

# APPENDIX 1: Literature Search Strategy for Clinical Effectiveness Studies

## Guide to Search Syntax (DIALOG)

- ! Explode the search term. Retrieve the search concept plus all narrower terms.
- ? Truncation symbol, single character. Retrieve plural and variant ending of search terms.
- " " Search phrases.
- () Proximity operator. Words must be adjacent.
- (l) Proximity operator. Links descriptors and subheadings.
- (n) Proximity operator. Words must be near each other in any order.
- (w) Proximity operator. Words must be adjacent.
- ab Search in article abstract.
- de Descriptor i.e., subject heading (a controlled, thesaurus term).
- dt Document type.
- id Identifier (includes CAS Registry Number and natural language indexing terms).
- rn CAS Registry Number.
- ti Search in titles.
- tn Brand name.
- tw Text word.

DATABASES	DATES / LIMITS	SUBJECT HEADINGS/KEYWORDS
DIALOG OneSearch  MEDLINE BIOSIS Previews EMBASE PASCAL	Human  1990 -	Insulin Long-Acting(l)aa/de <i>[MeSH heading for MEDLINE]</i>  OR  (Insulin Glargine OR Insulin Detemir)/de <i>[EMTREE terms for EMBASE]</i>  OR  TN=(Lantus OR Levemir) <i>[Brand names in EMBASE]</i>  OR  (glargine OR Lantus OR HOE()901 OR 160337()95()1)/ti,ab,id OR RN=160337-95-1 OR (detemir OR Levemir OR NN()304 OR 169148()63()4)/ti,ab,id OR RN=169148-63-4 <i>[Textwords searched in title, abstract, identifier, registry number]</i>  OR  (long()acting()insulin? OR slow?()acting()insulin? OR long()acting()analog? OR slow?()acting()analog?)/ti,ab <i>[Textwords searched in title, abstract]</i>  OR Insulin(l)aa/de <i>[MeSH heading for MEDLINE]</i>

DATABASES	DATES / LIMITS	SUBJECT HEADINGS/KEYWORDS
		<p><i>OR</i></p> <p>(Insulin Derivative OR Insulin Aspart OR Insulin(B28(Lysine)B29)Proline)/de [EMTREE terms for EMBASE]</p> <p><i>OR</i></p> <p>TN=(Humalog OR NovoLog OR NovoRapid OR NovoMix OR Apidra) [Brand names in EMBASE]</p> <p><i>OR</i></p> <p>Insulin Lispro/de [BIOSIS Previews thesaurus term]</p> <p><i>OR</i></p> <p>(insulin?(1n)analog? OR insulin?(1n)derivat? OR new()insulin? OR novel()insulin?)/ti,ab</p> <p><i>OR</i></p> <p>(133107)64)9 OR insulin?(2n)(Lys?)28)B) OR (28)B)Lys?)29)B)(2n)insulin? OR Lispro? OR Humalog? OR B28 OR 28)B)lysine)29)B)prolineinsulin?)/ti,ab,id OR Lyspro?/ti,ab OR insulin(Lys)B28)Pro)B29/id OR RN=133107-64-9</p> <p><i>OR</i></p> <p>(116094)23)6 OR insulin?()aspart? OR B28)asp? OR Asp()B28 OR NovoLog OR NovoRapid OR NovoMix?)/ti,ab OR insulin()Asp)B28/id OR RN=116094-23-6</p> <p><i>OR</i></p> <p>(insulin()glulisine OR apidra OR 207748)29)6 OR insulin(Lys)B3)Glu)B29 OR insulin()lysyl)B3)glutamyl)B29 OR B3)lysyl)B29)glutamylinsulin)/ti,ab,id OR RN=207748-29-6</p> <p><i>OR</i></p> <p>(quick()acting()insulin? OR rapid()acting()insulin? OR rapidly()acting()insulin? OR short()acting()insulin? OR fast()acting()insulin? OR quick()acting()analog? OR rapid()acting()analog? OR rapidly()acting()analog? OR short()acting()analog? OR fast()acting()analog?)/ti,ab</p> <p><b>AND</b></p> <p>Diabetes Mellitus!/de [MeSH heading for MEDLINE]</p>

DATABASES	DATES / LIMITS	SUBJECT HEADINGS/KEYWORDS
		<p><i>OR</i></p> <p>(Insulin-Dependent Diabetes OR Insulin-Dependent Diabetes Mellitus OR Diabetes OR Diabetes Insipidus OR Diabetes Mellitus OR "Maturity-Onset Diabetes of the Young" OR Non-Insulin-Dependent Diabetes Mellitus OR "Gestational Diabetes" OR "Gestational Diabetes Mellitus")/de  <i>[BIOSIS Previews thesaurus terms]</i></p> <p><i>OR</i></p> <p>(Diabetes Control OR Diabetes Insipidus! OR Diabetes Mellitus! OR Experimental Diabetes Mellitus! OR Pregnancy Diabetes Mellitus!)/de  <i>[EMTREE terms for EMBASE]</i></p> <p><i>OR</i></p> <p>(diabet? OR IDDM OR NIDDM OR MODY OR "type 1" OR "type I" OR "type 2" OR "type II" OR insulin()depend?()DM OR matur?()onset()DM OR late()life()DM OR gestational()DM OR juvenile()onset()DM OR juvenile()DM OR ketosis()prone()DM OR sudden()onset()DM OR non()insulin()depend?()DM OR adult()onset()DM)/ti,ab</p> <p><i>AND</i></p> <p>(Controlled Clinical Trials OR Multicenter Studies OR Randomized Controlled Trials OR Double-Blind Method OR Random Allocation OR Single-Blind Method OR Placebos)/de  <i>[MeSH headings for MEDLINE]</i></p> <p><i>OR</i></p> <p>dt=(Multicenter Study OR Randomized Controlled Trial OR Controlled Clinical Trial)  <i>[Document type in MEDLINE]</i></p> <p><i>OR</i></p> <p>(Multicenter Study OR Randomized Controlled Trial OR Randomized Clinical Trial OR Randomized Trial OR Evidence-Based Medicine)/de  <i>[BIOSIS Previews thesaurus terms]</i></p> <p><i>OR</i></p> <p>(Major Clinical Study OR Multicenter Study OR Controlled Study! OR Randomized Controlled Trial)/de  <i>[EMTREE terms for EMBASE]</i></p> <p><i>OR</i></p> <p>(random? OR sham? OR placebo? OR singl?()blind? OR dumm? OR mask?) OR doubl?()blind? OR dumm? OR mask?) OR tripl?()blind? OR dumm? OR mask?) OR trebl?()blind? OR dumm? OR mask?) OR</p>

DATABASES	DATES / LIMITS	SUBJECT HEADINGS/KEYWORDS
		<p>control?)(study OR studies OR trial?) OR RCT? ? OR (multicent? OR multi(cent?)(study OR studies OR trial?))/ti,ab</p> <p><b>OR</b></p> <p>(Meta-Analysis OR Technology Assessment, Biomedical)/de [MeSH headings for MEDLINE]</p> <p><b>OR</b></p> <p>dt=Meta-Analysis [Document type in MEDLINE]</p> <p><b>OR</b></p> <p>Meta-Analysis/de [BIOSIS Previews thesaurus term]</p> <p><b>OR</b></p> <p>(Meta Analysis OR Systematic Review OR Biomedical Technology Assessment)/de [EMTREE terms for EMBASE]</p> <p><b>OR</b></p> <p>(meta()analy? OR metaanaly? OR met()analy? OR metanaly? OR health()technology()assessment? OR meta()regression? OR metaregression? OR mega()regression? OR systematic?)(literature()review? OR review? OR overview?) OR methodologic?)(literature()review? OR review? OR overview?) OR quantitative()(review? OR overview? OR synthes?) OR research()(integration? OR overview?) OR integrative(2w)(review? OR overview?) OR collaborative()(review? OR overview?) OR pool?()analy? OR data()synthes? OR data()extraction? OR data()abstraction? OR handsearch? OR hand()search? OR mantel()haenszel OR peto OR der()simonian OR dersimonian OR fixed()effect? OR latin()square?)/ti,ab</p> <p><i>Search performed on 3 August 2005; monthly alerts set up on MEDLINE, EMBASE and BIOSIS Previews and were ongoing until June 2007. An economic filter was added to the disease and intervention search concepts to retrieve economic studies.</i></p> <p><i>Total Hits = 850 Records (817 'clinical' results+33 sys. review /meta-analysis results), 442 Unique Records after comparison with PubMed records (423 clinical' results+19 sys. review /meta-analysis results)</i></p>
Cochrane Library, Issue 3 2005, all issues 2006, Issue 2 2007	1990 -	<p>Same MeSH and keywords as per MEDLINE search, excluding study design filter. Appropriate syntax used.</p> <p><i>Initial search performed on 2 August 2005 and updated with subsequent database updates.</i></p> <p><u>Total Hits =</u></p>

DATABASES	DATES / LIMITS	SUBJECT HEADINGS/KEYWORDS
		<i>Cochrane Database of Systematic Reviews = 2 Records, 1 Unique</i> <i>DARE = 2 Records, 0 Unique</i> <i>CENTRAL = 276 Records, 13 Unique</i> <i>Abstracts by INAHTA and other HTAs = 6 Records, 3 Unique</i>
PubMed	Human 1990 -	Same MeSH and keywords as per MEDLINE search. Appropriate syntax used. <i>Total Hits = 407 Unique Records</i>
Web sites of health technology assessment (HTA) and related agencies; trial registries; other databases		AHRQ; National Research Register; University of York NHS Centre for Reviews and Dissemination – CRD databases; LILACS etc.

## APPENDIX 2: Data Extraction Form

Data Extraction Form					
<b>Reviewer's initials</b>					
<b>Reference (Ref ID, author, year, source, publication status)</b>					
<b>Trial characteristics</b>					
Study design					
Number of centres					
Country					
Sponsor					
Number of patients					
Type of diabetes					
Disease state					
Investigator's definition of hypoglycemia					
Procedure					
Other					
<b>Patients' characteristics</b>					
<b>Category</b>	<b>Unit</b>	<b>Treatment</b>	<b>Control</b>	<b>All arms combined</b>	<b>Comment</b>
Age					
Male or female					
Duration of diabetes					
Baseline A1c					
Baseline BMI					
Race or ethnicity					
Withdrawals or lost to follow-up					
Other					
<b>Outcomes and cost data</b>					
<b>Category</b>	<b>Units</b>	<b>Treatment</b>	<b>Control</b>	<b>Comment</b>	
A1c					
BG					
Hypoglycemia					
Diabetic complications					
Adverse events					
Mortality					
QoL					
Cost					
Other					

A1c=glycosylated hemoglobin; BG=blood glucose; BMI=body mass index; QoL=quality of life

## APPENDIX 3: Trial Quality Assessment Form

Reference		
Reviewer		
Number	Category	Score
1	<b>Randomization</b>	
	Was the study described as randomized (i.e., including words such as “randomly,” “random,” “randomization”)? A trial reporting that it is “randomized” receives one point. Yes=1, no=0.	
	Trials describing an appropriate method of randomization (table of random numbers, computer-generated) receive an additional point. Appropriate=1, not appropriate=0.	
	If the report describes the trial as randomized and uses an inappropriate method of randomization (e.g., date of birth, hospital numbers), a point is deducted. Inappropriate=-1.	
2	<b>Double-blinding</b>	
	Was the study described as double-blind? A trial reporting that it is “double-blind” receives one point. Yes=1, no=0.	
	Trials describing an appropriate method of double-blinding (identical placebo: colour, shape, taste) receive an additional point. Yes=1, no=0.	
	If the report describes a trial as double-blind and uses an inappropriate method (e.g., comparison of tablets versus injection with no dummy), a point is deducted. Inappropriate=-1.	
3	<b>Withdrawals and dropouts</b>	
	Was there a description of withdrawals and dropouts? A trial reporting the number and reasons for withdrawals or dropouts receives one point. If there is no description, no point is given. Yes=1, no=0.	
	<b>Total score</b> (for above three categories)	
		<b>Adequacy Level</b>
4	<b>Adequacy of allocation concealment</b>	
	Central randomization; numbered or coded bottles or containers; drugs prepared by a pharmacy, serially numbered, opaque, sealed envelopes=adequate	
	Alternation; reference to case record number or date of birth=inadequate	
	Allocation concealment is not reported or fits neither category=unclear	

## APPENDIX 4A: Characteristics of RCTs Involving Type 1 DM Patients

Study	Publication Type	Study Period	Sponsor	Countries	Number of Centres	Study Type	Comparison	Number of Patients	Withdrawals
De Leeuw <sup>25</sup>	journal article	12 months	Novo Nordisk	several European countries	42	open-label, parallel	IDet+IAsp versus NPH+IAsp	315	8
Fulcher <sup>26</sup>	journal article	30 weeks	Aventis	Australia	9	single-blind, parallel	IGlar+ILis versus NPH+ILis	125	18
Garg <sup>27</sup>	abstract	4 weeks	NR	US	NR	open-label, parallel	IGlar+HI versus NPH+HI	14	NR
Hermansen <sup>28</sup>	journal article	2×6 weeks	Novo Nordisk	Denmark	7	open-label, crossover	IDet+HI versus NPH+HI	59	3
Hershon <sup>29</sup>	journal article	28 weeks	Aventis	US	48	open-label, parallel	IGlar+HI versus NPH+HI	394	40
Home <sup>30</sup>	journal article	28 weeks	Aventis	UK, Europe	63	open-label, parallel	IGlar+HI versus NPH+HI	585	37
Home <sup>31</sup>	journal article	16 weeks	Novo Nordisk	Australasia, Europe	52	open-label, parallel	IDet <sub>12h</sub> +IAsp versus IDet <sub>m+b</sub> +IAsp versus NPH <sub>m+b</sub> +IAsp	408	17
Kawamura <sup>32</sup>	abstract	2×16 weeks	NR	Japan	NR	crossover	IGlar+IAsp versus NPH+IAsp	64	NR
Kølendorf <sup>33</sup>	poster	2×16 weeks	Novo Nordisk	multinational	multicentre	open-label, crossover	IDet+IAsp versus NPH+IAsp	130	NR
Kudva <sup>34</sup>	journal article	2×16 weeks	Aventis, Medtronic	US	NR	partial blinding, crossover	IGlar+IAsp versus UL+IAsp	24	2
Peiber <sup>35</sup>	journal article	4 weeks	Novo Nordisk	European countries	42	partial blinding, parallel	IGlar[30]+HI versus IGlar[80]+HI versus NPH+HI	333	0
Pieber <sup>36</sup>	journal article	16 weeks	Novo Nordisk	7 European countries	23	open-label, parallel	IDet <sub>m+d</sub> +IAsp versus IDet <sub>m+b</sub> +IAsp versus NPH <sub>m+b</sub> +IAsp	400	21
Porcellati <sup>37</sup>	journal article	1 year	National Ministry of Scientific	Italy	NR	open-label, parallel	IGlar(dinner time)+ILis versus NPH (4 times/day)+ILis	121	NR

Study	Publication Type	Study Period	Sponsor	Countries	Number of Centres	Study Type	Comparison	Number of Patients	Withdrawals
			Research						
Raskin <sup>38</sup>	journal article	16 weeks	Hoechst Marion Roussel	Canada, US	60	open-label, parallel	IGlar+ILis versus NPH+ILis	619	31
Ratner <sup>39</sup>	journal article	28 weeks	Hoechst Marion Roussel	US	49	open-label, parallel	IGlar+HI versus NPH+HI	534	53
Robertson <sup>40</sup>	poster	26 weeks	Novo Nordisk	European countries	multicentre	open-label, parallel	IDet+IAsp versus NPH+IAsp	347	NR
Rosenstock <sup>41</sup>	journal article	4 weeks	Aventis	US	multicentre	double-blind, parallel	IGlar[30]+HI versus IGlar[80]+HI versus NPH+HI	256	2
Rossetti <sup>42</sup>	journal article	3 months	National Ministry of Scientific Research	Italy	NR	open-label, parallel	IGlar(dinner time)+ILis versus IGlar(bedtime)+ILis versus NPH (4 times/day)+ ILis	51	NR
Russell-Jones <sup>43</sup>	journal article	6 months	Novo Nordisk	Europe, Australia	92	open-label, parallel	IDet+HI versus NPH+HI	749	49
Schober <sup>44</sup>	journal article	28 weeks	Aventis	9 European countries, South Africa	30	open-label, parallel	IGlar+HI versus NPH+HI	361	12
Standl <sup>45</sup>	journal article	6-month treatment+6-month extension	Novo Nordisk	Europe, Australia, New Zealand	47	open-label, parallel	IDet+HI versus NPH+HI	289	37
Vague <sup>46</sup>	journal article	6 months	Novo Nordisk	5 European countries	46	open-label, parallel	IDet+IAsp versus NPH+IAsp	447	22
Witthaus <sup>47</sup>	journal article	28 weeks	Aventis	10 European countries	multicentre	open-label, parallel	IGlar+HI versus NPH+HI	517	NR

12h=12-hour interval; HI=conventional human insulin; IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; IGlar[30]=insulin glargine containing 30 µg/ml zinc; IGlar[80]=insulin glargine containing 80 µg/ml zinc; ILis=insulin lispro; m+b=morning and bedtime; m+d=morning and before dinner; NPH=neutral protamine Hagedorn; UL=ultra lente

## APPENDIX 4B: Characteristics of RCTs Involving Type 2 DM Patients

Study	Publication Type	Study Period	Sponsor	Countries	Number of Centres	Study Type	Comparison	Number of Patients	Withdrawals
Fonseca <sup>48</sup> (subgroup analysis of Rosenstock) <sup>56</sup>	journal article	28 weeks	Aventis	US	38	open-label, parallel	IGlar+HI versus NPH+HI	100	7
Fritsche <sup>49</sup>	journal article	24 weeks	Aventis	13 European countries	111	open-label, parallel	IGlar (morning)+Glim versus IGlar (bedtime)+Glim versus NPH (bedtime)+Glim	695	55
Haak <sup>50</sup>	journal article	26 weeks	Novo Nordisk	5 European countries	63	open-label, parallel	IDet+IAsp versus NPH+IAsp	505	34
Hermansen <sup>51</sup> Kølendorf <sup>52</sup>	poster	24 weeks	Novo Nordisk	10 countries	58	open-label, parallel	IDet+OAD versus NPH+OAD	476	1
Massi Benedetti <sup>53</sup>	journal article	52 weeks	Aventis	14 European countries, South Africa	57	open-label, parallel	IGlar+OAD versus NPH+OAD	570	46
Meneghini <sup>54</sup>	abstract	48 weeks	NR	US	60	open-label, parallel	IGlar versus Pioglitazone	253	80
Riddle <sup>55</sup>	journal article	24 weeks	Aventis	US and Canada	80	open-label, parallel	IGlar+OAD versus NPH+OAD	756	65
Rosenstock <sup>56</sup>	journal article	28 weeks	NR	US	59	open-label, parallel	IGlar+HI versus NPH+HI	518	49
Rosenstock <sup>57</sup>	journal article	24 weeks	Aventis	US	42	open-label, parallel	IGlar+Sfu(max)+Metf versus Ros+Sfu(max)+Metf	216	17
Yki-Järvinen <sup>58</sup>	journal article	52 weeks	Hoechst Marion Roussel	European countries	NR	open-label, parallel	IGlar+OAD versus NPH+OAD	426	NR

Study	Publication Type	Study Period	Sponsor	Countries	Number of Centres	Study Type	Comparison	Number of Patients	Withdrawals
Yki-Järvinen <sup>59</sup>	journal article	36 weeks	Aventis	Finland, UK	7	open-label, parallel	IGlar+Metf versus NPH+Metf	110	2
HOE 901/2004 Study Group <sup>60</sup>	journal article	4 weeks	Aventis	Europe, South Africa	29	open-label, parallel	IGlar[30]+OAD versus IGlar[80]+OAD versus NPH+OAD	204	2

Glim=glimepiride (sulfonylurea); HI=conventional human insulin; IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; IGlar[30]=insulin glargine containing 30 µg/ml zinc; IGlar[80]=insulin glargine containing 80 µg/ml zinc; max=maximum dose; Metf=metformin; NPH=neutral protamine Hagedorn; OAD=oral anti-diabetic agent; Sfu=sulfonylurea

## APPENDIX 5A: Characteristics of Patients in RCTs Involving Type 1 DM

Study	Treatment Arm	Number of Patients	Age (years)	Male/Female, number (%)	Race or Ethnicity	Duration of Diabetes (years)	Baseline A1c (%)	Baseline BMI, kg/m <sup>2</sup> (weight, kg)	Baseline Rate of Hypoglycemia (episodes/patient/30 days)	Withdrawals or Lost to Follow-Up
De Leeuw <sup>25</sup>	IDet+IAsp	216	40.1±12.8*	116/100 (53.7/46.3)	all Caucasian	17.8±9.7*	8.18±1.14*	24.4±2.9*	NR	5
	NPH+IAsp	99	40.8±13.2*	52/47 (52.5/47.5)	all Caucasian	16.6±10.2*	8.03±1.11*	24.6±3.5*	NR	3
Fulcher <sup>26</sup>	All	125	40.5±13.5*	49/76 (39.2/60.8)	98.4% Caucasian	17.5±10.1*	NR	26.6±3.8*	NR	18
	IGlar+ILis	62	41.6±12.9*	24/38 (38.7/61.3)	NR	17.9±10.5*	9.2±1.1*	27.0±3.6*	NR	4
	NPH+ILis	63	39.3±13.9*	25/38 (39.7/60.3)	NR	17.1±9.7*	9.7±1.3*	26.0±3.9*	NR	14
Garg <sup>27</sup>	IGlar+HI	9	24.6±2.9 <sup>†</sup>	NR	NR	9.8±6.0	NR	NR	NR	NR
	NPH+HI	5	23.8±3.8	NR	NR	12.3±6.7	NR	NR	NR	NR
Hermansen <sup>28</sup>	all	59	34.5 [19 to 52] <sup>‡</sup>	46/10 (82/18)	all Caucasian	14.8 [2.6 to 47.8] <sup>‡</sup>	7.9 [5.7 to 8.7] <sup>‡</sup>	23.8±2.0*	NR	3
Hershon <sup>29</sup>	all	394	37.8±12.0*	195/199 (49.5/50.5)	95.7% Caucasian	17.4±10.6*	7.7±1.2*	25.9±4.5*	NR	40
	IGlar+HI	195	37.9±12.6*	98/97 (50.3/49.7)	94.9% Caucasian	18.2±11.5*	7.7±1.2*	25.6±4.2*	NR	24
	NPH+HI	199	37.8±11.4*	97/102 (48.7/51.3)	96.5% Caucasian	16.7±9.5*	7.7±1.1*	26.1±4.8*	NR	16
Home <sup>30</sup>	all	585	39±12	326/259 (55.7/44.3)	NR	16±11*	7.9±1.2*	24.9±3.2*	NR	37
	IGlar+HI	292	39±12	160/132 (54.8/45.2)	NR	16a±12*	7.9±1.2*	24.6±3.1*	NR	16
	NPH+HI	293	39±12	166/127 (56.7/43.3)	NR	15±9	8.0±1.2*	25.1±3.3*	NR	21
Home <sup>31</sup>	IDet <sub>12h</sub>	137	40.9±13.0*	71/66 (51.8/48.2)	NR	17.1±10.6*	8.55±1.20*	25.1±3.3*	NR	5
	IDet <sub>m+b</sub>	139	41.3±11.4*	79/60 (56.8/43.2)	NR	17.6±10.7*	8.74±1.20*	25.2±3.6*	NR	4

Study	Treatment Arm	Number of Patients	Age (years)	Male/Female, number (%)	Race or Ethnicity	Duration of Diabetes (years)	Baseline A1c (%)	Baseline BMI, kg/m <sup>2</sup> (weight, kg)	Baseline Rate of Hypoglycemia (episodes/patient/30 days)	Withdrawals or Lost to Follow-Up
	NPH <sub>m+b</sub>	132	38.3±12.4*	70/62 (53/47)	NR	15.1±10.6*	8.52±1.19*	25.2±3.7*	NR	8
Kawamura <sup>32</sup>	all	64	8 to 21	NR	NR	NR	NR	NR	NR	NR
	IGlar	NR	NR	NR	NR	NR	8.1±1.3	NR	NR	NR
	NPH	NR	NR	NR	NR	NR	8.3±1.3	NR	NR	NR
Kølendør <sup>33</sup>	all	130	39.2±12.3*	70/60 (53.8/46.2)	NR	16.6±10.2*	7.9±0.7*	25.3±3.5*	NR	NR
Kudva <sup>34</sup>	all	24 randomized, 22 evaluated	43 [24 to 72] <sup>‡</sup>	10/12 (45.5/54.5)	NR	16 [3 to 54] <sup>‡</sup>	6.94±0.14 <sup>†</sup>	25.9 [21.0 to 36.5] <sup>‡</sup>	NR	2
Peiber <sup>35</sup>	IGlar[30]+HI	110	35.6 [18 to 68] <sup>‡</sup>	61/49 (56/44)	NR	median 11 [1 to 36] <sup>‡</sup>	8.09±0.11 <sup>†</sup>	24 [18.7 to 28.3] <sup>‡</sup>	NR	0
	IGlar[80]+HI	113	37.5 [19 to 70] <sup>‡</sup>	74/39 (66/34)	NR	median 8 [1 to 48] <sup>‡</sup>	7.96±0.11 <sup>†</sup>	24 [18.6 to 30.0] <sup>‡</sup>	NR	0
	NPH+HI	110	35.7 [20 to 61] <sup>‡</sup>	68/42 (62/38)	NR	median 11 [2 to 48] <sup>‡</sup>	7.85±0.11 <sup>†</sup>	24 [18.9 to 29.1] <sup>‡</sup>	NR	1
Pieber <sup>36</sup>	IDet <sub>m+d</sub> +IAsp	139	39.0±12.4*	78/61 (56.1/43.9)	Caucasian	14.4±10.8*	8.01±1.24*	25.0±3.7*	NR	7
	IDet <sub>m+b</sub> +IAsp	132	40.4±11.4*	90/42 (68.2/31.8)	Caucasian	15.9±10.3*	8.13±1.37*	25.4±3.2*	NR	10
	NPH <sub>m+b</sub> +IAsp	129	41.1±11.9*	73/56 (56.6/43.4)	Caucasian	14.4±9.2*	8.08±1.15*	25.2±3.1*	NR	4
Porcellati <sup>37</sup>	IGlar(dinner time)+ILis	61	36±1.0 <sup>†</sup>	34/27 (55.7/44.3)	NR	13±0.3 <sup>†</sup>	7.1±0.1 <sup>†</sup>	22.9±0.14 <sup>†</sup>	NR	NR
	NPH(4 times/day)+ILis	60	34±1.0 <sup>†</sup>	33/27 (55/45)	NR	15±0.3 <sup>†</sup>	7.1±0.2 <sup>†</sup>	23.2±0.15 <sup>†</sup>	NR	NR
Raskin <sup>38</sup>	IGlar+ILis	310	38.9±12.2*	151/159 (48.7/51.3)	96.5% Caucasian	18.7±11.5*	7.59±1.19*	25.5±3.4*	211 pts (68.1%)	15
	NPH+ILis	309	39.5±12.2*	162/147 (52.4/47.6)	97.4% Caucasian	18.4±11.8*	7.71±1.2*	25.7±3.9*	200 pts (64.7%)	16
Ratner <sup>39</sup>	All	534	38.5±12.0*	270/264 (50.6/49.4)	NR	17.4±10.85*	7.7±1.2*	25.78±4.29*	NR	53
	IGlar+HI	264	38.2±12.2*	141/123	NR	17.9±11.66*	7.7±1.2*	25.63±4.01*	NR	31

Study	Treatment Arm	Number of Patients	Age (years)	Male/Female, number (%)	Race or Ethnicity	Duration of Diabetes (years)	Baseline A1c (%)	Baseline BMI, kg/m <sup>2</sup> (weight, kg)	Baseline Rate of Hypoglycemia (episodes/patient/30 days)	Withdrawals or Lost to Follow-Up
				(53.4/46.6)						
	NPH+HI	270	38.9±11.9*	129/141 (47.8/52.2)	NR	16.9±10.0*	7.7±1.1*	25.93±4.55*	NR	22
Robertson <sup>40</sup>	IDet+IAsp	232	11.9±2.8*	119/113 (51.3/48.7)	NR	5.1±3.1*	8.8±1.2*	19.2±2.8*	NR	NR
	NPH+IAsp	115	11.7±2.7*	55/60 (47.8/52.2)	NR	4.8±2.8*	8.8±1.2*	19.1±2.9*	NR	NR
Rosenstock <sup>41</sup>	All	256	37.5±11.9*	133/123 (52/48)	93.8% Caucasian	16.3±10.7*	7.9±1.1*	24.3±2.6*	NR	1
	IGlar[30]+HI	82	37.5±11.7*	42/40 (51/49)	92.7% Caucasian	16.7±11.3*	7.8±1.1*	23.9±2.5*	NR	0
	IGlar[80]+HI	86	37.0±11.5*	44/42 (51/49)	94.2% Caucasian	15.8±10.0*	7.9±1.2*	24.4±2.5*	NR	0
	NPH+HI	88	37.9±12.5*	47/41 (53/47)	94.3% Caucasian	16.3±10.8*	8.0±1.2*	24.5±2.7*	NR	1
Rossetti <sup>42</sup>	IGlar (dinnertime)+ILis	17	31.3±3.4 <sup>†</sup>	8/9 (47/53)	NR	12.9±2.3 <sup>†</sup>	6.8±0.2 <sup>†</sup>	22.9±1.0 <sup>†</sup>	12.8±0.2 <sup>†</sup>	NR
	IGlar (bedtime)+ILis	17	34.0±3.1 <sup>†</sup>	10/7 (59/41)	NR	14.8±2.3 <sup>†</sup>	7.0±0.2 <sup>†</sup>	23.2±0.9 <sup>†</sup>	13.6±0.2 <sup>†</sup>	NR
	NPH (4 times/day)+ILis	17	32.0±3.0 <sup>†</sup>	9/8 (53/47)	NR	13.1±1.9 <sup>†</sup>	6.9±0.1 <sup>†</sup>	23.1±0.8 <sup>†</sup>	13.9 ± 0.1 <sup>†</sup>	NR
Russell-Jones <sup>43</sup>	IDet+HI	491	40.9±12.4*	322/169 (65.6/34.4)	NR	17.1±11.3*	8.35±1.20*	25.1±3.4*	NR	27
	NPH+HI	256	39.8±12.3*	157/99 (61.3/38.7)	NR	16.4±9.5*	8.35±1.21*	25.4±3.4*	NR	22
Schober <sup>44</sup>	all	361 randomized; 349 evaluated	11.7±2.41*	181/168 (51.9/48.1)	NR	4.8±3.05*	NR	18.9±2.84*	NR	12 (before treatment)
	IGlar+HI	174	11.8±2.46*	97/77 (55.7/44.3)	NR	5.0±3.02*	8.48±0.11 <sup>†</sup>	18.8±2.76*	NR	NR
	NPH+HI	175	11.5±2.36*	84/91 (48/52)	NR	4.7±3.08*	8.81±0.11 <sup>†</sup>	18.9±2.93*	NR	NR
Standl <sup>45</sup>	IDet+HI	154	40.7±13.4*	95/59 (62/38)	NR	16.1±9.1*	7.72±1.26*	25.2±3.0*	NR	20

Study	Treatment Arm	Number of Patients	Age (years)	Male/Female, number (%)	Race or Ethnicity	Duration of Diabetes (years)	Baseline A1c (%)	Baseline BMI, kg/m <sup>2</sup> (weight, kg)	Baseline Rate of Hypoglycemia (episodes/patient/30 days)	Withdrawals or Lost to Follow-Up
	NPH+HI	134	42.5±12.3*	88/46 (66/34)	NR	16.0±10.6*	7.66±1.19*	25.6±3.3*	NR	17
Vague <sup>46</sup>	IDet+IAsp	301	38.9±13.3*	162/139 (53.8/46.2)	NR	17.1±9.9*	8.18±1.14*	24.5±3.2*	NR	17
	NPH+IAsp	146	41.8±14.2*	74/72 (50.7/49.3)	NR	17.4±11.0*	8.11±1.12*	24.6±3.4*	NR	5
Witthaus <sup>47</sup>	IGlar+HI	261	40.1±12.31*	142/119 (54.4/45.6)	NR	NR	7.82±1.15*	NR	NR	NR
	NPH+HI	256	39.4±11.9*	145/111 (56.6/43.4)	NR	NR	7.95±1.15*	NR	NR	NR

12h=12-hour interval; HI=conventional human insulin; IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; IGlar[30]=insulin containing 30 µg/ml zinc; IGlar[80]=insulin containing 80 µg/ml zinc; ILis=insulin lispro; m+b=morning and bedtime; m+d=morning and before dinner; NPH=neutral protamine Hagedorn; NR=not reported; pts=patients  
\*mean±SD, †mean±SE, ‡mean [range]

## APPENDIX 5B: Characteristics of Patients in RCTs Involving Type 2 DM

Study	Treatment Arm	Number of Patients	Age, years	Male/ Female (%)	Race or Ethnicity	Duration of Diabetes, years	Baseline A1c (%)	Baseline BMI, kg/m <sup>2</sup> (weight, kg)	Baseline Rate of Hypo- glycemia	Withdrawals or Lost to Follow-Up
Fonseca <sup>48</sup> subgroup analysis of Rosenstock <sup>56</sup>	all	100	57.9±9.21*	57/43 (57/43)	84% Caucasian	12.6±9.61*	8.39±1.09*	29.81± 5.06*	NR	7
	IGlar+HI	52	57.3±8.68*	25/27 (48.1/51.9)	82.7% Caucasian	12.4±10.02*	8.42±1.22*	30.34± 4.41*	NR	5
	NPH+HI	48	58.5±9.8*	32/16 (66.7/33.3)	85.4% Caucasian	12.7±9.25*	8.36±0.96*	29.94± 5.67*	NR	2
Fritsche <sup>49</sup>	IGlar (morning)+ Glim	236	61±9*	122/114 (51.7/48.3)	NR	9.0** [0 to 38]‡	9.1±1.0*	28.6±4.5*	NR	11
	IGlar (bedtime)+ Glim	227	60±9*	132/95 (58.1/41.9)	NR	8.2** [1 to 51]‡	9.1±1.0*	28.7±3.9*	NR	17
	NPH (bedtime)+ Glim	232	62±9*	119/113 (51.3/48.7)	NR	9.3** [1 to 39]‡	9.1±1.1*	28.9±3.9*	NR	27
Haak <sup>50</sup>	IDet+IAsp	341	60.6±8.7*	165/176 (48.4/51.6)	99% Caucasians	12.9±7.4*	7.9±1.3*	30.1±5.0*	NR	26
	NPH+IAsp	164	60.0±8.4*	93/71 (56.7/43.3)	98.8% Caucasian	13.7±8.0*	7.8±1.3*	31.1±5.8*	NR	8
Hermansen <sup>51</sup> Kølendir <sup>52</sup>	IDet+OAD	237	61.3±9.1*	117/120 (49.4/50.6)	NR	9.6±6.6*	8.61±0.78*	28.9±3.6*	NR	12
	NPH+OAD	238	60.4±9.3*	135/103 (56.7/43.3)	NR	9.8±6.2*	8.51±0.76*	29.0±3.6*	NR	12
Massi Benedetti <sup>53</sup>	IGlar	289	59.6±9.3*	154/135 (53.3/46.7)	NR	10.2±6.2*	9.0±1.2*	29.3±4.3*	NR	17
	NPH	281	59.4±9.1*	152/129 (54.1/45.9)	NR	10.5±6.0*	8.9±1.1*	28.8±4.3*	NR	29
Meneghini <sup>54</sup>	all	253	53	NR	NR	5.9	8 to 12	33.5	NR	80
Riddle <sup>55</sup>	IGlar+OAD	367	55±9.5*	202/165 (55/45)	84% Caucasian	8.4±5.55*	8.61±0.9*	32.5±4.64*	NR	33
	NPH+OAD	389	56±8.9*	218/171 (56/44)	83% Caucasian	9.0±5.57*	8.56±0.9*	32.2±4.80*	NR	32

Study	Treatment Arm	Number of Patients	Age, years	Male/Female (%)	Race or Ethnicity	Duration of Diabetes, years	Baseline A1c (%)	Baseline BMI, kg/m <sup>2</sup> (weight, kg)	Baseline Rate of Hypoglycemia	Withdrawals or Lost to Follow-Up
Rosenstock <sup>56</sup>	IGlar+HI	259	59.5±9.7*	150/109 (57.9/42.1)	80.6% Caucasian	13.4±8.3*	8.6±1.2*	30.7±5.0*	25.5% pts	28
	NPH+HI	259	59.2±9.9*	161/98 (62.2/37.8)	80.7% Caucasian	14.1±9.0*	8.5±1.2*	30.4±5.1*	29.7% pts	21
Rosenstock <sup>57</sup>	IGlar (bedtime)+ Sfu(max)+ Metf	104	55.9±10.5*	47/57 (45/55)	NR	8.5±5.8*	8.8±1.0*	34.6±7.0*	NR	6
	Ros+Sfu (max)+Metf	112	55.3±11.4*	65/47 (58/42)	NR	8.1±5.1*	8.7±1.0*	33.6±6.3*	NR	11
Yki-Järvinen <sup>58</sup>	IGlar+OAD	214	59±1 <sup>†</sup>	118/96 (55/45)	NR	10±1 <sup>†</sup>	9.1±0.1 <sup>†</sup>	29.3±0.3 <sup>†</sup>	NR	NR
	NPH+OAD	208	59±1 <sup>†</sup>	110/98 (53/47)	NR	10±1 <sup>†</sup>	8.9±0.1 <sup>†</sup>	28.5±0.3 <sup>†</sup>	NR	NR
Yki-Järvinen <sup>59</sup>	IGlar+Metf	61	56±1 <sup>†</sup>	38/23 (62/38)	NR	9±1 <sup>†</sup>	9.5±0.1 <sup>†</sup>	31.3±0.7 <sup>†</sup>	NR	1 (due to pancreatic cancer)
	NPH+Metf	49	57±1 <sup>†</sup>	32/17 (65/35)	NR	9±1 <sup>†</sup>	9.6 ± 0.1 <sup>†</sup>	32.0±0.8 <sup>†</sup>	NR	1 (due to pulmonary tumour, but benign)
HOE 901/2004 Study Group <sup>60</sup>	IGlar[30]+ OAD	64	58.9 [29 to 75] <sup>‡</sup>	37/27 (58/42)	NR	9.5	9.79±1.5*	26.84 [19.8 to 34.2] <sup>‡</sup>	1.6% pts	2
	IGlar[80]+ OAD	72	60.0 [38 to 78] <sup>‡</sup>	46/26 (64/36)	NR	9.9	9.71±1.2*	27.62 [19.6 to 35.3] <sup>‡</sup>	1.4% pts	0
	NPH+OAD	68	59.2 [30 to 78] <sup>‡</sup>	39/29 (57/43)	NR	9.1	9.47±1.4*	27.69 [20.1 to 39.0] <sup>‡</sup>	5.9% pts	0

Glim=glimepiride (sulfonylurea); HI=conventional human insulin; IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; IGlar[30]=insulin containing 30 µg/ml zinc; IGlar[80]=insulin containing 80 µg/ml zinc; Metf=metformin; NPH=neutral protamine Hagedorn; NR=not reported; OAD=oral anti-diabetic agent; pts=patients; Ros=rosiglitazone; Sfu(max)=sulfonylurea; \*mean±SD, <sup>†</sup>mean±SE, <sup>‡</sup>mean [range], <sup>§</sup>median [interquartile]

## APPENDIX 6: Inclusion and Exclusion Criteria for Selecting Patients in RCTs

Study	Inclusion Criteria	Exclusion Criteria	DM Type
De Leeuw <sup>25</sup>	age ≥ 18 years; type 1 DM < 1 year; basal-bolus therapy ≥ 2 months before study; BMI < 35 kg/m <sup>2</sup> ; A1c ≤ 12.0%; total daily basal insulin requirement < 100 IU/day; Caucasian	proliferative retinopathy; impaired hepatic or renal function; severe cardiac problems; uncontrolled hypertension; recurrent major hypoglycemia; allergy to insulin; pregnancy or lactation	1
Fonseca <sup>48</sup> (subgroup analysis of Rosenstock) <sup>56</sup>	age 40 to 80 years; insulin use ≥ 3 months before study	hepatic or renal impairment; oral antidiabetic drugs ≤ 3 months before study; night shift work	2
Fritsche <sup>49</sup>	age < 75 years; BMI < 35 kg/m <sup>2</sup> ; previous oral therapy; fasting blood glucose ≥ 6.7 mmol/L; A1c 7.5 to 10.5%	pregnancy or lactation; treatment with insulin or investigation drugs ≤ 3 months before study; clinically relevant somatic or mental diseases	2
Fulcher <sup>26</sup>	age 18 to 80 years; insulin use ≥ 1 year before study; A1c ≥ 12.0%	nightshift workers; known sensitivity to study drug or related drugs; impaired hepatic function or other clinically relevant physiological or psychological medical conditions; use of systemic corticosteroids and BG lowering drugs	1
Garg <sup>27</sup>	abstract, criteria unspecified	not reported	1
Haak <sup>50</sup>	age ≥ 35 years; type 2 DM ≥ 12 months; A1c ≤ 12.0%; insulin use ≥ 2 months before study	OAD use ≤ 2 months before trial; pregnancy or lactation; proliferative retinopathy; uncontrolled hypertension; recurrent major hypoglycemia; impaired renal or hepatic function; cardiac problems; total daily basal insulin dose > 100 IU/day	2
Hermansen <sup>28</sup>	age 15 to 55 years; Caucasian; type 1 DM > 2 years; use of basal-bolus treatment with NPH and HI ≥ 6 months before study; BMI ≤ 27.5 kg/m <sup>2</sup> ; A1c ≤ 8.7%; glucagon-stimulated C-peptide ≤ 0.1 nmol/L or fasting C-peptide ≤ 0.04 nmol/L; NPH dosage < 40 IU/day	proliferative retinopathy; impaired hepatic or renal function; decompensated heart failure; unstable angina pectoris; myocardial infarction within last year; hypertension (≥ 180/100 mm Hg); hypoglycemic unawareness; recurrent major hypoglycemia; allergy to insulin or any compositional component; abuse of alcohol or narcotics; use of systemic corticosteroids, beta-blockers, or hormones within last month; pregnancy or lactation or using inadequate contraceptive measures; treatment with other investigational products ≤ 3 months before study; previous use of insulin detemir	1
Hermansen, <sup>51</sup> Kølendorf <sup>52</sup>	insulin-naïve; type 2 DM inadequately controlled with 1 or 2 OADs ≥ 4 months	not reported	2
Hershon <sup>29</sup>	age 18 to 80 years; A1c ≤ 12.0%; postprandial C-peptide ≤ 0.5 mmol/L	hepatic or renal impairment; oral antidiabetic drugs ≤ 3 months before study; pregnancy; night shift work	1

Study	Inclusion Criteria	Exclusion Criteria	DM Type
Home <sup>30</sup>	adult; C-peptide<0.50 nmol/L or <1.50 µg/L when capillary BG ≥5.5 mmol/L (100 mg/dL); insulin use ≥1 year before study	not reported	1
Home <sup>31</sup>	age>8 years; type 1 diabetes >1 year before study; use of basal-bolus regimen >2 months before study with basal insulin dose <100 units/day; A1c ≤12.0%; BMI ≤35 kg/m <sup>2</sup>	proliferative retinopathy; recurrent major hypoglycemia; impaired hepatic or renal function; uncontrolled cardiovascular problems; use of medication known to interfere with glucose metabolism; pregnancy or lactation; other significant medical problems	1
Kawamura <sup>32</sup>	age 8 to 21 years; basal-bolus insulin treatment with NPH	not reported	1
Køglendørf <sup>33</sup>	basal-bolus treatment ≥4 months before study	not reported	1
Kudva <sup>34</sup>	age≥18 years; A1c ≤7.8%; fasting C-peptide <200 pmol/L; MIT with glargine or ultralente as basal insulin+rapid-acting insulin	not reported	1
Massi Benedetti <sup>53</sup>	diagnosis ≥3 years before study; oral antidiabetic drugs alone or combined with 1 × daily insulin ≥3 months before study	not reported	2
Meneghini <sup>54</sup>	A1c 8 to 12%; sulfonylurea dosage ≥½ maximal dose or metformin 1 to 2.5 g/day for ≥3 months before study	not reported	2
Pieber <sup>35</sup>	insulin therapy > 1 year before study	not reported	1
Pieber <sup>36</sup>	age≥18 years; BMI≤35 kg/m <sup>2</sup> ; A1c≤12.0%; type 1 DM ≥1 year; basal-bolus insulin treatment ≥2 months before study; total daily basal insulin requirement ≤100 IU/day	significant medical disorders; pregnancy or lactation; history of recurrent major hypoglycemia; known hypoglycemic unawareness; use of concomitant medications likely to interfere with glucose metabolism	1
Porcellati <sup>37</sup>	fasting C-peptide ≤0.15 nmol/L; MIT with lispro+ NPH ≥2 years	microangiopathic complications; autonomic neuropathy	1
Raskin <sup>38</sup>	age 18 to 80 years; use of NPH+insulin lispro ≥3 months before study; C-peptide≤0.5mmol/L; FBG≥5.5mmol/L; A1c≤12.0%	hepatic or renal impairment; pregnancy or lactation; use of any glucose-lowering drug other than insulin ≤4 weeks before study	1
Ratner <sup>39</sup>	age 18 to 80 years; postprandial C-peptide ≤0.5 nmol/L for ≥1 year before study; A1c≤12.0%	use of antidiabetic drugs other than insulin ≤1 month before study; pregnancy; impaired hepatic or renal function; nightshift work	1
Riddle <sup>55</sup>	age 30 to 70 years; diabetes ≥2 years before study; use of oral antidiabetic drugs ≥3 months before study; BMI 26 to 40 kg/m <sup>2</sup> ; A1c 7.5 to 10.0%; FBG≥7.8 mmol/L	prior use of insulin except for gestational diabetes or <1 week; current use of alpha-glucosidase inhibitor or rapid-acting insulin secretagogue; use of other agents affecting glycemic control; history of ketoacidosis or inability to recognize hypoglycemia; increased liver enzymes or serum creatinine; history of drug or alcohol abuse; positive anti-	2

Study	Inclusion Criteria	Exclusion Criteria	DM Type
		GAD antibody; fasting C-peptide $\leq 0.25$ pmol/mL	
Robertson <sup>40</sup>	age 6 to 17 years; insulin use $\geq 12$ months; A1c $\leq 12.0\%$ ; BMI indexed according to age: 6 to 7 years BMI $\leq 19$ kg/m <sup>2</sup> ; 8 to 9 years BMI $\leq 20$ kg/m <sup>2</sup> ; 10 to 11 years BMI $\leq 22$ kg/m <sup>2</sup> ; 12 to 13 years BMI $\leq 24$ kg/m <sup>2</sup> ; 14 to 17 years BMI $\leq 27$ kg/m <sup>2</sup>	not reported	1
Rosenstock <sup>41</sup>	age 18 to 70 years; BMI 18 to 28 kg/m <sup>2</sup> ; A1c $\leq 10.0\%$ ; postprandial C-peptide $< 0.2$ pmol/mL; basal-bolus daily insulin $\geq 2$ months before study	not reported	1
Rosenstock <sup>56</sup>	age 40 to 80 years; insulin treatment $\geq 3$ months before study; A1c 7.0 to 12.0%; BMI $< 40$ kg/m <sup>2</sup>	hepatic or renal impairment; oral antidiabetic drugs $\leq 3$ months before study	2
Rosenstock <sup>57</sup>	age $> 18$ years; A1c $\geq 7.5\%$ ; BMI $> 25$ kg/m <sup>2</sup> ; continuous oral use of $\geq 50\%$ of maximally labelled dose of sulfonylurea and $\geq 1,000$ mg metformin $\geq 3$ months before study	stroke; myocardial infarction; angina pectoris; coronary artery bypass graft; percutaneous transluminal coronary angioplasty within previous 12 months; history of congestive heart failure; use of nonselective beta-blockers; hypoglycemia unawareness; impaired renal or hepatic function; substance or alcohol abuse; malignancy and planned radiological examinations requiring administration of contrasting agents	2
Rossetti <sup>42</sup>	fasting C-peptide $\leq 0.15$ nmol/L; MIT	not reported	1
Russell-Jones <sup>43</sup>	age $\geq 18$ years; type 1 DM $\geq 1$ year; use of basal-bolus insulin $\geq 2$ months before study	A1c $> 12.0\%$ ; total basal insulin dose $> 100$ IU/day; pregnancy or lactation; proliferative retinopathy; impaired hepatic or renal function; recurrent major hypoglycemia; uncontrolled hypertension; severe cardiac problem; other significant medical problems; concomitant use of medications known to interfere with glucose metabolism	1
Schober <sup>44</sup>	age 5 to 16 years; insulin use $\geq 1$ year before study with $\geq 3$ daily injections of insulin; A1c $\leq 12.0\%$	treatment with blood glucose-lowering drugs other than insulin $\leq 1$ month before study; post-menarcheal, sexually active girls not using adequate contraception; treatment with hyperglycemic drugs; treatment with investigational drugs $\leq 2$ months before study; impaired hepatic or renal function	1
Standl <sup>45</sup>	age 18 to 74 years; type 1 DM $\geq 12$ months; twice daily basal insulin and meal-related bolus insulin $\geq 2$ months before study; BMI $< 35.0$ kg/m <sup>2</sup> ; A1c $\leq 12.0\%$ ; total basal insulin dosage $\leq 100$ IU/day	proliferative retinopathy; impaired hepatic or renal function; severe cardiac disease; uncontrolled hypertension; recurrent major hypoglycemia; insulin allergy; pregnancy or lactation	1
Vague <sup>46</sup>	type 1 DM $\geq 1$ year; use of basal-bolus insulin $\geq 2$ months before study; A1c $\leq 12.0\%$ ; BMI $\leq 35.0$ kg/m <sup>2</sup> ; total basal insulin dosage $\leq 100$ IU/day	proliferative retinopathy; impaired hepatic or renal function; severe cardiac problems; uncontrolled hypertension; recurrent major hypoglycemia; allergy to insulin; pregnancy or	1

Study	Inclusion Criteria	Exclusion Criteria	DM Type
		lactation	
Witthaus <sup>47</sup>	insulin use $\geq 1$ year before study	not reported	1
Yki-Järvinen <sup>58</sup>	age 40 to 80 years; BMI $< 40$ kg/m <sup>2</sup> ; A1c 7.5 to 12.0%; diabetes diagnosed $\geq 3$ years before study; oral antidiabetic therapy with sulfonylurea alone or +acarbose or metformin or with metformin alone $\geq 1$ year before study; negative history of ketoacidosis	women not using contraceptives; pregnancy; use of regular insulin $\leq 4$ weeks before study; diabetic retinopathy with surgery $\leq 3$ months before study or requiring treatment for this within 3 months of entering study; night shift work; cardiovascular, hepatic (ALT or AST $> 2 \times$ upper limit), neurologic, endocrine, or other major systemic diseases; history of drug or alcohol abuse; impaired renal function (serum creatinine $> 133$ $\mu$ mol/L)	2
Yki-Järvinen <sup>59</sup>	age 35 to 75 years; use of stable dose of sulfonylurea and metformin or metformin alone $\geq 3$ months before study; BMI 20 to 40 kg/m <sup>2</sup> ; A1c $\geq 8.0\%$ ; mean FPG $\geq 7$ mmol/L; fasting C-peptide $\geq 0.33$ nmol/L	use of other oral antihyperglycemic agents; prior use of insulin; positive GAD antibodies; history of ketoacidosis; non-compliance with regard to daily measurement of FPG; abnormal safety laboratory tests including liver enzymes, serum aspartate aminotransferase, serum alkaline phosphatase, $> 3$ times the upper limit of normal; serum creatinine $\geq 120$ $\mu$ mol/L; history of alcohol or drug abuse; night shift work; pregnancy; use of investigational drug $\leq 2$ months before study; use of drugs likely to interfere with glucose control; clinically relevant major systemic disease other than diabetes that would make implementation of study protocol or interpretation of result difficult; mental health condition rendering subject unable to understand nature, scope, and possible consequences of study; diabetic retinopathy requiring surgical treatment during study or $< 3$ months before study	2
HOE 901/2004 Study Investigators <sup>60</sup>	age 40 to 80 years; oral treatment $\geq 3$ months; A1c $\geq 7.0\%$	prior insulin treatment	2

A1c=glycated hemoglobin; BG=blood glucose; BMI=body mass index; FBG=fasting blood glucose; GAD=glutamic acid decarboxylase; HI=conventional human insulin; NPH=neutral protamine Hagedorn; OAD=oral anti-diabetic agent

## APPENDIX 7: Quality Assessment of RCTs

Study	Score on Jadad Scale for			Total Score on Jadad Scale	Allocation Concealment	Blinding of Outcome Assessor	Analyses: Intent-to-Treat
	Randomization	Double Blinding	Withdrawals and Dropouts				
<b>Type 1</b>							
De Leeuw <sup>25</sup>	1	0	1	2	unclear	NR	yes
Fulcher <sup>26</sup>	1	0	1	2	unclear	yes	yes
Hermansen <sup>28</sup>	1	0	1	2	unclear	partially	no
Hershon <sup>29</sup>	1	0	1	2	unclear	NR	yes
Home <sup>30</sup>	2	0	1	3	unclear	NR	yes
Home <sup>31</sup>	2	0	1	3	adequate	NR	yes
Kudva <sup>34</sup>	2	0	1	3	unclear	yes	no
Pieber <sup>35</sup>	1	0	1	2	unclear	partially	NR
Pieber <sup>36</sup>	2	0	1	3	unclear	NR	yes
Porcellati <sup>37</sup>	2	0	0	2	adequate	NR	yes
Raskin <sup>38</sup>	2	0	1	3	unclear	NR	NR
Ratner <sup>39</sup>	1	0	1	2	unclear	NR	yes
Rosenstock <sup>41</sup>	1	0	1	2	unclear	partially	yes
Rossetti <sup>42</sup>	1	0	0	1	unclear	NR	NR
Russell-Jones <sup>43</sup>	2	0	1	3	unclear	NR	yes
Schober <sup>44</sup>	1	0	0	1	unclear	NR	yes
Standl <sup>45</sup>	1	0	1	2	unclear	NR	yes
Vague <sup>46</sup>	2	0	1	3	adequate	NR	yes
Witthaus <sup>47</sup>	2	0	0	2	unclear	NR	yes
<b>Type 2</b>							
Fonseca <sup>48</sup>	1	0	1	2	unclear	No	NR
Fritsche <sup>49</sup>	2	0	1	3	unclear	NR	yes
Haak <sup>50</sup>	1	0	1	2	unclear	NR	yes
Massi Benedetti <sup>53</sup>	2	0	1	3	adequate	NR	yes
Riddle <sup>55</sup>	2	0	1	3	adequate	NR	yes
Rosenstock <sup>56</sup>	1	0	1	2	unclear	NR	yes
Rosenstock <sup>57</sup>	1	0	1	2	unclear	NR	yes
Yki-Järvinen <sup>58</sup>	1	0	0	1	adequate unclear	partially	yes
Yki-Järvinen <sup>59</sup>	2	0	1	3	unclear	NR	yes
HOE 901/2004 Study Investigators Group <sup>60</sup>	2	0	1	3	adequate	partially	yes

## APPENDIX 8A: HbA1c in Type 1 DM Patients

Study	Trial Type	Treatment Arm Number	Treatment Arm	Number of Patients at Baseline	A1c at Baseline (%)	Treatment Duration	A1c at End Point (%)	A1c (change from baseline)	p-value (post-tx versus baseline)	p-value (analogue versus control)
De Leeuw <sup>25</sup>	parallel	I	IDet+IAsp	216	8.18±1.14*	12 months	7.53±0.10 <sup>†</sup>	-0.64		I versus II, NS
		II	NPH+IAsp	99	8.03±1.11*	12 months	7.59±0.13 <sup>†</sup>	-0.56		
Fulcher <sup>26</sup>	parallel	I	IGlar+ILis	62	9.2±1.1*	30 weeks	8.3±0.14 <sup>†</sup>	-0.89	p<0.05	I versus II, p=0.01
		II	NPH+ILis	63	9.7±1.3*	30 weeks	9.1±0.14 <sup>†</sup>	-0.67	p<0.05	
Garg <sup>27</sup> abstract	parallel	I	IGlar+HI	9	NR	4 weeks	NR	-0.4%		I versus II, NS
		II	NPH+HI	5	NR	4 weeks	NR	-0.2%		
Hershon <sup>29</sup>	parallel	I	IGlar+HI	195	7.7±1.2*	28 weeks	NR	-0.09±0.07 <sup>†</sup>		I versus II, NS
		II	NPH+HI	199	7.7±1.1*	28 weeks	NR	-0.19±0.07 <sup>†</sup>		
Home <sup>30</sup>	parallel	I	IGlar+HI	292	7.9±1.2*	28 weeks	NR	0.21±0.05 <sup>†</sup>		I versus II, NS
		II	NPH	293	8.0±1.2*		NR	0.10±0.05 <sup>†</sup>		
Home <sup>31</sup>	parallel	I	IDet <sub>12h</sub> +IAsp	137	8.55±1.20*	16 weeks	7.75±0.07 <sup>†</sup>	-0.07 (-0.85%)		I and II versus III, p=0.027
		II	IDet <sub>m+b</sub> +IAsp	139	8.74±1.20*	16 weeks	7.78±0.07 <sup>†</sup>	-0.07 (-0.82%)		
		III	NPH <sub>m+b</sub> +IAsp	132	8.52±1.19*	16 weeks	7.94±0.07 <sup>†</sup>	-0.07 (-0.65%)		
Kawamura <sup>32</sup>	cross-over	I	IGlar+IAsp	64	NR	2×16 weeks	7.5±1.1	NR		I versus II, p<0.01
		II	NPH+IAsp	64	NR	2×16 weeks	8.2±1.3	NR		
Køglendørf <sup>33</sup> poster	cross-over	I	IDet+IAsp	130	7.9±0.7*	2×16 weeks	7.55 [-0.11, 0.11] <sup>‡</sup>	-0.3		I versus II, NS
		II	NPH+IAsp	130	7.9±0.8*	2×16 weeks	7.55 [-0.11, 0.11] <sup>‡</sup>	-0.3		

Study	Trial Type	Treatment Arm Number	Treatment Arm	Number of Patients at Baseline	A1c at Baseline (%)	Treatment Duration	A1c at End Point (%)	A1c (change from baseline)	p-value (post-tx versus baseline)	p-value (analogue versus control)
Kudva <sup>34</sup>	cross-over	I	IGlar+IAsp	24	6.94±0.14 <sup>†</sup>	2×16 weeks	6.82±0.13 <sup>†</sup>	NR		I versus II, p=0.03
		II	UL+IAsp	24	6.94±0.14 <sup>†</sup>	2×16 weeks	7.02±0.13 <sup>†</sup>	NR		
Peiber <sup>35</sup>	parallel	I	IGlar[30]+HI	110	8.09±0.11 <sup>†</sup>	4 weeks	7.85±0.10 <sup>†</sup>	-0.25±0.05 <sup>†</sup>	p=0.0001	
		II	IGlar[80]+HI	113	7.96±0.11 <sup>†</sup>	4 weeks	7.80±0.10 <sup>†</sup>	-0.15±0.05 <sup>†</sup>	p=0.0061	
		III	NPH+HI	110	7.85±0.11 <sup>†</sup>	4 weeks	7.79±0.09 <sup>†</sup>	-0.03±0.05 <sup>†</sup>	NS	
Pieber <sup>36</sup>	parallel	I	IDet <sub>m+d</sub> +IAsp	139	8.01±1.24 <sup>*</sup>	16 weeks	7.67±0.07 <sup>†</sup>	-0.43	p<0.05	I versus II, versus III, NS
		II	IDet <sub>m+b</sub> +IAsp	132	8.13±1.37 <sup>*</sup>	16 weeks	7.65±0.07 <sup>†</sup>	-0.49	p<0.05	
		III	NPH <sub>m+b</sub> +IAsp	129	8.08±1.15 <sup>*</sup>	16 weeks	7.73±0.07 <sup>†</sup>	-0.39	p<0.05	
Porcellati <sup>37</sup>	parallel	I	IGlar (dinner time)+ILis	61	7.1±0.1 <sup>†</sup>	1 year	6.7±0.1 <sup>†</sup>	NR	p<0.05	I versus II, p<0.05
		II	NPH (4 times/day)+ILis	60	7.1±0.2 <sup>†</sup>	1 year	7.1±0.1 <sup>†</sup>	NR	NS	
Raskin <sup>38</sup>	parallel	I	IGlar+ILis	310	7.59±1.19 <sup>*</sup>	16 weeks	7.53±1.19 <sup>*</sup>	NR		I versus II, NS
		II	NPH+ILis	309	7.71±1.2 <sup>*</sup>	16 weeks	7.60±1.14 <sup>*</sup>	NR		
Ratner <sup>39</sup>	parallel	I	IGlar+HI	264	7.7±1.2 <sup>*</sup>	28 weeks	7.54±1.2 <sup>*</sup>	-0.16±0.05 <sup>†</sup>		I versus II, NS
		II	NPH+HI	270	7.7±1.1 <sup>*</sup>	28 weeks	7.49±1.1 <sup>*</sup>	-0.21±0.05 <sup>†</sup>		
Robertson <sup>40</sup> poster	parallel	I	IDet+IAsp	232	8.8±1.2 <sup>*</sup>	26 weeks	8.06±1.2 <sup>*</sup>	-0.74	NR	I versus II, NS
		II	NPH+IAsp	115	8.8±1.2 <sup>*</sup>	26 weeks	7.98±1.2 <sup>*</sup>	-0.82	NR	
Rosenstock <sup>41</sup>	parallel	I	IGlar[30]+HI	82	7.8±1.1 <sup>*</sup>	4 weeks	7.4±1.1 <sup>*</sup>	-0.4±0.48 <sup>*</sup>		
		II	IGlar[80]+HI	86	7.9±1.2 <sup>*</sup>	4 weeks	7.5±1.2 <sup>*</sup>	-0.4±0.49 <sup>*</sup>		
		III	NPH+HI	88	8.0±1.2 <sup>*</sup>	4 weeks	7.6±1.2 <sup>*</sup>	-0.4±0.48 <sup>*</sup>		
Rossetti <sup>42</sup>	parallel	I	IGlar (dinnertime)+ILis	17	6.8±0.2 <sup>†</sup>	3 months	6.4±0.1 <sup>†</sup>	NR	p<0.04	
		II	IGlar (bedtime)+ILis	17	7.0±0.2 <sup>†</sup>	3 months	6.6±0.1 <sup>†</sup>	NR	p<0.04	
		III	NPH (4 times/day)	17	6.9±0.1 <sup>†</sup>	3 months	7.0±0.1 <sup>†</sup>	NR	NS	

Study	Trial Type	Treatment Arm Number	Treatment Arm	Number of Patients at Baseline	A1c at Baseline (%)	Treatment Duration	A1c at End Point (%)	A1c (change from baseline)	p-value (post-tx versus baseline)	p-value (analogue versus control)
			+ILis							
Russell-Jones <sup>43</sup>	parallel	I	IDet+HI	491	8.35±1.20*	6 months	8.30±1.08*	-0.06±0.92*		I versus II, NS
		II	NPH+HI	256	8.35±1.21*	6 months	8.41±1.32*	0.06±1.05*		
Schober <sup>44</sup>	parallel	I	IGlar+HI	174	8.48±0.11 <sup>†</sup> , p=0.04	28 weeks	8.76±0.11 <sup>†</sup>	0.28±0.09 <sup>†</sup>		I versus II, NS
		II	NPH+HI	175	8.81±0.11 <sup>†</sup>	28 weeks	9.08±0.11 <sup>†</sup>	0.27±0.09 <sup>†</sup>		
Standl <sup>45</sup>	parallel	I	IDet+HI	154	7.72±1.26*	12 months	7.88±0.082 <sup>‡</sup>	NR		I versus II, NS
		II	NPH+HI	135	7.66±1.19*	12 months	7.78±0.088 <sup>‡</sup>	NR		
Vague <sup>46</sup>	parallel	I	IDet+IAsp	301	8.18±1.14*	6 months	7.60±0.09 <sup>†</sup>	-0.55		I versus II, NS
		II	NPH+IAsp	146	8.11±1.12*	6 months	7.64±0.10 <sup>†</sup>	-0.55		

12h=12-hour interval; A1c=glycated hemoglobin; HI=conventional human insulin; IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; IGlar[30]=insulin containing 30 µg/ml zinc; IGlar[80]=insulin containing 80 µg/ml zinc; ILis=insulin lispro; m+b=morning and bedtime; m+d=morning and before dinner; NPH=neutral protamine Hagedorn; NR=not reported; NS=not significant; tx=treatment; \*mean±SD, <sup>†</sup>mean±SE, <sup>‡</sup>mean [95%CI]

## APPENDIX 8B: HbA1c in Type 2 DM Patients

Study	Trial Type	Treatment Arm Number	Treatment Arm	Number of Patients at Baseline	A1c at Baseline (%)	Treatment Duration	A1c at End Point (%)	A1c (change from baseline)	p value (post-tx versus baseline)	p value (analogue versus control)
Fonseca <sup>48</sup> (subgroup analysis of Rosenstock) <sup>56</sup>	parallel	I	IGlar+HI	52	8.42±1.22*	28 weeks	8.01±1.22*	-0.41	NR	I versus II, NS
		II	NPH+HI	48	8.36±0.96*	28 weeks	7.90±0.96*	-0.46	NR	
Fritsche <sup>49</sup>	parallel	I	IGlar (morning)+ Glim	236	9.1±1.0*	24 weeks	7.8±1.2*	-1.24 (90% CI, -1.10 to -1.38)		I versus II, p=0.008; I versus III, p<0.001
		II	IGlar (bedtime)+ Glim	227	9.1±1.0*	24 weeks	8.1±1.3*	-0.96 (90% CI, -0.81 to -1.10)		
		III	NPH (bedtime)+ Glim	232	9.1±1.1*	24 weeks	8.3±1.3*	-0.84 (90%CI, -0.69 to -0.98)		
Haak <sup>50</sup>	parallel	I	IDet+IAsp	341	7.9±1.3*	26 weeks	7.6±0.1 <sup>†</sup>	-0.2	p=0.004	I versus II, NS
		II	NPH+IAsp	164	7.8±1.3*	26 weeks	7.5±0.1 <sup>†</sup>	-0.4	p=0.0001	
Hermansen <sup>51</sup> Kølenorf <sup>52</sup>	parallel	I	IDet+OAD	237	8.61±0.78*	24 weeks	6.58±0.064 <sup>†</sup>	-1.8	p<0.05	I versus II, NS
		II	NPH+OAD	238	8.51±0.76*	24 weeks	6.46±0.063 <sup>†</sup>	-1.9	p<0.05	
Massi Benedetti <sup>53</sup>	parallel	I	IGlar+OAD	289	9.0±1.2*	52 weeks	8.54±1.2*	-0.46	NR	I versus II, NS
		II	NPH+OAD	281	8.9±1.1*	52 weeks	8.52±1.1*	-0.38	NR	
Meneghini <sup>54</sup> abstract	parallel	I	IGlar (with Metf or Sfu)	124	8 to 12	48 weeks	6.7	-2.6		I versus II, p≤0.05
		II	pioglitazone (with Metf or Sfu)	129	8 to 12	48 weeks	7.0	-2.3		

Study	Trial Type	Treatment Arm Number	Treatment Arm	Number of Patients at Baseline	A1c at Baseline (%)	Treatment Duration	A1c at End Point (%)	A1c (change from baseline)	p value (post-tx versus baseline)	p value (analogue versus control)
Riddle <sup>55</sup>	parallel	I	IGlar+OAD	367	8.61±0.9*	24 weeks	6.96±0.9*	NR		I versus II, NS
		II	NPH+OAD	389	8.56±0.9*	24 weeks	6.97±0.9*	NR		
Rosenstock <sup>56</sup>	parallel	I	IGlar+HI	259	8.6±1.2*	28 weeks	8.19±1.2*	-0.41±0.1*	p=0.0001	I versus II, NS
		II	NPH+HI	259	8.5±1.2*	28 weeks	7.91±1.2*	-0.59±0.1*	p=0.0001	
Rosenstock <sup>57</sup>	parallel	I	IGlar (bedtime)+ Sfu (max)+Metf	104	8.8±1.0*	24 weeks	7.14±1.0*	-1.66	NS	I versus II, NS
		II	Ros+ Sfu(max)+ Metf	112	8.7±1.0*	24 weeks	7.19±1.0*	-1.51	NS	
Yki-Järvinen <sup>58</sup>	parallel	I	IGlar+OAD	214	9.1±0.1 <sup>†</sup>	52 weeks	8.34±0.09 <sup>†</sup>	NR	p<0.001	I versus II, NS
		II	NPH+OAD	208	8.9±0.1 <sup>†</sup>	52 weeks	8.24±0.09 <sup>†</sup>	NR	p<0.001	
Yki-Järvinen <sup>59</sup>	parallel	I	IGlar+Metf	61	9.5±0.1 <sup>†</sup>	36 weeks	7.14±0.12 <sup>†</sup>	NR		I versus II, NS
		II	NPH+Metf	49	9.6±0.1 <sup>†</sup>	36 weeks	7.16±0.14 <sup>†</sup>	NR		
HOE 901/2004 Study Group <sup>60</sup>	parallel	I	IGlar[30]+ OAD	64	9.79±1.5*	4 weeks	8.98±1.5*	-0.82	p=0.0001	I versus II, versus III, NS
		II	IGlar[80]+ OAD	72	9.71±1.2*	4 weeks	8.84±1.2*	-0.86	p=0.0001	
		III	NPH+OAD	68	9.47±1.4*	4 weeks	8.68±1.4*	-0.79	p=0.0001	

A1c=glycated hemoglobin; CI=confidence interval; Glim=glimepiride (sulfonylurea); HI=conventional human insulin; IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; m+b=morning and bedtime; m+d=morning and before dinner; max=maximum dose; Metf=metformin; NPH=neutral protamine Hagedorn; NR=not reported; NS=not significant; OAD=oral anti-diabetic agent; Ros=rosiglitazone; Sfu=sulfonylurea; tx=treatment; \*mean±SD, <sup>†</sup>mean±SE

## APPENDIX 9A: Eight-Point Blood Glucose Profiles of Type 1

Eight-Point Blood Glucose Profiles of Type 1 (mmol/L)									
Study	Treatment	Pre-breakfast	Post-breakfast	Pre-lunch	Post-lunch	Pre-dinner	Post-dinner	Bedtime	Night
De Leeuw <sup>25</sup>	IDet+IAsp	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD
	NPH+IAsp	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD
Hermansen <sup>28</sup>	IDet+HI	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD
	NPH+HI	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD
Home <sup>31</sup>	IDet <sub>12h</sub> +IAsp	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD
	IDet <sub>m+b</sub> +IAsp	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD
	NPH <sub>m+b</sub> +IAsp	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD
Home <sup>30</sup>	IGlar+HI	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD
	NPH+HI	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD
Kølendorf <sup>33</sup>	IDet+IAsp	7.63±2.69 <sup>*</sup> , p<0.001		7.66±2.80, <sup>*</sup> p=0.003		8.21±2.89, <sup>*</sup> p=0.002			
	NPH+IAsp	8.66±3.23 <sup>*</sup>		7.76±3.03 <sup>*</sup>		7.87±3.26 <sup>*</sup>			
Pieber <sup>36</sup>	IDet <sub>m+d</sub> +IAsp	NSD	NSD	NSD	NSD	NSD	NSD	lower, p<0.05, versus NPH	lower, p<0.05, versus NPH
	IDet <sub>m+b</sub> +IAsp	NSD	NSD	NSD	NSD	NSD	NSD	lower, p<0.05, versus NPH	lower, p<0.05, versus NPH
	NPH <sub>m+b</sub> +IAsp	NSD	NSD	NSD	NSD	NSD	NSD	higher	higher
Porcellati <sup>37</sup>	IGlar (dinner time)+ILis	lower, <0.05	NSD	lower, <0.05	NSD	lower, <0.05	NSD	NSD	8.4±0.27, p<0.05
	NPH (4 times/day) + ILis	higher	NSD	higher	NSD	higher	NSD	NSD	7.5±0.11, p<0.05
Robertson <sup>40</sup> poster	IDet+IAsp	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD
	NPH+IAsp	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD
Rossetti <sup>42</sup>	IGlar+ILis	lower, p<0.05	lower, p<0.05	lower, p<0.05	lower, p<0.05	NSD	lower, p<0.05	NSD	higher, p<0.05
	NPH+ILis	higher	higher	higher	higher	NSD	higher	NSD	lower
Russell-Jones <sup>43</sup>	IDet+HI	lower, p<0.001	NSD	NSD	NSD	NSD	NSD	NSD	NSD
	NPH+HI	Higher	NSD	NSD	NSD	NSD	NSD	NSD	NSD

Eight-Point Blood Glucose Profiles of Type 1 (mmol/L)									
Study	Treatment	Pre-breakfast	Post-breakfast	Pre-lunch	Post-lunch	Pre-dinner	Post-dinner	Bedtime	Night
Standl <sup>45</sup>	IDet+HI	NSD	NSD	NSD	lower, p<0.05	NSD	lower, p<0.05	NSD	NSD
	NPH+HI	NSD	NSD	NSD	higher	NSD	higher	NSD	NSD

12h=12-hour interval; HI=conventional human insulin; IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; ILis=insulin lispro; m+b=morning and bedtime; m+d=morning and before dinner; NPH=neutral protamine Hagedorn; NSD=no significant difference; mean±SD

## APPENDIX 9B: Fasting Blood Glucose Levels in Type 1 DM

Study	Treatment	Fasting Blood Glucose mmol/l (mg/dl)
De Leeuw <sup>25</sup>	IDet+IAsp	10.7 (FPG)
	NPH+IAsp	10.8 (FPG)
Fulcher <sup>26</sup>	IGlar+ILis	7.84±0.37, † p<0.05
	NPH+ILis	9.03±0.36†
Garg <sup>27</sup>	IGlar+HI	6.17±1.61† (111.1±28.9)†, p<0.01
	NPH+HI	9.25±1.48† (166.5±26.6)†
Hermansen <sup>28</sup>	IDet+HI	8.32±3.58*
	NPH+HI	8.75±4.16*
Hershon <sup>29</sup>	IGlar+HI	-1.17±0.22† from baseline, p=0.015 versus NPH
	NPH+HI	-0.56±0.17† from baseline
Home <sup>30</sup>	IGlar+HI	-1.17±0.12† from baseline, NSD
	NPH+HI	-0.89±0.12† from baseline
Home <sup>31</sup>	IDet <sub>12h</sub> +IAsp	8.28±0.20, † p=0.004 versus NPH
	IDet <sub>m+b</sub> +IAsp	8.26±0.20, † p<0.001 versus NPH
	NPH <sub>m+b</sub> +IAsp	9.05±0.21†
Køglendørf <sup>33</sup>	IDet+IAsp	7.63, p=0.0001 versus NPH
	NPH+IAsp	8.66
Kudva <sup>34</sup>	IGlar+IAsp	8.61±0.78† (155±14), † p=0.047
	UL+IAsp	10.61±1.28† (191±23)†
Peiber <sup>35</sup>	HOE901[30]+HI	7.47±0.2†
	HOE901[80]+HI	7.18±0.18†
	NPH+HI	7.92±0.28, † p=0.0005 HOE901 pooled
Pieber <sup>36</sup>	IDet <sub>m+d</sub> +IAsp	9.83±0.35, † p<0.001 versus NPH (FPG)
	IDet <sub>m+b</sub> +IAsp	9.15±0.36, † p<0.006 versus NPH (FPG)
	NPH <sub>m+b</sub> +IAsp	11.14±0.35† (FPG)
Raskin <sup>38</sup>	IGlar+ILis	8.0±2.3, * p=0.0001
	NPH+ILis	9.0±2.4*
Ratner <sup>39</sup>	IGlar+HI	8.08±2.7, * NSD
	NPH+HI	8.76±3.0*
Robertson <sup>40</sup>	IDet+IAsp	8.44±3.32, * (FPG)p=0.002
	NPH+IAsp	9.58±4.29* (FPG)
Rosenstock <sup>41</sup>	IGlar+HI	7.6±2.1, * p<0.05
	NPH+HI	9.0±2.4*
Russell-Jones <sup>43</sup>	IDet+HI	7.56±1.8, * p<0.001
	NPH+HI	8.47±2.65*
Schober <sup>44</sup>	IGlar+HI	-1.29±0.19, † from baseline, p=0.0231 versus NPH
	NPH+HI	-0.68±0.20, † from baseline
Standl <sup>45</sup>	IDet+HI	10.1±0.45† (FPG) NSD
	NPH+HI	9.84±0.48† (FPG)
Vague <sup>46</sup>	IDet+IAsp	8.80±3.37, * p<0.001
	NPH+IAsp	9.23±3.78*

12h=12-hour interval; FPG=fasting plasma glucose; HI=conventional human insulin; IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; ILis=insulin lispro; m+b=morning and bedtime; NPH=neutral protamine Hagedorn; mean±SD, †mean±SE

## APPENDIX 9C: Eight-Point Blood Glucose Profiles of Type 2 DM

Eight-Point Blood Glucose Profiles of Type 2 Using LA (mmol/L)									
Study	Treatment	Pre-breakfast	Post-breakfast	Pre-lunch	Post-lunch	Pre-dinner	Post-dinner	Bedtime	Night
Fritsche <sup>49</sup>	IGlar (morning)+ Glim	NSD	lower, p<0.001, versus bedtime NPH and bedtime IGlar	lower, p<0.001, versus bedtime NPH and bedtime IGlar	lower, p<0.001, versus bedtime NPH and bedtime IGlar	lower, p<0.001, versus bedtime NPH and bedtime IGlar	lower, p<0.001, versus bedtime NPH and bedtime IGlar	lower, p=0.002, versus bedtime NPH and bedtime IGlar	lower, p<0.001, versus bedtime NPH and bedtime IGlar
	NPH (bedtime)+ Glim	NSD	higher	higher	higher	higher	higher	higher	higher
	IGlar (bedtime)+ Glim	NSD versus NPH	NSD versus NPH	NSD versus NPH	NSD versus NPH	NSD versus NPH	NSD versus NPH	NSD versus NPH	NSD versus NPH
Haak <sup>50</sup>	IDet+IAsp	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD
	NPH+IAsp	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD
Hermansen <sup>51</sup> Kølendorf <sup>52</sup>	IDet+OAD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD
	NPH+OAD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD
Yki-Järvinen <sup>58</sup>	IGlar+OAD	NSD	NSD	NSD	NSD	lower, p=0.0035	lower, p=0.0094	NSD	NSD
	NPH+OAD	NSD	NSD	NSD	NSD	higher	higher	NSD	NSD
Yki-Järvinen <sup>59</sup>	IGlar+Metf	NSD	NSD	NSD	NSD	8.6±0.3,* p=0.002	NSD	NSD	NSD
	NPH+Metf	NSD	NSD	NSD	NSD	10.1±0.3*	NSD	NSD	NSD

Glim=glimepiride (sulfonylurea); IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; LA=long-acting insulin analogues; Metf=metformin; NPH=neutral protamine Hagedorn; NSD=no significant difference; OAD=oral anti-diabetic agent; \* mean±SE

## APPENDIX 9D: Fasting Blood Glucose Levels in Type 2 DM Patients

Study	Treatment	Fasting Blood Glucose mmol/L (mg/dL)
Fonseca <sup>48</sup> (subgroup analysis of Rosenstock) <sup>56</sup>	IGlar+HI	8.23±2.57*
	NPH+HI	7.85±2.11*
Fritsche <sup>49</sup>	IGlar (morning)+Glim	7.0±1.9*
	IGlar (bedtime)+Glim	6.8±1.9*
	NPH (bedtime)+Glim	6.9±1.9*
Haak <sup>50</sup>	IDet+IAsp	9.7±0.2 <sup>†</sup> (FPG)
	NPH+IAsp	9.6±0.3 <sup>†</sup> (FPG)
Hermansen <sup>51</sup> Kølerdorf <sup>52</sup>	IDet+OAD	6.6 (FPG)
	NPH+OAD	6.3 (FPG)
Massi Benedetti <sup>53</sup>	IGlar+OAD	7.1±0.3 <sup>†</sup>
	NPH+OAD	7.4±0.2 <sup>†</sup>
Riddle <sup>55</sup>	IGlar+OAD	6.5, FPG
	NPH+OAD	6.7, FPG
Rosenstock <sup>56</sup>	IGlar+HI	NSD
	NPH+HI	NSD
Rosenstock <sup>57</sup>	IGlar (bedtime)+Sfu(max)+Metf	-3.60±0.23, p=0.001, (FPG)
	Ros+Sfu(max)+Metf	-2.57±0.22, (FPG)
Yki-Järvinen <sup>59</sup>	IGlar+Metf	5.7±0.02 <sup>†</sup> , (FPG)
	NPH+Metf	6.0±0.03 <sup>†</sup> , (FPG)
HOE 901/2004 Study Group <sup>60</sup>	IGlar[30]+OAD	7.00
	IGlar[80]+OAD	6.95
	NPH+OAD	6.53

FPG=fasting blood glucose; Glim=glimepiride (sulfonylurea); HI=conventional human insulin; IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; IGlar[30]=insulin containing 30 µg/ml zinc; IGlar[80]=insulin containing 80 µg/ml zinc; max=maximum dose; Metf=metformin; NPH=neutral protamine Hagedorn; NSD=no significant difference; OAD=oral anti-diabetic agent; \*mean±SD, <sup>†</sup>mean±SE

## APPENDIX 10A: Hypoglycemia in Type 1 DM Patients

Study	Study Type	Treatment Arm Number	Treatment Arm	Number of Points at Baseline	Treatment Duration	Type of Hypoglycemia	Hypoglycemia Rate at Baseline	Hypoglycemia Rate at End Point	Outcome Unit	Hypoglycemia (change from baseline)	p-value (post-tx versus baseline)	p-value Between Treatments
De Leeuw <sup>25</sup>	parallel	I	IDet+IAsp	216	12 months	overall minor major nocturnal	NR	207 (96) NSD 30 (14) 180 (1378)	pts (%)  pts (episodes)	NR		I versus II, p=0.016 for nocturnal
		II	NPH+IAsp	99	12 months	overall minor major nocturnal	NR	95 (96) NSD 21 (21) 87 (926)	pts (%)  pts (episodes)	NR		
Fulcher <sup>26</sup>	parallel	I	IGlar+ILis	62	30 weeks	overall nocturnal mild moderate severe nocturnal mild moderate severe	NR	62 (100) 50 (81) 10.78 6.82 0.87 4.49 2.36 1.71 0.22	pts (%)  episodes/ 100 pt-days	NR		I versus II, NS for overall, p=0.02 for mild nocturnal (IGlar>NPH), p=0.004 for moderate nocturnal, p=0.02 for severe nocturnal
		II	NPH+ILis	63	30 weeks	overall nocturnal  mild moderate severe nocturnal mild moderate severe	NR	59 (93.7) 54 (86)  10.34 7.31 0.99 4.73 1.96 2.21 0.37	pts (%)  episodes/ 100 pt-days	NR		
Hermansen <sup>28</sup>	cross-over	I	IDet+HI	59	2x6 weeks	overall minor	NR	54 (94.7) 53 (93)	pts (%)	NR		I versus II, NS for all

Study	Study Type	Treatment Arm Number	Treatment Arm	Number of Points at Baseline	Treatment Duration	Type of Hypoglycemia	Hypoglycemia Rate at Baseline	Hypoglycemia Rate at End Point	Outcome Unit	Hypoglycemia (change from baseline)	p-value (post-tx versus baseline)	p-value Between Treatments
						major		4 (7)				
		II	NPH+HI	59	2x6 weeks	overall minor major	NR	51 (91.1) 51 (91.1) 7 (12.5)	pts (%)	NR		
Hershon <sup>29</sup>	parallel	I	IGlar+HI	195	28 weeks	BG<2.8 mM BG<2.0 mM severe nocturnal	NR	143 (73.3) 71 (36.6) 5 (2.6) 139 (71.2)	pts (%)	NR		I versus II, p=0.021 for BG<2.8, p=0.033 for BG<2.0, NS for severe and nocturnal
		II	NPH+HI	199	28 weeks	BG<2.8 mM BG<2.0 mM severe nocturnal	NR	163 (81.7) 92 (46.2) 10 (5.1) 138 (69.5)	pts (%)	NR		
Home <sup>30</sup>	parallel	I	IGlar+HI	292	28 weeks	symptomatic severe nocturnal	NR	260 (89.0) 31 (10.6) 178 (61.0)	pts (%)	NR		I versus II, NS for all
		II	NPH+HI	293	28 weeks	symptomatic severe nocturnal	NR	248 (84.6) 44 (15.0) 179 (61.1)	pts (%)	NR		
Home <sup>31</sup>	parallel	I	IDet <sub>12h</sub> <sup>+</sup> IAsp	137	16 weeks	minor major nocturnal	NR	114 (84) 6 (4) 59 (44)	pts (%)	NR		I versus III, p=0.046 for minor, NS for major and nocturnal
		II	IDet <sub>m+b</sub> <sup>+</sup> IAsp	139	16 weeks	minor major nocturnal	NR	114 (83) 11 (8) 47 (34)	pts (%)	NR		II versus III, p=0.002 for minor, p<0.001 for nocturnal
		III	NPH <sub>m+b</sub> <sup>+</sup> IAsp	132	16 weeks	minor major nocturnal	NR	107 (84) 10 (8) 64 (50)	pts (%)	NR		
Køendorf <sup>33</sup>	cross-over	I	IDet+IAsp	130	2x16 weeks	overall major minor symptomatic	NR	116 (89) 12 (9) 103 (79) 78 (60)	pts (%)	NR		I versus II, p=0.001 for overall, NS for major,

Study	Study Type	Treatment Arm Number	Treatment Arm	Number of Points at Baseline	Treatment Duration	Type of Hypoglycemia	Hypoglycemia Rate at Baseline	Hypoglycemia Rate at End Point	Outcome Unit	Hypoglycemia (change from baseline)	p-value (post-tx versus baseline)	p-value Between Treatments
						nocturnal		58 (45)				p=0.019 for minor, p=0.012 for symptom, p<0.0001 for nocturnal
		II	NPH+IAsp	130	2x16 weeks	overall major minor symptomatic nocturnal	NR	118 (91) 16 (12) 108 (83) 84 (65) 81 (62)	pts (%)	NR		
Kudva <sup>34</sup>	cross-over	I	IGlar+IAsp	24	2x16 weeks	overall day nocturnal severe	NR	24.5±2.99* 19.9±2.48* 4.6±1.18* 0.1±0.07*	episodes/ pt/32 weeks	NR		I versus II, p=0.05 for overall, p=0.001 for day, p=0.07 for nocturnal.
		II	UL+IAsp	24	2x16 weeks	overall day nocturnal severe	NR	31.3±4.04* 28.6±3.89* 2.7±0.59* 0.1±0.07*	episodes/ pt/32 weeks	NR		
Peiber <sup>35</sup>	parallel	I	IGlar[30]+HI	110	4 weeks	symptomatic nocturnal severe	NR	87 (79) 39 (36) 7 (6)	pts (%)	NR		I, II versus III, p=0.0037 for nocturnal, NS for symptom and severe
		II	IGlar[80]+HI	113	4 weeks	symptomatic nocturnal severe	NR	82 (73) 41 (36) 5 (4)	pts (%)	NR		
		III	NPH+HI	110	4 weeks	symptomatic nocturnal severe	NR	87 (79) 61 (56) 5 (5)	pts (%)	NR		
Pieber <sup>36</sup>	Parallel	I	IDet <sub>m+d</sub> +IAsp	139	16 weeks	overall nocturnal major minor symptomatic	NR	100 (72) 60 (43) 5 (4) 88 (63) 69 (50)	pts (%)	NR		I versus II versus III, NS

Study	Study Type	Treatment Arm Number	Treatment Arm	Number of Points at Baseline	Treatment Duration	Type of Hypoglycemia	Hypoglycemia Rate at Baseline	Hypoglycemia Rate at End Point	Outcome Unit	Hypoglycemia (change from baseline)	p-value (post-tx versus baseline)	p-value Between Treatments
		II	IDet <sub>m+b</sub> + IAsp	132	16 weeks	overall nocturnal major minor symptomatic	NR	92 (70) 51 (39) 5 (4) 78 (59) 64 (48)	pts (%)	NR		
		III	NPH <sub>m+b</sub> + IAsp	129	16 weeks	overall nocturnal major minor symptomatic	NR	100 (78) 60 (47) 4 (3) 89 (69) 68 (53)	pts (%)	NR		
Porcellati <sup>37</sup>	parallel	I	IGlar(dinner time)+ILis	61	1 year	mild day nocturnal	NR	7.2±0.5 6.0±0.6* 1.2±0.2*	episodes/ pt/30 days	NR		I versus II, p<0.05 for mild, day and nocturnal
		II	NPH (4 times/day)+ ILis	60	1 year	mild day nocturnal	NR	13.2±0.6 10±0.8* 3.2±0.3*	episodes/ pt/30 days	NR		
Raskin <sup>38</sup>	parallel	I	IGlar+ILis	310	16 weeks	overall nocturnal severe	NR	281 (90.6) 214 (69.0) 20 (6.5)	pts (%)	NR		I versus II, NS
		II	NPH+ILis	309	16 weeks	overall nocturnal severe	NR	280 (90.6) 195 (63.1) 16 (5.2)	pts (%)	NR		
Ratner <sup>39</sup>	parallel	I	IGlar+HI	264	28 weeks	overall nocturnal severe	NR	105 (39.9) 48 (18.2) 5 (1.9)	pts (%)	NR		I versus II, p<0.05 for overall and nocturnal
		II	NPH+HI	270	28 weeks	overall nocturnal severe	NR	133 (49.2) 73 (27.1) 15 (5.6)	pts (%)	NR		
Robertson <sup>40</sup>	parallel	I	IDet+IAsp	232	26 weeks	overall nocturnal	NR	79.7 4.5	episodes/ pt-yr	NR		I versus II, NS for overall, p=0.011 (RR: 36%) for nocturnal
		II	NPH+IAsp	115	26 weeks	overall nocturnal	NR	91.1 7.1	episodes/ pt-yr	NR		

Study	Study Type	Treatment Arm Number	Treatment Arm	Number of Points at Baseline	Treatment Duration	Type of Hypoglycemia	Hypoglycemia Rate at Baseline	Hypoglycemia Rate at End Point	Outcome Unit	Hypoglycemia (change from baseline)	p-value (post-tx versus baseline)	p-value Between Treatments
Rosenstock <sup>41</sup>	parallel	I	IGlar[30]+HI	82	4 weeks	overall	NR	80 (97.6)	pts (%)	NR		
		II	IGlar[80]+HI	86	4 weeks	overall	NR	86 (100)	pts (%)	NR		
		III	NPH+HI	88	4 weeks	overall	NR	82 (93.2)	pts (%)	NR		III versus I, or III versus II, p=0.03
Rossetti <sup>42</sup>	parallel	I	IGlar (dinnertime)+ILis	17	3 months	overall nocturnal	12.80±0.2* NR	8.1±0.8* 1.7±0.2*	episodes/pt/30 days	NR	p<0.04	I versus II, NS I and II versus III, p<0.005
		II	IGlar (bedtime)+ILis	17	3 months	overall nocturnal	13.6±0.2* NR	7.7±0.9* 2.0±0.19*	episodes/pt/30 days	NR	p<0.04	
		III	NPH (4 times/day)+ILis	17	3 months	overall nocturnal	13.9±0.1* NR	12.2±1.3* 3.6±0.4*	episodes/pt/30 days	NR	NR	
Russell-Jones <sup>43</sup>	parallel	I	IDet+HI	491	6 months	overall major minor nocturnal	NR	448 (93.3) 31 (6.5) 414 (86.3) 339 (70.6)	pts (%)	NR		I versus II, p=0.003 for nocturnal
		II	NPH+HI	256	6 months	overall major minor nocturnal	NR	229 (92.7) 22 (8.9) 207 (83.8) 180 (72.9)	pts (%)	NR		
Schober <sup>44</sup>	parallel	I	IGlar+HI	174	6 months	overall severe nocturnal	NR	138 (79.3) 40 (23.0) 22 (12.6)	pts (%)	NR		I versus II, NS
		II	NPH+HI	175	6 months	overall severe nocturnal	NR	138 (78.9) 50 (28.6) 31 (17.7)	pts (%)	NR		
Standl <sup>45</sup>	parallel	I	IDet+HI	154	12 months	overall major minor nocturnal	NR	135 (2.45) 18 (0.02) 121 (1.24) 102 (0.45)	pts (episodes/pt/30 days)	NR		I versus II, p=0.067 for nocturnal

Study	Study Type	Treatment Arm Number	Treatment Arm	Number of Points at Baseline	Treatment Duration	Type of Hypoglycemia	Hypoglycemia Rate at Baseline	Hypoglycemia Rate at End Point	Outcome Unit	Hypoglycemia (change from baseline)	p-value (post-tx versus baseline)	p-value Between Treatments
						symptomatic		106 (1.18)				
		II	NPH+HI	135	12 months	overall major minor nocturnal symptomatic	NR	113 (3.48) 14 (0.01) 106 (1.79) 94 (0.63) 94 (1.68)	pts (episodes/ pt/30 days)	NR		
Vague <sup>46</sup>	parallel	I	IDet+IAsp	301	6 months	overall major minor nocturnal symptomatic	NR	271 (5.18) 24 (0.04) 259 (2.19) 198 (0.64) 236 (2.94)	pts (episodes/ pt/30 days)	NR		I versus II, p=0.029 for overall, p=0.011 for minor, p<0.005 for nocturnal
		II	NPH+IAsp	146	6 months	overall major minor nocturnal symptomatic	NR	138 (6.70) 21 (0.06) 129 (3.03) 110 (0.96) 121 (3.61)	pts (episodes/ pt/30 days)	NR		

12h=12-hour interval; BG=blood glucose; HI=conventional human insulin; IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; IGlar[30]=insulin containing 30 µg/ml zinc; IGlar[80]=insulin containing 80 µg/ml zinc; ILis=insulin lispro; m+b=morning and bedtime; m+d=morning and before dinner; NPH=neutral protamine Hagedorn; NR=not reported; NS=not significant; NSD=no significant difference; pt=patient; pt-days=patient days; pt-yr=patient year; pts=patients; tx=treatment; UL=ultra lente; mean±SE.

## APPENDIX 10B: Hypoglycemia in Type 2 DM Patients

Study	Study Type	Treatment Arm Number	Treatment Arm	Number of Points at Baseline	Treatment Duration	Type of Hypoglycemia	Hypoglycemia Rate at Baseline	Hypoglycemia Rate at End Point	Outcome Unit	Hypoglycemia (change from baseline)	p value (post-tx versus baseline)	p value Between Treatments
Fonseca <sup>48</sup> (subgroup analysis of Rosenstock) <sup>56</sup>	parallel	I	IGlar+HI	52	28 weeks	symptomatic severe nocturnal	NR	24 (46) 0 (0) 8 (15)	pts (%)	NR		I versus II, p<0.05 for symptomatic, p<0.10 for nocturnal
		II	NPH+HI	48	28 weeks	symptomatic severe nocturnal	NR	29 (60) 1 (2) 13 (27)	pts (%)	NR		
Fritsche <sup>49</sup>	parallel	I	IGlar (morning)+ Glim	236	24 weeks	overall symptomatic nocturnal severe	NR	175 (74) 133 (56) 39 (17) 5 (2.1)	pts (%)	NR		I versus III, p<0.001 for nocturnal
		II	IGlar (bedtime)+ Glim	227	24 weeks	overall symptomatic nocturnal severe	NR	155 (68) 98 (43) 52 (23) 4 (1.8)	pts (%)	NR		II versus III, p<0.001 for nocturnal II versus I, p=0.004 for symptomatic
		III	NPH (bedtime)+ Glim	232	24 weeks	overall symptomatic nocturnal severe	NR	173 (75) 135 (58) 89 (38) 6 (2.6)	pts (%)	NR		III versus II, p=0.001 for symptomatic
Haak <sup>50</sup>	parallel	I	IDet+IAsp	341	26 weeks	overall nocturnal	NR	152 (45) 52 (15)	pts (%)	NR		I versus II, NS
		II	NPH+IAsp	164	26 weeks	overall nocturnal	NR	80 (49) 38 (23)	pts (%)	NR		
Hermansen <sup>51</sup> Kølendorf <sup>52</sup>	parallel	I	IDet+OAD	237	24 weeks	overall nocturnal minor	NR	47% lower 55% lower 52% lower	relative risk (%) as compared with NPH	NR		I versus II, p<0.001 for overall, nocturnal, and minor
		II	NPH+OAD	238	24 weeks	overall nocturnal minor	NR			NR		

Study	Study Type	Treatment Arm Number	Treatment Arm	Number of Points at Baseline	Treatment Duration	Type of Hypoglycemia	Hypoglycemia Rate at Baseline	Hypoglycemia Rate at End Point	Outcome Unit	Hypoglycemia (change from baseline)	p value (post-tx versus baseline)	p value Between Treatments
Massi Benedetti <sup>53</sup>	parallel	I	IGlar+ OAD	289	52 weeks	overall nocturnal severe	NR	101 (35) 35 (12) 5 (1.7)	pts (%)	NR		I versus II, p=0.002 for nocturnal
		II	NPH+ OAD	281	52 weeks	overall nocturnal severe	NR	115 (41) 67 (24) 3 (1.1)	pts (%)	NR		
Meneghini <sup>54</sup>	parallel	I	IGlar (with Metf or Sfu)	124	48 weeks	overall severe	NR	49 (53.8) 7 (7.7)	pts (%)	NR		
		II	Pioglitazone (with Metf or Sfu)	129	48 weeks	overall severe	NR	19 (23.2) 1 (1.2)	pts (%)	NR		
Riddle <sup>55</sup>	parallel	I	IGlar+ OAD	367	24 weeks	overall symptomatic nocturnal severe	NR	13.9 9.2 4.0 14 episodes/9 pts	episodes/pt-yr	NR		I versus II, p<0.02 for overall, p<0.005 for symptom, p<0.001 for nocturnal, NS for severe
		II	NPH+ OAD	389	24 weeks	overall symptomatic nocturnal severe	NR	17.7 12.9 6.9 9 episodes/7 pts	episodes/pt-yr	NR		
Rosenstock <sup>56</sup>	parallel	I	IGlar+HI	259	28 weeks	overall nocturnal	25.5	159 (61.4) 81 (31.3)	pts (%)	NR		I versus II, NS for overall, p=0.016 for nocturnal
		II	NPH+HI	259	28 weeks	overall nocturnal	29.7	173 (66.8) 104 (40.2)	pts (%)	NR		
Rosenstock <sup>57</sup>	parallel	I	IGlar (bedtime)+ Sfu(max)+ Metf	104	24 weeks	overall symptomatic nocturnal severe	NR	57 26 29 3	pts	NR		I versus II, p=0.0528 for overall, p<0.0165 for symptomatic,

Study	Study Type	Treatment Arm Number	Treatment Arm	Number of Points at Baseline	Treatment Duration	Type of Hypoglycemia	Hypoglycemia Rate at Baseline	Hypoglycemia Rate at End Point	Outcome Unit	Hypoglycemia (change from baseline)	p value (post-tx versus baseline)	p value Between Treatments
		II	Ros+ Sfu(max)+ Metf	112	24 weeks	overall symptomatic nocturnal severe	NR	47 14 12 6	pts	NR		p=0.02 for nocturnal
Yki-Järvinen <sup>58</sup>	parallel	I	IGlar+ OAD	214	52 weeks	overall nocturnal	NR	70 (32.5) 21 (10)	pts (%)	NR		I versus II, p=0.04 for overall, p=0.0001 for nocturnal
		II	NPH+ OAD	208	52 weeks	overall nocturnal	NR	88 (42.5) 50 (23.8)	pts (%)	NR		
Yki-Järvinen <sup>59</sup>	parallel	I	IGlar+Metf	61	36 weeks	overall	3 (5)	33 (54) at weeks 25 to 36	pts (%)	NR		I versus II, NS
		II	NPH+Metf	49	36 weeks	overall	2 (4)	28 (57) at weeks 25 to 36		NR		
HOE 901/2004 Study Group <sup>60</sup>	parallel	I	IGlar[30]+ OAD	64	4 weeks	overall nocturnal	1.6	12 (18.8) 4 (6.3)	pts (%)	NR		I or II versus III, NS for overall, p=0.0123 for nocturnal
		II	IGlar[80]+ OAD	72	4 weeks	overall nocturnal	1.4	18 (25) 6 (8.3)	pts (%)	NR		
		III	NPH+ OAD	68	4 weeks	overall nocturnal	5.9	22 (32.4) 13 (19.1)	pts (%)	NR		

Glim=glimepiride (sulfonylurea); HI=conventional human insulin; IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; IGlar[30]=insulin containing 30 µg/ml zinc; IGlar[80]=insulin containing 80 µg/ml zinc; max=maximum dose; Metf=metformin; NPH=neutral protamine Hagedorn; NR=not reported; NS=not significant; OAD=oral anti-diabetic agent; pt-yr=patient-year; pts=patients; Sfu=sulfonylurea; tx=treatment

## APPENDIX 11A: Definition of Hypoglycemia as Reported by Investigators for Trials on Type 1 DM Patients

Study	Analogue	Definition of Hypoglycemia
DeLeeuw <sup>25</sup>	IDet	overall (minor): BG <2.8 mmol/L; symptoms only, if not confirmed with BG measurement severe (major): episode with severe central nervous system symptoms, requiring assistance and BG <2.8 mmol/L or symptom reversal achieved with food, glucose, or glucagon
Fulcher <sup>26</sup>	IGlar	symptomatic: symptoms consistent with hypoglycemia that was mild (2.8 to 3.6 mmol/L), moderate (<2.8 mmol/L), or severe severe: requiring assistance, with BG <2.8 mmol/L or prompt recovery after oral carbohydrate, intravenous glucose, or subcutaneous glucagon nocturnal: between evening insulin injection and morning insulin dose
Garg <sup>27</sup>	IGlar	NR
Hermansen <sup>28</sup>	IDet	overall (minor): BG <3.0 mmol/L, dealt with by patient severe (major): requiring third-party help or intravenous glucose or glucagon nocturnal: NR
Hershon <sup>29</sup>	IGlar	overall: symptoms of hypoglycemia confirmed by BG <2.8 mmol/L (50 mg/dL) severe: requiring assistance, with BG <2.0 mmol/L (36 mg/dL) or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration nocturnal: between evening basal insulin injection and before morning injection of basal insulin (if applicable) or determination of morning FBG
Home <sup>31</sup>	IDet	minor: BG <2.8 mmol/L symptomatic: symptoms of hypoglycemia with no BG measurement or BG >2.8 mmol/L major: requiring assistance nocturnal: between 2300 h and 0600 h
Home <sup>30</sup>	IGlar	symptomatic: symptoms of hypoglycemia confirmed by BG <2.8 mmol/L (50 mg/dL) asymptomatic: BG <2.8 mmol/L (50 mg/dL) without symptoms severe: requiring assistance, with BG <2.8 mmol/L (50 mg/dL) or prompt recovery after administration of oral carbohydrate, intravenous glucose, or glucagon nocturnal: during sleep, between bedtime and rising in the morning, or before morning pre-breakfast self-BG measurement and morning insulin injection
Kawamura <sup>32</sup>	IGlar	NR
Køglendørf <sup>33</sup>	IDet	symptoms only: symptoms of hypoglycemia without BG measurement or BG ≥3.1 mmol/L minor: BG <3.1 mmol/L major: requiring assistance
Kudva <sup>34</sup>	IGlar	overall: symptoms of hypoglycemia with BG <60 mg/dL serious: requiring assistance with BG <50 mg/dL
Pieber <sup>35</sup>	IGlar	overall: BG <2.8 mmol/L severe: requiring assistance
Pieber <sup>36</sup>	IDet	nocturnal: between 2300 h and 0600 h
Porcellati <sup>37</sup>	IGlar	overall: BG ≤4.0 mmol/L (72 mg/dL) severe: requiring assistance nocturnal: between 0100 h and 0730 h

Study	Analogue	Definition of Hypoglycemia
Raskin <sup>38</sup>	IGlar	overall (symptomatic): symptoms of hypoglycemia severe: requiring assistance, with BG<2.0 mmol/L (36 mg/dL) or associated with prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration nocturnal: between bedtime after evening injection and before performing BG measurement in morning
Ratner <sup>39</sup>	IGlar	overall: symptoms or BG<2.0 mmol/L (36 mg/dL) severe: requiring assistance nocturnal: occurring while asleep after bedtime insulin dose and before morning BG measurement
Robertson <sup>40</sup>	IDet	nocturnal: between 2200 h and 0700 h
Rosenstock <sup>41</sup>	IGlar	overall: symptoms or BG<2.8 mmol/L severe: symptoms or BG<2.8 mmol/L in which routine activities curtailed or assistance required, or prompt recovery of patient after administration of oral carbohydrate, intravenous glucose, or glucagon administration nocturnal: between bedtime basal insulin and BG measurement in morning
Rossetti <sup>42</sup>	IGlar	overall: BG≤4.0 mmol/L severe: requiring assistance nocturnal: NR
Russell-Jones <sup>43</sup>	IDet	overall (minor): BG<2.8 mmol/L (50 mg/dL); symptoms only if not confirmed by BG measurement severe: requiring assistance nocturnal: between 2300 h and 0600 h
Schober <sup>44</sup>	IGlar	overall: BG<2.8 mmol/L severe: BG<2.8 mmol/L, requiring assistance or experiencing prompt recovery after oral carbohydrate or intravenous glucose or glucagon administration nocturnal: NR
Standl <sup>45</sup>	IDet	overall (minor): BG<2.8 mmol/L; symptoms only if not confirmed by BG measurement severe (major): requiring assistance nocturnal: NR
Vague <sup>46</sup>	IDet	overall (minor): BG<2.8 mmol/L; symptoms only if not confirmed by BG measurement severe (major): requiring assistance nocturnal: NR
Witthaus <sup>47</sup>	IGlar	NR

BG=blood glucose; FBG=fasting blood glucose; IDet=insulin detemir; IGlar=insulin glargine; NR=not reported.

## APPENDIX 11B: Definition of Hypoglycemia as Reported by Investigators for Trials on Type 2 DM Patients

Study	Analogue	Definition of Hypoglycemia
Fonseca <sup>48</sup>	IGlar	overall: symptoms, confirmed by BG<2.8 mmol/L (50 mg/dL) severe: requiring assistance, and BG<2.0 mmol/L (36 mg/dL) or associated with prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration nocturnal: between bedtime basal insulin injection and before morning determination of FBG
Fritsche <sup>49</sup>	IGlar	overall: BG<4.2 mmol/L (75 mg/dL) severe: requiring assistance, and BG<2.8 mmol/L (50 mg/dL) or associated with prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration nocturnal: between bedtime after evening injection and before patient awakes in morning
Haak <sup>50</sup>	IDet	overall (minor): BG<2.8 mmol/L; symptoms only, not confirmed by BG measurement severe: requiring assistance nocturnal: between 2300 h and 0600 h
Hermansen <sup>51</sup>	IDet	minor: BG<3.1 mmol/L major: requiring assistance nocturnal: between 2300 h and 0600 h
Massi Benedetti <sup>53</sup>	IGlar	overall: BG<2.8 mmol/L (50 mg/dL), classified as symptomatic or asymptomatic severe: requiring assistance, and BG<2.8 mmol/L (50 mg/dL), or prompt recovery after oral carbohydrate or intravenous glucose or glucagon administration nocturnal: occurring during sleep, between evening injection, and before morning FBG measurement or morning injection
Meneghini <sup>54</sup>	IGlar	NR
Riddle <sup>55</sup>	IGlar	overall: BG≤4.0 mmol/L (72 mg/dL) severe: requiring assistance and BG<3.1 mmol/L (56 mg/dL), or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration nocturnal: between bedtime injection and before BG measurement, eating breakfast, or administration of oral antihyperglycemics in morning
Rosenstock <sup>56</sup>	IGlar	overall: symptoms and BG<2.8 mmol/L severe: requiring assistance and BG<2.0 mmol/L or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration nocturnal: occurring during sleep, after evening injection, and before rising in morning (before morning BG measurement and insulin injection)
Rosenstock <sup>57</sup>	IGlar	overall: BG<3.9 mmol/L (70 mg/dL), <2.8 mmol/L (50 mg/dL), or <2.0 mmol/L (36 mg/dL) severe: requiring assistance, with BG<2.0 mmol/L (36 mg/dL) or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration nocturnal: occurring after evening insulin injection and before getting up in morning
Yki-Järvinen <sup>58</sup>	IGlar	overall: BG<2.8 mmol/L (50 mg/dL), classified as symptomatic or asymptomatic severe: requiring assistance, with BG<2.8 mmol/L or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration nocturnal: occurring during sleep, between evening injection and rising in morning (i.e., before morning BG measurement)

Study	Analogue	Definition of Hypoglycemia
Yki-Järvinen <sup>59</sup>	IGlar	overall: BG $\leq$ 4.0 mmol/L severe: requiring assistance of another person and BG<3.1 mmol/L or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration
HOE 901/2004 Study Investigators Group <sup>60</sup>	IGlar	overall: BG<2.8 mmol/L, classified as symptomatic or asymptomatic severe: requiring assistance and BG<2.8 mmol/L or prompt recovery after administration of oral carbohydrate, intravenous glucose, or glucagon nocturnal: between bedtime basal insulin and FBG next morning

BG=blood glucose; FBG=fasting blood glucose; IGlar=insulin glargine; i.v.=intravenous; NR=not reported

## APPENDIX 12A: Adverse Events (Excluding Hypoglycemia) in Type 1 DM Patients

Study	Analogue	Number of Adverse Events in Each Arm	Description of Adverse Events
DeLeeuw <sup>25</sup>	IDet	IDet 72.7% of patients in 1st 6 months and 60.2% of patients in 2 <sup>nd</sup> 6 months experienced AEs; 12 severe AEs NPH 76.8% in 1st 6 months and 69.7% in 2 <sup>nd</sup> 6 months; 6 severe AEs	IDet: CNS complaints (including migraine) most frequent, other AEs included retinal edema and macular degeneration, 3 moderate episodes of hyperglycemia, 2 patients with ketosis, 1.9% of patients reported injection site reactions NPH: vision disturbances most frequent; other AEs included retinal disorder, 2 patients with ketosis, and 1.0 % of patients reported injection site reactions
Fulcher <sup>26</sup>	IGlar	IGlar 277 events in 57 patients; NPH 241 events in 56 patients	most common AEs were upper respiratory tract infections (IGlar 7.2%; NPH 11.2%), infections (IGlar 7.2%; NPH 6.2%), rhinitis (IGlar 7.2%; NPH 5.4%), headache (IGlar 9.8%; NPH 4.2%), and diarrhea (IGlar 4.3%; NPH 0.8%); injection site reactions were similar (IGlar 9 events in 5 patients; NPH 7 events in 7 patients); <5% of AEs considered to be severe, <10% considered to be related to study medication
Garg <sup>27</sup>	IGlar	NR	NR
Hermansen <sup>28</sup>	IDet	approximately 30% of patients had AEs during either treatment period	NR
Hershon <sup>29</sup>	IGlar	IDet 84.6% of patients experienced at least 1 treatment-related AE; 13.8% of patients experienced at least 1 serious AE NPH 85.9% of patients experienced at least 1 treatment-related AE; 13.1% of patients experienced at least 1 serious AE	increased body weight and injection site pain only AEs specified
Home <sup>31</sup>	IDet	IDet: serious AEs reported for 14 patients (5%) NPH: serious AEs reported for 4 patients (3%)	AEs not considered to be related to study medication
Home <sup>30</sup>	IGlar	IGlar 37/292 patients (13%) experienced AEs possibly related to study medication; 9% classified as serious NPH 39/293 patients (13%) experienced AEs possibly related to study medication; 10% classified as serious	IGlar 8 patients (3%) had injection site mass; 3 patients (1%) had injection site reaction NPH 9 patients (3%) had injection site mass; 6 patients (2%) had injection site reaction similar numbers of patients for each group developed retinopathy severity level >61 (ETDRS), clinically significant macular edema, or 3-step progression on ETDRS retinopathy scale
Kawamura <sup>32</sup>	IGlar	NR	NR
Kølendorf <sup>33</sup>	IDet	NR	NR

Study	Analogue	Number of Adverse Events in Each Arm	Description of Adverse Events
Kudva <sup>34</sup>	IGlar	NR	NR
Pieber <sup>35</sup>	IGlar	IGlar (HOE 901-30) 3 (3%) of patients with injection site reactions IGlar (HOE 901-80) 10 (9%) of patients with injection site reactions NPH: 3 (3%) patients with injection site reactions	only injection site reactions reported
Pieber <sup>36</sup>	IDet	approximately 63% of all patients reported AEs IDet 9 patients (3.3%) with serious AEs NPH 2 patients (1.6%) with serious AEs	IDet 1 serious AE considered to be related to study medication (1 transient ischemic attack); 4 patients experienced injection site reactions
Porcellati <sup>37</sup>	IGlar	NR	NR
Raskin <sup>38</sup>	IGlar	IGlar: treatment-emergent AEs regardless of relationship to study medication occurred in 250/310 patients (80.6%) NPH: treatment-emergent AEs regardless of relationship to study medication occurred in 236/309 patients (71.4%) in NPH group	most common AEs were injection site events (6.1% of IGlar patients and 0.3% NPH patients); other AEs included headache, retinal events, increase in body weight; 1 NPH patient withdrew because of cancer of pancreas
Ratner <sup>39</sup>	IGlar	frequency and types of AEs similar in both groups; IGlar 84.5%; NPH 86.7%	reported AEs were injection site reactions (15.2% in IGlar versus 10.4% in NPH) and 1 fall in each group (due to hypoglycemia) resulting in serious events
Robertson <sup>40</sup>	IDet	similar numbers of AEs in both groups	NR
Rosenstock <sup>41</sup>	IGlar	NR	most frequent AEs considered related to study medication were injection site reactions
Rossetti <sup>42</sup>	IGlar	NR	NR
Russell-Jones <sup>43</sup>	IDet	<2% of patients reported serious AEs with probable or possible relation to treatment.	NR except for 1 episode of severe hyperglycemia in NPH group
Schober <sup>44</sup>	IGlar	IGlar: 16 (9.2%) injection site reactions; 10 (5.7%) serious AEs; 4 (2.3%) systemic allergic reactions NPH: 15 (8.6%) injection site reactions; 24 (13.7%) serious AEs; 2 (1.1%) systemic allergic reactions	no allergic reactions considered related to study treatments; other AEs reported were infection, upper respiratory tract infection, pharyngitis, rhinitis, gastroenteritis; injection site reactions were only AEs considered to be related to treatment; serious AEs included hyperglycemia and ketoacidosis
Standl <sup>45</sup>	IDet	IDet 3 episodes of hyperglycemia due to missed doses; 4.5% of IDet patients had injection site reactions; 11.0% of patients experienced vision disorders; 5.2% retinal disorders	AEs included hyperglycemia (due to missed doses), injection site disorders, abnormal fundoscopies, vision disorders, retinal disorders

Study	Analogue	Number of Adverse Events in Each Arm	Description of Adverse Events
		NPH 0.7% of NPH patients had injection site reactions; 2 patients had abnormal fundoscopies after 12 months; 11.2% of patients experienced vision disorders; 8.2% retinal disorders	
Vague <sup>46</sup>		approximately 70% of patients in both groups had $\geq 1$ AE IDet 3 injection site reactions; 1 potentially allergic reaction to IDet NPH 1 injection site reaction	most common AEs were headache, upper respiratory tract infection, rhinitis; others included allergic reaction to IDet and injection site reactions in both treatment groups; 1 patient in IDet group withdrew due to headache, vomiting, and malaise (not considered to be treatment-related); 1 patient withdrew due to uterine carcinoma (not considered to be treatment-related)
Witthaus <sup>47</sup>	IGlar	NR	NR

AE=adverse event; CNS=central nervous system; ETDRS=Early Treatment Diabetic Retinopathy Study; IDet=insulin detemir; IGlar=insulin glargine; NPH=neutral protamine Hagedorn; NR=not reported.

## APPENDIX 12B: Adverse Events (Excluding Hypoglycemia) in Type 2 DM Patients

Study	Analogue	Number of Adverse Events in Each Arm	Description of Adverse Events
Fonseca <sup>48</sup>	IGlar	IGlar 43/52 patients (83%) experienced at least 1 AE, 7 (13.5%) of these possibly treatment-related; 5/52 patients (10%) experienced serious AE NPH 41/48 patients (85%) experienced at least 1 AE, 3 (6.3%) of these possibly treatment-related; 8/48 patients (17%) experienced serious AE	most common AEs included retinal vascular disorders, upper respiratory tract infections, neuropathy, peripheral edema, and injection site hemorrhage; most common serious AEs were cerebrovascular accidents, coronary artery disorders, myocardial infarct, hypertension, retinal vascular disorder, retinal hemorrhage, and skin carcinoma, of which only injection site hemorrhage was considered treatment-related; body weight increased in both groups
Fritsche <sup>49</sup>	IGlar	bedtime IGLar 414 (36 considered possibly treatment-related) morning IGLar 403 (45 considered possibly treatment-related) NPH 423 (55 considered possibly treatment-related)	only AEs specified were weight gain
Haak <sup>50</sup>	IDet	NR	most common AEs were gastrointestinal disorders in IDet patients; skin and appendage disorders in NPH patients; weight gain experienced by both groups
Hermansen <sup>51</sup> Kølendorf <sup>52</sup>	IDet	NR	NR
Massi Benedetti <sup>53</sup>	IGlar	IGlar 185 patients (65%) reported at least 1 AE; 5.5% possibly treatment-related NPH: 193 (69%) reported at least 1 AE; 7.5% possibly treatment-related	most common AEs were infection, upper respiratory tract infection, bronchitis, back pain, and injection site reactions; other AEs included increased insulin antibodies and development of <i>E. coli</i> antibodies
Meneghini <sup>54</sup>	IGlar	NR	IGlar: most common AEs 1 edema; 6 weight increase Pio: most common AEs 13 edema; 9 weight increase; 5 headache
Riddle <sup>55</sup>	IGlar	NR	weight gain reported for both groups.
Rosenstock <sup>56</sup>	IGlar	IGlar 27 patients (10.4%) experienced treatment-related AEs; 9 withdrew due to AEs NPH: 20 patients (7.7%) experienced treatment-related AEs; 7 withdrew due to AEs	mild pain or cellulitis at injection site were only AEs specified
Rosenstock <sup>57</sup>	IGlar	IGlar: 2 (2%) patients discontinued due to AEs; serious AEs in 5 (4.8%) patients, 0 considered to be related to treatment. Rosiglit: 9 (8%) patients discontinued due to AEs; serious AEs in 11 (9.8%) patients, 3 considered to be	IGlar: gastrointestinal infection (unrelated to treatment), average weight gain 1.7±0.4 kg; serious AEs NR Rosiglit: edema (12.5% of patients), average weight gain 3.0±0.4 kg, nausea, elevated liver function tests (considered to be related to treatment); serious AEs included overdose, fibroid tumours, iron

Study	Analogue	Number of Adverse Events in Each Arm	Description of Adverse Events
		possibly related to treatment	deficiency (considered to be possibly related to treatment)
Yki-Järvinen <sup>58</sup>	IGlar	no difference in treatment-emergent AEs possibly related to study medication	IGlar: mean weight gain of 2.57±0.23 kg NPH: mean weight gain of 2.34±0.23 kg
Yki-Järvinen <sup>59</sup>	IGlar	IGlar: 33 patients (54%); 1 serious AE, not considered to be related to treatment NPH: 24 patients (49%); 4 serious AEs, not considered to be related to treatment	most common AEs were infections and musculoskeletal and gastrointestinal disorders, with no differences between groups IGlar: mean weight gain of 2.6±0.6 kg; serious AE was endometriosis; 1 withdrawal due to pancreatic cancer NPH: mean weight gain 3.5±0.7 kg; serious AEs were anaphylactic reaction, atrial fibrillation and cardiac failure, gastroenteritis, pulmonary emphysema
HOE 901/2004 Study Investigators Group <sup>60</sup>	IGlar	IGlar 30: 3/64 patients (4.7%) experienced AEs possibly related to treatment IGlar 80: 3/72 patients (4.2%) experienced AEs possibly related to treatment NPH: 2/68 patients (2.9%) experienced AEs possibly related to treatment	IGlar 30: tachycardia, tongue edema, injection site reaction; 1 serious adverse event (myocardial infarction) not considered to be treatment-related IGlar 80: parasthesia, dyspepsia, increased appetite NPH: headache, nausea with asthenia 1 patient in each group experienced injection site reaction; mean body weight increased in all groups

AE=adverse event; IDet=insulin detemir; IGlar=insulin glargine; NR=not reported.

## APPENDIX 13A: Mortality in Type 1 DM Patients

Study	Study Type	Treatment Arm	Number of Patients at Baseline	Treatment Duration	Number of Deaths	Cause of Death
Pieber <sup>36</sup>	parallel	IDet <sub>m+d</sub> +IAsp	139	16 weeks	0	
		IDet <sub>m+b</sub> +IAsp	132	16 weeks	1	unknown
		NPH <sub>m+b</sub> +IAsp	129	16 weeks	0	
Raskin <sup>38</sup>	parallel	IGlar+ILis	310	16 weeks	0	
		NPH+ILis	309	16 weeks	0	
Ratner <sup>39</sup>	parallel	IGlar+HI	264	28 weeks	0	
		NPH+HI	270	28 weeks	1	death secondary to cardiopulmonary arrest, not considered to be related to study medication

HI=conventional human insulin; IAsp=insulin aspart; IGlar=insulin glargine; ILis=insulin lispro; m+b=morning and bedtime; m+d=morning and before dinner; NPH=neutral protamine Hagedorn

## APPENDIX 13B: Mortality in Type 2 DM Patients

Study	Study Type	Treatment Arm	Number of Patients at Baseline	Treatment Duration	Number of Deaths	Cause of Death
Fritsche <sup>49</sup>	parallel	IGlar (morning)+ Glim	236	24 weeks	0	
		IGlar (bedtime)+ Glim	227	24 weeks	2	unrelated to study medication
		NPH (bedtime)+ Glim	232	24 weeks	1	unrelated to study medication
Haak <sup>50</sup>	parallel	IDet+IAsp	341	26 weeks	1	patient had history of coronary heart disease; death not considered to be related to study medication
		NPH+IAsp	164	26 weeks	0	
Massi Benedetti <sup>53</sup>	parallel	IGlar	289	52 weeks	1	not considered to be related to study medication
		NPH	281	52 weeks	6	not considered to be related to study medication
Meneghini <sup>54</sup>	parallel	IGlar+OAD versus Pioglitazone +OAD	253	48 weeks	1	patient in IGlar+OAD treatment arm died from multiple blunt trauma
HOE 901/2004 Study group <sup>60</sup>	parallel	IGlar[30]+OAD	64	4 weeks	0	
		IGlar[80]+OAD	72	4 weeks	0	
		NPH+OAD	68	4 weeks	0	

Glim=glimepiride (sulfonylurea); IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; IGlar[30]=insulin containing 30 µg/mL zinc; IGlar[80]=insulin containing 80 µg/mL zinc; NPH=neutral protamine Hagedorn; OAD=oral anti-diabetic agent.

## APPENDIX 14: QOL in Type 1 DM Patients

Study	Treatment	Diabetes Treatment Satisfaction Questionnaire					Well-Being Questionnaire					
		Total (scale)	Satisfaction (scale)	Convenience (scale)	Flexibility (scale)	Willingness to Continue (scale)	Total	Depression	Anxiety	Energy	Positive Well-Being	Others (perceived frequency of hyperglycemia)
Witthaus <sup>47</sup>	IGlar+HI	+1.27 (from baseline), p<0.001	0.37, p=0.002	0.32, p<0.001	0.25, p<0.001	0.39, p<0.001	1.22 (from baseline), NS	-0.19, NS	-0.31, NS	0.33, NS	0.39, NS	-0.55, p=0.038
	NPH+HI	-0.56	0.08	0.09	0.00	-0.24	1.57	-0.24	-0.53	0.40	0.35	-0.30

HI=conventional human insulin; IGlar=insulin glargine; NPH=neutral protamine Hagedorn; NS=not significant

## APPENDIX 15: Literature Search Strategy for Cost-Effectiveness Studies

Databases	Dates/Limits	Subject Headings/Keywords
DIALOG OneSearch  MEDLINE BIOSIS Previews EMBASE PASCAL	Human  1990 -	Insulin Long-Acting(l)aa/de <i>[MeSH heading for MEDLINE]</i>  OR  (Insulin Glargine OR Insulin Detemir)/de <i>[EMTREE terms for EMBASE]</i>  OR  TN=(Lantus OR Levemir) <i>[Brand names in EMBASE]</i>  OR  (glargine OR Lantus OR HOE()901 OR 160337()95()1)/ti,ab,id OR RN=160337-95-1 OR (detemir OR Levemir OR NN()304 OR 169148()63()4)/ti,ab,id OR RN=169148-63-4 <i>[Textwords searched in title, abstract, identifier, registry number]</i>  OR  (long()acting()insulin? OR slow?()acting()insulin? OR long()acting()analog? OR slow?()acting()analog?)/ti,ab <i>[Textwords searched in title, abstract]</i>  OR  Insulin(l)aa/de <i>[MeSH heading for MEDLINE]</i>  OR  (Insulin Derivative OR Insulin Aspart OR Insulin()B28()Lysine()B29()Proline)/de <i>[EMTREE terms for EMBASE]</i>  OR  TN=(Humalog OR NovoLog OR NovoRapid OR NovoMix OR Apidra) <i>[Brand names in EMBASE]</i>  OR  Insulin Lispro/de <i>[BIOSIS Previews thesaurus term]</i>  OR

Databases	Dates/Limits	Subject Headings/Keywords
		<p>(insulin?(1n)analog? OR insulin?(1n)derivat? OR new()insulin? OR novel()insulin?)/ti,ab</p> <p><i>OR</i></p> <p>(133107()64()9 OR insulin?(2n)(Lys?()28()B) OR (28()B)(Lys?()29()B)(2n)insulin? OR Lispro? OR Humalog? OR B28 OR 28()B()lysine()29()B()prolineinsulin?)/ti,ab,id OR Lyspro?/ti,ab OR insulin()Lys()B28()Pro()B29/id OR RN=133107-64-9</p> <p><i>OR</i></p> <p>(116094()23()6 OR insulin?()aspart? OR B28()asp? OR Asp()B28 OR NovoLog OR NovoRapid OR NovoMix?)/ti,ab OR insulin()Asp()B28/id OR RN=116094-23-6</p> <p><i>OR</i></p> <p>(insulin()glulisine OR apidra OR 207748()29()6 OR insulin()Lys()B3()Glu()B29 OR insulin()lysyl()B3()glutamyl()B29 OR B3()lysyl()B29()glutamylinsulin)/ti,ab,id OR RN=207748-29-6</p> <p><i>OR</i></p> <p>(quick()acting()insulin? OR rapid()acting()insulin? OR rapidly()acting()insulin? OR short()acting()insulin? OR fast()acting()insulin? OR quick()acting()analog? OR rapid()acting()analog? OR rapidly()acting()analog? OR short()acting()analog? OR fast()acting()analog?)/ti,ab</p> <p><b>AND</b></p> <p>Diabetes Mellitus!/de [MeSH heading for MEDLINE]</p> <p><i>OR</i></p> <p>(Insulin-Dependent Diabetes OR Insulin-Dependent Diabetes Mellitus OR Diabetes OR Diabetes Insipidus OR Diabetes Mellitus OR "Maturity-Onset Diabetes of the Young" OR Non-Insulin-Dependent Diabetes Mellitus OR "Gestational Diabetes" OR "Gestational Diabetes Mellitus")/de [BIOSIS Previews thesaurus terms]</p> <p><i>OR</i></p> <p>(Diabetes Control OR Diabetes Insipidus! OR Diabetes Mellitus! OR Experimental Diabetes Mellitus! OR Pregnancy Diabetes Mellitus!)/de [EMTREE terms for EMBASE]</p> <p><i>OR</i></p> <p>(diabet? OR IDDM OR NIDDM OR MODY OR "type 1" OR "type I" OR "type 2" OR "type II" OR insulin(depend?())DM OR</p>

Databases	Dates/Limits	Subject Headings/Keywords
		<p>matur?(onset)DM OR late()life()DM OR gestational()DM OR juvenile(onset)DM OR juvenile()DM OR ketosis()prone()DM OR sudden(onset)DM OR non(insulin)depend?()DM OR adult(onset)DM)/ti,ab</p> <p><b>AND</b></p> <p>(Economics OR "Costs and Cost Analysis"! OR "Value of Life" OR Economics, Medical! OR Economics, Hospital! OR Economics, Nursing OR Economics, Pharmaceutical OR "Fees and Charges"! OR Budgets OR Models, Economic! OR Markov Chains OR Monte Carlo Method OR Decision Trees OR "Quality of Life" OR Patient Satisfaction OR Quality-Adjusted Life Years)/de  <i>[MeSH headings for MEDLINE]</i></p> <p><b>OR</b></p> <p>(Economic Impact OR Economic Value OR Pharmacoeconomics OR Health Care Cost OR Economic Factors OR Economics OR Cost Analysis OR Cost OR Economic Analysis OR Cost-Effectiveness OR Costs OR "Quality of Life" OR Health Care Cost OR Cost Savings OR Cost-Benefit Analysis OR Hospital Costs OR Medical Costs OR Quality-of-Life)/de  <i>[BIOSIS Previews thesaurus terms]</i></p> <p><b>OR</b></p> <p>(Health economics! OR Economic Evaluation! OR Pharmacoeconomics! OR Economic Aspect! OR Quality Adjusted Life Year OR "Quality of Life!")/de  <i>[EMTREE terms for EMBASE]</i></p> <p><b>OR</b></p> <p>(Economics OR Economic Model OR Pharmacoeconomics OR Cost Benefit Analysis OR Cost Utility Analysis OR Health Care Economics OR Medical Cost OR Expenditure OR Budget OR Budgeting OR Cost Estimation OR Cost Evaluation OR Cost Lowering OR Cost Minimization OR Cost Savings OR Cost Utility Analysis OR Cost Price)/de  <i>[PASCAL thesaurus terms]</i></p> <p><b>OR</b></p> <p>(econom? OR cost OR costly OR costing OR costed OR costs OR price OR prices OR pricing OR priced OR discount OR discounts OR discounted OR discounting OR expenditure OR expenditures OR budget? OR afford? OR pharmacoeconomic? OR pharmaco(1n)economic? OR decision(1n)(tree? OR analy? OR model?) OR (value OR values OR valuation)(2n)(money OR monetary OR life OR lives) OR QOL OR QOLY OR QOLYs OR HRQOL OR QALY OR QALYs OR quality(1n)life OR willingness(1n)pay OR quality(1n)adjusted()life()year?)/ti,ab</p>

Databases	Dates/Limits	Subject Headings/Keywords
		<p><i>Search performed on 3 August 2005; monthly alerts set up on MEDLINE, EMBASE and BIOSIS Previews and were ongoing until Mar/6/2006.</i></p> <p><i>Total Hits = 326 Unique Records (i.e. records remaining after 'clinical' records from 1-A search NOT'd out)</i></p>
Cochrane Library Issue 3 2005	1990 -	<p>Same MeSH and keywords as per MEDLINE search, excluding study design filter. Appropriate syntax used.</p> <p><i>Initial search performed on 2 August 2005 and updated with subsequent database updates. Last update performed on Feb/06/2006.</i></p> <p><i>Total Hits =</i> <i>NHS EED = 5 Records, 1 Unique</i></p>
PubMed	Human 1990 -	Same MeSH and keywords as per MEDLINE search. Appropriate syntax used.
OHE-IFPMA Database Ltd.  HEED: Health Economic Evaluations Database August 2005		glargine OR Lantus OR detemir OR Levemir OR lispro OR Humalog OR aspart OR NovoLog OR NovoRapid OR NovoMix OR glulisine OR Apidra[all fields], 2 <i>Unique Relevant Results</i>
Websites of health economics research groups		Health Economics Research Group (HERG); Health Economics Research Unit (HERU); etc.

## APPENDIX 16: Quality Assessment Results Using BMJ Checklist

BMJ Checklist	Palmer <i>et al.</i> <sup>71</sup>	Bullano <i>et al.</i> <sup>72</sup>	Zhang <i>et al.</i> <sup>73</sup>
<b>Study design</b>			
1. research question is stated	y	y	y
2. economic importance of research question is stated	n	n	y
3. viewpoints of analysis stated and justified	y	y	y
4. rationale for choosing alternative programs or interventions compared is stated	y	y	n
5. alternatives being compared are described	y	y	p
6. form of economic evaluation used is stated	y	y	y
7. choice of form of economic evaluation justified in relation to questions addressed	p	y	p
<b>Data collection</b>			
8. sources of effectiveness estimates used are stated	y	y	na
9. details of design and results of effectiveness study are given (if based on 1 study)	na	na	na
10. details of method of synthesis or meta-analysis of estimates are given (if based on overview of a number of effectiveness studies)	y	na	na
11. primary outcome measures for economic evaluation are clearly stated	y	y	y
12. methods to value health states and other benefits are stated	y	na	na
13. details of subjects from whom valuations were obtained are given	y	na	na
14. productivity changes (if included) are reported separately	na	na	na
15. relevance of productivity changes to study question is discussed	na	na	na
16. quantities of resources are reported separately from unit costs (attention: resources)	p	n	n
17. methods for the estimation of quantities and unit costs are described (p: if sources are mentioned)	y	y	p
18. currency and price are recorded	y	p	p
19. details of currency of price adjustments for inflation or currency conversion are given	y	n	n
20. details of any model used are given	y	y	na
21. choice of model used and key parameters on which it is based are justified (y=if relevant assumptions are detailed)	y	y	na
<b>Analysis and interpretation of results</b>			
22. time horizon of costs and benefits is stated	y	y	y
23. discount rate(s) is stated	y	n	n
24. choice of rate(s) is justified	y	na	na
25. explanation is given if costs or benefits are not discounted	na	n	n
26. details of statistical tests and confidence intervals are given for stochastic data	p	p	n
27. approach to sensitivity analysis is given	y	y	na
28. choice of variables for sensitivity analysis is justified	y	p	na

<b>BMJ Checklist</b>	<b>Palmer et al.<sup>71</sup></b>	<b>Bullano et al.<sup>72</sup></b>	<b>Zhang et al.<sup>73</sup></b>
(yes=if cited previous relevant studies as base)			
29. range over which variables are varied are stated	y	y	na
30. relevant alternatives are compared	y	y	p
31. incremental analysis is reported	y	y	y
32. major outcomes are presented in disaggregated and aggregated forms	y	y	y
33. answer to study question is given	y	y	y
34. conclusions follow from data reported	y	y	y
35. conclusions accompanied by appropriate caveats	y	n	y

n=no; na=not applicable; p=partial; y=yes.

## APPENDIX 17: Characteristics of Economic Studies

Study	Study Type (CEA, CUA); Analysis Type (model-based, trial-tailed)	Intervention Versus Comparator	Study Population	Analysis Horizon	Study Perspective	Geographic Location
Palmer <sup>71</sup>	model-based CUA	detemir-based basal-bolus therapy versus NPH-based basal-bolus therapy	DM1	lifetime	NHS reimbursement perspective	UK
Bullano <sup>72</sup>	cost-consequence study with medical claim data	glargine versus NPH	appears to involve both types of DM, although not mentioned	1 year	managed care perspective	southeastern US
Zhang <sup>73</sup>	cost comparison study with reimbursement data	glargine versus non-glargine agents	DM	1 year	medical program in California	California US

CEA=cost-effectiveness analysis; CUA=cost utility analysis; NHS=National Health Service; NPH=neutral; protamine Hagedorn

## APPENDIX 18: Results of Economic Studies

Study	Cost	Baseline Results	Sensitivity Analysis Results	Conclusion
Palmer <sup>71</sup>	total lifetime cost per patient (discounted at 3.5%): detemir-based basal-bolus group £34,405 (SD £953), NPH-based basal-bolus group £32 698 (SD £1,007); difference is £1,707 per patient	ICER (incremental \$/life-year gained) £22,474; ICER (incremental \$/QALY gained) £19,285	only with A1c improvement assumption, ICER rose to £20,910 per QALY gained from £19,285 per QALY gained; with discounting rate varying from 0% to 6%, ICER ranged from £18,105 per QALY gained to £20,253; with time horizon varying from 5 years to 15 years, ICER ranged from £36,885 to £22,776.	detemir-based basal-bolus therapy would fall under adoption threshold range of £35,000 to £57,000 if its effects compared to NPH-based basal-bolus therapy used in this analysis could stay in UK real-life clinical setting
Bullano <sup>72</sup>	mean cost for index medication per patient per year \$390 (95% CI: \$351 to \$429) for glargine cohort, \$343 (95% CI: \$320 to \$367) for NPH cohort	hypoglycemia event rate (per 100 patients per year) 18.3 for NPH group, 7.3 for glargine group	if target A1c was 8% and 9%, number needed to treat was 9 and 10 respectively	in study population, savings associated with reduced hypoglycemic events in glargine group more than offset increased acquisition cost of glargine
Zhang <sup>73</sup>	use of insulin glargine associated with incremental savings of -21.9% for emergency department claims and -36.9% for in-patient claims, but with incremental cost of 3.5% for outpatient claims and 15.7% for pharmacy claims	total cost for glargine group \$1,824.35 per patient for 6 months before glargine initiation, \$1,639.17 for 6 months afterwards; for reference group, \$680.08 per patient before index date and \$608.55 thereafter	no sensitivity analysis	data suggest short-term cost benefits of glycemic control associated with insulin glargine in patients with diabetes; total pharmacy cost increased with initiation of glargine, but was offset by reductions of diabetes-related in-patient claims that were associated proportionally with reduction of hypoglycemia-related in-patient care

ICER=incremental cost-effectiveness ratio; NPH=neutral protamine Hagedorn; QALY=quality-adjusted life-year

## APPENDIX 19: RCTs on Type 1 DM Patients, Published After Completion of Our Assessment

Study	Number of Patients, Age	Type of Trial, Duration	Results				Conclusion
			Outcomes	IGlar+IAsp	NPH+IAsp	p value	
Chatterjee <sup>97</sup>	60, 42.7 years	RCT crossover, 2 × 16 weeks	Outcomes	IGlar+IAsp	NPH+IAsp	p value	combination of IGlar and IAsp is effective basal bolus regimen in type 1 DM
			A1c (%)	8.07	8.26	0.04	significant
			BG	descriptive	descriptive		no difference
			hypoglycemia (%)	80.7	77.2	0.63	no difference
			AE	NR	NR		
			mortality	NR	NR		
			QoL (DTSQ):				
			satisfaction	descriptive: greater by 4 points	descriptive		
			perception of hypoglycemia	descriptive	descriptive	0.76	no difference
			perception of hyperglycemia	descriptive	descriptive	0.34	no difference
QoL (ADDQoL)	descriptive	descriptive		no difference			
Kølendorf <sup>98</sup>	130, 39.2 years	RCT crossover, 2 × 16 weeks	outcomes	IDet+IAsp	NPH+IAsp	p value	IDet significantly lowers risk of hypoglycemia compared with NPH at similar HbA1c
			A1c	7.6	7.6		no difference
			BG				
			fasting PG (nmol/L)	7.6	8.7	<0.0001	significant
			hypoglycemia				
			nocturnal (%)	13	23	<0.0001	significant
			AE	descriptive	descriptive		no difference
			mortality	NR	NR		
QoL	NR	NR					

Study	Number of Patients, Age	Type of Trial, Duration	Results				Conclusion
Robertson <sup>99</sup>	347, 11.8 years	RCT parallel, 26 weeks	Outcomes	IDet+IAsp	NPH+IAsp	p value	basal bolus IDet+IAsp or NPH+IAsp similar in improving A1c in children and adolescents with type 1 DM
			A1c (%)	8.0±0.1 <sup>†</sup>	7.9±0.1 <sup>†</sup>	--	no difference
			BG				
			fasting PG (nmol/L)	8.4±0.3 <sup>†</sup>	9.6±0.4 <sup>†</sup>	0.022	significant
			nocturnal PG (nmol/L)	10.4±0.4 <sup>†</sup>	9.6±0.4 <sup>†</sup>	0.194	no difference
			hypoglycemia				
			24-hour (%)	96.1	98.3	0.351	no difference
			nocturnal (%)	75	87.8	0.041	significant
			severe 24-hour (%)	15.9	20.0	0.799	no difference
			AE (%)	87	90	NR	no difference
			mortality	NR	NR		
QoL	NR	NR					

A1c=glycated hemoglobin; ADDQoL=Audit of Diabetes-Dependent Quality Questionnaire; AE=adverse event; BG=blood glucose; DTSQ=Diabetes Treatment Satisfaction Questionnaire; HbA1c=glycated hemoglobin; IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; NPH=neutral protamine Hagedorn; NR=not reported; PG=plasma glucose; QoL=quality of life; RCT=randomized controlled trial; <sup>†</sup> mean±SE

## APPENDIX 20: RCTs on Type 2 DM Patients, Published After Completion of Our Assessment

Study	Number of Patients, Age	Type of Study, Duration	Results				Conclusion	
			Outcome	IGlar+Glim	NPH+Glim	p value		
Eliaschewitz <sup>100</sup>	481, 56.6 years	RCT parallel, 24 weeks	Outcome	IGlar+Glim	NPH+Glim	p value	in type 2 DM inadequately controlled on OAD, IGlar+Glim effective in improving metabolic control with reducing incidence of nocturnal hypoglycemia	
			A1c (%)	7.65±1.30*	7.78±1.29*	0.795		no difference
			BG					
			fasting BG (nmol/L)	6.4±2.0*	6.6±2.5*	0.298		no difference
			hypoglycemia					
			symptomatic (%)	52.8	62.8	0.042		significant
			nocturnal (%)	20.4	34.8	<0.001		significant
			severe (%)	2.6	4.4	0.303		no difference
			AE (%)	59	60			no difference
			mortality	0	0			
QoL (DTSQ)	16.6±2.6	16.0±3.3	<0.02	significant				
Gerstein <sup>101</sup>	405, 56.5 years	RCT parallel, 24 weeks	outcomes	IGlar	OAD	p value	IGlar more likely to achieve lower HbA1c than OAD	
			A1c (% change)	-1.55	-1.25	0.005		significant
			BG					
			fasting PG (nmol/L change)	-3.89	-2.31	0.0001		significant
			hypoglycemia					
			overall (%)	48.5	42.2	0.23		no difference
			AE	descriptive	descriptive			no difference
			mortality	NR	NR			
			QoL	NR	NR			
Hermansen <sup>102</sup>	476, 61 years	RCT parallel, 24 weeks	Outcomes	IDet+OAD	NPH+OAD	p value	IDet compared with NPH achieves recommended A1c	

Study	Number of Patients, Age	Type of Study, Duration	Results				Conclusion
							with reduced hypoglycemia
			A1c (%)	6.58±0.06 <sup>†</sup>	6.46±0.06 <sup>†</sup>		no difference
			fasting PG (mmol/L)	6.9	6.6		no difference
			hypoglycemia				
			overall (RR)	47% lower than with NPH	--	<0.001	significant
			nocturnal (RR)	55% lower than with NPH	--	<0.001	significant
			AE	descriptive	descriptive		no difference
			mortality	NR	NR		
			QoL	NR	NR		
Philis-Tsimikas <sup>103</sup>	504, 58.5 years	RCT parallel, 20 weeks	Outcomes	IDet+OAD	NPH+OAD	p value	IDet given either in the morning or evening can be used to improved glycemic control and is better than NPH.
			A1c				
			IDet morning (% change)	-1.58	-1.74		no difference
			IDet evening (% change)	-1.48	-1.74		no difference
			fasting PG (nmol/L)				
			IDet morning	7.97	6.78	<0.001	significant
			IDet evening	6.50	6.78		no difference
			hypoglycemia				
			IDet morning (overall, %)	19.4	32.3	<0.05	significant
			IDet evening (overall, %)	16.0	32.3	<0.05	significant
			IDet morning (nocturnal, %)	2.4	13.4	<0.05	significant
			IDet evening (nocturnal, %)	4.7	13.4	<0.05	significant
			AE	descriptive	descriptive		no difference

Study	Number of Patients, Age	Type of Study, Duration	Results				Conclusion
			mortality	1	1		
			QoL	NR	NR		
Reynolds <sup>105</sup>	40	RCT parallel, 24 weeks	Outcomes	IGlar	OAD	p-value	IGlar and OAD (rosiglitazone) had similar effects on A1c reduction and hypoglycemia frequency
			A1c (% change)	-1.5	-1.4		no difference
			hypoglycemia (episodes/patient)	2.85±0.7	3.30±1.0	0.71	no difference
			AE	edema (1)	cerebrovascular event (1)		
			mortality	NR	NR		
			QoL	NR	NR		
Yokoyama <sup>104</sup>	62, 61.5 years	RCT parallel, 6 months	Outcomes	IGlar+IAsp/ILis	NPH+IAsp/ILis	p value	conversion bedtime NPH to morning IGlar seems to be efficacious in reducing HbA1c
			A1c (%)	6.6	7.0	0.007	significant
			fasting PG (nmol/L)	8.4±1.4	8.6±2.3		no difference
			hypoglycemia-overall (%)	48	42		no difference
			AE	NR	NR		
			mortality	NR	NR		
			QoL	NR	NR		

A1c=glycated hemoglobin; AE=adverse event; BG=blood glucose; DTSQ=Diabetes Treatment Satisfaction Questionnaire; Glim=glimepiride (sulfonylurea); HbA1c=glycated hemoglobin; IAsp=insulin aspart; IDet=insulin detemir; IGlar=insulin glargine; ILis=insulin lispro; NPH=neutral protamine Hagedorn; NR=not reported; OAD=oral anti-diabetic agent; PG=plasma glucose; QoL=quality of life; RCT=randomized controlled trial; RR=risk reduction; mean±SD, †mean±SE.

## APPENDIX 21: Economic Studies Published After Completion of Our Assessment

Study, Geographic Location, Industry Funding	Intervention versus Comparator	Study Population	Study Design (Study Type, Perspective, and Time Horizon)	Study Results (Baseline Results and Sensitivity Analysis)	Conclusion
Grima <sup>106</sup> Canada, funded by Sanofi-Aventis Canada	IGlar versus NPH	type 1 DM and type 2 DM, did not reach recommended target (HbA1c≤7%) with multiple daily injections of NPH insulin; 2 types analyzed separately	model-based CEA and CUA from public payer (ministries of health) perspective; for type 1 DM, from 27 years old until death or 63 years old; for type 2 DM, from 53 years old until death or 89 years old	for type 1 DM, ICER C\$18,661 per life-year gained or C\$20,799 per QALY gained; in 1-way sensitivity analysis, ICER from C\$6,754 to C\$122,300 per life-year gained or C\$7,875 to C\$143,178 per QALY; for type 2 DM, ICER C\$8,041 per life-year gained or C\$8,618 per QALY gained; in 1-way sensitivity analysis, ICER from C\$579 to C\$59,005 per life-year gained or C\$620 to C\$63,581 per QALY	ICER provided evidence for IGLar adoption from Canadian health care payer perspective
McEwan <sup>107</sup> UK, funded by Sanofi-Aventis UK	IGlar versus NPH	type 1 DM with characteristics similar to patients in DCCT study	model-based CUA from UK National Health Service (NHS) perspective over 40 years	ICER estimated for 5 base-case scenarios; scenarios 1 to 3 considered only different hypoglycemia risks due to treatment; scenarios 4 and 5 considered only different A1c reductions due to treatment (£/QALY) scenario 1: 8,807 scenario 2: 8,668	IGlar resulted in significant health benefits and represents excellent value for money in treatment of type 1 diabetes

Study, Geographic Location, Industry Funding	Intervention versus Comparator	Study Population	Study Design (Study Type, Perspective, and Time Horizon)	Study Results (Baseline Results and Sensitivity Analysis)	Conclusion
				scenario 3: 7,391 scenario 4: 9,767 scenario 5: 3,189; ICER most sensitive to price of IGlAr, utility decrement due to hypoglycemia, cohort mean weight; also sensitive to duration of treatment effect on A1c	
Brande <sup>108</sup> Switzerland, funded by Sanofi-Aventis (Suisse) sa, Geneva, Switzerland	IGlAr versus NPH	type 2 DM	model-based CEA and CUA over 10 years; appears to be perspective of Switzerland health care system	ICER of IGlAr versus NPH 1) for IGlAr pessimistic scenario (i.e., $\Delta A1c = -0.12\%$ ), ICER from CHF27,742 to CHF41,620 per event prevented and CHF40,441 to CHF45,701 per QALY gained (depending on baseline A1c of 10% to 8%) 2) for IGlAr optimistic case scenario (i.e., $\Delta A1c = -0.40\%$ ), ICER from dominant to CHF4,899 per event prevented and dominant to CHF5,711 per QALY gained (depending on baseline A1c of 10% to 8%) 1-way sensitivity analysis on 2 variables conducted: discount rate	IGlAr proved to be cost-effective and represents good to excellent value for money compared with NPH insulin

Study, Geographic Location, Industry Funding	Intervention versus Comparator	Study Population	Study Design (Study Type, Perspective, and Time Horizon)	Study Results (Baseline Results and Sensitivity Analysis)	Conclusion
				(0%, 5%); the level of baseline HbA1c (8% to 10%)	
McEwan <sup>109</sup> UK, funded by Sanofi-Aventis UK.	IGlar versus NPH	type 2 DM	model-based CUA from perspective of UK National Health Service (NHS) over 40 years	ICER estimated for 2 base-case scenarios; scenario 1 considered impact of treatment on hypoglycemia risk; scenario 2 considered impact of treatment on A1c reductions; £/QALY scenario 1: 10,027 scenario 2: 13,921; 1-way sensitivity analysis showed that most mean ICER values within £20,000/QALY; it was most sensitive to price of IGlar, utility decrement associated with hypoglycemia, and cohorts' mean weight	IGlar showed excellent value for money in treatment of DM2 in UK

A1c=glycated hemoglobin; CEA=cost-effectiveness analysis; CHF=Swiss franc; CUA=cost utility analysis; DCCT=Diabetes Control and Complications Trial; HbA1c=glycated hemoglobin; ICER=incremental cost-effectiveness ratio; IGlar=insulin glargine; NPH=neutral protamine Hagedorn; QALY=quality-adjusted life-year.

## APPENDIX 22: Formulary Status After Completion of Our Assessment

Description	DIN_PDIN	Brand_Name	BC	AB	SK	MB	ON	NB	NS	NL	FNIHB	Health Canada Status
INSULIN (HUMAN)	00984299	GE NPH PENFILL VIAL ONLY										
INSULIN (HUMAN)	00908991	HUMLIN NPH VIAL ONLY									B	
INSULIN (HUMAN)	00646148	HUMULIN LENTE INJ MEDIUM 100 U/mL susp ER	B	B	B			B	B	B	B	
INSULIN (HUMAN)	02241310	HUMULIN N 100 U/mL sol	B								B	
INSULIN (HUMAN)	01959239	HUMULIN N 100 U/mL susp	B	B	B	B		B	B	B	B	
INSULIN (HUMAN)	09853804	HUMULIN N 100 U/mL susp 3 mL CARTRIDGE					B				B	
INSULIN (HUMAN)	00587737	HUMULIN N INJ 100 U/mL sol	B	B	B	B	B	B	B	B	B	
INSULIN (HUMAN)	00977675	INSULIN NOVOLIN GE NPH										
INSULIN (HUMAN)	02024241	NOVOLIN GE LENTE INJ SC 100 U/mL susp	B			B				B		inactive DIN
INSULIN (HUMAN)	02024225	NOVOLIN GE NPH INJ 100 U/mL susp	B	B	B	B	B	B	B	B	B	
INSULIN (HUMAN)	02024268	NOVOLIN GE NPH PENFILL INJ 100 U/mL susp	B	B	B	B		B	B	B		
INSULIN (HUMAN)	09853782	NOVOLIN GE NPH PENFILL INJ 100 U/mL susp 3 mL					B				B	
INSULIN (PORK)	00514535	LENTE PURIFIED PORK INSULIN INJ 100 U/mL susp ER	B			B		B		B		inactive DIN
INSULIN (PORK)	00514551	NPH PURIFIED PORK INSULIN INJ 100 U/mL sol	B	B	B			B	B	B		inactive DIN
INSULIN (HUMAN)	00733075	HUMULIN ULTRALENTE INJ 100 U/mL susp ER	B	B	B			B	B	B		inactive DIN
INSULIN GLARGINE	02245689	LANTUS 100 U/ML 10 mL VIAL										
INSULIN GLARGINE	02251930	LANTUS 100 U/ML 3 mL CARTRIDGE										
INSULIN DETEMIR	02271842	LEVEMIR 100 U/ML 3 mL PENFILL										
INSULIN DETEMIR	02271850	LEVEMIR FLEX-PEN										
INSULIN DETEMIR	02271869	LEVEMIR INNOLET										

Source: National Prescription Drug Utilization Information System (NPDUIS), Canadian Institute for Health information (CIHI), 2007. For product with "B" status, no justification required for reimbursement; B=benefit; DIN=drug identification number.