondary publications were searched in order to identify any further primary publications. The search for relevant secondary publications (systematic reviews, meta-analyses, and HTA reports) was conducted in the databases Medline and EMBASE parallel to the search for relevant primary literature by appropriate formulation of

[‡] Medical Literature Analysis and Retrieval System Online
[§] Excerpta Medica Database
[**] Cochrane Central Register of Controlled Trials
[††] Health technology assessment

the search strategy (see Appendix B). In addition, a search was conducted in the specialised CDSR,[‡‡] DARE,[§§] and HTA databases.

4.2.2 Search for further published and unpublished studies

The following procedures were conducted in order to identify further published or unpublished studies:

- Query in writing to the companies Novo Nordisk Pharma GmbH, Mainz (insulin aspart); Aventis Pharma Deutschland GmbH, Bad Soden am Taunus (insulin glulisine); and Lilly Deutschland GmbH, Bad Homburg (insulin lispro). Date of query: 29 April 2005.
- Search for clinical study reports of completed studies via the Internet in publicly accessible study registers of manufacturers (http://www.lillytrials.com; access on 12 June 2005) and the US association "Pharmaceutical Research and Manufacturers of America" (PhRMA), (http://www.clinicalstudyresults.org; access on 12 June 2005).
- Search of the websites http://www.emea.eu.int and http://www.fda.gov (access on 12 June 2005) for publicly accessible documents of regulatory authorities (European Medicines Agency [EMEA]; US Food and Drug Administration [FDA]).

4.2.3 Search for additional information on relevant studies

The documents retrieved by the procedures described in Section 4.2.2 were searched for additional information on the previously identified published studies. Furthermore, the main authors Altuntas, Anderson, Bastyr, Dailey, and Ross were contacted in writing on 20/21 June 2005 and asked to provide additional information. A reminder was sent on 29 July 2005.

4.2.4 Acquisition of statements / scientific hearing

Statements could be made up to four weeks after the publication of the preliminary report. A form was provided to allow for comments on two main aspects:

1. Missing original studies in the preliminary report.
2. Incorrect evaluation of original studies in the preliminary report.

[‡‡] Cochrane Database of Systematic Reviews
[§§] Database of Abstracts of Reviews of Effects

After the deadline for statements, a scientific hearing was held where the aspects of the statements received were discussed with regard to their relevance for the final report.

4.3 Evaluation of studies

The evaluation of the studies included was conducted on the basis of the information available and was therefore strongly dependent on the quality of the respective publications and the additional sources of information.

The evaluation was conducted in three steps:

- Data extraction,
- Evaluation of the quality of the studies and publications,
- Evaluation of the consistency of data within the publication itself and between the publication and other sources of information (e.g. information provided in the publication and in regulatory documents).

At the end of this three-step procedure, it was finally decided for each study, under consideration of the quality of the study and publication, and the consistency of the available information, whether the respective study was to be included in the evaluation and whether therefore a detailed description of the study was to be presented in the final report.

4.3.1 Data extraction

Data extraction from published studies was conducted by two reviewers independently with standardised data extraction forms. A sample extraction form is included in Appendix C. The two reviewers then completed a joint data extraction form on the basis of the individual forms. Any discrepancies during this first evaluation step were resolved by discussion beforehand. The extraction form generated by consensus, together with the publications available on the relevant studies, formed the basis of the production of this report.

4.3.2 Quality of studies and publications

Information on the following main aspects of study quality was systematically extracted:

- Randomisation process,
- Allocation concealment,
- Blinding of treating staff, patients, and endpoint evaluations.

Furthermore, an overall evaluation of the study and publication quality was conducted by means of a four-graded scale (biometric quality) under consideration of the above and additional aspects, which are if necessary presented for the individual studies in the respective sections.

Possible grades were:

- No identifiable deficiencies,
- Minor deficiencies,
- Serious deficiencies,
- Unclear.

The grades were predefined as follows: “minor deficiencies”: it is assumed that their correction will not substantially influence the results and the overall conclusion of the study; “serious deficiencies”: if these deficiencies were corrected, the overall conclusion of the study would in principle be questioned. As previously stated, the evaluation of the quality of a study is directly influenced by the quality and consistency of the information available. Therefore “serious deficiencies” do not necessarily refer to the quality of the study itself, but may be due to the quality of the publication.

4.3.3 Consistency of information

Following the data extraction, where appropriate, a comparison of these data and of data obtained by the additional searches described in Sections 4.2.2 and 4.2.3 took place.

Insofar as discrepancies were detected (also discrepancies between multiple data provided on a topic within the publication itself) that may have had a substantial effect on the study results or on their interpretation, this is presented in the respective parts of the results section.

4.4 Study summary

Aspects of study design, quality, and results are presented as a summary for the total study pool.

4.4.1 Meta-analysis

An aggregation of data by means of meta-analysis following the Institute's methods was to be conducted provided that this was seen as a meaningful methodological and textual procedure.

4.4.2 Sensitivity analysis

Sensitivity analyses were preplanned:

- For the biometric evaluation of quality (see Section 4.3.2);
- If possible for the per-protocol evaluations vs. the ITT evaluations presented in the publications;
- For a (statistical) model with fixed effects (vs. a model with random effects) if a meta-analysis was to be conducted.

4.4.3 Subgroup analysis

Subgroup analyses were planned for the following characteristics, if possible and meaningful:

- Gender,
- Age,
- Concomitant diseases,
- Different definitions of diabetes,
- Additional blood glucose-lowering therapy,
- If marked heterogeneity was detected between studies within the framework of a meta-analysis, and, if identified, for the characteristics responsible for this heterogeneity.

4.5 Amendments to the report plan

During the production of the report, some amendments in the methodology predefined in the report plan were made. These amendments refer on the one hand to the necessity of a specification or clarification of an issue (without substantial amendments to the preplanned methodological procedure) and on the other, to the methodological procedure itself. The most relevant amendments are listed below (for the period before the completion of the preliminary report and for the period after publication of the preliminary report).

4.5.1 Amendments made before the completion of the preliminary report

Amendments of content compared with the preplanned procedure

- Search for unpublished studies and for additional information on published studies in study registers and in publicly accessible documents of regulatory authorities (EMEA and FDA).
- No direct access to the database of the Cochrane Metabolic and Endocrine Disorders Review Group.
- Exclusion of studies was possible after evaluation of the study and publication quality and consistency of data.

Amendments without relevant consequences with regard to content as they were in line with the preplanned procedure

- Standardisation of the formulation of the patient-relevant outcomes.
- Specification of the inclusion criteria for studies including premixed insulin formulations.
- Provision of details about the possibility of including non-blinded studies in the evaluation (according to the report plan these studies were not excluded, but this point is now specifically noted).
- Addition of the inclusion criterion I9 to the overview table of inclusion criteria. This criterion was previously noted in the text of the report plan, but not listed in the overview table.
- Specification of the term “full-text publication” for studies that were not published in a scientific journal at the time of report production.
- Provision of explicit details on the assessment of the consistency of information.

- Provision of explicit details about the data sources used to search for systematic reviews, meta-analyses, and HTA reports.

4.5.2 Amendments made after the publication of the preliminary report

Amendments of content compared with the preplanned procedure

- Extension of the inclusion criteria for studies including premixed insulin formulations to those with similar, but not exactly identical proportions of insulin (of rapid-acting insulin analogues or short-acting RHI combined with longer-acting insulins).

Amendments without relevant consequences for the content (since they were in accordance with the preplanned procedures)

- Specification of the term “additional blood glucose-lowering therapy”.
- Specification of the duration of treatment for cross-over studies.
- Inclusion of a separate section describing the acquisition of statements and the conduct of a scientific hearing.

5. Results

In the following the results of the literature search are first presented, i.e. the search for published and unpublished studies, as well as for additional information on these studies from other sources. The relevant studies are then summarised. In addition, information is provided as to whether and to what extent preplanned meta-analyses and sensitivity and subgroup analyses were conducted, and on the respective results.

5.1 Results of the literature search

5.1.1 Literature search procedures

The search in the bibliographic databases was conducted in three steps:

1. First search on 15 April 2005,
2. Correction of the first search in the CENTRAL database on 14 May 2005,[***]
3. Additional search on 10 June 2005 after finalisation of the report plan.

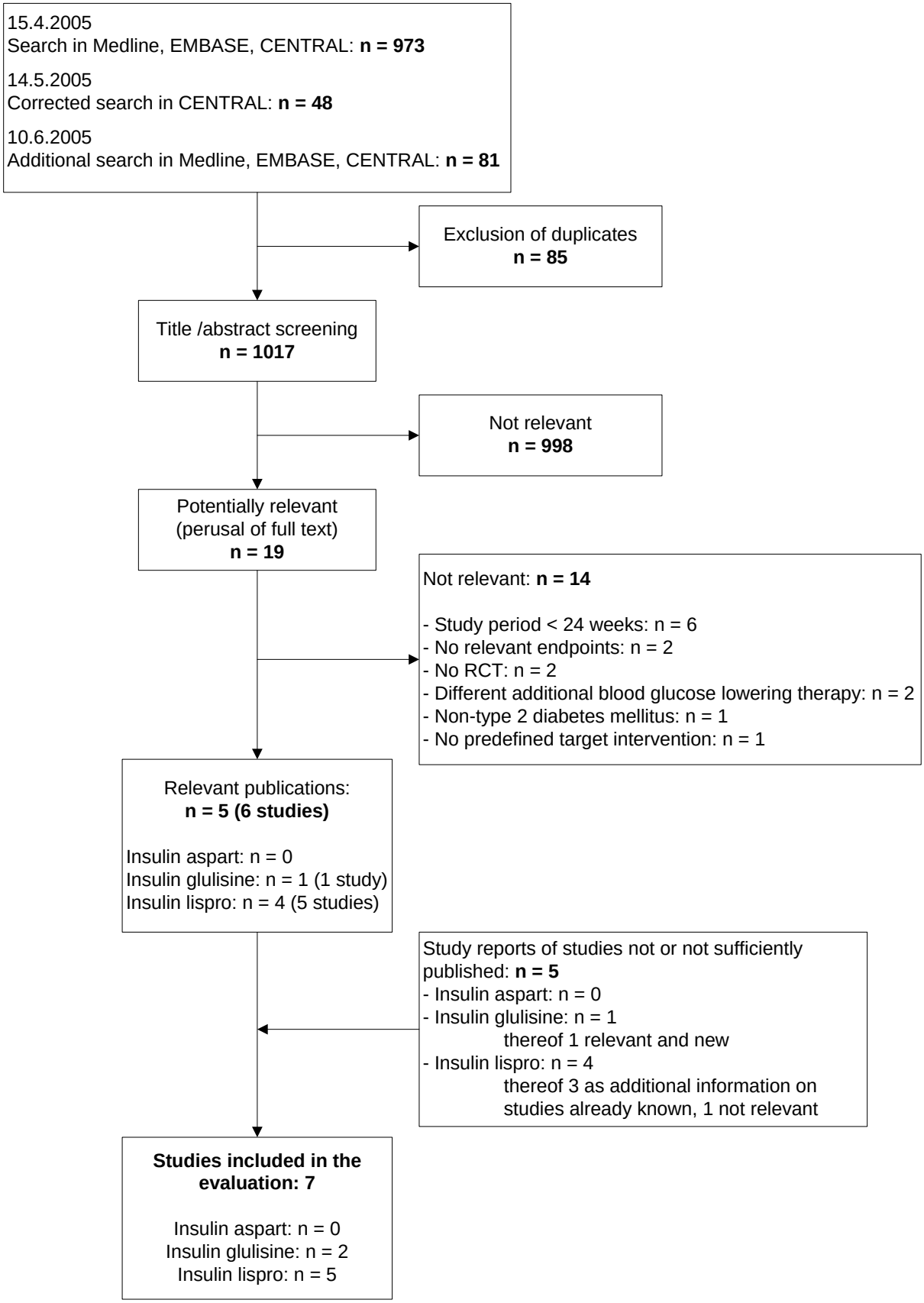
All search strategies are presented in Appendix B.

The results of the search are presented in Figure 1. After excluding duplicate publications, initially 1017 publications were identified of which 995 were classified concordantly by both reviewers as not relevant. After discussion, three further publications were also classified concordantly as not relevant. Of the remaining 19 publications, 5 publications were concordantly classified by both reviewers as relevant (Appendix A.1). The titles of the other 14 non-relevant publications perused in full text are listed in Appendix A.2, including the reason for exclusion.

The search for relevant secondary literature conducted on 15 April 2005 (repeated on 10 June 2005) identified a total of 19 systematic reviews, meta-analyses, and HTA reports (see Appendix A.3). No additional relevant primary studies were identified in these publications.

[***] In the first search on 15 April 2005, an "AND" operation was erroneously also used for the CENTRAL database for the query "study type". The references affected by these limitations were identified by means of a corrected search and were added to the search results.

Figure 1: Results of the search in bibliographical databases



5.1.2 Study registers

In http://www.lillytrials.com, synopses of studies were identified that fulfilled the inclusion criteria and that had already been identified by the literature search (Z012, Z014, and Z016 studies). The Z012 and Z014 studies were summarised in the publication by Anderson (1997); Study Z016 was published by Bastyr (2000).

The following documents providing additional information for the report were identified in http://www.clinicaltrialresults.org:

- On insulin aspart: information on a potentially relevant, previously unpublished study (according to the information provided in the study register; BIASP-1466).
- On insulin glulisine: no additional information provided.
- On insulin lispro: reference to the Lilly study register, no additional information provided.

5.1.3 Publicly accessible documents from regulatory authorities

Additional documents were identified on the EMEA website (http://www.emea.eu.int):

- On insulin aspart: scientific discussion on NovoRapid (1 September 2004). Reference to a potentially relevant Phase III study: ANA/DCD/037/USA (referred to as “037” in the following); no publication source named.
- On insulin glulisine: scientific discussion (date unknown; last change: 16 February 2005). Reference to a relevant study (3002) already identified in the literature search (Dailey 2004).
- On insulin lispro
  - Scientific discussion on Humalog (1 July 2004); references to four potentially relevant clinical studies not yet published in the Lilly study register (IOBJ, IOCF, IODQ, IONS); no publication source named. Lilly was asked to provide further information on these studies on 17 June 2005. According to information provided by Lilly on 21 June 2005, all four studies have been published. After perusal of these publications, all four studies were excluded due to lack of relevance for this report (no study included patients with diabetes mellitus type 2).
  - Scientific discussion on Humalog Mix (date unknown; last change: 23 April 2001). Reference to a potentially relevant study without specification of the study number; no publication source named. A request for information was sent to Lilly on 4 July 2005. According to the information provided by Lilly on 14 July 2005,

this study is the IODI study. The publication by Roach et al. (2001) was named as the respective publication, which had already been identified in the literature search and excluded because of the different additional blood glucose-lowering therapies in the treatment groups (see Appendix A.2).

Additional information relevant to this report was found on the FDA website http://www.fda.gov.

- On insulin aspart:
  - With regard to the new drug application (NDA) No. 20-986: Medical review on the 13 August 1999 and statistical review on 10 August 1999. Reference to Study 037 already quoted in the EMEA documents. No publication source named.
  - With regard to the NDA No. 20-986/SE3-003: Medical review on 20 December 2001; no reference to relevant studies included.
- On insulin glulisine: Medical review und statistical review for the NDA No. 21-629. Reference to Study 3002 (already quoted in the EMEA documents), additional reference to a further potentially relevant study (3005); no publication source named.
- On insulin lispro: Medical review on the NDAs Nos. 21-017 und 21-018; reference to the IODI study already quoted in the EMEA documents. No publication source named.

5.1.4 Query to manufacturers

The following documents on potentially relevant studies, whose contents with regard to the evaluation are not confidential and therefore may be referred to in this report, were provided by the manufacturers of rapid-acting insulin analogues.

- Sanofi-Aventis Deutschland GmbH, Bad Soden (insulin glulisine): study report (Study 3005) provided on 15 September 2005.
- Lilly Deutschland GmbH, Bad Homburg (insulin lispro): study reports on Z012, Z014, Z016, and IODI studies (provided on 29 August 2005).

Despite several requests for information, no relevant non-confidential information was provided by Novo Nordisk Pharma GmbH, Mainz (insulin aspart). For Study 037, only an abstract was referred to, which had been published in 1999 [15]. The information in this abstract was insufficient to be included in this evaluation.

5.1.5 Query to authors

Additional relevant information provided by the following authors was available at the time of production of the final report:

- George Dailey (on Study 3002).

The information provided by the author is included in Appendix D.

All other authors either did not provide additional relevant information or did not respond to the Institute's queries; this is also documented in Appendix D.

5.1.6 Information from statements provided and from the scientific hearing

The following additional relevant information was collected via the acquisition of statements and the subsequent scientific hearing:

- With regard to Study BIASP-1466, an abstract publication [16] was presented, which showed that the study did not fulfil the inclusion criteria as the study period was too short.

Other aspects presented in the statements and the scientific hearing are described in Section 7 (Discussion) and in Appendix E (Meeting minutes of the scientific hearing).

5.1.7 Study pool

The study pool of potentially or definitely relevant studies resulting from the various search steps is shown in Table 1. All relevant studies for which full-text publications were available according to the definition in Section 4.1.6 were included in the evaluation.

Table 1: Study pool

Insulin analogue Study	**Relevant**	**Full-text publication available**[a]		**Inclusion in report**
		Publication[b]	Study report	
Insulin aspart				
037	Potentially	No	No	No
Insulin glulisine				
3002	Yes	Yes: Dailey 2004	No	Yes
3005	Yes	No	Yes	Yes
Insulin lispro				
Z012	Yes	Yes: Anderson 1997[c]	Yes	Yes
Z014	Yes	Yes: Anderson 1997[c]	Yes	Yes
Z016	Yes	Yes: Bastyr 2000	Yes	Yes
Canadian Lispro Study	Yes	Yes: Ross 2001	No	Yes
Altuntas 2003	Yes	Yes: Altuntas 2003	No	Yes

a: As defined in Section 4.1.6.
b: Refers to publicly accessible publications in scientific journals.
c: Only limited usability, as the analysis included is a pooled analysis of Studies Z012 and Z014.

The following terms are used for the accessed sources of information: “publication” for publicly accessible articles in scientific journals; “study report” for detailed clinical study reports provided by the manufacturers (see Section 5.1.4).

As a general rule, the publication (if available), being a publicly accessible source, was regarded as the primary source of information. Additional information provided by the respective authors was also considered. Study reports were only considered if the information provided in the respective publications was insufficient, unclear, or inconsistent. The

existence of inconsistent information between publication and study report is presented in the respective sections, if considered relevant for this report. Information from other documents (e.g. publicly accessible regulatory documents) was only considered in exceptional cases; this is also noted in the respective sections.

5.2 Studies included

5.2.1 Study design and population

Details on the design of the seven studies included in this report and the respective patient populations are presented in Tables 2 – 5.

In all studies, a rapid-acting insulin analogue was compared with RHI (in addition to a longer-acting insulin, whose composition and scheme of administration were identical in both treatment groups) in an open-label design. Five of the seven studies compared insulin lispro vs. RHI; two studies compared insulin glulisine vs. RHI. No relevant fully published study was found on insulin aspart. In the three-arm study by Altuntas (2003), a combination therapy of insulin lispro and metformin was also investigated. An evaluation of this treatment arm is not included in this report.

Relevant studies on premixed formulations of rapid-acting insulin analogues or short-acting RHI combined with longer-acting insulins or direct comparator studies between insulin analogues were not found.

The maximum study period was 12 months (exclusively studies on insulin lispro: Z012, Z014, and Z016); therefore no study was designed to provide evidence of the efficacy or safety of the respective study drug over a period of several years. Both studies on insulin glulisine covered a study period of 26 weeks.

The number of patients included in studies on insulin lispro lay between 40 (Altuntas 2003) and 375 (Z016). The total number of patients (n=858) in all five studies on insulin lispro was lower than in the two studies on insulin glulisine (n=1766).

The available studies on insulin lispro included either patients with existing insulin therapy, insulin-naïve patients, or patients with OAD failure (insufficient lowering of blood glucose levels despite maximum doses of OAD). In contrast, both studies on insulin glulisine only included patients who had previously been treated with insulin for a period of at least 6 months. None of the seven studies investigated patients with newly diagnosed diabetes.

The gender distribution was similar in all studies. The mean age in all studies lay between 55 and 60 years.

Table 2: Overview of studies included

Insulin analogue Study	**Study design**	**Study period**	**Number of patients**	**Location and dates of study**	**Relevant endpoints**[a]
Insulin lispro					
Z012	RCT, parallel, open-label	*12 months + 2-4 weeks run-in phase*	*72 [Lispro] 73 [RHI]*	*USA, Canada, South Africa, Belgium 1992-1993*	*Primary endpoint: unclear.*[b] *Relevant: frequency of hypoglycaemic episodes (also including details on severity), HbA_{1c},, adverse events.*
Z014	RCT, parallel, open-label	*12 months + 2-4 weeks run-in phase*	*73 [Lispro] 77 [RHI]*	*USA, Germany, Netherlands, South Africa, Australia, Israel 1992-1993*	*Primary endpoint: unclear.*[b] *Relevant: frequency of hypoglycaemic episodes (also including details on severity), HbA_{1c}, adverse events.*
Z016	RCT, parallel, open-label	12 months	*186 [Lispro]*[c] *189 [RHI]*[c]	USA, Canada, Europe, South Africa 1993-1994	*Primary endpoint: unclear.*[b] *Relevant: frequency of hypoglycaemic episodes (also including details on severity), HbA_{1c}, QoL, adverse events.*
Canadian Lispro Study	RCT, parallel, open-label	5.5 months[d]	70 [Lispro] 78 [RHI]	Canada Dates of study period unclear	Primary endpoint: not stated. Relevant: rate of hypoglycaemia (total and nocturnal), HbA_{1c}[e], QoL (DQOL).
Altuntas 2003	RCT, parallel, open-label	6 months	20 [Lispro] 20 [RHI]	Turkey Dates of study period unclear	Primary endpoint: not stated. Relevant: rate of hypoglycaemia, HbA_{1c}[e], adverse events.
Insulin glulisine					
3002	RCT, parallel, open-label	26 weeks + 4-week run-in phase	435 [Glulisine][f] 441 [RHI][f]	USA, Canada, Australia Dates of study period unclear	Primary: change in HbA_{1c}. In addition: rate of hypoglycaemia (including nocturnal and severe), adverse events, treatment satisfaction.[g]
3005	*RCT, parallel, open-label*	*26 weeks + 4-week run-in phase*	*448 [Glulisine][f] 442 [RHI][f]*	*Europe, Oceania, Argentina, South Africa, Israel 2001-2003*	*Primary: change in GHb. In addition: rate of hypoglycaemia (including nocturnal and severe), adverse events, treatment satisfaction (DTSQ).*

continued

Table 2: Overview of studies included (continued)

a: Specification of the respective primary endpoint and of other endpoints that provide information on the patient-relevant outcomes noted (Section 4.1.3).
b: Inconsistent information in the respective study reports; see also following text.
c: Data according to study report; according to publication: n=182 (insulin lispro), n=183 (RHI).
d: Duration of study period not specified in weeks: 5.5 months correspond to min. 23.6 weeks, max. 24.1 weeks.
e: No details provided on the ranking of endpoints (primary/secondary endpoints).
f: Number of patients who received at least one dose of study medication. In both the 3002 and 3005 studies, 2 patients were additionally randomised; these patients did not receive study medication and were not included in the primary evaluation.
g: According to consistent information in the publicly accessible FDA and EMEA regulatory documents (see Section 5.1.3).
QoL: quality of life; DQOL: Diabetes Quality Of Life Questionnaire; DTSQ: Diabetes Treatment Satisfaction Questionnaire. GHb: glycosylated haemoglobin; RCT: randomised controlled trial.
Italics: information according to the respective study report; no or insufficient information available in publicly accessible publications.

Table 3: Diabetes-related inclusion and exclusion criteria in the relevant studies

Insulin analogue Study	**Diabetes diagnosis according to**	**Relevant inclusion and exclusion criteria**
Insulin lispro		
Z012	*WHO 1980*	*I: Insulin treatment for at least 2 months before study entry.* *E: OAD therapy; insulin pump therapy.*
Z014	*WHO 1980*	*I: Insulin treatment for at least 2 months before study entry.* *E: OAD therapy, insulin pump therapy.*
Z016	WHO 1980	I: Insulin treatment < 2 months before study entry. E: Insulin pump therapy.
Canadian Lispro Study	n.d.	I: OAD failure. E: Long-term insulin therapy, severe retinopathy or neuropathy, > 2 severe hypoglycaemic episodes in the last 12 months.
Altuntas 2003	ADA 1997	I: OAD failure (insufficient lowering of blood glucose levels despite using maximum doses of sulfonylurea).
Insulin glulisine		
3002	n.d.	I: Insulin therapy for at least 6 months before study entry; HbA_{1c} 6%-11%.
3005	*Diabetes mellitus type 2 (according to patient file)*	*I: Insulin therapy for at least 6 months before study entry; HbA_{1c} 6%-11%.* *E: Glinide or glitazone therapy in the 4 weeks before study entry; active proliferative retinopathy.*

OAD: oral antidiabetics; ADA: American Diabetes Association; WHO: World Health Organization; n.d.: no details provided; I: inclusion criteria; E: exclusion criteria.
Italics: information according to the respective study report; no or insufficient information available in publicly accessible publications.

Table 4: Target values and therapy regimens of the blood glucose-lowering treatments

Insulin analogue Study	**Target values**[a]	**Insulin administration** **Rapid-acting insulin analogue**[b]	**Longer-acting insulin**	**Other blood glucose-lowering treatments**
Insulin lispro				
Z012	*Fasting blood glucose values < 140 mg/dl; 2-hour postprandial values < 180 mg/dl (self-monitoring).*	*Before each meal*	*UL 1-2x/day*	*Not permitted*
Z014	*Fasting blood glucose values < 140 mg/dl; 2-hour postprandial values < 180 mg/dl (self-monitoring).*	*Before each meal*	*NPH 1-2x/day*	*Not permitted*
Z016	Fasting blood glucose values < 140 mg/dl; 2-hour postprandial values < 180 mg/dl (self-monitoring).	Before each meal	NPH or UL 1-2x/day	*Not permitted*
Canadian Lispro Study	2-hour postprandial values < 160 mg/dl (self-monitoring).	Mornings and evenings	NPH mornings and evenings	Unclear
Altuntas 2003	2-hour postprandial values < 160 mg/dl (self-monitoring).	Before each meal	NPH evenings	Unclear
Insulin glulisine				
3002	2 hours postprandial: 120-160 mg/dl (self-monitoring); in addition, NPH titration (aim: 90-120 mg/dl preprandial [self-monitoring]).	Mornings and evenings	NPH 2x/day	OAD permitted
3005	*2 hours postprandial: 120-160 mg/dl (self-monitoring); in addition, NPH titration (aim: 90-120 mg/dl preprandial [self-monitoring])*	*Mornings and evenings*	*NPH 2x/day*	*OAD permitted (except for glinides and glitazones); if possible, dosing was not to be changed during the study.*

a: Blood glucose levels.
b: Time of administration: insulin lispro directly before meals, except in the Canadian Lispro Study (15 minutes before meals); insulin glulisine: 0-15 minutes before meals; RHI: 30-45 minutes before meals.
NPH: Neutral Protamin Hagedorn; UL: Ultralente; OAD: oral antidiabetics.
Italics: information according to the respective study report; no or insufficient information provided in publicly accessible publications.

Table 5: Baseline demographic and diabetes-related data

Insulin analogue Study	**N**	**Age [years][a]**	**Gender f[%]**	**m[%]**	**Duration of diabetes illness [years][a]**	**HbA_{1c} [%][a]**	**BMI [kg/m²][a]**
Insulin lispro							
Z012							
Lispro	*72*	*56*	*50*	*50*	*11*	*8.7 (1.5)*	*29*
RHI	*73*	*57*	*44*	*56*	*12*	*8.8 (1.8)*	*28*
Z014							
Lispro	*73*	*56*	*48*	*52*	*14*	*8.8 (1.4)*	*28*
RHI	*77*	*55*	*51*	*49*	*12*	*9.0 (1.6)*	*29*
Z016[b]		56 (10)[c]			8 (7)[c]		28 (4)[c]
Lispro	*186*	*55*	*43*	*57*	*8*	*9.5 (1.9)*[d]	*28*
RHI	*189*	*57*	*44*	*56*	*8*	*9.6 (1.8)*[d]	*28*
Canadian Lispro Study							
Lispro	70	59 (8)	63	37	11 (8)	10.7 (1.7)	28 (8)
RHI	78	58 (9)	62	38	11 (7)	10.6 (1.8)	27 (9)
Altuntas 2003							
Lispro	20	55 (34)	n.d.		6	unclear[e]	31
RHI	20	55 (34)	n.d.		10	unclear[e]	31
Insulin glulisine							
3002							
Glulisine	435	59 (10)	44	56	15 (8)	7.6 (0.9)	35 (7)
RHI	441	58 (10)	50	50	13 (8)	7.5 (1.0)	35 (7)
3005							
Glulisine	*448*	*60 (9)*	*52*	*48*	*14 (8)*	*7.6 (0.9)*[f]	*31 (5)*
RHI	*442*	*60 (10)*	*49*	*51*	*13 (7)*	*7.5 (0.9)*[f]	*31 (5)*

continued

Table 5: Baseline demographic and diabetes-related data (continued)

a: Mean values (rounded off where necessary); standard deviation in brackets, if available.
b: Data for the single groups according to study report, as these data were not provided in the publication (Bastyr 2000).
c: Data for the total population; no standard deviations available for the single groups.
d: Time point of measurement: 2 weeks after randomisation.
e: Inconsistent information on baseline data in the publication (Tables 1 and 3, as well as information in the text).
f: GHb.
f: female; m: male; BMI: body mass index; n.d.: no details provided; GHb: glycosylated haemoglobin.
Italics: information according to the respective study report; no or insufficient information provided in publicly accessible publications.

5.2.2. Quality of studies and publications

An overview of study and publication quality (including the assessment criteria used) is presented in Table 6.

Five of the seven studies showed serious, and two studies showed minor deficiencies of quality (both studies on insulin glulisine; 3002 and 3005). However, in all seven studies (including 3002 and 3005), serious deficiencies were found with regard to single relevant endpoints. These deficiencies are presented in the respective sections and evaluated with regard to their consequences for the validity of results.

The classification as a study with “serious deficiencies” for the studies Z012, Z014, and Z016 was mainly due to inconsistent information on the primary endpoint of the study in the respective study report. For example, in one section, “postprandial blood glucose level excursions” were named as the “primary efficacy variables”, whereas this parameter was not regarded as relevant for the sample size calculation/power analysis. Instead, the following three parameters were: “fasting blood glucose levels”, “HBA_{1c}”, and “hypoglycaemic episodes”. In addition, in the section describing the study protocol, a reference to various primary efficacy variables was found (“postprandial blood glucose excursions”, “hypoglycaemic episodes in relation to glycaemic control”, and “metabolic control”). These inconsistencies apply to all three studies in equal measure. The publication by Ross in 2001 (Canadian Lispro Study) and by Altuntas (2003) did not contain any information on which endpoint was the primary one. Information on simple size planning was also not found in these publications. Furthermore, in the publication on the Canadian Lispro Study, no results were provided on the predefined endpoint “severe hypoglycaemia”.

More detailed information on the whole randomisation process including the specification of the allocation procedures (e.g. by means of a randomisation list) were only found in the study reports for the Z012, Z014, Z016, and 3005 studies, as well as in the publication of the 3002 study. In the Z012, Z014, and Z016 studies, allocation to treatment groups was conducted centrally by means of a computer-generated randomisation list. No information in this regard was found for the two other studies on insulin lispro. In both studies on insulin glulisine, stratified randomisation was conducted centrally according to OAD treatment.

In all studies, patients and treating staff were not blinded. The reason given in all studies was the differing injection-meal interval. The lack of blinding of patients and treating staff is a serious deficiency in quality with regard to the evaluation of the various endpoints reported in the studies, in particular hypoglycaemia; the more so as double-blinded short-term studies with rapid-acting insulin analogues have already been conducted [17]. These deficiencies are

increased by the fact that the primary endpoint evaluations relevant to this report were not blinded. No explanation for this procedure was provided in any of the publications available.

Sample size planning was adequately described for all studies, except for the Canadian Lispro Study and the study by Altuntas (2003).

The information provided on discontinuations of therapy in the Z012 and Z014 studies was adequately transparent. In contrast, the information provided on discontinuations in Study Z016 in the publication by Bastyr (2000) and in the study report was extremely inconsistent. The respective information provided on the Canadian Lispro Study (Ross, 2001) and on Study 3002 (Dailey, 2004) was also not adequately transparent. Information provided on Study 3005 (study report) was transparent; however, the rate of study discontinuations differed markedly between treatment groups, which was especially relevant for the evaluation of the endpoint "severe hypoglycaemia" (see respective section).

Furthermore, for all studies, inconsistent information was found on all main parameters within the available publications (including the respective study reports) and/or between publications. The main discrepancies are presented in detail in the respective sections of this report (in particular in the results section).

Table 6: Quality of studies and publications

Insulin analogue Study	**Randomisation process / Concealment of allocation**	**Blinding**			**Sample size planning**	**Discontinuations of therapy**	**Consistency of information**	**Study / publication quality[a]**
		Patient	**Treating staff**	**Evaluation of endpoints**				
Insulin lispro								
Z012	*Adequate/ adequate*	No	No	*With regard to laboratory parameters: yes*	*Adequately described*	*[L]: 2 (3%); [RHI]: 2 (3%); (reasons stated).*	No[b]	Serious deficiencies[c]
Z014	*Adequate/ adequate*	No	No	*With regard to laboratory parameters: yes*	*Adequately described*	*[L]: 5 (6%); [RHI]: 6 (7%); (reasons stated).*	No[b]	Serious deficiencies[c]
Z016	*Adequate/ adequate*	No	No	*With regard to laboratory parameters: yes*	*Adequately described*	According to publication: [L]: 25 (14%) [RHI]: 19 (10%); *according to study report: [L]: 30 (16%), [RHI]: 28 (15%), (reasons stated).*	No[d]	Serious deficiencies[e]
Canadian Lispro Study	n.d./ n.d.	No	No	n.d.	n.d.	In total 3% (n=5); distribution in groups unclear; reasons stated.	No	Serious deficiencies[f]
Altuntas 2003	n.d./ n.d.	No	No	n.d.	n.d.	None	No	Serious deficiencies[g]

continued

Table 6: Quality of studies and publications (continued)

Insulin analogue Study	**Randomisation process / Concealment of allocation**	**Blinding**			**Sample size planning**	**Discontinuations of therapy**	**Consistency of information**	**Study / publication quality**[a]
		Patients	**Treating staff**	**Evaluation of endpoints**				
Insulin glulisine								
3002	Adequate/ adequate	No	No	With regard to HBA_{1c}: yes; otherwise n.d.	Adequately described	[G]: 28 (6%); [RHI]: 36 (8%); reasons stated.[h]	Yes	Minor deficiencies[i]
3005	*Adequate/ adequate*	*No*	*No*	With regard to HBA_{1c}: yes; otherwise n.d.	*Adequately described*	*[G]: 28 (6%); [RHI]: 14 (3%); reasons stated.*	Yes	Minor deficiencies[i]

a: For grades: see Section 4.3.2.
b: Inconsistent information on the primary endpoint. In the publication by Anderson (1997), only a pooled analysis of the Z012 and Z014 studies was provided without reference in this regard.
c: As the information provided on the primary endpoint is inconsistent and this issue is therefore unclear.
d: With regard to the endpoint "nocturnal hypoglycaemia": inconsistency between text and figure (Bastyr 2000; Kaplan-Meier Analysis); however, relevant information in the figure is not provided (numbers at risk). According to the study report, the endpoint "nocturnal hypoglycaemia" was not predefined. The information on the number of randomised patients is inconsistent between publication and study report.
e: Because the information on the primary endpoint is inconsistent and this issue is therefore unclear. In addition, an endpoint was reported in the publication (Bastyr 2000) that was not predefined (nocturnal hypoglycaemia); this endpoint was not found in the study report. Inconsistent information is provided on the QoL subgroup.
f: As the primary endpoint was not stated and information on the randomisation process and on allocation concealment are missing. In addition, information is missing on the predefined endpoint "severe hypoglycaemia".
g: As the primary endpoint was not stated and information on the randomisation process and allocation concealment is missing. In addition, there is a relevant inconsistency of data in the publication.
h: Data source: FDA statistical review [18].
i: With regard to the overall study. In addition, there are specific deficiencies with regard to the evaluation of single endpoints. These are presented in the respective sections.
n.d. no details provided; [L]: insulin lispro; [RHI]: regular human insulin; [G]: insulin glulisine; QoL: quality of life; FDA: Food and Drug Administration.
Italics: information according to the respective study report, no or insufficient information in publicly accessible publications.

5.3 Study results

5.3.1 Diabetic late complications and mortality

None of the studies included, in respect of their design and duration of study period, was designed to investigate the effect of treatment with rapid-acting insulin analogues compared with RHI with regard to the prevention of micro- and macrovascular late complications of diabetes type 2.

These include:

- Cardiac morbidity and mortality,
- Cerebral morbidity and mortality,
- Vascular non-cardiac and non-cerebral morbidity and mortality,
- Rate of blinding,
- Rate of terminal renal insufficiencies requiring dialysis,
- Rate of amputations (minor and major amputations).

In this regard, for the three insulin analogues investigated, it therefore remains unclear whether they have a more positive or negative, or no effect compared with RHI.

The same applies to total mortality. Information on mortality in the single studies is presented in Table 7. None of the studies was designed and suited to show the effect of rapid-acting insulin analogues on total mortality compared with RHI. It cannot be derived from the single or summarised mortality rates observed in the studies that one of the treatment options was superior or equivalent.

Table 7: Mortality rates in the single studies

Insulin analogue Study	**Mortality rate**	
	Insulin analogue [N (%)]	**Regular human insulin** [N (%)]
Insulin lispro		
Z012	0 (0%)	0 (0%)
Z014	0 (0%)	0 (0%)
Z016	2 (1%)	0 (0%)
Canadian Lispro Study	n.d.	n.d.
Altuntas 2003	n.d.	n.d.
Insulin glulisine		
3002	1 (0.2%)	2 (0.5%)
3005	*2 (0.4%)*	*1 (0.2%)*

n.d.: no details provided.
Italics: information according to the respective study report, no or insufficient information in publicly accessible publications.

5.3.2 Hospitalisations

No information was found in any of the publicly accessible publications on diabetes-related hospitalisations or hospitalisations due to other causes.

In the study reports on insulin lispro, information was provided in part on single cases of hospitalisations, e.g. due to an adverse drug effect; however, cumulative evaluations were not provided. It therefore remains unclear whether the rate of hospitalisations due to diabetes or other causes differed between treatment groups.

In the study report on Study 3005 (insulin glulisine), it was stated that hospitalisations due to serious adverse events occurred in 33 patients (7.4%) treated with insulin glulisine and 36 patients (8.1%) treated with RHI; 0 (0%) and 3 (0.7%) of these events were due to hypoglycaemia, respectively. Definite evidence of a superiority of one of the treatment options cannot be concluded from these findings.

5.3.3 Hyperglycaemia

Detailed information on the rate of hyperglycaemic or ketoacidotic comas was neither found in the publicly accessible nor in the publicly inaccessible documents.

In the study report on Study Z016, it was stated that one patient (0.5%) experienced a ketoacidotic coma while receiving insulin lispro.

Information on symptomatic hyperglycaemia was provided in the sections on adverse drug effects in the study reports (see Table 8). Definite evidence of the superiority of a treatment option cannot be concluded from this information.

Table 8: Symptomatic and/or severe hyperglycaemia

Insulin analogue Study	**Symptomatic and/or severe hyperglycaemia**	
	Insulin analogue [N (%)]	**Regular human insulin** [N (%)]
Insulin lispro		
Z012	*0 (0%)*	*1 (1.4%)*
Z014	*1 (1.4%)*	*1 (1.3%)*
Z016	*3 (1.6%)*	*3 (1.6%)*
Canadian Lispro Study	n.d.	n.d.
Altuntas 2003	n.d.	n.d.
Insulin glulisine		
3002	n.d.	n.d.
3005	*1 (0.2%)*	*0 (0%)*

n.d.: no details provided.
Italics: information according to the respective study report, no or insufficient information in publicly accessible publications.

5.3.4 Hypoglycaemia and control of blood glucose levels

Extent of blood glucose lowering

Controlled studies comparing insulin-based intensive and less intensive lowering of blood glucose levels have repeatedly shown that intensive lowering of blood glucose levels is associated with a higher risk of severe hypoglycaemia [4-6]. A supposedly lower hypoglycaemia rate in one of the treatment groups in an intervention study may possibly be due only to a less intensive lowering of blood glucose levels and may not necessarily be due to a substance-specific effect. Therefore, the prerequisite for the interpretation of hypoglycaemia rates in a controlled study comparing different blood glucose-lowering agents is knowledge of the extent of blood glucose lowering in the respective treatment groups.

This information, provided in the publications, is shown in Table 9.

Table 9: HbA_{1c} (%) levels throughout the study period

Insulin analogue Study	**Baseline**[a]	**3 months**[a]	**6 months**[a]	**12 months**[a]	**Final visit**[a,b]	**Change: baseline-final visit**[a]
Insulin lispro						
Z012[c]						*p=0.857*
Lispro	*8.7 (1.5)*	*8.0 (1.3)*	*7.8 (1.4)*	*8.0 (1.2)*	*8.0 (1.2)*	*-0.7 (1.2)*
RHI	*8.8 (1.8)*	*8.3 (1.5)*	*8.3 (1.6)*	*8.2 (1.7)*	*8.2 (1.6)*	*-0.6 (1.4)*
Z014[d]						*p=0.465*
Lispro	*8.8 (1.4)*	*8.0 (1.2)*	*8.1 (1.5)*	*8.3 (1.6)*	*8.4 (1.5)*	*-0.4 (1.5)*
RHI	*9.0 (1.6)*	*8.3 (1.5)*	*8.5 (1.9)*	*8.5 (1.8)*	*8.5 (1.7)*	*-0.5 (1.7)*
Z016[e]						
Lispro	*9.5 (1.9)*[f]	*8.2 (1.4)*	*7.9 (1.3)*	*8.2 (1.5)*	*8.3 (1.6)*	*n.d.*
RHI	*9.6 (1.8)*[f]	*8.1 (1.5)*	*7.9 (1.4)*	*8.1 (1.5)*	*8.1 (1.5)*	*n.d.*
Canadian Lispro Study						n.d.
Lispro	10.7 (0.2)[g]	n.d.	8.0 (0.1)[g,h]	-	n.d.	-2.5 (0.2)[g]
RHI	10.6 (0.2)[g]	n.d.	8.0 (0.1)[g,h]	-	n.d.	-2.3 (0.2)[g]
Altuntas 2003						
Lispro	unclear[i]	n.d.	unclear[i]	-	unclear[i]	unclear[i]
RHI	unclear[i]	n.d.	unclear[i]	-	unclear[i]	unclear[i]
Insulin glulisine						
3002						p=0.0029[m]
Glulisine	7.6 (0.9)	7.0[j]	7.1[k]	-	7.1[l]	-0.46
RHI	7.5 (1.0)	7.0[j]	7.2[k]	-	7.2[l]	-0.3
3005[n,o]						p=0.5726[p]
Glulisine	*7.6 (0.9)*	*7.2*	*7.3*	-	*7.3*	-0.32
RHI	*7.5 (0.9)*	*7.1*	*7.2*	-	*7.2*	-0.35

continued

Table 9: HbA_{1c} (%) levels throughout the study period (continued)

a: Mean values, rounded off where necessary; standard deviations in brackets, if available.
b: Value at the time of the last visit.
c: For all visits: comparison between groups p > 0.05; number of evaluated patients varies: n = 60-72 for insulin lispro, n = 65-72 for RHI.
d: For all visits: comparison between groups p > 0.05; number of evaluated patients varies: n = 67-73 for insulin lispro, n = 70-77 for RHI.
e: For all visits: comparison between groups p > 0.05; number of evaluated patients varies: n = 155-179 for insulin lispro, n = 159-182 for RHI.
f: 2 weeks after start of study.
g: Standard error in brackets.
h: After 5.5 months.
i: Inconsistent information on baseline data in the publication (Tables 1 and 3, and text).
j: Number of patients included in this evaluation unclear; p = 0.0165: unclear whether this refers to the comparison of mean values at the respective visits or the comparison of the HbA_{1c} changes since start of study.
k: Number of patients included in this evaluation unclear; p = 0.0341: unclear whether this refers to the comparison of mean values or the comparison of mean changes.
l: Number of patients included in the evaluation: n=404 (insulin glulisine) and n=403 (RHI) (according to information provided by Dailey on 29 August 2005).
m: Primary endpoint: comparison of baseline-adjusted HbA_{1c} changes; difference: -0.16% (95%-CI: -0.05% – -0.26%).
n: All data for glycosylated total haemoglobin (GHb).
o: For all visits: comparison between groups p > 0.05; number of evaluated patients varies: n=393-429 for insulin glulisine and n=397-431 for RHI.
p: Primary endpoint: comparison of baseline-adjusted HbA_{1c} changes; difference: 0.03% (95%-CI: -0.07% – 0.13%).
CI: confidence interval; n.d. no details provided; RHI: regular human insulin.
Italics: information according to the respective study report, no or insufficient information in publicly accessible publications.

Insulin lispro

Transparent information was provided for all studies on long-term lowering of blood glucose levels, measured by HbA_{1c} levels (except for the study by Altuntas 2003: inconsistent information, see Table 9). In summary, no statistically significant or clinically relevant differences between treatment groups were shown at any visit.

Insulin glulisine

In both studies on insulin glulisine, sufficient transparent information was available on the effect of the respective blood glucose-lowering treatment on HbA_{1c} levels. Both studies were designed to show evidence of a non-inferiority of insulin glulisine compared to RHI; in both studies, a change in mean HbA_{1c} or GHb of 0.4% was predefined as the relevance margin. In both studies the non-inferiority of insulin glulisine was confirmed. The subsequent test for superiority (insulin glulisine vs. RHI) was statistically significant in Study 3002 in favour of insulin glulisine; in Study 3005, a statistically non-significant difference was shown in favour of RHI. In both studies, the respective effect estimates for the difference in HbA_{1c} lowering between treatment groups (0.16% and 0.03%) as well as the lower and upper level of the respective 95% confidence interval lay under the predefined level of 0.4% for clinical relevance (see Table 9). In summary, with regard to the two studies available on insulin glulisine (independent of any existing statistical significance), no clinically relevant difference compared with RHI with regard to its effectiveness on long-term blood glucose lowering can be concluded.

Therefore, a meta-analytical summary of results was not conducted.

Definition of hypoglycaemia

In all studies, both patients and treating staff were not blinded with regard to the type of blood glucose-lowering treatment used. The reliability of the results obtained therefore strongly depends on whether the definition of the event “hypoglycaemia” allows little or much room for interpretation concerning subjective intentional or unintentional influences. A possible measure to minimise bias due to intentional influences would for example be the blinded evaluation of endpoints by an independent body. This applies even more so if symptoms are unspecific, and the hypoglycaemic episode is not so severe that it requires third-party assistance. The definition of “severe hypoglycaemia” based only on a patient’s recollection of third-party assistance is also vulnerable to subjective influences as this can, for example, also mean the administration of glucose by a third party to a patient with unspecific symptoms.

Conversely, the definition “i.v. administration of glucose or glucagon, and/or coma and/or death, as well as evidence of a blood glucose level < 36 mg/dl” allows less room for subjective interpretation.

The definition of a hypoglycaemic event and its susceptibility to potential bias is shown in Table 10. It was not described in any study that efforts had been made to minimise systematic bias of results, e.g. by means of an independent validation of results. Therefore all studies were susceptible to this type of bias (also with regard to severe hypoglycaemia).

Table 10: Definition of the event "hypoglycaemia" in the studies evaluated

Insulin analogue Study	**Definition**	**Susceptibility to systematic bias**
Insulin lispro		
Z012	*General: blood glucose level < 36 mg/dl (self-monitoring) or hypoglycaemia-related symptoms.* *In addition (among other things):* [a] *Treatment with glucagon/i.v. glucose by a third-party, hypoglycaemic coma.*	Possible, also for coma, as based on patient statements.
Z014	*As in Study Z012.*	Possible, also for coma, as based on patient statements.
Z016	General: blood glucose level < 63 mg/dl (self-monitoring) or hypoglycaemia-related symptoms. *In addition (among other things):* [a] *Treatment with glucagon/i.v. glucose by a third-party, hypoglycaemic coma.* Nocturnal: [b] as under "general"; occurring between 0:00 a.m-6:00 a.m.	Possible, also for coma, as based on patient statements.
Canadian Lispro Study	General: blood glucose level < 60 mg/dl (self-monitoring) or typical hypoglycaemic symptoms. Nocturnal: the corresponding definition is missing. Severe: as under "general" but requiring third-party assistance, or coma / unconsciousness.	Possible; for coma / unconsciousness: unclear.[c]
Altuntas 2003	General: blood glucose level < 60 mg/dl (self-monitoring) or symptoms associated with hypoglycaemia.	Possible
Insulin glulisine		
3002	General: hypoglycaemia-associated symptoms. Nocturnal: like general, occurring during sleep. Severe: as under "general" but requiring third-party assistance and confirmed by blood glucose < 36 mg/dl, or with prompt recovery following oral carbohydrate, iv. glucose, or glucagon administration.	Possible; for severe hypoglycaemia: unclear[c]
3005	*As in Study 3002.* *In addition (among other things):*[a] *hypoglycaemia-related unconsciousness / coma; for nocturnal hypoglycaemic episodes: two endpoints ("symptomatic" and "severe").*	Possible, also for severe hypoglycaemia and coma, as based on patient statements.

a: E.g. within the framework of a safety evaluation.
b: In the publication by Bastyr 2000. This category (nocturnal hypoglycaemia) was not found in the study report on Study Z016; apparently post hoc evaluation (not preplanned).
c: No information on the type of data collection (patient statements or patient files?) and whether a validation by study staff was conducted.
i.v. intravenous.
Italics: information according to the respective study report, no or insufficient information in publicly accessible publications.

Severe hypoglycaemia

"Severe hypoglycaemia" was a separate endpoint in the Canadian Lispro Study and in both studies (3002 and 3005) on insulin glulisine.

Furthermore, corresponding information was provided in the study reports on the studies Z012, Z014, Z016, and 3005 within the framework of the safety evaluation.

The results are presented in Table 11.

Table 11: Information on the endpoint "severe hypoglycaemia"

Insulin analogue Study	**Endpoint**	**Results**	**Number of patients with missing data**
Insulin lispro			
Z012	yes[a]	*Coma: 1 (1.4%) [L] vs. 1 (1.4%) [RHI]* *Treatment with i.v. glucose: 2 (2.8%) [L] vs. 2 (2.7%) [RHI]* *Treatment with glucagon: 0 (0%) [L] vs. 0 (0%) [RHI]*	*[L]: 0/72 (0%)* *[RHI]: 1/73 (1%)*
Z014	yes[a]	*Coma: 1 (1.4%) [L] vs. 2 (2.7%) [RHI]* *Treatment with i.v. glucose: 1 (1.4%) [L] vs. 1 (1.4%) [RHI]* *Treatment with glucagon: 0 (0%) [L] vs. 0 (0%) [RHI]*	*[L]: 0/73 (0%)* *[RHI]: 0/77 (0%)*
Z016	yes[a]	*Coma: 0 (0%) [L] vs. 2 (1.1%) [RHI]* *Treatment with i.v. glucose: 1 (0.5%) [L] vs. 1 (0.5%) [RHI]* *Treatment with glucagon: 1 (0.5%) [L] vs. 1 (0.5%) [RHI]*	*[L]: 4/186 (2%)* *[RHI]: 6/189 (3%)*
Canadian Lispro Study	yes	n.d.	n.d.
Altuntas 2003	no	-	-
Insulin glulisine			
3002	yes	Treatment period Month 4 until Month 6:[b] Number of patients with $\geq$ 1 episode:[c,d] 6 (1.4%) [G] vs. 5 (1.2%) [RHI]	[G]: 19/435 (4%)[d] [RHI]: 21/441 (5%)[d]
3005	yes[e]	*Within total study period:* *Number of patients with $\geq$ 1 episode:*[f] *6 (1.3%) [G] vs. 14 (3.2%) [RHI]* *Number of patients with $\geq$ 1 episode (only coma):*[g,h] *4 (0.9%) [G] vs. 7 (1.6%) [RHI]* *Treatment period Month 4 until Month 6:* *Number of patients with $\geq$ 1 episode:*[i] *2 (0.5%) [G] vs. 7 (1.6%) [RHI]*	*[G]: 21/448 (5%)*[j] *[RHI]: 8/442 (2%)*[j]

continued

Table 11: Information on the endpoint “severe hypoglycaemia” (continued)

a: Within the framework of the safety evaluation.
b: No information provided on the first half of the study period; the additional information provided by the author also refers to the second half of the study period.
c: Number of total episodes: 6 [G] vs. 5 [RHI].
d: According to additional information provided by Dailey.
e: Both as an efficacy criterion and also within the framework of the safety evaluation.
f: Number of total episodes: 9 [G] vs. 16 [RHI].
g: Number of total episodes unclear.
h: Coma/unconsciousness, based on information from the safety evaluation.
i: Number of total episodes: 4 [G] vs. 8 [RHI].
j: The data on the rates under “total study period” refer however to the whole study population, as these data correspond to the data in the study report. See also following text.
[L]: insulin lispro; [G]: insulin glulisine; [RHI]: regular human insulin; i.v.: intravenous.
Italics: information according to the respective study report, no or insufficient information in publicly accessible publications.

Insulin lispro

No information on "severe hypoglycaemia" was found in the publication on the Canadian Lispro Study, even though this was a predefined endpoint. Data from the study reports on the studies Z012, Z014, and Z016 (safety evaluation) are presented in Table 11. In summary, no definite evidence of a difference between treatment groups was shown (with an overall low event rate: 2 [insulin lispro] vs. 5 [RHI] for "coma", 4 vs. 4 for "i.v. glucose").

Insulin glulisine

In the publication by Dailey 2004 (Study 3002), no significant difference between treatment groups was shown for severe hypoglycaemia (Table 11). However, only data on the second half of the study period, not on the acclimatisation phase (first three months), were presented in the publication. The additional information on severe hypoglycaemia (provided by the main author Dailey on request) also referred only to the second half of the study period. It remains unclear whether the initial stronger lowering of blood glucose under insulin glulisine (see Table 9) was associated with a higher rate of severe hypoglycaemia.

According to the study report on Study 3005, there was a tendency towards fewer cases of severe hypoglycaemia with insulin glulisine compared with RHI (see Table 11). However, for the second half of the study period, which mainly accounts for the differences between treatment groups, there were no data available for noticeably more patients in the insulin glulisine group than in the RHI group (21 patients [5%] vs. 8 patients [2%], respectively). This difference of 13 patients (3%) between groups is higher than the difference described between groups with regard to the event rate (8 patients, [2%]). The results are therefore neither robust in a worst-case analysis nor in a less conservative analysis; on the contrary, in both analyses the results reverse in favour of RHI (worst case: all 21 missing insulin glulisine patients, but none of the 8 missing RHI patients experienced a hypoglycaemia episode; less conservative analysis: all patients with missing data are evaluated as therapy failures with regard to this endpoint [i.e. all 21 missing insulin glulisine patients, and all 8 missing RHI patients experienced an episode]). Furthermore, according to the study report, two patients in the insulin glulisine group (but none in the RHI group) were prematurely withdrawn from the study due to recurring episodes of hypoglycaemia. In one patient, six of the eight episodes were classified as severe; in the other patient one of the nine episodes was classified as severe. When considering the total number of episodes occurring in all patients, these events cannot (at least completely) have been included in the analysis.

In addition to the information in Table 11, both in the publication on Study 3002 and in the study report on Study 3005, rates of patients with $\geq$ 1 episode were listed (including data on the mean event rates per patient per month). Due to the extremely skewed distribution (no event occurred in over 95% of patients in both groups), the information value of these data is low. In summary, no advantage of either treatment option with regard to the occurrence of symptomatic severe hypoglycaemia was shown in either study.

Total hypoglycaemia rate

The results for the endpoint "total hypoglycaemia rate" are presented in Table 12. No information was provided for any study on whether an independent and blinded validation of results (with regard to treatment) was conducted. Therefore the results are of low informative value, due also to the differing definitions of the endpoint "hypoglycaemia" (symptoms only / symptoms or a blood glucose level below a predefined level [self-monitoring]).

Table 12: Total hypoglycaemia rate

Insulin analogue Study	**Definition**	**Results**
Insulin lispro		
Z012	Symptoms; or BG < 36 mg/dl	*Events / Patient / 30 days:* [a] *Start of study: 2.3±4.5 [L] vs. 3.4±5.3 [RHI]; p=0.61* *End of study: 2.1±3.2 [L] vs. 2.5±4.6 [RHI]; p=0.51* *Change: -0.2±4.0 [L] vs. -0.9±4.1 [RHI]; p=1.0*
Z014	Symptoms; or BG < 36 mg/dl	*Events / Patient / 30 days:* [a] *Start of study: 1.9±2.9 [L] vs. 1.6±3.2 [RHI]; p=0.61* *End of study: 0.8±2.3 [L] vs. 0.8±2.1 [RHI]; p=0.65* *Change: -1.1±2.5 [L] vs. -0.8±2.3 [RHI]; p=0.32*
Z016[b]	Symptoms; or BG < 63 mg/dl	*Events / Patient / 30 days:* [a] *Start of study:*[c] *1.3±2.7 [L] vs. 1.3±2.8 [RHI]; p=0.6* *End of study: 0.9±2.1 [L] vs. 0.8±1.9 [RHI]; p=0.39* *Change: n.d.*
Canadian Lispro Study	Symptoms; or BG < 60 mg/dl	Events / Patient / 30 days: [d] 1.8±0.3 [L] vs. 1.7±0.3 [RHI]; p: n.d.
Altuntas 2003	Symptoms; or BG < 60 mg/dl	0.57% [L] vs. 0.009% [RHI][e], p = 0.012
Insulin glulisine		
3002	Symptoms	Total treatment period:[f] Events / patient / month:[a] 1.2±2.1 [G] vs. 1.3±2.4 [RHI]; p: n.d. Number of patients with ≥ 1 episode: 317 (72.9%) [G] vs. 322 (73%) [RHI]; p: n.d.
3005	*Symptoms*	*Total treatment period:* *Events / patient / month:* [a] *0.7±1.4 [G] vs. 0.6±1.5 [RHI]; p: n.d.* *Number of patients with ≥ 1 episode / 6 months:* *226 (50.4%) [G] vs. 240 (54.3%) [RHI]; p: n.d.*

a: Mean value ± standard deviation, rounded off where necessary.
b: Inconsistent information between study report and publication by Bastyr; in the following data from the study report are presented, as this is more transparent.
c: Two weeks after start of study.
d: Mean value ± standard error, rounded off where necessary.
e: Reference unclear (% of what?); information on symptomatic hypoglycaemia is not provided.
f: According to additional information provided by Dailey.
BG: blood glucose level (self-monitoring); [L]:insulin lispro; [RHI]: regular human insulin; [G] insulin glulisine; n.d.: no details provided.
Italics: information according to the study report, no or insufficient information in publicly accessible publications.

Insulin lispro

In all studies on insulin lispro, hypoglycaemia was defined as follows: occurrence of hypoglycaemia-related symptoms (independent of the actual blood glucose value) or self-monitoring of a blood glucose value lower than a predefined value (36, 60, or 63 mg/dl;

according to study). Therefore in all studies, asymptomatic cases of hypoglycaemia were also allocated to this endpoint.

The change in hypoglycaemia rate between start of study and end of study was comparable between groups in the Z014 and Z016 studies. In Study Z012, the hypoglycaemia rate was noticeably more reduced in patients receiving RHI than in those receiving insulin lispro. In this study, ultralente was used in both groups as the longer-acting insulin (in all other studies, NPH-insulin was used; in Study Z016, both NPH insulin and ultralente were used). Whether, and if yes, to what extent this contributed to the observed difference is however unclear (also due to the general problem of the validity of the endpoint). Likewise, the noticeably higher baseline level in the RHI group at the start of the study could sufficiently explain the observed difference.

In the Canadian Lispro Study (Ross 2001), the hypoglycaemia rate was similar between treatment groups (a significance test was not conducted).

In the publication by Altuntas in 2003, even though a corresponding definition of hypoglycaemia was provided (hypoglycaemia-associated symptoms or a blood glucose level < 60 mg/dl), results were only presented for the latter category. Significantly more episodes of hypoglycaemia occurred in patients treated with insulin lispro compared with RHI.

However in this study, the reference (% of what?) and therefore the absolute frequency per time unit is unclear. Furthermore, due to the described deficiencies with regard to the description of changes in HbA_{1c} levels, it is unclear whether the higher hypoglycaemia rate under insulin lispro is the result of a more intensive lowering of blood glucose levels.

In summary, with regard to the hypoglycaemia rate, the studies on insulin lispro do not show a clear advantage in favour of one of the two treatment options.

Insulin glulisine

In both studies on insulin glulisine, the event “hypoglycaemia” was defined by the existence of corresponding symptoms; asymptomatic cases of hypoglycaemia were therefore not recorded.

The publication detailing Study 3002 (Dailey 2004) only included information on the second study period for “hypoglycaemia”, whereas the information provided separately by Dailey referred to the whole study period.

The event rate per person per month, as well as the rate of patients with $\geq$ 1 episode during the study period, was comparable between treatment groups in both studies (3002 and 3005).

In summary, in the studies on insulin glulisine, no definite advantage in favour of either treatment option was shown with regard to the hypoglycaemia rate.

Nocturnal hypoglycaemia

The results for the endpoint “nocturnal hypoglycaemia” are shown in Table 13.

Table 13: Nocturnal hypoglycaemia

Insulin analogue Study	**Endpoint**	**Results**
Insulin lispro		
Z012	*No*	-
Z014	*No*	-
Z016	*In the study report: no;* in Bastyr 2000: as defined under "general" and occurring between 0:00 und 6.00 a.m.	Number of patients with = 1 episode/year: 10.4% [L] vs. 13.7% [RHI][a] Number of patients with > 1 episode/year: 9.3% [L] vs. 8.2% [RHI][a]
Canadian Lispro Study	Yes (0:00 to 6:00 a.m.).	0.08 [L] vs. 0.16 [RHI]; p = 0.057 (Events / patient / 30 days).
Altuntas 2003	No	-
Insulin glulisine		
3002	Yes (as defined under "general" and occurring during sleep).	Treatment period Month 4 to Month 6:[b] Rate of patients ≥ 1 episode:[c] 21.4% [G] vs. 24.5% [RHI]; p = 0.3
3005	*Yes (occurring at night; two different endpoints: "severe" and "symptomatic").*	*Endpoint "severe":* *Total study period:* *Number of patients with ≥ 1 episode:*[d] *3 (0.7%) [G] vs. 5 (1.1%) [RHI]; p: n.d.* *Treatment period Month 4 to Month 6:* *Number of patients with ≥ 1 episode:*[e] *0 (0%) [G] vs. 3 (0.7%) [RHI]; p: n.d.* *Endpoint: "symptomatic":* *Total study period:* *Number of patients with ≥ 1 episode:*[f] *95 (21.2%) [G] vs. 100 (22.6%) [RHI]; p: n.d.* *Treatment period Month 4 to Month 6:* *Number of patients with ≥ 1 episode:*[g] *39 (9.1%) [G] vs. 63 (14.5%) [RHI]; p=0.029*

a: No significance test provided for the noted comparisons; for "freedom of events": p=0.69
b: No information provided for the first half of the study period.
c: Absolute numbers not provided.
d: Total number of episodes: 3 [G] vs. 6 [RHI].
e: Total number of episodes: 0 [G] vs. 4 [RHI].
f: Total number of episodes: 256 [G] vs. 347 [RHI].
g: Total number of episodes: 87 [G] vs. 158 [RHI].
[L]: insulin lispro; [RHI]: regular human insulin; [G] insulin glulisine.
Italics: information according to the respective study report; no or insufficient information available in publicly accessible publications.

Insulin lispro

Information on nocturnal hypoglycaemia was found in the publications by Bastyr 2000 (Study Z016) and Ross 2001 (Canadian Lispro Study). In both publications, this endpoint referred to hypoglycaemia (including asymptomatic hypoglycaemia) that occurred between 0.00 and 6:00 a.m.

In the study report on Study Z016, no information was provided on the endpoint "nocturnal hypoglycaemia"; therefore the information provided in Bastyr 2000 apparently refers to a post-hoc evaluation.

In the Canadian Lispro Study, few hypoglycaemia episodes occurred; fewer episodes occurred in patients receiving insulin lispro compared with RHI. This difference was not statistically significant. Data on variability were not provided. For the endpoint "nocturnal hypoglycaemia", no information was provided on the frequency of severe episodes.

In summary, in the studies on insulin lispro no clear advantage for either treatment option was shown for the endpoint "nocturnal hypoglycaemia".

Insulin glulisine

For both studies on insulin glulisine, information was provided on nocturnal hypoglycaemia, without defining the precise period when this episode was recorded (e.g. between 0:00 and 6:00 a.m.). The term "nocturnal" was defined as "occurring while the patient was asleep (between bedtime and rising in the morning)" in the publication by Dailey.

In Study 3002, no significant difference with regard to the occurrence of nocturnal hypoglycaemia was shown between groups. Again, only the results for the second study period were reported. No information was provided on whether and, if yes, how often these hypoglycaemia episodes were severe. The additional data forwarded by the author (Dailey) did not provide further information in this regard.

In Study 3005, the rate of patients who experienced at least one episode of nocturnal hypoglycaemia was similar between groups throughout the whole study period. This also applies to episodes of severe nocturnal hypoglycaemia. For the treatment period Month 4 to Month 6 (second half of study), a noticeable, statistically significant difference with regard to symptomatic nocturnal hypoglycaemia was shown in favour of insulin glulisine. This difference can only partially be explained by the higher dropout rate in the insulin glulisine group and the premature withdrawal (instructed by the treating physician) of two insulin glulisine patients due to recurring hypoglycaemia episodes (see above under "severe hypoglycaemia"). However, according to the study report, there was already a noticeable

difference between treatment groups with regard to the endpoint “nocturnal symptomatic hypoglycaemia” before the start of the treatment period (in the screening/run-in phase). In the insulin glulisine group, the event rate of 0.16±0.59 events per patient per month and the variance were noticeably lower than in the RHI group (0.23±0.76).

The event rates converged over the course of the study (0.1±0.33 in the insulin glulisine group and 0.13±0.39 in the RHI group). Therefore, in Study 3005, a reduction of the event rate (difference between mean values) of 0.06 in the insulin glulisine group was shown vs. 0.1 in the RHI group. Furthermore, on average there was a tendency towards a more intensive lowering of blood glucose levels over the whole study period in patients treated with RHI compared with insulin glulisine (according to the study report: between 0.05% and 0.1% [glycosylated haemoglobin]). Besides the general problem of a lack of blinding of patients and treating staff, as well as a lack of an independent validation of the endpoint “hypoglycaemia”, this observation strongly qualifies the noticeable differences in the second half of the study described above.

In summary, the studies on insulin glulisine, especially when considering the whole study period, did not show a clear advantage for either treatment option with regard to the endpoints “nocturnal hypoglycaemia”, “severe hypoglycaemia”, and “symptomatic hypoglycaemia”.

Summary – rate of hypoglycaemia episodes under consideration of the lowering of blood glucose levels

The data available do not show a clear advantage for any treatment option with regard to the occurrence of severe and non-severe hypoglycaemia. This also applies to nocturnal hypoglycaemia.

5.3.5 Quality of life and treatment satisfaction

Insulin lispro

QoL instruments were employed in two studies (Z016 and Canadian Lispro Study).

Whereas in the publication on Study Z016 (Bastyr 2000), it was explicitly stated this evaluation was only conducted in the study centres in the USA and Canada (in 195 patients [53%]), in the study report it was noted that this evaluation was also conducted in France (additionally 92 patients [26%]). Neither a description of characteristics of the QoL subgroup (demographic data, diabetes-related baseline data, etc.) nor information on whether event rates (e.g. for severe hypoglycaemia) differed between this subgroup and the overall study population were provided. This clearly limits the usability of results. No detailed QoL data was provided in the publication by Bastyr or in the study report on Study Z016; however in the study report it was stated that no statistically significant differences between treatment groups were found for the primary domains of the instrument, including “treatment satisfaction” and “treatment flexibility”. This also applies to the secondary domains; no statistically significant differences between treatment groups were found after baseline adjustment.

Likewise, in the Canadian Lispro Study (Ross 2001), a QoL assessment (DQOL, Diabetes Quality of Life Measure questionnaire [a disease-specific instrument]) was only conducted in a subgroup (approx. 69% of the total population) at the start and end of the study. No information was provided on how this subgroup was selected, or on subgroup-specific baseline and endpoint data. Therefore, all in all, the results are hardly interpretable. No significant difference was shown between treatment groups for the total score. A statistically significant difference was shown in one of the four subscales in favour of insulin lispro (diabetes-related worries [7 out of 55 questions] absolute change: +7 points in the insulin lispro group vs. -1 point in the RHI group [read off Figure 3, Ross 2001], $p = 0.008$]). In summary, in all publications on insulin lispro, robust data were not available for the QoL and treatment satisfaction endpoints. On the basis of the available information, no clear advantage for either treatment option can be concluded.

Insulin glulisine

In both studies on insulin glulisine, data on treatment satisfaction were collected (this information was included in the FDA and EMEA regulatory documents [19,20]). No such information was provided in the publication by Dailey 2004. For Study 3002, no detailed results were provided in any of the available publications.

The study report on Study 3005 included a detailed presentation of the results on treatment satisfaction (Diabetes Treatment Satisfaction Questionnaire; DTSQ). The DTSQ includes eight questions on treatment satisfaction including the perceived frequency of hypo- and hyperglycaemia. Only 611 of the originally 890 randomised patients were included in this analysis (69%). Two reasons for exclusion were reported in the study report: missing validation of the instrument employed in the respective national language, and exclusion of patients who participated in the study for less than eight weeks. In particular, the second criterion may possibly have led to a bias in the selection of patients. It is unclear how relevant this criterion was for the two respective treatment groups. The subgroup of 611 patients is described as an "QoL-ITT population", without an ITT-analysis actually being available. Furthermore, the information provided in the study report on the number of patients evaluated is inconsistent; according to the results tables, only 606 (instead of 611) patients were included in the QoL-ITT population. Data on the "Treatment Satisfaction Score" (made up out of six of the eight questions[†††]) were only available for 548 (90.4%) of these patients. For the other two questions included, the response rate was lower (528 [87%] and 531 [88%]); no explanation was provided in the study report for these lower rates. For the "Treatment Satisfaction Score", relating to the mean change from baseline, a statistically significant difference was shown in favour of insulin glulisine *(*+0.9 points [median: 0 points] vs. +0.4 points [median: 0 points], p=0.033). For both other questions, only minor differences were shown relating to the change from baseline (0.2 points in favour of insulin glulisine; 0.1 points in favour of RHI). Furthermore, for the analyses described, the "DTSQs" version of the questionnaire (primarily suited to describe a status, not a change) was also employed; the "DTSQc" version (suited to describe a change) was only employed in 384 patients (43%). Overall, with regard to treatment satisfaction, the results of Study 3005 are of little informative value due to a strong selection bias, a high dropout rate within the selected subgroup, inconsistent information on the number of patients analysed, as well as unexplained missing answers to single questions of the (only limitedly suitable) questionnaire.

In summary, in the studies on insulin glulisine, no clear advantage was shown for either treatment option with regard to treatment satisfaction. General QoL assessments were not available.

[†††] Excluding the questions on the perceived frequency of hypo- and hyperglycaemia episodes.

5.3.6 Other adverse drug effects

The information provided on other adverse drug effects (except for hypoglycaemia) in the publicly accessible publications was overall insufficient, whereas in part in the study reports, detailed information was provided. None of the studies was designed primarily to investigate the safety of rapid-acting insulin analogues. In Table 14, a synoptic comparison of results for the following safety endpoints is shown: weight increase, rate of discontinuations due to adverse drug effects, and rate of serious unexpected adverse events.

Table 14: Other adverse drug effects

Insulin analogue Study	**Weight increase during the course of the study**[a]	**Rate of discontinuations due to adverse drug effects** **N (%)**	**Serious unexpected adverse events**[b] **N (%)**
Insulin lispro			
Z012	*p=0.10*		
Lispro	*1.9±4.3 kg*	*0 (0%)*	*0 (0%)*
RHI	*2.3±3.9 kg*	*1 (1.4%)*	*0 (0%)*
Z014	*p=0.99*		
Lispro	*1.6±4.0 kg*	*3 (4.1%)*	*3 (4.1%)*
RHI	*2.1±3.8 kg*	*3 (3.9%)*	*0 (0%)*
Z016	*p=0.25*		
Lispro	*4.3±5.4 kg*	*3 (1.6%)*[c]	*2 (1.1%)*
RHI	*4.7±5.2 kg*	*4 (2.1%)*	*0 (0%)*
Canadian Lispro S.	p=n.d.	n.d.	n.d.
Lispro	5 kg[d]		
RHI	4 kg[d]		
Altuntas 2003	unclear[e]	n.d.	n.d.
Insulin glulisine			
3002	p=0.37	n.d.	n.d.
Glulisine	1.8 kg[f]		
RHI	2.0 kg[f]		
3005	*p=0.15*		
Glulisine	*1.3 kg*[f]	*9 (2.0%)*	*38 (8.5%)*
RHI	*1.6 kg*[f]	*3 (0.7%)*	*40 (9.0%)*

a: Mean value ± standard deviation, rounded off if necessary.
b: Except for hypo- and hyperglycaemia.
c: Including 2 deaths.
d: Calculated from weight at baseline and end of study. Insulin lispro: baseline 79±2 kg, end of study 84±2 kg; RHI: baseline 77±2 kg, end of study 81±2 kg; (mean values ± standard error).
e: Inconsistent information in the publication.
f: No data provided on variance.
RHI: regular human insulin; n.d.: no details provided.
Italics: information according to the respective study report; no or insufficient information available in publicly accessible publications.

Insulin lispro

Information on weight changes was provided in the study reports on studies Z012, Z014, and Z016, as well as in the publication by Ross 2001 (Canadian Lispro Study). The information provided in the publication by Altuntas (2003) cannot definitely be allocated to the individual treatment groups due to the inconsistencies between the respective table and text; the results therefore remain unclear. In summary, the increase in weight throughout the course of the study was comparable between treatment groups (between 2 kg and approx. 5 kg).

Information on both the endpoints discontinuations of therapy due to adverse drug effects and serious unexpected adverse events was only found in the study reports of the studies Z012, Z014, and Z016. Whereas rates of discontinuations of therapy due to adverse drug effects were similar in all three studies, serious unexpected adverse events other than hypo- or hyperglycaemia were only reported for patients in the insulin lispro group; however, the rate was low (in total five events).

In summary, no clear advantage for either treatment option was shown for these two endpoints.

Insulin glulisine

In the publication by Dailey in 2004 (Study 3002), detailed information was found on the number and severity of adverse events, but sufficient information on the type of event was not provided. Forty patients in both the insulin glulisine group (9.2%) and in the RHI group (9.1%) experienced a serious non-hypoglycaemic event. How many of these events were classified as serious unexpected adverse events is unclear. Both groups experienced a similar increase in weight during the course of the study (+ 1.8 kg [insulin glulisine]; + 2.0 kg [RHI]; $p = 0.369$).

In Study 3005, discontinuations of therapy due to adverse drug effects occurred more frequently in patients treated with insulin glulisine compared with RHI (the overall rate of events was low). This supports the argument that the results in the study report on “severe hypoglycaemia” are of questionable validity. The rate of serious unexpected adverse events was comparable between groups. In Study 3005, as in the other studies, no statistically significant difference for weight change was shown between groups.

In summary, no advantage for either treatment option was shown with regard to the endpoints noted above.

5.4 Meta-analysis / sensitivity analysis

Data aggregation for the relevant endpoints by means of meta-analysis was either not meaningful or possible on the basis of the available data.

5.5 Subgroup analyses

5.5.1 Gender

No gender-specific conclusions can be drawn from the data available, and no indications can be inferred that the results presented should be assessed differently for men or women.

5.5.2 Age

No age-specific conclusions can be drawn from the data available. The mean age in all studies lay between 55 and 60 years (a wide variance was shown; the standard deviation in the larger studies was approx. 10 years). No further information on age distribution was found in any publication. No studies were available that had been specifically conducted in certain age groups (e.g. in geriatric patients).

5.5.3 Concomitant diseases

Conclusions for patient subgroups with or without specific rare or frequent diabetes-related diseases cannot be made on the basis of the available data.

6. Summary

A total of seven relevant studies were identified by an extensive search in bibliographic databases, reference lists of relevant review papers and HTA reports, as well as publicly accessible study registers, and regulatory documents. Sufficient transparent information was available for these studies and they were therefore included in the evaluation. In addition, a further potentially relevant study was found, which was not included in the evaluation process as a full-text publication was not available.

In five of the studies included, insulin lispro was compared with RHI (both in combination with longer-acting insulin); for three of these studies, study reports were available which provided substantially more information than the publications. In the other two studies, insulin glulisine was compared with RHI (both in combination with longer-acting insulin). For one of these studies, the results of which had not previously been published, the evaluation was mainly conducted on the basis of the study report provided by the manufacturer. No relevant and fully published study was found on insulin aspart. The results on Study 037 were only published as an abstract in 1999. Novo Nordisk was not prepared to provide study data under the prerequisite that these data were to be published in this report. Therefore no detailed, publicly accessible results were available on a randomised long-term intervention study in patients with type 2 diabetes mellitus treated with insulin aspart. Furthermore, no relevant studies were found on premixed formulations of rapid-acting insulin analogues or short-acting RHI combined with longer-acting insulins or on direct comparisons between rapid-acting insulin analogues.

Overall, the quality of reporting in the publicly accessible publications was insufficient. In part, the information presented on study methods and results deviated substantially from the information presented in the study reports.

With a study period between 5.5 and 12 months, none of the studies was designed to investigate the effect of rapid-acting insulin analogues with regard to the reduction of diabetic late complications or total mortality. Information on hospitalisations was only provided within the framework of safety evaluations.

The hypoglycaemia rate was recorded in all studies; however, due to the open-label study design and the lack of blinding of the endpoint evaluation, all studies were susceptible to systematic bias. Furthermore, the missing or unclear consideration of premature discontinuations of therapy, in particular in the studies on insulin glulisine, strongly limited the informative value of the results. In summary, under consideration of these problems, no

clear advantage was shown for any of the investigated treatment options, neither with regard to severe, symptomatic, nor nocturnal hypoglycaemia.

Only limited QoL data were available (only for two studies on insulin lispro). In the largest study on insulin lispro (approx. 350 patients), no difference was shown between treatment groups. In the shortest study included (5.5 months; approx. 150 patients), a statistically significant difference in favour of insulin lispro in a subcategory of the employed QoL instrument was shown; however, for the total score of this instrument, no statistically significant difference between groups was demonstrated. In summary, no clear advantage was shown for either treatment option.

Treatment satisfaction was assessed in both studies on insulin glulisine; however, the publication on Study 3002 did not include information on the respective results. The results provided in the study report on Study 3005 are of little informative value due to substantial selection bias, methodological deficiencies, and inconsistent data. Therefore, no definite statements can be made on the effects of long-term therapy with rapid-acting insulin analogues (compared with RHI) on treatment satisfaction.

Information on adverse non-hypoglycaemia events was scarce in the publicly accessible publications, but was provided in the study reports. In the safety evaluation, no clear advantage or disadvantage was shown for insulin lispro or for insulin glulisine compared with RHI; however, there was a tendency towards more discontinuations due to adverse drug effects in patients treated with insulin glulisine and towards more serious unexpected adverse events in patients treated with insulin lispro compared with RHI.

In all studies, insofar as reported, similar weight increases occurred for both patients receiving the study drug (insulin analogue) and the control (RHI): the weight gain ranged from approx. between 1.5 kg and 5 kg throughout the study periods.

With a maximum study period of 12 months, no study was suited to show the safety of long-term therapy with insulin analogues in patients with type 2 diabetes mellitus. In particular, the question of potential consequences of a potential mitogenic potency of insulin analogues described in preclinical trials with regard to the long-term treatment of diabetic type 2 patients remains unanswered.

7. Discussion

This systematic analysis of randomised long-term intervention studies did not provide evidence of an additional patient-relevant benefit of rapid-acting insulin analogues compared with RHI. This refers to the single agents included in the evaluated studies, as well as to the whole substance class.

It is noticeable that no high-quality long-term studies are available that primarily aim to show evidence of a patient-relevant benefit, even though one of the drugs investigated (insulin lispro) has been approved and marketed for about ten years. This does not only apply to the endpoints “morbidity” and “mortality” but also to other aspects of patient-relevant benefits; e.g. rate of severe hypoglycaemic episodes, QoL, and treatment satisfaction. All patient-relevant outcomes were, if at all, investigated within the framework of the secondary or further endpoint evaluation or in the safety evaluation. It was not discernable for any study that an attempt to minimise bias for non-primarily evaluated patient-relevant outcomes by employing adequate instruments had been made. On the contrary, for some studies there were indications of a selective publication of partial results, whereas results for predefined endpoints were sometimes missing without explanation. Furthermore, some substantial inconsistencies between the information in journal publications, other publicly accessible sources, and/or study reports were noticeable.

The publications provided in the statements on the preliminary report did not change these findings.

Two retrospective US register studies [21, 22] and a health economical analysis from German-language countries [23] were provided by Lilly. The written statements provided by Lilly on these publications were selective and partially incorrect. In both register studies, the primary objective was the assessment of the frequency of use of health care services, comparing patients treated with insulin lispro vs. patients treated with RHI. The risk profile between both treatment groups differed substantially. A comparable collective with regard to risk profile was to be selected from the total population by means of “Propensity Score Matching”. With regard to study results, the two studies neither differentiated between patients with type 1 or type 2 diabetes, nor was this a criterion for the matching procedure. According to the results of one study, patients treated with insulin lispro had significantly more outpatient visits, received significantly more prescriptions, and experienced significantly fewer hospitalisations than patients treated with RHI. In the second study, this tendency was also shown; however, the differences between groups were not statistically significant. Both studies are not suited to provide evidence of an increased frequency of

outpatient visits due to insulin lispro, or an increased frequency of hospitalisations due to RHI. They may however be used for the formulation of a hypothesis in this regard. This also applies to the third publication [23], which bases its analyses primarily on a Markov model that was not transparently described. The validity of this model strongly needs to be queried, also due to the claim by the authors that treatment with insulin lispro promises a significant lowering of HbA_{1c} levels, and that the danger of hypoglycaemia is avoided [23]. Neither claim is supported by the publication. The derivable hypotheses from the provided publications, either in favour of or against insulin lispro, could have been, can be, and should be assessed in adequately designed intervention studies. This equally applies to other rapid-acting insulin analogues, and would in principle be meaningful prior to any widespread introduction of novel drugs.

The publication on treatment satisfaction (also provided by Lilly) in which patients were questioned who had switched from RHI to insulin analogue therapy, is also not suited to provide evidence of a superiority of insulin lispro [24]. This was discussed in the scientific hearing (see meeting minutes; Appendix E). In this context, it was shown in the scientific hearing that no convincing evidence could be provided for the lack of the necessity of a fixed injection-meal interval for rapid-acting insulin analogues. On the basis of pharmacokinetic and pharmacodynamic data, a shortened fixed injection-meal interval may be inferred, but not no interval at all. In addition, this applies to an RHI concentration of 100 units per ml (U100), but only to a lesser extent to an RHI concentration of 40 units per ml (U40) [25-28]. In all studies included in this report, RHI was used in a concentration of 100 units per ml. Relevant direct comparator studies including U40 RHI were neither identified by the literature search nor were such studies known to the representatives of the pharmaceutical industry. This point, and the lack of pen systems with U40 RHI on the German market, was criticised in statements on the preliminary report.

Furthermore, the clinical relevance of a fixed injection-meal interval beyond the pharmacodynamic effect is unclear. It may be postulated that a long injection-meal interval is associated with an increased risk of hypoglycaemia, insofar as the meal following the injection is not taken as planned. No evidence was available (and was also not presented in the statements submitted or in the scientific hearing) showing that compliance with a fixed injection-meal interval of 30-45 minutes is necessary with RHI therapy, e.g. to improve metabolic control (measured by means of HbA_{1c} levels), and/or to reduce the risk of diabetic late complications.

Lilly supplied several studies on adverse drug effects including a summary of clinical study results [29-31]. These publications, which are mainly based on information from studies included in this report, are consistent with the conclusions on adverse drug effects in this report. They are not suited to answer the questions raised in preclinical studies about a potentially increased mitogenic potency and/or carcinogenicity of individual insulin analogues. This also applies to the numerous original publications on rapid-acting insulin analogues referenced in the submitted statements, which in part refute and in part support these concerns [9,11,32-40]. In the "National Care Guideline for Type 2 Diabetes Mellitus" (Nationale Versorgungsleitlinie Typ 2 Diabetes mellitus; status: April 2003), generated with the collaboration of the German Diabetes Association, it is stated that an increased mitogenic effect cannot be definitely excluded for insulin analogue therapy [41]. This statement in the guideline is not supported by scientific references. It is, however, supported at least for insulin aspart and insulin glulisine, by statements made by the EMEA and/or FDA in documents on the respective drug approval procedures summarised in Table 15 [19,42-48]. In this regard, no relevant statements were provided on insulin lispro in the FDA documents. However, an increased IGF-receptor affinity has also been described for this drug [11,32]. In summary, the clinical relevance of the preclinical findings is still unclear. Therefore, unless proven otherwise by means of adequately designed studies, they are to be seen as a potential safety risk for long-term insulin analogue therapy. Studies on this topic were neither brought forward in the written statements submitted nor in the scientific hearing.

Table 15: Extract from publicly accessible FDA and EMEA statements on the mitogenic/carcinogenic potency of rapid-acting insulin analogues

Drug	**Extract from EMEA statements**[a]	**Extract from FDA statements**[a]
Insulin lispro	**July 2004 (date of the last scientific assessment)** - *"…the company was requested to submit new additional 'in vitro cell' studies to assess the stimulation on DNA synthesis of insulin lispro compared to human insulin and Aspartate B 10 insulin in Hep G2 human hepatoma cells…. The overall results of all replicates did not demonstrate any mitogenic properties."* - *"As the result of the mutagenic potential assessed through several series of tests was uniformly negative, and no proliferative effect has been observed, there was no need to conduct conventional carcinogenicity data."*	**February 1999 (review completion date)** No relevant details.
Insulin glulisine	**October 2004 (date of the last scientific assessment according to Module 8 of the EPAR[b] documents)** - *"The in vitro data on receptor binding and on mitogenicity and the in vitro proliferation studies on mammary glands indicated a lack of mitogenic potential of insulin glulisine."* - *"Conventional carcinogenicity studies are not warranted.… One-year study in rats was performed especially aimed at investigating the carcinogenic potential of insulin glulisine. The tumours detected were not considered to be treatment related."*	**January 2004 (review completion date)** - *"The IGF-1 receptor affinity of HMR 1964* [insulin glulisine] *was lower than that of human insulin." "… it appears that a general mitogenic effect on mammary gland related to the compound HMR 1964* [insulin glulisine] *or HR 1799* [human insulin] *is not likely."* - *"Standard 2-year carcinogenicity studies in animals have not been performed.… There was a non-dose dependent higher incidence of mammary gland tumors in female rats administered insulin glulisine compared to untreated controls. The incidence of mammary tumours for insulin glulisine were similar to human insulin. The relevance of these findings to human is not known."* - *"There was only a statistically significant increased tumor incidence in dose groups receiving 5 or 40 IU/kg insulin glulisine or 40 IU/kg HR 1799* [human insulin]*…, but not in high dose groups receiving 100 IU/kg insulin glulisine or 100 IU/kg HR 1799* [human insulin]*."*

continued

Table 15: Extract from publicly accessible FDA and EMEA statements on the mitogenic/carcinogenic potency of rapid-acting insulin analogues (continued)

Drug	Extract from EMEA statements	Extract from FDA statements
Insulin aspart	**September 2004 (date of the last scientific assessment)** - *"It was concluded that the presented information on receptor affinities… provided evidence that there were no relevant differences between IAsp and human insulin."* - *"Data on the mitogenic activity of IAsp relative to HI and the insulin analogue AspB10 as obtained in human MCF-7 cells and in CHO K1 cells was presented. The results in CHO K1 cells were essentially similar to those of HI whereas the mitogenic activity of IAsp in MCF-7 cells indicated differences to HI.… the results in MCF-7 cells were not sufficiently robust for proper assessment."* - The tumourigenicity of insulin aspart and human insulin was investigated in two dose-dependent 52-week toxicity studies in rats: *"It is concluded that both HI and IAsp have the capability to produce mammary tumours in the Sprague-Dawley rat upon prolonged exposure at supraphysiological doses.…Although the design of the 52-week studies with IAsp can be criticised, it was concluded that the results…did not indicate any significant or relevant difference in tumourigenic potential between IAsp and HI. The overall evidence from in vitro and in vivo data thus suggests that the mammary tumours observed are not relevant for the proposed therapeutic use of IAsp."* - *"No carcinogenicity study was performed and this was accepted in view of the tumour findings in the 52-week repeat dose toxicity studies in rats…"*	**March 2000 (review completion date)** - *"The affinity of X14* [insulin aspart]*…. for the IGF-1 receptor is slightly higher but not significantly different from human insulin (0.05% with X14* [insulin aspart]*, 0.03% with human insulin… vs. 100% with IGF)."* - *"The standard 2-year bioassay to determine the carcinogenicity of the drug (X14)* [insulin aspart]*… have not been performed."* - *"Study A (non-QA[c] study):… the first exploratory 1-year toxicity study in rats…..indicated that the tumourigenic potential of X14* [insulin aspart] *was no greater than endogenous insulin…"* - *Study B (QA study): One Year-Toxicity Study in Rats...suggests that the incidence of mammary tumors with X14* [insulin aspart] *may be higher than with human insulin, and further studies may be required to clearly establish its role in the induction of mammary gland tumours."* **Addendum to the Novomix 70/30 review of August 2000** - *"Standard 2-year carcinogenicity studies in animals have not been performed.… At a dose of 200 U/kg/day, NovoLog increased the incidence of mammary gland tumours in females when compared to untreated controls. The incidence of mammary tumours for NovoLog was not significantly different than for regular human insulin. The relevance of these findings to humans is not known."*

[a]Direct quotes in italics. Additional comments in normal font; [b]EPAR: European Public Assessment Report; [c]QA: Quality assurance.

All in all, the questions raised in the statements on the methodological aspects of this report did not have a relevant influence on the report, even after their discussion in the scientific hearing.

Any resulting amendments are described in Section 5.1.6. The minimum study period of 24 weeks for the inclusion of studies in this report, queried in several statements, is consistent with EMEA requirements (required minimum study period of 6-12 months for confirmatory studies on insulin analogues [49]). Furthermore, the results of a recently published systematic review of randomised trials, which also included studies with a study period > 4 weeks, were qualitatively consistent with the results of this report [17].

In summary, it can be concluded from the results presented in this report that most patient-relevant questions, including those concerning the potential damage caused by long-term treatment with insulin analogues, cannot be answered on the basis of the current available studies of higher quality.

8. Conclusion

For patient-relevant outcomes, there is no convincing evidence of a superiority of rapid-acting insulin analogues compared with RHI in diabetes mellitus type 2 therapy. Rapid-acting insulin analogues have not been sufficiently investigated with regard to their potential long-term beneficial and harmful effects.

9. List of included studies

Insulin lispro:

Study Z012

- Anderson JH, Brunelle RL, Koivisto VA, Trautmann ME, Vignati L, DiMarchi R, and the Insulin Lispro Study Group. Improved mealtime treatment of diabetes mellitus using an insulin analogue. Clin Ther 1997; 19: 62-72.
- Clinical Study Report, Study F3Z-MC-IOAB(b). LY275585 versus Humulin® R: Pre-Meal Therapy in Type II Diabetes. 7 July 1994 (provided by Lilly Deutschland GmbH).

Study Z014

- Anderson JH, Brunelle RL, Koivisto VA, Trautmann ME, Vignati L, DiMarchi R, and the Insulin Lispro Study Group. Improved mealtime treatment of diabetes mellitus using an insulin analogue. Clin Ther 1997; 19: 62-72.
- Clinical Study Report, Study F3Z-MC-IOAD(b)(1). LY275585 versus Humulin® R: Pre-Meal Therapy in Type II Diabetes. 10 August 1994 (provided by Lilly Deutschland GmbH).

Study Z016

- Bastyr EJ, Yuang H, Brunelle RL, Vignati L, Cox DJ, Kotsanos JG. Factors associated with nocturnal hypoglycemia among patients with type 2 diabetes new to insulin therapy: experience with insulin lispro. Diabetes Obes Metab 2000; 2: 39-46.
- Clinical Study Report, Study F3Z-MC-IOAF. LY275585 versus Humulin® R: Pre-Meal Therapy in New Patients with Type II Diabetes. 31 August 1994 (provided by Lilly Deutschland GmbH).

Canadian Lispro Study

- Ross SA, Zinman B, Campos RV, Strack T. Canadian Lispro Study Group. A comparative study of insulin lispro and human regular insulin in patients with type 2 diabetes mellitus and secondary failure of oral hypoglycemic agents. Clin Invest Med 2001; 24: 293-298.

Altuntas (2003) Study

- Altuntas Y, Ozen B, Ozturk B, et al. Comparison of additional metformin or NPH insulin to mealtime insulin lispro therapy with mealtime human insulin therapy in secondary OAD failure. Diabetes Obes Metab 2003; 5: 371-378.

Insulin glulisine:

Study 3002

- Dailey G, Moses RG, Rosenstock J, Ways K. Insulin Glulisine provides improved glycemic control in patients with type 2 diabetes. Diabetes Care 2004; 27: 2363-2368.

Study 3005

- Clinical Study Report, HMR1964-3005. 26-week, multinational, multicenter, controlled, open, 1:1 randomized, parallel, clinical trial to assess noninferiority between HMR1964 and regular human insulin injected subcutaneously in subjects with type 2 diabetes mellitus also using NPH insulin. 16 January 2004 (provided by Sanofi-Aventis Deutschland GmbH).
- A summary of the study is provided in the documents [19] and [20].

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http://www.fda.gov/cder/foi/nda/2000/20-986_NovoLog_medr_P5.pdf;
Access on 12 June 2005.

48. Center for Drug Evaluation and Research. Application-Number 21172. Pharmacological Review. http://www.fda.gov/cder/foi/nda/2001/21172_Novolog_pharmr.pdf.
Access on 12 June 2005.

49. Committee for proprietary medicinal products (CPMP). Note for guidance on clinical investigation of medicinal products in the treatment of diabetes mellitus. London, 30 May 2002. CPMP/EWP/1080/00.

Appendix A.1: Non-relevant publications (reviewed in full text)

Study period < 24 weeks

1. Chan WB, Chow CC, Yeung VT, Chan JC, So WY, Cockram CS. Effect of insulin lispro on glycaemic control in Chinese diabetic patients receiving twice-daily regimens of insulin. Chin Med J 2004; 117: 1404-1407.
2. Laube H. Experience with Lispro-insulin in the intensified therapy of IDDM and NIDDM patients. Diabetes Stoffwechsel 1996; 5: 273-276.
3. Perriello G, Pampanelli S, Porcellati F, et al. Insulin aspart improves meal time glycaemic control in patients with type 2 diabetes: a randomized, stratified, double-blind and cross-over trial. Diabet Med 2005; 22: 606-611.
4. Rami B, Schober E. Postprandial glycaemia after regular and lispro insulin in children and adolescents with diabetes. Eur J Pediatr 1997; 156: 838-840.
5. Skrha J, Smahelova A, Andel M, et al. Insulin lispro improves postprandial glucose control in patients with diabetes mellitus. Sbornik Lekarsky 2002; 103: 15-21.
6. Vignati L, Anderson JH, Jr., Iversen PW. Efficacy of insulin lispro in combination with NPH human insulin twice per day in patients with insulin-dependent or non-insulin-dependent diabetes mellitus. Multicenter Insulin Lispro Study Group. Clin Ther 1997; 19: 1408-1421.

No relevant endpoints

1. Fineberg NS, Fineberg SE, Anderson JH, Birkett MA, Gibson RG, Hufferd S. Immunologic effects of insulin lispro [Lys (B28), Pro (B29) human insulin] in IDDM and NIDDM patients previously treated with insulin. Diabetes 1996; 45: 1750-1754.
2. Lindholm A, Jensen LB, Home PD, Raskin P, Boehm BO, Rastam J. Immune responses to insulin aspart and biphasic insulin aspart in people with type 1 and type 2 diabetes. Diabetes Care 2002; 25: 876-882.

No RCT

1. Boehm BO, Vaz JA, Brondsted L, Home PD. Long-term efficacy and safety of biphasic insulin aspart in patients with type 2 diabetes. Eur J Intern Med 2004; 15: 496-502.

(Extension of a previously randomised study, with further participation without a renewed randomisation of patients.)

2. Howorka K, Pumprla J, Schlusche C, Wagner-Nosiska D, Schabmann A, Bradley C. Dealing with ceiling baseline treatment satisfaction level in patients with diabetes under flexible, functional insulin treatment: assessment of improvements in treatment satisfaction with a new insulin analogue. Qual Life Res 2000; 9: 915-930.

No patients with type 2 diabetes mellitus

1. Kaplan W, Rodriguez LM, Smith OE, Haymond MW, Heptulla RA. Effects of mixing glargine and short-acting insulin analogs on glucose control. Diabetes Care 2004; 27: 2739-2740.

Different additional blood glucose-lowering treatments

1. Roach P, Strack T, Arora V, Zhao Z. Improved glycaemic control with the use of self-prepared mixtures of insulin lispro and insulin lispro protamine suspension in patients with types 1 and 2 diabetes. Int J Clin Pract 2001; 55: 177-182.

2. Schernthaner G, Kopp HP, Ristic S, Muzyka B, Peter L, Mitteregger G. Metabolic control in patients with type 2 diabetes using Humalog Mix50 injected three times daily: crossover comparison with human insulin 30/70. Horm Metab Res 2004; 36: 188-193.

No predefined target intervention

1. Boivin S B. Assessment of in vivo stability of a new insulin preparation for implantable insulin pumps. A randomized multicenter prospective trial. EVADIAC Group. Evaluation Dans le diabete du Traitement par Implants Actifs. Diabetes Care 1999; 22: 2089-2090.

Appendix A.2: Systematic reviews, meta-analyses, and HTA-reports

1. Campbell RK, Campbell LK, White JR. Insulin lispro: its role in the treatment of diabetes mellitus. Ann Pharmacother 1996; 30: 1263-1271.
2. Davey P, Grainger D, MacMillan J, Rajan N, Aristides M, Gliksman M. Clinical outcomes with insulin lispro compared with human regular insulin: a meta-analysis. Clin Ther 1997; 19: 656-674.
3. Puttagunta AL, Toth EL. Insulin lispro (Humalog), the first marketed insulin analogue: indications, contraindications and need for further study. CMAJ 1998; 158: 506-511.
4. Toth EL, Lee KC. Guidelines for using insulin lispro. Can Fam Phys 1998; 44: 2444-2449.
5. Heinemann L. Hypoglycemia and insulin analogues: is there a reduction in the incidence? J Diabetes Complications 1999; 13: 105-114.
6. Setter SM, Corbett CF, Campbell RK, White JR. Insulin aspart: a new rapid-acting insulin analog. Ann Pharmacother 2000; 34: 1423-1431.
7. Heise T, Heinemann L. Rapid and long-acting analogues as an approach to improve insulin therapy: An evidence-based medicine assessment. Curr Pharm Des 2001; 7: 1303-1325.
8. Campbell RK, White JR, Jr. Insulin therapy in type 2 diabetes. J Am Pharm Assoc 2002; 42: 602-611.
9. Colquitt J, Royle P, Waugh N. Are analogue insulins better than soluble in continuous subcutaneous insulin infusion? Results of a meta-analysis. Diabetic Med 2003; 20: 863-866.
10. Plum M-B, Sicat BL, Brokaw DK. Newer insulin therapies for management of type 1 and type 2 diabetes mellitus. Consultant Pharmacist 2003; 18: 454-465.
11. Daugherty KK. Review of Insulin Therapy. J Pharm Pract 2004; 17: 10-19.
12. Haycox A. Insulin aspart: An evidence-based medicine review. Clin Drug Invest 2004; 24: 695-717.

13. Siebenhofer A, Plank J, Berghold A, et al. Meta-analysis of short-acting insulin analogues in adult patients with type 1 diabetes: continuous subcutaneous insulin infusion versus injection therapy. Diabetologia 2004; 47: 1895-1905.

14. Siebenhofer A, Plank J, Berghold A, Narath M, Gfrerer R, Pieber TR. Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus. The Cochrane Database of Systematic Reviews 2004, Issue 4. Art. No.: CD003287. DOI: 10.1002/14651858.CD003287.pub3.

15. Vivian EM, Olarte SV, Gutierrez AM. Insulin strategies for type 2 diabetes mellitus. Ann Pharmacother 2004; 38: 1916-1923.

16. Braunstein SN, White JR. Trends in the management of type 2 diabetes: an emerging role for insulin. J Manag Care Pharm 2005; 11: S2-S11.

17. Hirsch IB. Insulin analogues. N Engl J Med 2005; 352: 174-183.

18. Emerging Drug List: Insulin Aspart. No. 20, February 2002. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 2002.

19. Shukla VK, Otten N. Insulin lispro: a critical evaluation. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 1999.

Appendix B: Search strategies

Search date: 15 April 2005

Search mask: Ovid

Databases: Medline 66, Pre-Medline, EMBASE 88, CENTRAL

#	Query	Hits
1	(Lyspro$ or Lispro$).ti,ab,ot.	1058
2	(Lys$B28 or B28Lys$ or (lys$ adj1 B28)).ti,ab,ot.	107
3	(Pro$B29 or B29Pro$ or (pro$ adj1 B29)).ti,ab,ot.	166
4	humalog$.ti,ab,ot,tn.	618
5	133107-64-9.rn.	1591
6	1 or 2 or 3 or 4 or 5	2024
7	(insulin$ adj1 aspart$).ti,ab,ot.	308
8	(Asp$B28 or B28Asp$ or (asp$ adj1 B28)).ti,ab,ot.	54
9	(Novorapid$ or Novolog$).ti,ab,ot,tn.	214
10	116094-23-6.rn.	417
11	7 or 8 or 9 or 10	669
12	(Glulisine$ or Glulysin$).ti,ab,ot.	17
13	(Glu$B29 or B29Glu$ or (glu$ adj1 B29)).ti,ab,ot.	6
14	(Lys$B3 or B3Lys$ or (lys$ adj1 B3)).ti,ab,ot.	22
15	Apidra$.ti,ab,ot,tn.	18
16	207748-29-6.rn.	19
17	12 or 13 or 14 or 15 or 16	60
18	6 or 11 or 17	2357
19	(insulin$ adj6 (analog$ or derivat$)).ti,ab,ot.	4240
20	((shortacting or fastacting or rapidacting) adj6 insulin$).ti,ab,ot.	8
21	((short$ or fast$ or rapid$) adj1 acting adj6 insulin$).ti,ab,ot.	1219
22	((novel or new) adj6 insulin$).ti,ab,ot.	5859
23	19 or 20 or 21 or 22	10052
24	exp insulin/aa	1909
25	exp Insulin Derivative/	928
26	24 or 25	2837
27	23 or 26	11429
28	exp Diabetes Mellitus/	310557
29	diabet$.ti,ab,ot.	330905
30	mellitu$.ti,ab,ot.	109729
31	IDDM.ti,ab,ot.	12193
32	MODY.ti,ab,ot.	825

33	NIDDM.ti,ab,ot.	12968
34	(T1DM or T2DM or ((T1 or T2) adj1 DM)).ti,ab,ot.	913
35	(insulin$ depend$ or insulin?depend$ or noninsulin$ or noninsulin?depend$).ti,ab,ot.	47808
36	((matury or late) adj onset$ adj6 diabet$).ti,ab,ot.	339
37	(typ$ adj6 diabet$).ti,ab,ot.	74287
38	30 or 31 or 32 or 33 or 34 or 35 or 36 or 37	172756
39	exp Diabetes Insipidus/	7722
40	insipid$.ti,ab,ot.	6779
41	39 or 40	9285
42	28 or 38	344766
43	42 or (29 not (41 not 42))	391141
44	controlled clinical trial.pt.	133623
45	controlled clinical trials/	331109
46	randomized controlled trial.pt.	387133
47	randomized controlled trials/	134263
48	random allocation/	86908
49	cross-over studies/	43604
50	double-blind method/	196659
51	single-blind method/	19233
52	44 or 45 or 46 or 47 or 48 or 49 or 50 or 51	939549
53	((singl$ or doubl$ or trebl$ or tripl$) adj6 (blind$ or mask$)).ti,ab,ot.	230122
54	((random$ or cross-over or crossover) adj25 (trial$ or study or studies or intervention$ or investigat$ or experiment$ or design$ or method$ or group$ or evaluation or evidenc$ or data or test$ or condition$)).ti,ab,ot.	672686
55	(random$ adj25 (cross over or crossover)).ti,ab,ot.	44900
56	53 or 54 or 55	745618
57	52 or 56	1237743
58	exp meta-analysis/	26967
59	meta analysis.pt.	10659
60	(metaanaly$ or meta analy$).ti,ab,ot.	25815
61	58 or 59 or 60	46468
62	exp biomedical technology assessment/	9843
63	hta.ti,ab,ot.	840
64	((biomed$ or health$) adj6 technolog$ adj6 assessment$).ti,ab,ot.	1522
65	62 or 63 or 64	11222
66	exp "Review Literature"/	8377
67	((review$ or search$) adj25 (medical databas$ or medline or	46292

	pubmed or embase or cochrane or systemat$)).ti,ab,ot.	
68	66 or 67	53905
69	addresses.pt.	2396
70	bibliography.pt.	12134
71	biography.pt.	108214
72	case reports.pt.	1165447
73	clinical conference.pt.	4390
74	comment.pt.	276703
75	conference abstract.pt.	1126
76	conference paper.pt.	520784
77	congresses.pt.	41229
78	consensus development conference nih.pt.	489
79	consensus development conference.pt.	4514
80	dictionary.pt.	476
81	directory.pt.	6273
82	editorial.pt.	313373
83	festschrift.pt.	912
84	historical article.pt.	216400
85	interview.pt.	16286
86	lectures.pt.	3289
87	legal cases.pt.	6746
88	legislation.pt.	1649
89	letter.pt.	818677
90	newspaper article.pt.	13560
91	note.pt.	175296
92	patient education handout.pt.	1351
93	periodical index.pt.	300
94	review of reported cases.pt.	51728
95	technical report.pt.	1214
96	69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95	3243486
97	exp Animals/	11688850
98	exp animal/	11684209
99	exp animals/	11688850
100	animal experiment.sh.	677564
101	97 or 98 or 99 or 100	12323065
102	exp Humans/	8742154
103	exp human/	13101954
104	102 or 103	13101954

105	101 not 104	3518823
106	18 or 27	12353
107	106 and 43	6599
108	57 not 96	1148575
109	61 or 65 or 68	101745
110	107 and 108	1621
111	107 and 109	136
112	110 or 111	1659
113	112 not 105	1651
114	**remove duplicates from 113**	**973**

Search date: 14 May 2005

Search mask: Ovid

Data base: CENTRAL

#	Query	Hits
1	(Lyspro$ or Lispro$).ti,ab,ot.	174
2	(Lys$B28 or B28Lys$ or (lys$ adj1 B28)).ti,ab,ot.	15
3	(Pro$B29 or B29Pro$ or (pro$ adj1 B29)).ti,ab,ot.	14
4	humalog$.ti,ab,ot,tn.	26
5	133107-64-9.rn.	0
6	1 or 2 or 3 or 4 or 5	184
7	(insulin$ adj1 aspart$).ti,ab,ot.	51
8	(Asp$B28 or B28Asp$ or (asp$ adj1 B28)).ti,ab,ot.	8
9	(Novorapid$ or Novolog$).ti,ab,ot,tn.	2
10	116094-23-6.rn.	0
11	7 or 8 or 9 or 10	56
12	(Glulisine$ or Glulysin$).ti,ab,ot.	0
13	(Glu$B29 or B29Glu$ or (glu$ adj1 B29)).ti,ab,ot.	0
14	(Lys$B3 or B3Lys$ or (lys$ adj1 B3)).ti,ab,ot.	0
15	Apidra$.ti,ab,ot,tn.	0
16	207748-29-6.rn.	0
17	12 or 13 or 14 or 15 or 16	0
18	6 or 11 or 17	234
19	(insulin$ adj6 (analog$ or derivat$)).ti,ab,ot.	223
20	((shortacting or fastacting or rapidacting) adj6 insulin$).ti,ab,ot.	0
21	((short$ or fast$ or rapid$) adj1 acting adj6 insulin$).ti,ab,ot.	161
22	((novel or new) adj6 insulin$).ti,ab,ot.	161
23	19 or 20 or 21 or 22	424
24	exp insulin/aa	219
25	exp Insulin Derivative/	0
26	24 or 25	219
27	23 or 26	499
28	exp Diabetes Mellitus/	2903
29	diabet$.ti,ab,ot.	10301
30	mellitu$.ti,ab,ot.	3358
31	IDDM.ti,ab,ot.	514
32	MODY.ti,ab,ot.	2
33	NIDDM.ti,ab,ot.	874
34	(T1DM or T2DM or ((T1 or T2) adj1 DM)).ti,ab,ot.	37

35	(insulin$ depend$ or insulin?depend$ or noninsulin$ or noninsulin?depend$).ti,ab,ot.	2361
36	((matury or late) adj onset$ adj6 diabet$).ti,ab,ot.	4
37	(typ$ adj6 diabet$).ti,ab,ot.	3658
38	30 or 31 or 32 or 33 or 34 or 35 or 36 or 37	6804
39	exp Diabetes Insipidus/	33
40	insipid$.ti,ab,ot.	42
41	39 or 40	47
42	28 or 38	8241
43	42 or (29 not (41 not 42))	10732
44	controlled clinical trial.pt.	66520
45	controlled clinical trials/	53
46	randomized controlled trial.pt.	192735
47	randomized controlled trials/	4520
48	random allocation/	19991
49	cross-over studies/	12365
50	double-blind method/	66444
51	single-blind method/	5420
52	44 or 45 or 46 or 47 or 48 or 49 or 50 or 51	254829
53	((singl$ or doubl$ or trebl$ or tripl$) adj6 (blind$ or mask$)).ti,ab,ot.	92085
54	((random$ or cross-over or crossover) adj25 (trial$ or study or studies or intervention$ or investigat$ or experiment$ or design$ or method$ or group$ or evaluation or evidenc$ or data or test$ or condition$)).ti,ab,ot.	184284
55	(random$ adj25 (cross over or crossover)).ti,ab,ot.	16582
56	53 or 54 or 55	214806
57	52 or 56	317330
58	exp meta-analysis/	149
59	meta analysis.pt.	382
60	(metaanaly$ or meta analy$).ti,ab,ot.	820
61	58 or 59 or 60	1025
62	exp biomedical technology assessment/	62
63	hta.ti,ab,ot.	32
64	((biomed$ or health$) adj6 technolog$ adj6 assessment$).ti,ab,ot.	15
65	62 or 63 or 64	108
66	exp "Review Literature"/	12
67	((review$ or search$) adj25 (medical databas$ or medline or pubmed or embase or cochrane or systemat$)).ti,ab,ot.	372
68	66 or 67	380

69	addresses.pt.	3
70	bibliography.pt.	4
71	biography.pt.	10
72	"case reports".pt.	1207
73	"clinical conference".pt.	2
74	comment.pt.	1379
75	"conference abstract".pt.	1125
76	"conference paper".pt.	1
77	congresses.pt.	40
78	"consensus development conference nih".pt.	0
79	"consensus development conference".pt.	8
80	dictionary.pt.	0
81	directory.pt.	0
82	editorial.pt.	267
83	festschrift.pt.	0
84	"historical article".pt.	44
85	interview.pt.	2
86	lectures.pt.	5
87	"legal cases".pt.	3
88	legislation.pt.	0
89	letter.pt.	4012
90	"newspaper article".pt.	129
91	note.pt.	0
92	"patient education handout".pt.	6
93	"periodical index".pt.	0
94	"review of reported cases".pt.	117
95	"technical report".pt.	8
96	69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95	7162
97	exp Animals/	4718
98	exp animal/	0
99	exp animals/	4718
100	"animal experiment".sh.	0
101	97 or 98 or 99 or 100	4718
102	exp Humans/	0
103	exp human/	0
104	102 or 103	0
105	101 not 104	4718
106	18 or 27	527

107	106 and 43	415
108	57 not 96	311506
109	61 or 65 or 68	1402
110	107 and 108	370
111	107 and 109	3
112	110 or 111	370
113	112 not 105	367
114	**107 not 113**	**48**

Search date: 10 June 2005

Search mask: Ovid

Data bases: Medline 66, Pre-Medline, EMBASE 88, CENTRAL

#	Query	Hits
1	(Lyspro$ or Lispro$).ti,ab,ot.	1082
2	(Lys$B28 or B28Lys$ or (lys$ adj1 B28)).ti,ab,ot.	108
3	(Pro$B29 or B29Pro$ or (pro$ adj1 B29)).ti,ab,ot.	166
4	humalog$.ti,ab,ot,tn.	639
5	133107-64-9.rn.	1636
6	1 or 2 or 3 or 4 or 5	2082
7	(insulin$ adj1 aspart$).ti,ab,ot.	325
8	(Asp$B28 or B28Asp$ or (asp$ adj1 B28)).ti,ab,ot.	56
9	(Novorapid$ or Novolog$).ti,ab,ot,tn.	230
10	116094-23-6.rn.	444
11	7 or 8 or 9 or 10	709
12	(Glulisine$ or Glulysin$).ti,ab,ot.	24
13	(Glu$B29 or B29Glu$ or (glu$ adj1 B29)).ti,ab,ot.	7
14	(Lys$B3 or B3Lys$ or (lys$ adj1 B3)).ti,ab,ot.	23
15	Apidra$.ti,ab,ot,tn.	23
16	207748-29-6.rn.	26
17	12 or 13 or 14 or 15 or 16	71
18	6 or 11 or 17	2440
19	(insulin$ adj6 (analog$ or derivat$)).ti,ab,ot.	4298
20	((shortacting or fastacting or rapidacting) adj6 insulin$).ti,ab,ot.	8
21	((short$ or fast$ or rapid$) adj1 acting adj6 insulin$).ti,ab,ot.	1248
22	((novel or new) adj6 insulin$).ti,ab,ot.	5980
23	19 or 20 or 21 or 22	10223
24	exp insulin/aa	1950
25	exp Insulin Derivative/	944
26	24 or 25	2894
27	23 or 26	11626
28	exp Diabetes Mellitus/	315371
29	diabet$.ti,ab,ot.	336273
30	mellitu$.ti,ab,ot.	111264
31	IDDM.ti,ab,ot.	12298
32	MODY.ti,ab,ot.	839
33	NIDDM.ti,ab,ot.	13000
34	(T1DM or T2DM or ((T1 or T2) adj1 DM)).ti,ab,ot.	970

35	(insulin$ depend$ or insulin?depend$ or noninsulin$ or noninsulin?depend$).ti,ab,ot.	48037
36	((matury or late) adj onset$ adj6 diabet$).ti,ab,ot.	344
37	(typ$ adj6 diabet$).ti,ab,ot.	76328
38	30 or 31 or 32 or 33 or 34 or 35 or 36 or 37	175719
39	exp Diabetes Insipidus/	7786
40	insipid$.ti,ab,ot.	6838
41	39 or 40	9370
42	28 or 38	350172
43	42 or (29 not (41 not 42))	397518
44	controlled clinical trial.pt.	134828
45	controlled clinical trials/	337569
46	randomized controlled trial.pt.	393584
47	randomized controlled trials/	136895
48	random allocation/	87967
49	cross-over studies/	44547
50	double-blind method/	199192
51	single-blind method/	19642
52	44 or 45 or 46 or 47 or 48 or 49 or 50 or 51	955580
53	((singl$ or doubl$ or trebl$ or tripl$) adj6 (blind$ or mask$)).ti,ab,ot.	233257
54	((random$ or cross-over or crossover) adj25 (trial$ or study or studies or intervention$ or investigat$ or experiment$ or design$ or method$ or group$ or evaluation or evidenc$ or data or test$ or condition$)).ti,ab,ot.	685806
55	(random$ adj25 (cross over or crossover)).ti,ab,ot.	45612
56	53 or 54 or 55	759388
57	52 or 56	1259154
58	exp meta-analysis/	27700
59	meta analysis.pt.	11010
60	(metaanaly$ or meta analy$).ti,ab,ot.	26440
61	58 or 59 or 60	47734
62	exp biomedical technology assessment/	9979
63	hta.ti,ab,ot.	867
64	((biomed$ or health$) adj6 technolog$ adj6 assessment$).ti,ab,ot.	1541
65	62 or 63 or 64	11378
66	exp "Review Literature"/	8597
67	((review$ or search$) adj25 (medical databas$ or medline or pubmed or embase or cochrane or systemat$)).ti,ab,ot.	47747
68	66 or 67	55555

69	addresses.pt.	2444
70	bibliography.pt.	12203
71	biography.pt.	108777
72	case reports.pt.	1173599
73	clinical conference.pt.	4532
74	comment.pt.	281461
75	conference abstract.pt.	1125
76	conference paper.pt.	524632
77	congresses.pt.	41651
78	consensus development conference nih.pt.	493
79	consensus development conference.pt.	4596
80	dictionary.pt.	477
81	directory.pt.	6315
82	editorial.pt.	318543
83	festschrift.pt.	927
84	historical article.pt.	217572
85	interview.pt.	16564
86	lectures.pt.	3346
87	legal cases.pt.	6852
88	legislation.pt.	1649
89	letter.pt.	827070
90	newspaper article.pt.	13917
91	note.pt.	178297
92	patient education handout.pt.	1428
93	periodical index.pt.	301
94	review of reported cases.pt.	52194
95	technical report.pt.	1207
96	69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95	3274836
97	exp Animals/	11790715
98	exp animal/	11785997
99	exp animals/	11790715
100	animal experiment.sh.	683740
101	97 or 98 or 99 or 100	12430025
102	exp Humans/	12986496
103	exp human/	12986496
104	102 or 103	12986496
105	101 not 104	3550990
106	cn$.an.	446156

107	(18 or 27) and 43	6763
108	57 not (96 or 105)	1110225
109	107 and (108 or 106)	1713
110	(in-data-review or in-process).st. and (200504$ or 200505$ or 200506$).up.	119733
111	pubmed-not-medline.st. and (200504$ or 200505$ or 200506$).up.	10992
112	medline.st. and (200504$ or 200505$ or 200506$).up.	151133
113	((20051$ or 20052$) not ("200510" or "200511" or "200512")).ew.	114091
114	new.uf. or ("2005".yr. and cn$.an.)	12884
115	110 or 111 or 112 or 113 or 114	408833
116	**109 and 115**	**81**

Appendix C: Sample extraction form

IQWiG Assignment No.	
Assessor	
Name of study	
Source	
Year	
Indication	
Research question / objective	
Setting	
Relevant inclusion and exclusion criteria	
Number of groups	
Treatment (study drug)	
Treatment (controls)	
Other treatment groups, if any	
Design	
Number of centres	
Details (if >1 centre)	
Randomisation	
Concealment	
Blinding	
Duration of observation	
Primary endpoints	
Secondary endpoints	
Planned subgroup analyses	
Sample size determination, including calculated sample size	

Statistical methodology	
Number of screened patients	
Run-in phase	
Number of randomised patients	
Number of analysed patients	
Flow of patients	
Comparability of groups	
Results	
Presentation of results	
Comments	
Evaluation	

Biometric quality	no identifiable deficits	slight deficits	serious deficits	unclear

For quantitative endpoints

Definition:_____

Endpoint:_____

		Study drug		Controls		
	Type	N	Value	N	Value	Source
Location measure						
Variability measure						

Measure for difference between groups:_____

Estimate	Source	95% confidence interval	Source	p-value (optional)

For binary (dichotomous) endpoints

Definition: _____

Endpoint: _____

Study drug		Controls		
Total number of patients	Number of patients with an event	Total number of patients	Number of patients with an event	Source

Measure for difference between groups:_____

Estimate	Source	95% confidence interval	Source	p-value (optional)

For censored data (survival times - ST)

Definition:_____

Endpoint:_____

Measure for difference between groups:_____

Estimate	Source	95% confidence interval	Source	p-value (optional)

Event rates from the Kaplan-Meier analysis

	Study drug		Controls		
Point in time	Number of patients at risk	Rate	Number of patients at risk	Rate	Source

Median survival time from the Kaplan-Meier analysis

Study drug	Controls	Source

Measure for follow-up times: _____

Study drug	Controls	Source

Information on age and gender distribution in the total groups (for age: location and variability measures)

Appendix D: Queries to authors and authors' responses

The dates of queries and responses are shown in Table D.1.

Table D.1: Queries to and responses from authors of relevant publications

Author	Date of first query	Date of reminder	Date of response	Content of response
Altuntas	20 June 2005	29 July 2005	no	-
Anderson	21 June 2005	29 July 2005	no	-
Bastyr	20 June 2005	29 July 2005	29 July 2005	"Will look for data."
Dailey	20 June 2005	29 July 2005	29 July 2005 29 August 2005	"Query will be processed." Provision of a response document
Ross	21 June 2005	29 July 2005	31 July 2005	"No access to data."

The document provided by Dailey on 29 August 2005 with additional information on Study 3002 is attached below.

HMR 1964A-3002 study published as

Insulin Glulisine Provides Improved Glycemic Control in patients With Type 2 Diabetes

Dailey et al., Diabetes Care 27: 2363-2368, 2004

Why did 2 of the 878 randomized patients not receive study medication?

After randomization but prior to receiving treatment, 2 subjects (both randomized to treatment with insulinglulisine) were withdrawn, in one case because the subject did not wish to continue, and in the other because of a protocol violation (violation not specified by the investigator). Note that this frequency of randomized/non treated subjects is very low and in line or even below with what is generally observed in trials of this size.

How many patients are included in the primary analysis and how are missing values dealt with?

The primary analysis was the analysis of change in HbA1c from baseline to endpoint (primary efficacy variable) using the ITT population, where endpoint was defined as the subject's last available measurement after start of treatment. The PP population was used to check for the consistency of the analyses based on the ITT population for each efficacy variable.
As the ITT population for each variable included only those subjects who had both a baseline and an on-treatment value for the given variable within the variable-specific time window, the number of subjects analyzed differed for each variable. The overall ITT population was 876 subjects (435 Glulisine, 441 RHI). The ITT Population for evaluation of "change in HbA1c at endpoint" included 807 patients (404 Glulisine, 403 RHI)

There were 31 insulinglulisine and 38 regular insulin subjects in the ITT population who were not included in the primary GHb evaluation. These subjects were excluded from the analysis either because their baseline (19,19) or endpoint was missing or the baseline values were obtained after first dose of study treatment, or the endpoint values were outside the 14-day window after the last dose (12,19).
Sensitivity analyses were performed, including an analysis using specific imputation rules (see box) and the non-inferiority of insulinglulisine compared to regular insulin was maintained in this imputed analysis.

- For subjects with a missing baseline (visit 6) GHb value the HbA1c value collected at screening (visit 1) was used to impute the missing baseline GHb value.
- Subjects who had their only post baseline GHb measurement more than 14 days after last dose of study medication were not evaluable for the primary efficacy analysis due to missing endpoint GHb (see also *Section 4.1, p057*). For these subjects the rule of taking a follow-up phase of 14 days into account was dropped which makes the respective GHb value evaluable as endpoint.
- For all remaining subjects without available endpoint value the following conservative imputation rules were applied for the primary efficacy variable, the change in GHb from baseline at endpoint:
  - For glulisine treated subjects the 75th percentile of the change from baseline to endpoint seen in the glulisine group was used.
  - For regular insulin treated subjects the 25th percentile of the change from baseline to endpoint seen in the regular insulin group was used.

We would like to see the numbers of the hypoglycaemic events. A measure of variance for the hypoglycaemia-rates would also be helpful.

1. Frequency of symptomatic hypoglycemia:
The table summarizes the hypoglycemic events during the time period from month 4 to study end (period after acclimatization to treatment) to which the publication refers now including the absolute numbers of episodes and SD values. The frequency represents number of subjects (%) reporting at least one episode of symptomatic hypoglycemia (ITT population).

Type of symptomatic hypoglycemia	Glulisine			Regular insulin		
	n/N	% 95% CI	Episodes (n)	n/N	% 95% CI	Episodes (n)
All	215/416	51.7 (46.8% , 56.6%)	1294	225/420	53.6 (48.7% , 58.4%)	1429
Nocturnal	89/416	21.4 (17.6%, 256.5%)	189	103/420	24.5 (20.5%, 28.8%)	293
Severe	6/416	1.4 (0.6%, 3.0%)	6	5/420	1.2 (0.5%, 2.7%)	5
Note: n = number of subjects reporting at least one episode of symptomatic hypoglycemia; N = number of ITT subjects evaluable.						

Table 20 below summarizes the frequency of all symptomatic hypoglcyemia during the ***entire*** treatment period (26 weeks) showing no between-treatment differences within the first 3 months and the entire treatment period.

Table 20 – Frequency of all symptomatic hypoglycemia

Treatment phase	Glulisine			Regular insulin		
	n/N	(%)	Number of episodes	n/N	(%)	Number of episodes
ITT population						
Screening/Run-in phase	270/435	(62.1)	1084	267/441	(60.5)	1069
Month 1	213/435	(49.0)	776	216/441	(49.0)	839
Month 2 to end	289/430	(67.2)	2396	288/431	(66.8)	2542
Month 4 to end	215/416	(51.7)	1294	225/420	(53.6)	1429
Entire phase	317/435	(72.9)	3172	322/441	(73.0)	3381
PP population						
Screening/Run-in phase	219/342	(64.0)	919	217/356	(61.0)	866
Month 1	176/342	(51.5)	640	182/356	(51.1)	705
Month 2 to end	245/342	(71.6)	2111	243/356	(68.3)	2166
Month 4 to end	186/342	(54.4)	1138	195/356	(54.8)	1238
Entire phase	263/342	(76.9)	2751	269/356	(75.6)	2871

Note: n = number of subjects reporting at least one episode of symptomatic hypoglycemia; N = number of ITT subjects evaluable.

2. Rates of symptomatic hypoglycemia per patient month

The table summarizes the symptomatic hypoglycemia rates during the time period from month 4 to study end (period after acclimatization to treatment) to which the publication refers including SD values. The monthly rate was calculated as: 365.25/12 x number of severe hypoglycemia episodes)/(number of days exposed in the time window).

Type of symptomatic hypoglycemia	Glulisine		Regular insulin	
	Mean	SD	Mean	SD
All	0.95	2.013	1.04	2.072
Nocturnal	0.14	0.356	0.21	0.543
Severe	***0.0041***	**0.034**	***0.0037***	**0.034**

Table 21 below summarizes the frequency of all symptomatic hypoglcyemia during the ***entire*** treatment period (26 weeks) showing no significant between-treatment differences within the first 3 months and the entire treatment period.

Table 21 – Rate of all symptomatic hypoglycemia per patient month

Time period	Glulisine			Regular insulin		
	N	Mean	SD	N	Mean	SD
ITT population						
Screening/run-in phase	435	1.86	2.906	441	1.82	2.766
Month 1	435	1.94	3.399	441	2.09	3.670
Month 2 to end	430	1.11	2.025	431	1.19	2.219
Month 4 to end	416	0.95	2.013	420	1.04	2.072
Entire treatment phase	435	1.23	2.087	441	1.34	2.363
PP population						
Screening/run-in phase	342	2.00	3.012	356	1.83	2.646
Month 1	342	2.03	3.336	356	2.15	3.607
Month 2 to end	342	1.20	2.129	356	1.18	2.139
Month 4 to end	342	1.00	2.120	356	1.04	2.073
Entire treatment phase	342	1.33	2.167	356	1.32	2.216

Note: N = number of ITT subjects evaluable
The monthly rate was calculated as (365.25/12 x number of hypoglycemia episodes)/(number of days exposed in the time window).

In table 1 and figure 1 of the publication there are varying values for HbA1c.

The HbA1c values given in table 1 are the mean baseline values in the entire ITT population, which was defined as all subjects randomized and treated with study medication, and consisted of 876 subjects (435 Glulisine and 441 RHI). The HbA1c values included in figure 1 are the mean baseline values in the ITT population for the primary efficacy analysis, which consisted of 807 subjects (404 Glulisine and 403 RHI). Note that the values are very closed.

The values for daily basal insulin are differing in table 1 (59.6±34.7) and the text (59.1)

The mean daily basal insulin doses given in table 1 (**59.6 Glulisine, 57.1 RHI**) are the observed mean values from the entire ITT population (descriptive statistics, see table 15 below). The mean daily basal doses given in the text (**59.1 [Glulisine] vs 57.3 [RHI]** ; p = 0.4025) are the adjusted means from an ANCOVA model (see table 12-57 below) with an adjustment for centre effect.

Table 15 – Mean daily insulin dose (IU) during treatment (ITT population)

Insulin type	Glulisine		Regular insulin	
	N	Mean[a]	N	Mean[a]
Baseline				
Total daily insulin	433	92.1	431	88.4
Daily short-acting insulin	433	32.5	431	31.3
Daily basal insulin	433	59.6	431	57.1
Adjusted mean change from baseline at endpoint				
Total daily insulin	433	9.3	431	11.1
Daily short-acting insulin	433	3.7	431	5.0
Daily basal insulin	433	5.7	431	6.0

[a] Means are presented for baseline and adjusted means for the change from baseline; adjusted means are from an ANCOVA model.

Table 12-57 Insulin doses (IU): ANCOVA results - ITT population

Timepoint	HMR1964 N	HMR1964 Adjusted Mean	HMR1964 SE	Regular insulin N	Regular insulin Adjusted Mean	Regular insulin SE	Difference: HMR1964 - Regular Adjusted Mean	Difference: HMR1964 - Regular 95% CI	Difference: HMR1964 - Regular SE	P-value for treatment effect
Baseline [a]										
Total daily insulin dose	433	91.58	2.495	431	88.57	2.509	3.02	(-3.68 ; 9.71)	3.412	0.3770
Daily short-acting insulin dose	433	32.50	1.196	431	31.31	1.203	1.20	(-2.01 ; 4.41)	1.636	0.4644
Daily basal insulin dose	433	59.08	1.588	431	57.26	1.597	1.82	(-2.44 ; 6.08)	2.172	0.4025
Change from baseline at week 12 [b]										
Total daily insulin dose	391	8.00	1.088	390	9.37	1.091	-1.37	(-4.27 ; 1.52)	1.475	0.3516
Daily short-acting insulin dose	391	3.23	0.630	390	3.62	0.632	-0.39	(-2.07 ; 1.28)	0.854	0.6464
Daily basal insulin dose	391	4.79	0.717	390	5.70	0.719	-0.91	(-2.81 ; 1.00)	0.972	0.3517
Change from baseline at week 26 [b]										
Total daily insulin dose	359	10.06	1.203	362	11.99	1.202	-1.92	(-5.14 ; 1.29)	1.639	0.2408
Daily short-acting insulin dose	359	3.78	0.796	362	5.47	0.784	-1.69	(-3.81 ; 0.44)	1.084	0.1204
Daily basal insulin dose	359	6.30	0.847	362	6.41	0.845	-0.11	(-2.38 ; 2.15)	1.153	0.9230
Change from baseline at endpoint [b]										
Total daily insulin dose	433	9.33	1.102	431	11.10	1.108	-1.76	(-4.72 ; 1.20)	1.507	0.2427
Daily short-acting insulin dose	433	3.69	0.707	431	5.00	0.711	-1.31	(-3.21 ; 0.59)	0.967	0.1756
Daily basal insulin dose	433	5.73	0.766	431	6.03	0.771	-0.30	(-2.36 ; 1.76)	1.048	0.7741

Note: ITT = intention-to-treat; N = Number of evaluable subjects; SE = standard error; 95% CI = 95% confidence interval for difference of adjusted means.
Change from baseline was calculated as difference: endpoint or week x - baseline.
Subjects are included only if they had both a baseline and a post-baseline value.
[a] Baseline was compared between treatments using an analysis of variance with treatment and pooled center as fixed effects.
[b] Change from baseline at week 12, week 26 and endpoint was analyzed using an analysis of covariance with treatment and pooled center as fixed effects and the corresponding baseline value as covariate.

We would like to receive more information on OAD-therapy

508 subjects were treated by OAD at baseline and 512 subjects received OAD during the study. Of the 508 subjects on OHA at randomization, 133 (26.2%) were on sulfonylurea and the treatments were balanced in SU use at baseline (61, 14.0% insulinglulisine and 72, 16.3% regular insulin subjects).

OHA use at randomization or during the study is shown in table 12-35:

HMR1964A/3002 Aventis Pharma 1dm0012t.1st / (

Table 12-35 Oral hypoglycemic agents (OHA) use at randomization or during the study - ITT population

Frequency of OHA use	Number (%) of subjects		
	Total	HMR1964	Regular insulin
Total number of ITT subjects	876 (100.0)	435 (100.0)	441 (100.0)
Total number of subjects with oral hypoglycemic agents at randomization or during the study	512 (58.4)	246 (56.6)	266 (60.3)
Combination of OHA used:			
One type of OHA	367 (41.9)	171 (39.3)	196 (44.4)
Combination of 2 different OHA types	130 (14.8)	67 (15.4)	63 (14.3)
Combination of 3 different OHA types	14 (1.6)	8 (1.8)	6 (1.4)
Combination of >3 different OHA types	1 (0.1)	- (-)	1 (0.2)

Note: ITT = intention-to-treat. A dash (-) indicates that no subject was reported.

A subgroup comparison of patients using OADs at baseline vs those who did not is shown in table 12-52

Table 12-52 Efficacy in subgroups defined by stratification factor used at randomization (OHA use vs. no OHA use at randomization)

Variable		OHA use at randomization		No OHA use at randomization	
		HMR1964	Regular insulin	HMR1964	Regular insulin
GHb (%) - ITT population					
Number of evaluable subjects		231	241	173	162
Baseline:	Mean (SD)	7.6 (0.96)	7.4 (0.91)	7.5 (0.89)	7.6 (1.00)
	Median (range)	7.5 (5.6-10.2)	7.3 (5.7-10.3)	7.4 (5.4-10.2)	7.4 (5.7-11.2)
Endpoint:	Mean (SD)	7.1 (0.95)	7.2 (0.93)	7.1 (0.93)	7.2 (1.11)
	Median (range)	7.0 (5.2-10.8)	7.1 (5.4-10.7)	7.0 (5.2-10.9)	6.9 (5.2-12.0)
Change from baseline:	Mean (SD)	-0.5 (0.80)	-0.2 (0.85)	-0.4 (0.76)	-0.4 (0.96)
	Median (range)	-0.5 (-2.9-2.1)	-0.2 (-3.1-2.1)	-0.3 (-2.7-3.0)	-0.4 (-3.3-2.6)
Treatment x stratum interaction P=0.1112 [a]					
GHb (%) - PP population					
Number of evaluable subjects		197	214	145	142
Baseline:	Mean (SD)	7.6 (0.93)	7.5 (0.90)	7.5 (0.91)	7.5 (0.91)
	Median (range)	7.4 (5.6-10.2)	7.4 (5.8-10.3)	7.4 (5.4-10.2)	7.3 (5.7-10.5)
Endpoint:	Mean (SD)	7.1 (0.95)	7.3 (0.90)	7.1 (0.96)	7.2 (1.04)
	Median (range)	7.0 (5.2-10.8)	7.1 (5.4-10.7)	7.0 (5.2-10.9)	6.9 (5.2-11.5)
Change from baseline:	Mean (SD)	-0.5 (0.80)	-0.2 (0.82)	-0.4 (0.78)	-0.3 (0.91)
	Median (range)	-0.5 (-2.9-2.1)	-0.2 (-2.4-2.0)	-0.3 (-2.7-3.0)	-0.3 (-3.1-2.6)
Treatment x stratum interaction P=0.0931 [a]					
Hypoglycemia (entire treatment phase) - ITT population					
Total number (%) of ITT subjects		245 (100.0)	263 (100.0)	190 (100.0)	178 (100.0)
Number (%) of subjects with at least one episode of					
Symptomatic hypoglycemia (P=0.1111 [b])		188 (76.7)	191 (72.6)	129 (67.9)	131 (73.6)
Severe symptomatic hypoglycemia (P=0.6504 [b])		8 (3.3)	5 (1.9)	9 (4.7)	7 (3.9)
Nocturnal symptomatic hypoglycemia (P=0.3780 [b])		94 (38.4)	96 (36.5)	70 (36.8)	73 (41.0)
Severe nocturnal symptomatic hypoglycemia (P=0.7888 [b])		3 (1.2)	2 (0.8)	5 (2.6)	4 (2.2)
Hypoglycemia (entire treatment phase) - PP population					
Total number (%) of PP subjects		197 (100.0)	214 (100.0)	145 (100.0)	142 (100.0)
Number (%) of subjects with at least one episode of					
Symptomatic hypoglycemia (P=0.6853 [b])		156 (79.2)	164 (76.6)	107 (73.8)	105 (73.9)
Severe symptomatic hypoglycemia (P=0.8141 [b])		5 (2.5)	4 (1.9)	8 (5.5)	5 (3.5)
Nocturnal symptomatic hypoglycemia (P=0.5273 [b])		83 (42.1)	81 (37.9)	60 (41.4)	60 (42.3)
Severe nocturnal symptomatic hypoglycemia (P=0.9022 [b])		2 (1.0)	1 (0.5)	5 (3.4)	2 (1.4)

Note: ITT = intention-to-treat; PP = per protocol; OHA = oral hypoglycemic agent; SD = standard deviation.
A dash (-) indicates that no subjects were reported.
[a] P-value from ANCOVA of change from baseline with an ANCOVA model including treatment, baseline, subgroup factor, and treatment by subgroup factor interaction.
[b] P-values for the treatment by subgroup factor interaction from a logistic regression model applied on the frequencies with treatment, subgroup factor and treatment by subgroup factor interaction included in the model.

The study was not designed to formally evaluate the differences in the efficacy of insulinglulisine when used together with OHAs or not. To further assess the use of insulinglulisine in a regimen with OHAs, data were summarized in subgroups of subjects who had been using OHAs at randomization and those who were not. Treatment groups were compared in each of these subgroups for the change in GHb as well as the number of subjects who reported at least one episode of any type of symptomatic hypoglycaemia between treatments.
The results of these exploratory analyses showed that there was no difference seen between the treatment groups in the two subgroups. As was seen in the population as a whole, there was a consistently larger decrease in GHb in the insulinglulisine group compared to the regular insulin group regardless of whether the subjects were using insulinglulisine with or without OHAs. Furthermore, the incidence of subjects reporting any type of symptomatic hypoglycaemia was similar in the two treatment groups regardless of whether the subjects were using insulinglulisine with OHAs or not. Thus, the efficacy of insulinglulisine was seen in these subgroups as assessed by these parameters.
Comparison of the demographic characteristics of the subjects, who were using OHAs at randomization, with those, who were not, demonstrated that these subjects were all comparable for these characteristics.

If possible, we would like to see more detailed information on randomization and concealment

This was an open study and the treatment was not blinded .The different times of insulin administration in relation to meals precluded blinding the study. In addition, major differences in the size and shape of the vials and the colour of the gasket and caps also prevent blinding. Repackaging of the insulins is not an option as this would result in a modification of the respective insulin products. The majority of studies comparing insulins are conducted using an open label design and this is accepted by the different agencies.
Subjects were randomized using a centralized randomization centre, which prevents inclusion bias that might arise from an open study design. Furthermore, except for the week –5 screening visit, HbA1c results determined in the central laboratory for the purposes of the study remained blinded to the investigative site during the conduct of the study.
Randomization was stratified according to whether or not the subjects were being treated with OHAs at the time of randomization to assure a balance between treatment allocations.
Two randomization schedules were used: one for subjects who had prior treatment with OHAs and one for those who did not.
At the end of the screening/run-in phase, once it had been established that a subject met the inclusion criteria, the investigator telephoned the independent agency so that the subject could be randomized. In accordance with the randomization schedule held by the agency, the investigator was informed about the study medication the subject was to receive and the randomization number of the subject. Each subject was given only the study medication assigned by the agency. The investigator documented the study medication and the randomization number in the CRF. After completing the screening/run-in phase, subjects were randomized in the order in which they qualified for inclusion in the study.

Appendix E: Meeting minutes of the scientific hearing

Meeting minutes of the scientific hearing

Statements on preliminary report A05-04: Rapid-acting insulin analogues for the treatment of diabetes mellitus type 2

08 September 2005

(Start: 10:15 a.m.; end: 13:30 p.m.)

Location: Institute for Quality and Efficiency in Health Care, Cologne

Participants:

Name	Company/Institution
Dr. Marion Braun-Schlüchtern	Federal Association of Office-based Diabetologists (Bundesverband Niedergelassener Diabetologen e. V., BVND)
Manfred Wölfert	German Diabetes Federation (Deutscher Diabetiker Bund, DDB)
Jie Shen	Lilly Deutschland GmbH
Dr. Christof Kazda	Lilly Deutschland GmbH
Dr. Nick Schulze-Solce	Lilly Deutschland GmbH
Dr. Marcel Kaiser	Novo Nordisk Pharma GmbH
Dr. Johannes Knollmeyer	Sanofi-Aventis Deutschland GmbH
Dr. Heinz Riederer	Sanofi-Aventis Deutschland GmbH
Prof. Dr. Jürgen Sandow	External expert
Dr. Karl Horvath	University of Graz
Univ. Doz. Dr. Andrea Siebenhofer-Kroitzsch	University of Graz

Dr. Ulrike Götting	German Association of Research-based Pharmaceutical Companies (Verband Forschender Arzneimittelhersteller e.V., VFA)
Priv. Doz. Dr. Bernd Richter	Peer reviewer
Hr. Tscheuschner	Patient representative
Dr. Cornelia Beimfohr	IQWiG
Katharina Biester	IQWiG
Dr. Anna Sabine Ernst	IQWiG
Doris Hemmann	IQWiG
Dr. Annegret Herrmann-Frank	IQWiG
Dr. Thomas Kaiser	IQWiG
Prof. Dr. Peter T. Sawicki	IQWiG
Frank Schmalfuß	IQWiG
Elke Vervölgyi	IQWiG
Markos Dintsios, MA, MPH	IQWiG (Minute taker)
Dr. Beate Wieseler	IQWiG (Minute taker)

Name	**Contribution**
Sawicki	• Greeting of participants • Comments on the procedure of the discussion: aim of the discussion is not consensus, but to discuss, understand, and present potential differences of opinion, and where necessary clarify the need for further research. • The German Diabetes Association submitted a statement. However, the persons who submitted the statement did not want to disclose their potential conflicts of interest. Therefore, following legal requirements, they were not invited to the scientific hearing as external experts. • Query on amendments to the agenda.
Knollmeyer	• Proposal to include an additional query (When should a drug be evaluated for the first time?)

Name	Contribution
TOP 1	**General vs. specific methods to evaluate the effects of drugs**
Sawicki	• Under TOP1, project-specific methodological issues should be discussed. General methodological aspects of the Institute's work should not be discussed in this hearing, but in a separate meeting with participation of the scientific advisory board (this meeting is held once a year).
Knollmeyer	• The "Council of Advisors for the Concerted Action in Health Care" (Sachverständigenrat für die Konzertierte Aktion im Gesundheitswesen) has also pointed out that an evaluation of the effects of newly approved drugs is difficult, as the necessary studies are not yet available. In many cases the data situation of the drugs to be compared will differ. This needs to be taken into account in the evaluation.
Sawicki	• The amount of valid data is not always proportional to the period since drug approval. • For the different agents investigated, the period since drug approval will be presented in the report by IQWiG. • IQWiG does not decide on the time point of an evaluation; it performs an evaluation on the basis of an assignment.
TOP 2	**Limitation to randomised controlled trials in the preliminary report on hand**
Götting	• Queries that only RCTs were included in the evaluation of rapid-acting insulin analogues; in the IQWiG methods paper, it is also planned to include studies with a lower evidence level.
Schulze-Solce	• Sees the necessity to include controls in studies and regards the principle of randomisation to be essential for the conduct of clinical studies. The problem of RCTs is that, due to the inclusion and exclusion criteria, only a small section of the real patient population is investigated, which does not reflect the realities in health care. He therefore demands the consideration

Name	Contribution
	of studies with other designs, in addition to RCTs. As an example of meaningful supplements, two studies (retrospective observational studies that use billing data from the US managed care section) were presented by Lilly, which include data on hospitalisation rates; this type of study is also viewed by Cochrane as reliable. • The evaluation of a drug's safety aspects should also be based on other sources, in addition to RCTs. • For some endpoints, the exclusive consideration of RCTs is unproblematic; for others, other study designs should also be considered.
Shen	• RCTs are intervention trials and are conducted in a controlled setting; therefore this design is not appropriate for evaluating hospitalisation rates. Hospitalisation rates should be evaluated on the basis of data collected in real conditions. The studies presented by Lilly have a high methodological level, which covers a large part of the variability (> 90%) between treatment groups; these data were also evaluated as being reliable in a Cochrane Review.
Richter	• Cochrane is a big organisation with different opinions and differences in the quality of reviews. • The effectiveness in real conditions can also be represented in RCTs. Therapeutic interventions primarily need to be evaluated by RCTs, as other designs do not allow for a sufficient control of confounding variables. Other designs can possibly be meaningful for single specific endpoints, but this is dependent on the type of parameters investigated.
T Kaiser	• In principle, real health care conditions can be represented in RCTs; however, unfortunately these studies have so far rarely been conducted. • Queries that hospitalisation rates cannot be validly represented

Name	Contribution
	in RCTs; there are examples of RCTs where hospitalisation rates were investigated. • In the studies presented by Lilly, there was a tendency towards fewer hospitalisations but to more outpatient visits under insulin analogues. These results bring up the question as to whether the study investigated comparable patient groups (even though a matching procedure was employed), or whether the differences observed were due to a different treatment of patients (not of therapies investigated, but of care provided with regard to outpatient visits). This issue cannot ultimately be answered because of the study design chosen.
Sawicki	• Asks whether the US data presented on hospitalisations can be transferred to the German health care situation.
Shen	• Lilly sees the advantages of RCTs. However, no RCTs are available on the issue of hospitalisation rates. An investigation of hospitalisation rates in RCTs would be critical due to ethical reasons, therefore cohort studies should also be considered.
Kazda	• Lilly was prepared, following the results of a pharmacokinetic/pharmacodynamic preliminary study conducted by Dr. Heise on Novorapid, to finance a study on patient-relevant endpoints in geriatric patients. This study was not conducted due to implementation problems.
Shen	• The study presented by Lilly is based on US data; unfortunately such data are not available for Germany. A modelling analysis under consideration of the German health care situation shows the same tendency; however, no real health care data were used. • Both the studies quoted are based on the use of resources. The cost-benefit evaluation indicates different hospitalisation rates due to different hypoglycaemia rates. • In the light of a lack of data from RCTs; “best available evidence” should be drawn on for the evaluation of the effects

Name	Contribution
	of drugs.
Sawicki	• Points out that the procedure to draw on studies of lower evidence levels when RCTs are lacking can lead to wrong conclusions (example: menopausal hormone therapy).
Riederer	• It is a problem that the studies were conducted at a time when the queries that IQWiG would raise were not known. Therefore to date, not all relevant information is available; the past is being evaluated with future methods. The demand for respective studies will be met in the future; that is, the required data will be available at a later point in time.
Sawicki	• IQWiG cannot apply different standards to older studies than to newer ones. To evaluate the effects of drugs, the standards valid today have to be used, which is also consistent with the requirements of the Federal Joint Committee.
T Kaiser	• The IQWiG methods paper intends that non-RCTs can also be used, but do not necessarily have to be used. The issue whether non-RCTs can meaningfully be considered is project-dependent, and e.g. depends on the underlying disease. • The NICE[‡‡‡]-HTA report on the evaluation of insulin glargine, also only included RCTs. • The limitation to RCTs for the evaluation of insulin analogues is meaningful, as it is a long-term therapy, the disease is chronic, and the endpoints can only be investigated in an unbiased manner in RCTs. • The inclusion of other data is only meaningful if decisions can be made on the basis of these data. • Describes the problem of the inclusion of such data, presenting the example of the ROSSO[§§§] study (retrolective study), which, with its naturalistic design, showed more events under more

[‡‡‡] National Institute for Clinical Excellence
[§§§] Retrolective Study Self-Monitoring of Blood Glucose and Outcome in Patients with Type 2 Diabetes

Name	Contribution
	intensive lowering of blood glucose levels. States that the consequences of the inclusion of such results in evaluations need to be considered.
Sawicki	• In addition, the ROSSO study describes more cases of microangiopathic events in patients who self-monitored blood glucose levels.
Knollmeyer	• For the evaluation on insulin glargine, non-RCT data for the evaluation of costs and safety was submitted to NICE, and also considered by NICE. • Thinks a harmonisation of the requirements of the European agencies is necessary. The generation of documents for the evaluation of drug effects represents a high expenditure for companies; therefore a harmonisation within Europe similar to the ICH**** approach, would be helpful.
Sawicki	• Also thinks a harmonisation of requirements is meaningful; this harmonisation is already envisaged; there will be a meeting including IQWiG, NICE, and Haute Autorité de Santé in November.
Knollmeyer	• Sees a problem if different drugs are evaluated differently due to the different data situation. • Proposes to allow for time to generate data before conducting an evaluation of drug effects.
Sawicki	• IQWIG can point this out to the Federal Joint Committee and propose suspending an evaluation if major studies are shortly before completion.
Shen	• The Canadian agency and NICE also consider data from pharmacoeconomic studies. Proposes to consider data from non-RCTs for specific endpoints.
Kazda	• The conclusions of the preliminary report have only limited

**** International Conference on Harmonisation

Name	Contribution
	validity; they only apply to patient groups included in the study on the basis of the inclusion and exclusion criteria of the respective studies and represent a section of the total diabetes mellitus type 2 collective. • Phase II and III studies on insulin lispro that showed postprandial differences were already conducted in 1994. A large prospective endpoint study on insulin lispro, which will be completed in 2007, is currently being conducted.
Sawicki	• If new results from pivotal studies become available, IQWiG can revise evaluations already completed, also within the framework of its general assignment.
Richter	• Methods must be up to date; when applying “best available evidence”, the question must be asked: “According to which quality criteria are the included studies to be evaluated?” No poor-quality studies should be considered under the cloak of effectiveness.
Sawicki	• If studies of a lower evidence level are included, not only selected studies of this evidence level can be taken into account; a systematic inclusion of these studies must take place.
TOP 3	**Evaluation of subgroups**
M Kaiser	• The study by Boehm et al. (2004) should be considered; in the publication a subgroup of type 2 diabetes mellitus patients who were treated for a period of 24 months is presented.
Siebenhofer	• In the study, patients were treated 3 months after randomisation. Subsequently, a voluntary follow-up of 21 months was possible in which only 65% of originally randomised patients participated. The follow-up period cannot be regarded as an RCT, therefore the study was excluded. The reason for exclusion will be included in the report in order to clarify this issue (duration of treatment under RCT conditions too short).

Name	Contribution
T Kaiser	• Some patients discontinued this study. Furthermore the voluntary follow-up may bias the study results.
Richter	• Methodologically, this is then no longer an RCT.
Wölfel	• The statement of the German Diabetes Federation is sufficient; no addenda.
TOP 4	**Blinding**
Knollmeyer	• Incongruity of the evaluation compared with the methods paper. • A blinding of studies is difficult due to the different application schemes; therefore in the evaluation of the quality of the studies the issue of blinding should only be considered subordinately.
T Kaiser	• The importance of blinding depends on the type of endpoint. In particular for subjective endpoints, blinding is important to minimise bias of results. A lack of blinding with regard to the evaluation of subjective endpoints is therefore a deficiency of the study. In situations where endpoints can hardly be subjectively influenced, blinding may be less important. With regard to the research question on hand, blinding is possible and has already been conducted in short-term studies. Therefore this argument doesn't count. This relation between endpoints and the importance of blinding has also been presented in the preliminary report.
Knollmeyer	• In large studies, the influence of blinding is not ascertainable.
Richter	• It is possible in nearly all studies to blind the evaluator of the endpoints; this possibility should be adequately used.
TOP 5	**Minimum study period**
Kazda	• Which evidence is available for the suitability of the chosen study period of 24 weeks?
T Kaiser	• This IQWiG evaluation investigates patient-relevant endpoints; in addition, statements should be made on long-term therapies.

Name	Contribution
	• The systematic review by Siebenhofer, which considered studies with a shorter duration, had a different research question. This review investigated the effect of insulin analogues on the lowering of blood glucose levels; this issue was not relevant for the IQWiG evaluation. The results of the Siebenhofer review with regard to patient-relevant endpoints are similar to the results of the IQWiG report. • The CPMP[††††] "Note for guidance" for studies on diabetes presented by Lilly also demands a minimum study period of 6 months for studies on insulin analogues; furthermore, additional 12-month studies should be available.
Kazda	• Sees a contradiction that HbA_{1c} is described in the preliminary report even though it is not an endpoint. Shorter studies are available that characterise HbA_{1c} levels well, but they were not taken into account.
T Kaiser	• In the IQWiG report, HbA_{1c} levels are only assessed in combination with hypoglycaemia; an isolated assessment would not be meaningful. When assessing hypoglycaemia rates, it is also necessary to consider the long-term control of blood glucose levels in order to determine whether a low hypoglycaemia rate is possibly due to poor control of blood glucose levels.
Richter	• The minimum study period of 24 weeks is arbitrary. No literature is available that supports this choice. However, the chosen study period is still meaningful, as a minimum period exists in which the treatment regimen has to level out. • When choosing a study period, it also needs to be considered that the time needs to be long enough for the effectiveness to adapt to reality. • A longer study period is also important because drop-out rates

[††††] Committee for Proprietary Medicinal Products

Name	Contribution
	(e.g. due to adverse drug effects) approach rates in reality well within 6 months.
M Kaiser	• Why 24 weeks and not 6 months?
T Kaiser	• 24 weeks are regarded as 6 months (6x4 weeks), also for drug approval issues.
Knollmeyer	• There are also examples that patient-relevant endpoints can be investigated in shorter studies. There is a study on diabetes type 1 patients using pumps, which shows a difference between groups with regard to the rate of catheter occlusions.
Sawicki	• This difference should also be noticeable in longer-term studies.
Wölfert	• The German Diabetes Federation accedes to the statement of the German Diabetes Association.
TOP 6	**Evaluation of regular human insulin**
Sawicki	• Asks whether the office-based diabetologists query the benefit of RHI in patients with type 2 diabetes.
Braun	• Only the UKPDS[‡‡‡‡] and the Kumamoto Study are available as studies to show evidence of a benefit of RHI therapy. The UKPDS study has methodological problems. For the Kumamoto Study, it is unclear whether the results can be transferred to German patients (BMI of the study population < 22 kg/m^2); therefore, there is no definite evidence of a benefit of RHI. • Supports the reproduction of the Kumamoto Study in Germany to clarify whether the effect with regard to microangiopathy endpoints also applies to patients in Germany.
Sawicki	• Assumes that the reproduction of the Kumamoto Study will not be permitted by the ethics committees. From his point of view, no reasonable reason exists to conduct this study again in

[‡‡‡‡] UK Prospective Diabetes Study

Name	Contribution
	Germany.
Braun	• Only the question of transferability is posed.
Knollmeyer	• To completely compare analogues and RHI, the literature search should be widened to studies including only RHI.
Richter	• Reproducibility of results is a correct demand, but in contrast to physics, in medicine this is far more difficult. • The research question could be extended to the comparison between animal and human insulin.
T Kaiser	• The objective of the assignment was the direct comparison between insulin analogues and RHI. Therefore the aim of the literature search was to identify studies that directly compared analogues and RHI. • A wider search strategy would have lead to the identification of studies that would not have been relevant to the research question.
Tscheuschner	• Which RHI concentration was to be investigated: U40 or U100?
Siebenhofer	• There was no limitation of the literature search with regard to the concentration of RHI; however, the studies identified all investigated U100.
Schulze-Solce	• The statement from the Federal Association of Office-based Diabetologists shows that for RHI, there is no evidence of a benefit according to current criteria; the correct conclusion of the report would therefore be that for both RHI and for insulin analogues, evidence of a benefit has not been shown.
Sawicki	• Queries whether there really is no evidence of a benefit for RHI in type 2 diabetes. • Refers to a further assignment which is to evaluate the effects of different concepts of lowering blood glucose levels in patients with type 2 diabetes mellitus.

Name	Contribution
Knollmeyer	• Is this evaluation going to be stratified according to treatment regimens?
Sandow	• Comprehension question: evaluation of the extent of blood glucose lowering?
T Kaiser	• The assignment asks the question, whether, and if yes, to what extent the lowering of blood glucose levels in patients with type 2 diabetes is meaningful, investigating different treatment regimens.
TOP 7	**Mitogenic potency of insulin analogues**
Sandow	• The assessment of mitogenic potency is not a matter of the assignment. Why is this issue presented in the report plan? Why does IQWiG refer to preclinical data? • There is an abundance of preclinical data from the development phase of insulin analogues; some of these data generated the hypothesis of an increased mitogenic potency. This issue has been clarified completely and should therefore not be noted in the IQWiG report.
T Kaiser	• Information on a mitogenic potency is so far only found in the section “Background”. It is pointed out that the clinical relevance of the preclinical data is unclear.
Sandow	• The clinical relevance was assessed by the regulatory authorities. Sanofi-Aventis presented the documents; the authorities made a statement on the relevance of the issue of mitogenic potency.
T Kaiser	• The conclusions of the authorities are included in the “Background” section of the report. IQWiG did not evaluate mitogenic potency, but would like to relay this information to the Federal Joint Committee, physicians, and patients.
M Kaiser	• If IQWiG agrees with the authorities’ conclusions, the section on mitogenic potency could be omitted completely; otherwise it

Name	Contribution
	evokes a suspicion that is not justified.
Sawicki	• The “mitogenic potency aspect” is part of the weighing of benefits and harms and will therefore still be presented in the report.
Kazda	• There are safety data on insulin lispro from RCTs; these should be included in the report; a clinical relevance of the preclinical data cannot be inferred from the RCTs.
Sawicki	• The evaluation of mitogenic potency is not IQWiG’s task; the results of the mitogenic potency trials will therefore not be presented in the results section of the report.
T Kaiser	• Safety data from included studies will be considered within the framework of the assignment.
Tscheuschner	• Reports two cases of cancer under insulin analogue therapy from the University of Düsseldorf; suggests assessing these cases.
Sandow	• The relevance of preclinical studies on mitogenic potency is unclear; direct studies on mitogenic potency in humans are not possible; single temporal correlations between insulin analogue therapy and cases of cancer are not a definite indication; Sanofi also knows of single cases and has investigated them.
Kazda	• Insulin lispro has been on the market for about 10 years, therefore Lilly has an extensive database on drug safety of insulin lispro; this database is regularly submitted to the authorities. So far no indications of a mitogenic potency of insulin lispro can be inferred from these data.
Richter	• The system of spontaneous reporting is insufficient. Suggestion to Lilly: Investigate the research question with an adequate case-control study on the basis of the Lilly database and publish the results.

TOP 8	**Injection-meal interval**
Knollmeyer	• In a three-arm study, two administration schemes of an analogue (short-acting; 15 min) and an RHI (recombinant; 30 min) were compared. The results (HbA_{1c}) differed depending on the time of application. • The scheme of administration, in particular the injection-meal interval should be considered in the presentation and evaluation.
Siebenhofer	• The influence of the administration scheme is included in the report, but is not quantified.
T Kaiser	• Asks whether relevant studies are available for the report that show the effect of the injection-meal interval on the risk of hypoglycaemia; no such studies were found in the literature search.
Knollmeyer	• The Sanofi-Aventis Study 3005 shows these results; the study should be provided to IQWiG.
Sawicki, T Kaiser	• Internal agreement will be reached for the modalities in this regard.
Kazda	• Studies on insulin lispro with different application schemes showed no difference with regard to HBA_{1c} and hypoglycaemia. It is crucial how the schemes are evaluated by patients and whether patient satisfaction differs; in this regard, there is a study in 2500 patients, which was included in the statement by Lilly.
Sawicki	• The patient-relevant endpoint for this research question is patient satisfaction.
Richter	• An adequate comparison needs to include an arm in which RHI is administered without an injection-meal interval; subsequently, QoL and patient satisfaction should be evaluated. This comparison is not available in the information found.
Shen	• There are no primary endpoint data available from RCTs on

	QoL and patient satisfaction. However, there is a survey with a different evidence level in >2500 German patients with diabetes mellitus types 1 and 2; these data should be considered in the report.
T Kaiser	• In principle, it would be possible methodologically to collect data on QoL and patient satisfaction in RCTs. The survey provided by Lilly is methodologically inadequate. • For example, no patients treated with RHI were questioned, and the patients were dissatisfied with their previous treatment regimen and were questioned after a switch in therapy. The influence of the fact that therapy was switched is not ascertainable in this study. Even the authors of the publication indicate that the survey is not a scientific work.
Knollmeyer	• Queries whether differences are to be expected by switching from U40 to U100; the pharmacokinetic data and product information for both concentrations is the same.
Sawicki	• The differences between U40 and U100 were discussed under TOP 11. Asks for the available scientific evidence that one does not need an injection-meal interval for analogues. Asks which data are available.
Sandow	• The shorter injection-meal interval was inferred from the studies on insulin monomers.
Kazda	• The option to use analogues without an injection-meal interval is confirmed by pharmacokinetic and pharmacodynamic data.
Sawicki	• There are data that e.g. justify a shorter injection-meal interval of approx. 25 minutes for analogues (compared with approx. 60 minutes for RHI) on the basis of their pharmacokinetic properties; but they do not justify no injection-meal interval at all.
Kazda	• There are Phase 3 studies that show good results with no injection-meal interval at all. However, with analogues the results are also better with an injection-meal interval. No

	interval is better than an over-long interval with a hypoglycaemia risk.
M Kaiser	• The shorter injection-meal interval of the analogues is based on pharmacokinetic studies and on studies that show a good progression of blood glucose levels with a short injection-meal interval.
Sandow	• Theoretical concept: the molecular structure of analogues is suited for a shorter injection-meal interval; this however has not been investigated in patients.
Sawicki	• Good studies are lacking that measure results without an injection-meal interval of RHI compared with insulin analogues. Therefore this is not an appropriate argument for the manufacturers of insulin analogues.
T Kaiser	• For analogues, it was shown in studies that a shorter injection-meal interval is possible. The same research question should however also be tested for RHI, e.g. in a four-arm study.
Sawicki	• A study by Lefèbvre showed that compliance with an injection-meal interval showed as good as no effects on the control of blood glucose levels.
TOP 9	**Progression of blood glucose levels (fasting, postprandial, preprandial)**
Knollmeyer	• Many studies collect data on the progression of blood glucose levels; this parameter is important for physicians and patients.
Sawicki	• Why is the progression of blood glucose levels a patient-relevant endpoint?
Knollmeyer	• The progression of blood glucose levels is patient-relevant, because the dose titration is orientated towards it. In addition, it covers safety aspects, for example, changes of the fundus of the eye are associated with blood glucose levels.
Sawicki	• The blood glucose level is a diagnostic parameter.

Kazda	• The Kumamoto Study showed a correlation between fasting, post-, and preprandial blood glucose levels and retinopathy and nephropathy. • Asks whether the equivalence of two therapies is accepted if the postprandial blood glucose levels are unphysiologic under therapy. Asks whether it is ethically justifiable to wait for studies with patient-relevant endpoints.
Sawicki	• The question is whether the postprandial blood glucose level is a valid surrogate parameter for complications.
T Kaiser	• There are examples that the achievement of a physiologic condition is not necessarily suited to be a patient-relevant endpoint. • In the CAST[§§§§] Study, it was shown that a drug that prevents ventricular extrasystoles can still increase mortality.
Kazda	• A study is currently being conducted to investigate the association between postprandial blood glucose levels and patient-relevant endpoints (the abstract is available). • The CAST Study involved high-risk patients. • The epidemiological data situation on this research question is good. • Asks about the probability that this association does not exist.
Richter	• Patients with type 2 diabetes mellitus are also high-risk patients. • Association measures are not sufficient. Controlled studies are needed that investigate the surrogate as a primary endpoint and show the association between the blood glucose level and the endpoint; at the moment the associations only serve to generate hypotheses.
Horvath	• No concluding evaluation of the causality between blood glucose levels and patient-relevant endpoints is possible on the basis of epidemiological observational studies.

[§§§§] Cardiac Arrhythmia Suppression Trial

Sawicki	• The opposite false conclusion is also possible. • At IQWiG, we are currently generating a methodology on the structured differentiation between valid and non-valid surrogate parameters.
TOP 10	**Mixing ratio between rapid-acting and longer-acting insulin in the study groups**
T Kaiser	• The objection of this statement is justified; the determination of a fixed mixing ratio is inappropriate; comparable mixing ratios, e.g. a largely predominant proportion of one component, are sufficient. The report will be amended accordingly.
Knollmeyer	• All usual schemes should be compared.
T Kaiser	• A certain comparability of the schemes should be ensured; otherwise the influence of the treatment scheme cannot be distinguished.
Knollmeyer	• The mixed insulins are losing ground in diabetology. Therefore the usual therapeutic concepts should be permitted as comparator groups.
T Kaiser	• This would be a different research question that goes beyond the original assignment.
TOP 11	**Differences in the pharmacokinetics and pharmacodynamics between U40 and U100 insulin**
Tscheuschner	• Has followed the development of insulin therapy; in the sixties: CR/CS***** (Hoechst); in the eighties: use of RHI in two concentrations. Has experience with injections, pens, and pumps. • There are patients that need little insulin per meal. He himself uses 3 units of U40. Physicians have been trying for the last couple of years to switch him to analogues. He has also tested analogues but had unsatisfactory experiences with regard to the

***** CR= Rinderinsulin (bovine insulin); CS=Schweineinsulin (pork insulin).

	progression of blood glucose levels (no smoothing of levels achieved). • From his point of view, U40 is still needed. He hopes that this concentration is also available in the long-term so that no shortages in supply for patients who are optimally adjusted to U40 occur. He sees a lack of support for this therapy option by diabetologists; prescription numbers for U40 have been going down substantially for some time. • U40 has a comparable pharmacokinetic profile to insulin analogues.
Sawicki	• Asks whether the analogues also have to be tested versus U40 and, if such studies do not exist, asks whether there are methodological reasons for this.
Knollmeyer	• Studies are conducted multi-nationally. In many countries only U100 is available; therefore the comparison with U100 seems obvious. • Study data should be generally valid. • Dosages have changed over the course of time; U100 is however still the most common concentration on an international level. • In case of a shortage of supplies with U40 in Germany, he recommends importing it or producing it by diluting the U100 concentration.
Sawicki	• Until now, organisational or market-related reasons have been shown for the use of U100, not scientific ones. • If data are available that show that U40 and insulin analogues have a comparable pharmacokinetic profile, it may be possible that the difference between U40 and analogues is smaller than the difference between U100 and analogues, or that no such difference exists.
Kazda	• The decision in favour of U100 was made by the International Diabetes Federation (IDF). The aim is to have comparable

	insulin concentrations in all countries to reduce the rate of adverse effects due to the use of wrong concentrations when visiting foreign countries. • As a result, companies switched production to U100 and conducted studies with U100. • He does not know of studies that compare U40 and analogues. • Lilly provides dilution solutions free of charge, e.g. for children. • Analogues were developed with the aim to adapt the insulin curves to the physiologic profile by means of the monomer molecular structure. This question was tested by the industry; it does not work with every patient.
Sawicki	• The IDF's objective was to adapt the insulin concentrations to avoid incorrect dosing, not primarily to develop insulins with a monomer molecular structure.
Tscheuschner	• The statutory health insurance funds do not reimburse imported pharmaceuticals.
Knollmeyer	• According to § 73 (3), the health insurance fund can reimburse a drug available outside Germany.
Sawicki	• Question to the German Diabetes Federation: Does the Federation support Mr. Tscheuschner's wish that U40 should continue to be made available in the future? • Question to the Federal Association of Office-based Diabetologists: does the Association support Mr. Tscheuschner's wish?
Wölfert	• Will propose a survey among members of the German Diabetes Federation to assess whether the availability of U40 is a problem.
Sawicki	• Proposal: conduct of the survey together with diabetologists.
Braun	• She herself doesn't switch patients' treatment if they are well-adjusted with U40. The problem therefore doesn't exist in this

	way for her; the patients' wishes have priority here.
Tscheuschner	• In every federal state the prescription numbers for U40 are going down.
Sandow	• The majority of patients can be adjusted better with the insulin pen.
Sawicki	• It is an issue of exact dosing.
Knollmeyer	• Previous studies have demonstrated the superiority of pen systems compared with injections.
Richter	• Maybe the affected persons should suggest a review by Cochrane.
TOP 12	**Miscellaneous**
Sandow	• Asks how long, in IQWiG's opinion, a randomised controlled study in patients with type 2 diabetes including patient-relevant endpoints should last.
T Kaiser	• This depends, among other things, on the frequency of the events to be investigated. Proposal: targeted investigation of a high-risk group in which specific events occur relatively often; single studies do not have to include all conceivable endpoints.
Sandow	• Proposals for studies in the final report would be meaningful.
Sawicki	• IQWiG currently does not have the capacity to provide this sort of advice. These responsibilities are envisaged in the future, but cannot be conducted in the construction phase of the Institute. The Institute currently also does not have a budget for such a task. • Also proposes studies in high-risk groups where results are relatively frequent; therefore shorter study periods are possible.
Richter	• Supports the idea that IQWiG should develop recommendations for studies. • In the final report, factors should be identified and explicitly named that can improve the quality of studies.

Kazda	• The preliminary report described quality deficits of the studies or of the study publications. Lilly subsequently provided study reports. Asks whether the points criticised could be clarified from the reports or whether further information is needed.
T Kaiser	• The quality problems were mainly a problem of the quality of the publications; the majority of open issues were clarified by the study reports.
Horvath	• A minimum requirement for a good publication is that the number of patients evaluated is reported; that is often not the case.
Richter	• Also important: sample size planning. • The requirements for a publication are defined in the CONSORT statement. He suggests that companies check the publications on their studies with regard to the fulfilment of the CONSORT statements (e.g. regarding the adequate publication of sample size calculations and the intention-to-treat analysis).
Kazda	• In publications there is often insufficient space for the complete description of the methodology.
T Kaiser	• Nowadays there is the option to publish additional information on the Internet; this is therefore not an argument with regard to newer publications.
Sawicki	• The lack of publication quality applies to all authors of study publications; in fact the quality of reporting of industry-sponsored studies is usually of better quality.
Shen	• Proposes a revision of the graph on page 30 of the preliminary report on the basis of the study reports; proposes the inclusion of the p-value.
Götting	• Praises the well-prepared event; the discussion was on a high level and led to a creative exchange of opinions. • Suggests also conducting such discussion rounds in connection with the report plan and the general discussion of the methods

	paper of the Institute.
Sawicki	• The development of the methods of the Institute is a dynamic learning process in which there will always be new developments. The procedure of supplying statements in writing before the discussion is helpful and should be maintained.
Götting	• For the preliminary report it should be made clearer that this is not already the final report. • Report plans should be published swiftly after completion.
T Kaiser	• A clearer labelling of the preliminary plan is envisaged. • Faster publication of the report plans has already been achieved.
Sawicki	• Thanks the external experts and the Institute's staff for the generation of the report on insulin analogues and thanks all participants at the hearing for the constructive discussion.

Appendix F: Substantial statements

The following persons, companies, institutions, and societies made substantial statements on the preliminary report.

- Sanofi-Aventis Deutschland GmbH: Dr. Knollmeyer, Dr. Riederer;
- The Federal Association of Office-based Diabetologists: Prof. Kusterer (substituted by Dr. Braun-Schlüchtern in the scientific hearing);
- German Diabetes Association: Prof. Kerner and Prof. Klein (no participation in the scientific hearing as external experts as no disclosure of potential conflicts of interest);
- German Diabetes Federation: Mr. Wölfert;
- Lilly Deutschland GmbH: Dr. Kazda, PD Dr. Kretschmer, Dr. Schulze-Solce, Ms. Shen, Dr. Weber (participants of the scientific hearing: Dr. Kazda, Dr. Schulze-Solce, and Ms. Shen);
- Novo Nordisk Pharma GmbH: Dr. M. Kaiser;
- Prof. Sandow;
- Mr. Tscheuschner;
- German Association of Research-based Pharmaceutical Companies: Dr. Götting, Dr. Vorderwülbecke.

The (German-language) statements can be found in the German final report (page 125 onwards) on the Institute's website under:
http://www.iqwig.de/media/auftr_ge/files/abschlussbericht/05-12-15_A05-04_Abschlussbericht-KW-Analoga-T2DM.pdf