National PBM Drug Monograph
Insulin detemir (Levemir®)
**VHA Pharmacy Benefits Management Strategic Healthcare Group
and Medical Advisory Panel**

EXECUTIVE SUMMARY

Insulin detemir was approved in 2005 (marketed March 2006) and is the second long-acting basal insulin analog on the market to join insulin glargine. It is approved to treat type 1 diabetes in adult and pediatric patients and type 2 diabetes in adults requiring basal insulin to manage hyperglycemia.

Type 1 diabetes

There are 7 randomized, open-label parallel studies comparing insulin detemir to NPH (16-52 weeks). Detemir or NPH was administered twice daily in all but 1 study. Four trials used insulin aspart and 2 used regular insulin for mealtime coverage and 1 compared detemir/aspart to NPH/regular. In general, the change in HbA1c was comparable between groups; 2 studies did show that reduction in HbA1c was significantly better with detemir than NPH (difference of 0.2%). The majority of studies showed no significant difference in the risk of all hypoglycemia and severe hypoglycemia between detemir and NPH. However, the majority of studies did show that the relative risk for nocturnal hypoglycemia was significantly lower with detemir. Most studies showed weight loss with insulin detemir with mean difference from NPH ranging from 0.52 -1.66kg. The difference persisted in those studies that were of 12-months duration. With the exception of 1 study which used a different formulation of detemir, the total daily dose of insulin for detemir and NPH was comparable.

Type 2 diabetes

Two randomized, open-label studies compared detemir + aspart to NPH + aspart or NPH + regular insulin (22-26 weeks) in patients using insulin pre-study. In one study, oral hypoglycemic agents (OHA) were discontinued and in the other, use of OHA 2-months prior to study entry was an exclusion criterion. Basal insulin was administered once or twice daily depending on pretrial treatment. Those not achieving glycemic goals on once daily may be switched to twice daily. There was no difference in HbA1c or fasting plasma glucose (FPG). There was no significant difference between detemir and NPH for any of the measured hypoglycemia parameters. There was less weight gain with insulin detemir compared to NPH (approximately 0.7kg difference). The percentage of patients requiring once or twice daily basal was similar for both groups; however, in the first study, a higher daily dose of basal insulin was required with detemir. The daily dose of aspart was slightly higher in the detemir groups.

Two 24-week studies, presented as abstracts, compared the addition detemir or NPH to OHAs.

- The addition of once daily detemir or NPH to metformin was evaluated. The decrease in HbA1c was significantly lower with NPH (difference 0.56%). Additionally, the 9-point blood glucose profile significantly favored NPH. There was no difference in mean FPG between groups. The relative risk of hypoglycemia with detemir, especially nocturnal, was about half of that in the NPH group (data not shown). Weight was maintained in the detemir group and increased with the NPH group (data not shown). The mean daily insulin dose was about 0.1units/kg higher in the detemir group.

- The addition of twice daily detemir or NPH to prestudy OHAs was evaluated. Change in HbA1c and percentage of patients achieving HbA1c $\leq$ 7% was similar in both groups; however, approximately 10% more patients in the detemir group achieved HbA1c $\leq$ 7% in the absence of hypoglycemia. Fasting blood glucose and 10-point blood glucose were comparable. The incidence of hypoglycemia and nocturnal hypoglycemia was lower with detemir. There was less weight gain with insulin detemir (1.6kg difference). Mean daily insulin dose was about 0.25units/kg higher in the detemir group.

Insulin detemir vs. insulin glargine (presented as abstracts)

- In type 1 diabetes, the administration of twice daily detemir was compared to bedtime administration of glargine (26-weeks). Insulin aspart was used for mealtime coverage. Change in HbA1c and 9-point blood glucose profiles were comparable between groups. Mean FPG was approximately 13mg/dL higher with insulin detemir. The incidence of overall hypoglycemia was similar with both groups; however, the annualized rate of major hypoglycemia and nocturnal hypoglycemia was lower with insulin detemir. The daily insulin dose was higher in the detemir group. Baseline adjusted change in weight was similar in both groups.

- In type 2 diabetes, the addition of detemir or glargine to existing oral hypoglycemics was evaluated (52-weeks). Detemir was administered once or twice daily and glargine was administered once daily. Approximately 55% of patients (per-protocol group) required twice daily detemir. Change in HbA1c, percent of patients achieving HbA1c ≤ 7% (including those who had done so in the absence of hypoglycemia), FPG, 10-point blood glucose, and nocturnal hypoglycemia were similar in both groups. There was no significant difference in minor, major or nocturnal hypoglycemia. There was less weight gain in the detemir group; however, this was primarily seen with once daily administration. Insulin analog-specific antibodies were found in the detemir group and not the glargine group. The daily insulin dose was higher in the detemir group (0.52, 0.85, and 0.44 units/kg for detemir QD, detemir BID, and glargine respectively).

INTRODUCTION

Insulin detemir was approved in 2005 (marketed March 2006) and is the second long-acting basal insulin analog on the market to join insulin glargine.

PHARMACOLOGY

Insulin detemir is produced using recombinant DNA technology in baker's yeast (*Saccharomyces cerevisiae*).

Insulin detemir differs from human insulin in that it the amino acid threonine has been removed at position B30 and a fatty acid side chain, covalently bound to lysine at position B29, has been added. This side chain allows for greater self-association and for reversible binding of detemir to albumin, which results in delayed absorption from the injection site and delayed distribution to target tissues.

In the subcutaneous tissue, detemir self-associates and exists as hexamers and as monomers that are bound to albumin. The monomers are slowly released from albumin in the subcutaneous tissue and cross into the plasma compartment where 98-99% of the monomers now bind to plasma albumin, further delaying distribution of detemir to target tissues. Finally, the monomers cross over to the interstitial fluid and bind to insulin receptors.

Insulin detemir differs from NPH and glargine in that it does not exist as or form precipitates once injected. NPH is a preformed crystalline/precipitate and insulin glargine precipitates in the subcutaneous tissue after it is administered. The lack of precipitation formation or precipitation dissolution of detemir may contribute to less within-patient variability in day-to-day blood glucose values.

PHARMACOKINETICS

The plasma concentration of detemir is linear and dose-proportional. Duration of action of detemir is dose-dependent.

Table 1: Pharmacokinetics of insulin detemir

Tmax	6-8 hours
Vd	0.1L/kg
half-life	5-7 hours (dose dependent)
Protein binding	98% to albumin

- Area under the curve for a single dose of detemir was up to 35% higher in healthy elderly subjects ($\geq$ 68years) compared to healthy younger subjects (25-35 years), due to reduced clearance.
- Non-diabetic subjects with severe hepatic dysfunction had lower detemir AUC compared to healthy volunteers.
- No significant differences in pharmacokinetic parameters were noted based on gender.
- There was no difference in pharmacokinetic parameters between subjects with renal impairment compared to healthy volunteers. However, it has been shown with human insulin that clearance is decreased in patients with renal impairment.

PHARMACODYNAMICS

In a double-blind, randomized, parallel study in patients with type 1 diabetes (n=51), the within-subject variability of glucose lowering effects of detemir, NPH, and glargine were compared using euglycemic clamp methods. A single-dose of 0.4 units/kg of detemir, NPH, or glargine was administered on 4 separate days. Insulin detemir had the least within-subject variability for the area under the curve for glucose infusion rate (GIR-AUC_{0-12h}) with a coefficient of variation of 27%, 59%, and 46% for detemir, NPH, and glargine respectively.[1]

In a 24-hour glucose clamp study in patients with type 1 diabetes, doses of detemir 0.2U/kg, 0.4U/kg and NPH at 0.3U/kg were compared. The AUC_{GIR} (mg/kg) was 419, 1184, and 743 and the GIRmax (mg/kg/min) was 1.1, 1.7, and 1.6 respectively.[2]

In a 16-hour glucose clamp study in patients with type 2 diabetes, detemir 0.6U/kg and 1.2U/kg were compared to NPH at the same 2 doses. The AUC_{GIR} (mg/kg) for the 0.6U/kg doses were 1359 and 1900 for detemir and NPH respectively. For the 1.2U/kg dose the values were 2333 and 3220 respectively for detemir and NPH. The GIRmax (mg/kg/min) for the 0.6U/kg doses were 2.3 and 3.2 and for the 1.2U/kg doses were 3.7 and 4.8 for detemir and NPH respectively.[16]

FDA INDICATIONS

- Treatment of type 1 diabetes in adult and pediatric patients
- Treatment of type 2 diabetes in adults requiring basal insulin to manage hyperglycemia

VA FORMULARY ALTERNATIVES

NPH insulin

DOSING

Each milliliter contains 100 units of insulin detemir. Insulin detemir can be administered once- or twice-daily.

- If given once daily, the dose should be administered with the evening meal or at bedtime.
- If given twice-daily, the evening dose can be administered either with the evening meal, at bedtime, or 12 hours after the morning dose.
- For patients with type 1 or type 2 diabetes on basal-bolus treatment, changing the basal insulin to detemir can be done on a unit-to-unit basis. The dose of detemir should then be adjusted to achieve glycemic targets. Some patients with type 2 diabetes may require higher doses of detemir than NPH.
- For patients currently receiving only basal insulin, changing the basal insulin to detemir can be done on a unit-to-unit basis.
- For insulin-naïve patients with type 2 diabetes who are inadequately controlled on oral antidiabetic drugs, detemir should be started at a dose of 0.1 to 0.2 U/kg once-daily in the evening or 10 units once- or twice-daily, and the dose adjusted to achieve glycemic targets.
- Close glucose monitoring is recommended during the transition and in the initial weeks thereafter. Dose and timing of concurrent short-acting insulins or other concomitant antidiabetic treatment may need to be adjusted.
- The requirements of detemir may need to be adjusted in patients with renal or hepatic impairment and in elderly patients.

ADMINISTRATION
- Insulin detemir should be administered by subcutaneous injection in the thigh, abdominal wall, or upper arm. Injection sites should be rotated within the same region.
- Insulin detemir should not be diluted or mixed with any other insulin preparation
- Do not use insulin detemir in insulin infusion pumps
- Use only if solution is clear and colorless

STORAGE
Unopened vials of insulin detemir should be refrigerated (36°F to 46°F). Once used, vials should be stored in the refrigerator; however, it may be kept at room temperature (below 86°F) away from direct heat and light for up to 42 days.

Unopened prefilled syringes (Flex Pen, InnoLet) and cartridges (PenFill) should be refrigerated. Once in use, it must not be stored in the refrigerator; it must be stored at room temperature away from direct heat and light (for up to 42 days) and must not be stored with the needle in place.

Insulin detemir should not be frozen. Do not use detemir if it has been frozen.

EFFICACY

Type 1 diabetes (see appendix 1)
There are 7 randomized, open-label parallel studies comparing insulin detemir to NPH.[3-9] Inclusion criteria were as follows: type 1 DM $\geq$ 1 year, $\geq$ 18 years old, used basal/bolus insulin therapy for $\geq$ 2 months, BMI $\leq$ 35 kg/m^2, HbA1c $\leq$ 12%, total basal insulin dose $\leq$ 100 units/day. Patients were excluded if they had proliferative retinopathy, impaired hepatic/renal function, severe cardiac problems, uncontrolled HTN, recurrent major hypoglycemia, insulin allergy, or if pregnant/breastfeeding.

Detemir or NPH were administered twice daily in all but 1 study (Russell-Jones compared bedtime administration of detemir or NPH). Four trials used insulin aspart[3, 4, 7, 9] and 2 used regular insulin[5, 6] for mealtime coverage and one compared detemir/aspart to NPH/regular.[8]

In general, change in HbA1c was comparable between groups. Two studies did show that reduction in HbA1c was statistically significantly better than NPH (difference of 0.2%); however, this difference is probably not clinically meaningful.[4, 8] Three out of 7 studies showed that FPG was significantly lower with detemir.[4, 5, 9] There was less within subject variation of self-monitored fasting blood glucose (obtained during the last 7 days of the study) with insulin detemir.[3-5, 8, 9] With the exception of 1 study which used a different formulation of detemir[2], the total daily dose of insulin for detemir and NPH was comparable.

In a 26-week study (abstract) comparing insulin detemir twice daily + aspart to glargine once daily at bedtime + aspart, change in HbA1c was similar and FPG was slightly higher in the detemir group (139mg vs. 126mg/dL). The daily basal/bolus insulin dose was 0.47/0.36 units/kg for detemir and 0.35/0.39 units/ kg for glargine.[13] (see appendix 3)

Table 2: Change in HbA1c in patients with type 1 diabetes

	Duration	Treatment arms	Detemir	Comparator	Adjusted difference vs. control [95%CI]
Vague[3]	6-months	Detemir + aspart vs. NPH + aspart	-0.55%	-0.55%	-0.04 [-0.218, 0.128]
Home[4]	16-weeks	Detemir + aspart vs. NPH + aspart	-0.85% (q12h) -0.82% (am/hs)	-0.65%	-0.2 [-0.34, -0.02]*
Russell-Jones[5]#	6-months	Detemir + regular vs. NPH + regular	-0.06%	+0.06%	-0.12% [-0.25, 0.02]
Standl[6]	6-months 12-months	Detemir + regular vs. NPH + regular	7.88%^	7.78%^	-
DeLeeuw[7]	12-months	Detemir + aspart vs. NPH + aspart	-0.64%	-0.56%	-
Hermansen[8]	18-weeks	Detemir + aspart vs. NPH	-0.5%	-0.28%	-0.22%[-0.34, -0.10]*

		+ regular			
Pieber[9]	16-weeks	Detemir + aspart vs. NPH + aspart	-0.43% (am/dinner) -0.49% (am/hs)	-0.39	-
Study 1372[13]¶	26-weeks	Detemir + aspart vs. glargine + aspart	-0.6%	-0.6%	

*significant vs. comparator
^change from baseline not shown
#detemir and NPH were dosed once daily at bedtime
¶detemir was dosed twice daily and glargine once daily

<u>Type 2 diabetes (see appendix 2)</u>
There are 2 published clinical trials evaluating basal/bolus administration of insulin detemir + aspart to NPH + aspart[11] or NPH + regular insulin.[10] Trials presented as abstracts or posters in patients with type 2 diabetes are also shown in appendix 3.[12, 14, 15]

In Raslova et al (n=394), patients were required to have been on insulin $\pm$ oral agents prior to the study.[10] Insulin aspart was used for bolus dosing in the detemir group and regular insulin was used in the NPH group. Oral hypoglycemic agents were discontinued. Baseline HbA1c was approximately 8.1%. Patients with total daily insulin dose > 1.4 units/kg/day, hypoglycemia unawareness, and recurrent major hypoglycemia were excluded. There was no significant difference between treatment arms for change in HbA1c, fasting plasma glucose, or 8-point blood glucose profile using SMBG. The mean basal/bolus dose for detemir + aspart was 0.58/ 0.37 units/kg/day and 0.46/0.33 units/kg/day for NPH/regular. Approximately 1/3 of patients in either group used once daily basal administration.

In a non-inferiority trial, Haak et al (n=505) randomized patients 2:1 to detemir or NPH.[11] Insulin aspart was used as the bolus insulin for both groups. Baseline HbA1c was approximately 7.9%. Patients who had been receiving oral hypoglycemic agents within 2 months of the study were excluded as were those who had recurrent major hypoglycemia, proliferative retinopathy, impaired renal/hepatic/cardiac function, or basal insulin dose > 100 units/day. There was no significant difference between treatment arms for change in HbA1c, fasting plasma glucose, or 9-point blood glucose profile using SMBG. The mean basal/bolus dose for detemir/aspart was 36.4/ 40.2 units/day and 35.3/ 35.8 units/day for NPH/aspart. Approximately 40% of patients in either group used once daily basal administration.

In both trials, there was less within-person day-to-day variation in FPG with detemir than NPH. HbA1c was not significantly affected by once daily or twice daily basal insulin dosing in either group.

Table 3: Change in HbA1c in patients with type 2 diabetes

	Duration	Treatment arms	Detemir	Comparator	Adjusted difference vs. control [95%CI]
Raslova[10]	22-weeks	Detemir + aspart vs. NPH + regular	-0.65%	-0.58%	-0.062% [-0.249, 0.125]
Haak[11]	26-weeks	Detemir + aspart vs. NPH + aspart	-0.2%	-0.4%	0.16% [0.003, 0.312]
Study 1337[15]	6-months	Detemir + metformin vs. NPH + metformin	-0.9%	-1.5%	0.56% [0.326, 0.784]*
Study 1530[12]	24-weeks	Detemir + OHA vs. NPH + OHA	-1.8%	-1.9%	
Study 1373[14]¶	52-weeks	Detemir + OHA vs. glargine + OHA	-1.45%	-1.45%	

¶detemir was dosed once or twice daily and glargine once daily
*Significant vs. detemir

There are 3 trials (abstracts/poster) that evaluated the addition of detemir to oral agents. One trial compared the addition of once daily detemir or NPH to metformin.[15] HbA1c and 9-point blood glucose profile favored NPH + metformin; both FPG and within-person FPG variability was similar for both groups.

In study 1530, Hermansen compared the addition of morning and evening detemir or NPH to existing oral agents. Change in HbA1c was similar between groups; however, 25.7% of the detemir patients achieved an HbA1c $\leq$ 7% in the absence of hypoglycemia compared to 15.5% with NPH.[12] Fasting plasma glucose and

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10-point glucose profiles were comparable, although there was slightly less within-person FPG variability with detemir.

Lastly, a study comparing once or twice daily detemir + oral agents to glargine once in the evening + oral agents, found no difference between groups for change in HbA1c, the percentage of patients achieving HbA1c less than 7% (including in the absence of hypoglycemia), FPG, and 10-point glucose profile.[14] There was no difference in within-patient FPG variation when the entire detemir group was compared to glargine. However, in the subgroup of once daily detemir patients, slightly less variability was noted pre-breakfast and pre-dinner. In the detemir group, the dose was divided into twice daily administration if FPG was < 126mg/dL AND pre-dinner glucose was > 126mg/dl and/or hypoglycemia limited once daily titration. The glargine group did not undergo this titration scheme and remained on once daily dosing throughout the study. A little more than half the patients in the detemir group required twice daily basal insulin dosing. (See appendix 3)

In all 3 studies, the daily insulin dose was higher with detemir versus the comparator.[12, 14 15]

Observational Studies
The PREDICTIVE trial is an observational, open-label prospective study conducted in patients with type 2 diabetes. Three separate groups were studied:
- OHA → detemir ± OHAs
- NPH ± OHAs → detemir ± OHAs
- Glargine ± OHAs → detemir ± OHAs

Table 4: PREDICTIVE study results (3-months)

	OHA → detemir ± OHAs	NPH ± OHAs → detemir ± OHAs	Glargine ± OHAs → detemir ± OHAs
Daily insulin dose	19.1 units	25.7 → 27.8 units	23.8 → 27.3 units
HbA1c	-1.29%	-0.58%	-0.59%
Weight	-0.9kg	-0.87kg	-0.78kg
All hypoglycemia	no significant increase in	-663 events/100pt-yrs	7.8 events/pt yr → 0.5 events/ pt yr
Major hypoglycemia	minor hypoglycemia; no	-39 events/100 pt-yrs	0.3 events/pt yr → 0 events/pt yr
Nocturnal hypoglycemia	major hypoglycemia	-429 events/100pt-yrs	2.2 events/pt yr → 0.1 events/ pt yr

Data from Novo Nordisk
Glargine to detemir data from Dornhorst A, Merilainen M. Abstract number 614-P ADA meeting 2006

SAFETY
Safety information, with exception of hypoglycemia and weight change, was not well described in the clinical trials or in the product package insert. Mild injection site reactions occurred more frequently in patients receiving detemir than NPH; however, actual numbers were not shown in the package insert.

Hypoglycemia
In general, hypoglycemia was defined as:
- Major if the assistance of another was needed
- Minor if blood glucose was < 50mg/dl (< 60mg/dl in Hermansen and Raslova) and patient was able to deal with the episode unaided
- Symptoms only – symptoms only, patient managed episode unaided, not confirmed by blood glucose reading

Generally, in type 1 diabetes there was no significant difference in the risk of all hypoglycemia between detemir and NPH. Two studies did show a significant difference; however, one study used a different formulation of insulin detemir[3] and the other compared detemir + aspart to NPH + regular.[8] There was no significant difference in major hypoglycemia between detemir and NPH. The majority of studies did show that the relative risk for all nocturnal hypoglycemia was significantly lower with detemir; however the difference in major nocturnal hypoglycemia was not significant except for the study that compared detemir + aspart to NPH + regular. In the abstract comparing detemir to glargine, there was no difference between groups for all hypoglycemia; however, the annualized rate of nocturnal hypoglycemia and major hypoglycemia was significantly lower in the detemir group.[13]

Table 5: Hypoglycemic events in type 1 diabetes

	All hypoglycemia	All major hypoglycemia	All nocturnal	Major nocturnal
Vague[3]				not shown
• detemir + aspart	5.18 events/pt-month	0.04 events/pt-month	0.64 events/pt-month	
• NPH + aspart	6.70 events/pt-month	0.06 events/pt-month	0.96 events/pt-month	
	RR=0.78[0.62, 0.97]*	RR= 0.65[0.28, 1.50]	RR=0.66 [0.5, 0.87]*	
Home[4]	**all minor**		**nocturnal minor**	
• detemir + aspart (q12h)	114 (84%) / 842	6 (4%) / 9	59 (44%) / 125	3 (2%) / 4
• detemir + aspart (am/hs)	114 (83%) / 780	11 (8%) / 24	47 (34%) / 82	5 (4%) / 9
• NPH + aspart	107 (84%) / 1074	10 (8%) / 12	64 (50%) / 166	4 (3%) / 4
	RR=0.75 [0.56, 1.0]*		RR=0.74 [0.50, 1.08]	
	0.68 [0.56, 0.84]*		0.47 [0.36, 0.62]*	
Russell-Jones[5]				
• detemir + regular	448 (93.3%) / 9922	31 (6.5%) / 68	339 (70.6%) / 1552	14 (2.9%) / 24
• NPH + regular	229 (92.7%) 5367	22 (8.9%) / 32	180 (72.9%) / 1062	10 (4%) / 13
	RR=0.94[0.79, 1.13]	RR=0.97 [0.45, 2.10]	RR=0.74[0.60, 0.90]*	RR=0.8 [0.28, 2.31]
Standl[6]				
• detemir + regular	2.45 events/pt-month	0.02 events/pt-month	0.45 events/pt-month	0.005 events/pt-month
• NPH + regular	3.48 events/pt-month	0.01 events/pt-month	0.63 events/pt-month	0.003 events/pt-month
	RR=0.71[0.44, 1.12]	RR=1.56[0.67, 3.64]	RR=0.71[0.49, 1.02]	RR=1.63[0.37, 7.07]
DeLeeuw[7]				
• detemir + aspart	RR=0.78[0.56, 1.08]	14%	180 (83%) / 1378*	5.1% / 20
• NPH + aspart		21%	87 (88%)/ 926	9.1% / 14
				RR=0.65[0.21, 1.99]
Hermansen[8]				
• determir + aspart	219 (75%) / 2497	19 (6.5%) / 40	113 (38.7%) / 271	3 (1%) / 4
• NPH + regular	238 (82.9) / 3192	18 (6.3%) / 45	173 (60.3%) / 608	12 (4.2%) / 24
	RR=0.79[0.63, 0.98]*	RR=0.89[0.35, 2.22]	RR=0.45[0.35, 0.58]*	RR=0.17[0.04, 0.63]*
Pieber[9]				
• detemir + aspart (am/dinner)	100 (72%)/ 876	5 (3.5%)/12	60 (43%)/184	3 (2.2%)/4
• detemir + aspart (am/hs)	92 (70%)/1005	5 (3.8%)/6	51(37%)/142	1(0.8%)/2
• NPH + aspart	100 (77%)/842	4 (3.1%)/5	60 (46%)/167	2 (1.6%)/2
Study 1372[13]				
• detemir BID + aspart	similar	0.1 events/pt-year*	4.3 events/pt-year*	
• glargine QD + aspart		0.3 events/pt-year	6.6 events/pt-year	

Data shown as # patients (% patients)/ # events
*Significant vs. comparator

In the 2 published studies in type 2 diabetes (insulin only studies), there was no significant difference between detemir and NPH for any of the measured hypoglycemia parameters, although numerically, the numbers favor detemir.[10, 11] However, in 2 of the unpublished studies where detemir or NPH is combined with oral agents, the incidence of hypoglycemia was lower with detemir.[12, 15] In the abstract comparing the addition of detemir or glargine to oral agents, there was no significant difference in the incidence of hypoglycemia between the 2 agents.[14]

Table 6: Hypoglycemic events in type 2 diabetes

	All hypoglycemia	All major hypoglycemia	All nocturnal	Major nocturnal
Raslova[10]				
detemir + aspart	65 (34.6%) / 269	2 (1.1%) / 2	28 (14.9%) / 49	0
NPH + regular	70 (36.1%) / 317	1 (0.5%) / 1	34 (17.5%) / 82	1 (0.5%) / 1
	RR=0.89 [0.54, 1.45]		RR=0.62 [0.32, 1.17]	
Haak[11]				
detemir + aspart	152 (46.2%) / 1218	<2%	52 (15.8%) / 166	
NPH + aspart	80 (49.7%) / 708	<2%	38 (23.6%) / 80	
	RR=0.84[0.52, 1.36]		RR=1.02 [0.55, 1.89]	
Study 1337[15]				
detemir + metformin	Relative risk of hypoglycemia (esp. nocturnal) ~ half of that in the NPH group (data not shown)			
NPH + metformin				
Study 1530[12]				
• detemir + OHA	8.6 events/pt-year*	1 episode	1.5 episodes/pt-year*	
• NPH + OHA	15.9 events/pt-year	8 episodes	3.3 episodes/pt-year	
Study 1373[14]	**all minor**			

• detemir QD/BID + OHA	46.4%	5 (1.7%)	95 (32.6%)
• glargine QD+ OHA	51.9%	8 (2.7%)	93 (32%)

Data shown as # patients (% patients)/ # events
*Significant vs. comparator

Weight
There was weight loss or less weight gain with insulin detemir compared to regimens that included NPH insulin.[3-9] In general, the mean difference between insulin detemir and NPH in type 1 diabetes ranged from 0.52 -1.66kg. The difference persisted in those studies that were of 12-months duration. In type 2 diabetes (insulin only studies), the difference ranged from 0.62-0.79kg.[10, 11]

The change in weight was similar for the type 1 diabetes study comparing twice daily detemir to once daily glargine.[13] In the type 2 diabetes study, there was less weight gain with detemir when given once daily compared to glargine once daily. When detemir was given twice daily, the change in weight was similar to glargine.

When detemir or NPH was added to metformin, weight was maintained in the detemir group and slightly increased in the NPH group.[15] When the addition of morning and evening detemir or NPH to oral agents was compared, there was less weight gain in the group receiving detemir.[12]

Table 7: Change in weight

		Duration	Treatment arms	Detemir	Comparator	Adjusted difference vs. control 95%CI]
Vague[3]	Type 1	6-months	Detemir + aspart vs. NPH + aspart	-0.2kg	+0.7kg	-0.98kg*
Home[4]	Type 1	16-weeks	Detemir + aspart vs. NPH + aspart	+0.02 ± 0.22 (q12h) +0.24 ± 0.22 (am/hs)	+0.86 ± 0.23kg	-0.8[-1.44, -0.24]* -0.6 [-1.23, -0.03]*
Russell-Jones#[5]	Type 1	6-months	Detemir + regular vs. NPH + regular	-0.23 ± 2.83kg	+0.32 ± 2.93kg	-0.52*
Standl[6]	Type 1	6-months 12-months	Detemir + regular vs. NPH + regular	-0.4kg -0.3kg	+0.9kg +1.4kg	-1.22* -1.66*
DeLeeuw[7]	Type 1	12-months	Detemir + aspart vs. NPH + aspart	-0.1kg	+1.2kg	-1.34kg [-2.12, -0.56]*
Hermansen[8]	Type 1	18-weeks	Detemir + aspart vs. NPH + regular	-0.95 ± 0.14	+0.07 ± 0.14	-1.0kg [-1.37, -0.66]*
Pieber[9]	Type 1	16-weeks	Detemir + aspart vs. NPH + aspart	-0.6kg (am/dinner)* +0.1kg (am/hs)*	+0.7kg	-
Study 1372^[13]	Type 1	26-weeks	Detemir + aspart vs. glargine + aspart	+0.52kg	+0.96kg	-
Raslova[10]	Type 2	22-weeks	Detemir + aspart vs. NPH + regular	+0.51 ± 0.22kg*	+1.13 ± 0.21kg	-
Haak[11]	Type 2	26-weeks	Detemir + aspart vs. NPH + aspart	+1kg	+1.8kg	-0.79kg [-1.44, -0.14]*
Study 1337[15]	Type 2	6-months	Detemir + metformin vs. NPH + metformin	maintained with detemir and slightly increased with NPH (data not shown)		
Study 1530[12]	Type 2	24-weeks	Detemir + OAD vs. NPH + OAD	+1.2kg*	+2.8kg	-
Study 1373¶[14]	Type 2	52-weeks	Detemir + OAD vs. glargine + OAD	+3.02kg (QD/BID) +2.25kg (QD) +3.71 (BID)	+3.93kg	-0.91kg [-1.62, -0.20]*

*Significant vs. comparator
#detemir and NPH were dosed once daily at bedtime
^In study 1372, detemir was dosed twice daily and glargine once daily.
¶detemir was dosed once or twice daily and glargine once daily

Insulin antibodies
The data on detemir, insulin, and cross-reacting antibodies were obtained from the FDA transcripts. In one study of patients with type 1 diabetes, detemir specific antibodies increased from a baseline of 2.71 to 7.81 after 12 months of treatment with detemir; cross-reacting antibodies increased from 14.1 to 20.2, while insulin antibodies were unchanged from baseline. In patients receiving NPH, there was no significant increase in any of these antibodies.

This was also shown in another study of type 1 diabetes where detemir specific antibodies rose from 1.55 to 4.88 and cross-reacting antibodies rose from 12.9 to 16.6 after 6 months of treatment with detemir. No significant changes were noted in patients receiving NPH.

In the abstract of the study comparing detemir to glargine in type 2 diabetes, insulin analog specific antibodies were detected in the detemir group and not in the glargine group.[14]

Change in antibodies does not appear to correlate with change in HbA1c or FPG; however, there was a correlation between change in antibodies and change in detemir dose.

LOOK-ALIKE/SOUND-ALIKE DRUGS

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

Insulin detemir: care should be taken not to confuse detemir with other insulin products
Levemir: Insulin lispro, sevelemer.

COST
Table 8: Acquisition Cost

	10mL vial	Cartridge 5 x 3mL	Disposable pre-filled pens 5 x 3mL	Innolet (prefilled/ disposable device) 5 x 3mL
Detemir	$24.12		$41.81	
Glargine	$27.96	$83.66		
NPH	$6.85		$45.71	$16.75

Examples of cost of insulin per day based on mean doses used in type 2 diabetes studies combining insulin and OHAs. These cost estimates are based on an 85kg weight, which is an average weight seen in patients with type 2 diabetes and use of the 10ml vial.

Table 9: Examples of insulin cost per day

	Cost per day	Cost per day
Study 1337	47.6 units = $1.15 (detemir)	38.2 units = $0.26 (NPH)
Study 1530	65 units = $1.56 (detemir)	44 units = $0.30 (NPH)
Study 1373	44.2 units = $1.07 (detemir QD) 85 units = $2.05 (detemir BID)	37.4 units = $1.06 (glargine)

Mean insulin dose obtained from combination insulin + OHA trials
Based on 85kg weight and use of 10 ml vial
Does not take into account cost of syringes, needles, etc. or cost savings due to differences in hypoglycemia/weight, etc.

SUMMARY

For type 2 diabetes, the percentage of patients requiring twice daily detemir or NPH was the similar (~63%) in the insulin only studies. In the 2 studies that combined detemir or NPH with OHAs, basal insulin was given once daily in the evening in 1 study and twice daily in the other study. In the once daily study, the HbA1c results favored NPH, whereas in the twice daily study, the results for detemir and NPH were similar. In the study combining detemir or glargine with OHAs, over half the detemir patients received twice daily dosing and all glargine patients received once daily glargine.

In the type 1 diabetes studies, all but once study administered detemir or NPH twice daily. In the detemir vs. glargine study, all detemir patients were dosed twice daily and all glargine patients once daily. Change in HbA1c was similar in both groups.

Table 10: Summary of pertinent results

	HbA1c	All hypoglycemia and major hypoglycemia	Nocturnal hypoglycemia	Weight
Type 2 diabetes	No difference between detemir and NPH except for study with metformin + NPH/detemir where NPH was significantly better No difference vs. glargine	No significant difference vs. NPH in the insulin only studies No difference vs. glargine Less hypoglycemia with detemir vs. NPH in combination with OHAs	No significant difference vs. NPH in the insulin only studies No difference vs. glargine Less nocturnal hypoglycemia with detemir vs. NPH in combination with OHAs	Less weight gain vs. NPH Less weight gain with once daily detemir vs. glargine (similar results for detemir BID and glargine)
Type 1 diabetes	No difference vs NPH (except for 2 studies showing tx diff of 0.2%) No difference vs. glargine	Majority of studies showed no significant difference vs. NPH No difference vs. glargine for all hypoglycemia; less major hypoglycemia with detemir	Significantly less nocturnal hypoglycemia vs. NPH Less nocturnal hypoglycemia vs. glargine	Weight loss or less weight gain vs. NPH No difference in weight gain vs. glargine

- Studies suggest that twice daily dosing of detemir will be needed for the majority of patients
- Detemir may be an alternative for patients with type 1 diabetes who have major or nocturnal hypoglycemia with insulin glargine.
- Detemir when combined with OHAs may be an alternative for patients who have hypoglycemia or nocturnal hypoglycemia using NPH.
- Detemir consistently showed less weight gain compared to NPH
- In type 2 diabetes, patients using once daily detemir gained less weight than those using glargine; however, this advantage appears to be lost when detemir is dosed twice daily.
- In type 2 diabetes, a higher dose of detemir was required versus the comparator

References:

1. Heise T, Nosek L, Ronn BB, et al. Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1 diabetes. Diabetes. 2004 Jun; 53(6):1614-20.

2. Plank J, Bodenlenz M, Sinner F, et al. A double-blind, randomized, dose-response study investigating the pharmacodynamic and pharmacokinetic properties of the long-acting insulin analog detemir. Diabetes Care. 2005 May; 28(5):1107-12.

3. Vague P, Selam JL, Skeie S, et al. Insulin detemir is associated with more predictable glycemic control and reduced risk of hypoglycemia than NPH insulin in patients with type 1 diabetes on a basal-bolus regimen with premeal insulin aspart. Diabetes Care 2003 Mar; 26(3):590-6.

4. Home P, Bartley P, Russell-Jones D, et al. Study to Evaluate the Administration of Detemir Insulin Efficacy, Safety and Suitability (STEADINESS) Study Group. Insulin detemir offers improved glycemic control compared with NPH insulin in people with type 1 diabetes: a randomized clinical trial. Diabetes Care 2004 May; 27(5):1081-7.

5. Russell-Jones D, Simpson R, Hylleberg B, et al. Effects of QD insulin detemir or neutral protamine Hagedorn on blood glucose control in patients with type I diabetes mellitus using a basal-bolus regimen. Clin Ther 2004 May; 26(5):724-36.

6. Standl E, Lang H, Roberts A. The 12-month efficacy and safety of insulin detemir and NPH insulin in basal-bolus therapy for the treatment of type 1 diabetes. Diabetes Technol Ther 2004 Oct; 6(5):579-88.

7. De Leeuw I, Vague P, Selam JL, et al. Insulin detemir used in basal-bolus therapy in people with type 1 diabetes is associated with a lower risk of nocturnal hypoglycemia and less weight gain over 12 months in comparison to NPH insulin. Diabetes Obes Metab. 2005 Jan; 7(1):73-82.

8. Hermansen K, Fontaine P, Kukolja KK, et al. Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes. Diabetologia 2004 Apr; 47(4):622-9.

9. Pieber TR, Draeger E, Kristensen A, et al. Comparison of three multiple injection regimens for Type 1 diabetes: morning plus dinner or bedtime administration of insulin detemir vs. morning plus bedtime NPH insulin. Diabet Med 2005 Jul; 22(7):850-7.

10. Raslova K, Bogoev M, Raz I, et al. Insulin detemir and insulin aspart: a promising basal-bolus regimen for type 2 diabetes.

Diabetes Res Clin Pract 2004 Nov; 66(2):193-201.

11. Haak T, Tiengo A, Draeger E, et al. Lower within-subject variability of fasting blood glucose and reduced weight gain with insulin detemir compared to NPH insulin in patients with type 2 diabetes. Diabetes Obes Metab 2005 Jan; 7(1):56-64.

12. Hermensen K, Derezinski T, Kim H, et al. Treatment with insulin detemir in combination with oral agents is associated with less risk of hypoglycemia and less weight gain than NPH insulin at comparable levels of glycemic improvement in people with type 2 diabetes. Diabetologia 2004; 47 (supplement 1): PS 64, poster number 754.

13. Study NN304-1372. Data from Levemir AMCP Dossier. Novo Nordisk, Inc. 2005.

14. Study NN304-1373. Data from Levemir AMCP Dossier. Novo Nordisk, Inc. 2005.

15. Study NN304-1337. Data from Levemir AMCP Dossier. Novo Nordisk, Inc. 2005.

16. Product package insert for Levemir ® October 19, 2005.

Prepared by: Deb Khachikian, PharmD
Date: May 2006

Appendix 1: Clinical trials in type 1 diabetes (see p.19 for list of abbreviations)

Trial	Inclusion/exclusion	Treatment regimen	Baseline information	Results
Vague 2003 R, OL, PR, MC Europe n=448 (n=301 detemir; n= 146 NPH) 6-month ITT Subgroup of patients (n=88 detemir; n=41 NPH) also provided an 8-h plasma glucose profile between 11p-7a on the last day of tx	Type 1 DM $\geq$1 year Basal/bolus insulin tx $\geq$2mos. HbA1c $\leq$12% BMI < 35kg/m^2 total basal insulin dose $\leq$ 100 IU/ day Exclusions: proliferative retinopathy, impaired hepatic/renal function, severe cardiac problems, uncontrolled HTN, recurrent major hypoglycemia, insulin allergy, pregnancy/breastfeeding	2:1 randomization (detemir:NPH) **Detemir + aspart vs. NPH + aspart** detemir or NPH administered before breakfast and at bedtime and insulin aspart before each main meal During 1st 2 weeks, the dose of basal insulin was optimized based on results of SMBG. During the next 2 weeks, the dose ratio of aspart and basal was adjusted. Starting doses of insulin was not described Target glucose levels: • Fasting, preprandial, and nocturnal (2-4am) 72-126mg/dl • postprandial < 180mg/dl	**Values for detemir / NPH** **age (years):** 38.9 ± 13.3 / 41.8 ± 14.2 **% males:** 53.8% / 50.7% **DM duration (years):** 17.1 ± 9.9 / 17.4 ± 11 **HbA1c (%):** 8.18 ± 1.14 / 8.11 ± 1.12 **FPG (mg/dl):** 208.8 ± 93.8 / 208.8 ± 94.9 **weight (kg):** 71.5 ± 11.9 / 71.2 ± 11.5 **BMI (kg/m^2):** 24.5 ± 3.2 / 24.6 ± 3.4 **total basal insulin dose (units/day):** 27.4 ± 12.5 / 25.2 ± 13.7 **total bolus insulin dose (units/day):** 30.9 ± 15.5 / 29.6 ± 15.8 mean ± SD	(see results table below)

Vague 2003 Results

	Detemir + aspart	NPH + aspart
completed trial	94.4%	96.6%
HbA1c (%)	-0.55	-0.55
HbA1c (%)	7.6 ± 0.09	7.64 ± 0.1
HbA1c detemir-NPH (95%CI)	-0.04 (-0.218, 0.128)	
FPG (mg/dl)	165.42 ± 7.92	178.92 ± 9.36
FPG detemir-NPH (95%CI)	-10.8 mg/dl (-29.7, 2.52)	
FPG within-person variability (SD)	60.66mg/dl*	68.04mg/dl
daily insulin dose (basal/ bolus)	59.2 U / 30.7 U	31.7 U / 26 U
Weight (kg)	-0.2kg*	+0.7kg
8-h BG curve	AUC similar between both groups; however, from 11p-0400 the NPH group had lower BG values whereas from 4-7am, the detemir group had lower BG values	

Hypoglycemia (# events/ # pts./ events per pt-month)		
all events	7522/ 271/ 5.18*	4820/138/ 6.70
major events	56/ 24/ 0.04	41/ 21/ 0.06
minor events	3184/ 259/ 2.19*	2180/ 129/ 3.03
symptoms only	4271/ 236/ 2.94	2595/ 121/ 3.61
all nocturnal	923/ 198/ 0.64*	689/ 110/ 0.96

mean ± SE
*Significant vs. NPH

Trial	Inclusion/exclusion	Treatment regimen	Baseline information	Results
Home 2004 R, OL, PR, MC Australasia, Europe n=408 (n=127 detemir 12h; n= 139 detemir am-hs; n=132 NPH) 16-weeks ITT Subgroup of patients (n=206) underwent CGMS x 72 hours after 12 weeks tx	Type 1 DM $\geq$1 year $\geq$ 18 years old Basal/bolus insulin tx $\geq$2mos. HbA1c $\leq$12% BMI < 35.5kg/m^2 total basal insulin dose < 100 IU/ day Exclusions: proliferative retinopathy, impaired hepatic/renal function, uncontrolled cardiovascular problems, recurrent major hypoglycemia, using meds known to interfere with glucose metabolism, pregnancy/ breastfeeding	**Detemir before breakfast and bedtime vs. Detemir every 12 hours vs. NPH before breakfast and bedtime** All patients used mealtime insulin aspart Starting dose for all basal insulin was 70% of the basal insulin dose at trial entry. Basal dose titrated based on SMBG results If pre- breakfast or dinner glucose: 126mg/dl = no change 126-180mg/dl = +10% change 180-270mg/dl= +20% change	**Values for detemir (12h)/ detemir (am-hs) / NPH** **age (years):** 40.9 ± 13 / 41.3 ± 11.4 / 38.3 ± 12.4 **% males:** 51.8% / 56.8% / 53% **DM duration (years):** 17.1 ± 10.6 / 17.6 ± 10.7 / 15.1 ± 10.6 **HbA1c (%):** 8.55 ± 1.2 / 8.74 ± 1.2 / 8.52 ± 1.19 **FPG (mg/dl):** 208.7 ± 83.7/ 209.7 ± 83 / 219.6 ± 98.8 **weight (kg):** 74.2 ± 12.6 / 75 ± 12.3 / 75.5 ± 14 **BMI (kg/m^2):** 25.1 ± 3.3 / 25.2 ± 3.6 /25.2 ± 3.7 **total basal insulin dose (units/day):** 26.4 ± 10.8 / 28.1 ± 12.5 / 29.5 ±	(see results table below)

Home 2004 Results

	Detemir 12h + aspart	Detemir am-hs + aspart	NPH + aspart
completed trial	96%	97%	93%
HbA1c (%)	-0.85 ± 0.07*	-0.82 ± 0.07*	-0.65± 0.07
HbA1c (%)	7.75 ± 0.07	7.78 ± 0.07	7.94 ± 0.07
clinic FPG (mg/dl)	175.5 ± 6.7*	160.92 ± 6.7*	202.32 ± 6.8
SMBG FPG	149± 3.6*	149 ±3.6*	163 ± 3.8
FPG within-person variability (SD)	53.1mg/dl*	52.38mg/dl*	62.82mg/dl
10-pt SMBG	Shape of profile similar. Glucose from dinner-breakfast was slightly lower for detemir q12h		
CGMS			

			≥270mg/dl = +25% change Details not provided on dosing of insulin aspart Target glucose levels: • Fasting, and night 72-126mg/dl • postprandial ≤ 180mg/dl	13.7 **total bolus insulin dose (units/day):** 30.9 ± 12.9/ 29.4 ± 13.4 / 30.5 ± 13.4 **% using once daily basal**: 47% **% using > once daily basal:** 46% **% using premix insulin:** 7% mean ± SD	(mmol/l•h) ¶

• >24h	54.9 ± 2.95	63.7 ± 2.92	8.7 ± 2.92
• overnight	15.9 ± 0.98	17.7 ± 1.01	16.2 ± 1.0
daily insulin dose (basal/ bolus)	36.7 ± 16.4/ 27.9 ± 15	36.3 ± 16.5/ 29.4 ± 12.2	34.8 ± 13.5/ 29.4 ± 12.5
Weight (kg)	+0.02 ± 0.22 *	+0.24 ± 0.22*	+0.86 ± 0.23
Hypoglycemia n (%) / E			
All minor	114 (84%) / 842 *	114 (83%) / 780*	107 (84%) / 1074
nocturnal minor	59 (44%) / 125	47 (34%) / 82*	64 (50%) / 166
All major	6 (4%) / 9	11 (8%) / 24	10 (8%) / 12
major nocturnal	3 (2%) / 4	5 (4%) / 9	4 (3%) / 4

mean ± SE
mean ± SD for insulin doses
*Significant vs. NPH
¶deviation from the individual mean

Russell-Jones 2004 R, OL, PR, MC Europe, Australia n=747 (n=491 detemir; n= 256 NPH) 6-months (1 month stabilization, 5-month maintenance) ITT Subgroup of patients (n=138) underwent CGMS x 72 hours during the last month of treatment	Type 1 DM ≥1 year ≥ 18 years old using QD basal or pre-mixed insulin in the evening and bolus insulin before meals for ≥ 2 months Exclusions: HbA1c > 12% basal insulin dose > 100u/day proliferative retinopathy, impaired hepatic/renal function, recurrent major hypoglycemia, uncontrolled HTN, severe cardiac problems, using meds known to interfere with glucose metabolism, pregnancy/ breastfeeding	**2:1 randomization** **detemir at bedtime + regular vs. NPH at bedtime + regular** starting detemir dose- 50% of basal dose pretrial dose NPH dose – pretrial basal insulin dose basal dose titrated based on SMBG to achieve pre- breakfast and dinner glucose 72-126mg/dl and 90-min postprandial glucose of ≤ 180mg/dl starting dose or adjustment of bolus insulin not described	**Values for detemir / NPH** **age (years):** 40.9 ± 12.4 / 39.8 ± 12.3 **% males:** 65.6% / 61.3% **DM duration (years):** 17.1 ± 11.3 / 16.4 ± 9.5 **HbA1c (%):** 8.35 ± 1.2 / 8.35 ± 1.2 **FPG (mg/dl):** 223.8 ± 95.6 / 207.9 ± 83.2 **weight (kg):** 76.5 ± 12.3 / 76.1 ± 12.5 **BMI (kg/m²):** 25.1 ± 3.4 / 25.4 ± 3.4 **total basal insulin dose (units/kg/day):** 0.31 ± 0.12 for both groups **total bolus insulin dose (units/kg/day):** 0.44 ± .15 / 0.44 ± 0.14 mean ± SD	

	Detemir + regular	NPH + regular
completed trial	94.7%	91.8%
d/c due to AE (n)	5	2
HbA1c (%)	-0.06 ± 0.92	0.06 ± 1.05
HbA1c (detemir – NPH) [95%CI]	-0.12% [-0.25, 0.02]	
FPG (mg/dl)	-28.98 ± 107.6*	-2.7 ±112.3
Fasting SMBG	-22.5 ± 77.4*	-11.34 ± 80
9-pt SMBG	only FPG was significantly lower with detemir	
FPG within-person variability [SD (CV%)]	50.76mg/dl* (37.4%)	64.8mg/dl (43%)
CGMS (mmol/l•h) ¶		
• >24h	55.11 ± 2.2*	62.99 ± 2.55
• overnight	14.71 ± 0.74*	17.09 ± 0.85
Weight (kg)	-0.23*	+0.31
basal insulin dose (units/kg/day)	0.27 ± 0.12	0.33 ± 0.14
bolus insulin dose (units/kg/day)	0.47 ± 0.16	0.44 ± 0.15
Hypoglycemia n (%) / E		
all	448 (93.3%) / 9922	229 (92.7%) 5367
all major	31 (6.5%) / 68	22 (8.9%) / 32
nocturnal (all)	339 (70.6%) /	180 (72.9%) / 1062

	1552*	
nocturnal (major)	14 (2.9%) / 24	10 (4%) / 13
symptoms only (all)	368 (76.7%)/ 4202	182 (73.7%)/2254
symptoms only (nocturnal)	212 (44.2%)/664	114 (46.2%)/ 432

mean ± SD
mean ± SE for CGMS
*Significant vs. NPH
¶deviation from the individual mean

Standl 2004 R, OL, PR, MC Europe, Australia, New Zealand 6-months randomized (1st month titration phase) N=461(n=237 detemir; n=224 NPH) 6-months extension n= 289 (n=154 detemir; n=135 NPH) Data presented for the 289 patients continuing the extension trial ITT	Type 1 DM ≥1 year 18-74 years old Treated with twice daily basal insulin and meal-related bolus insulin for ≥2 months BMI ≤ 35 kg/m² HbA1c ≤12% Total basal insulin dose ≤ 100 units/day Exclusions: proliferative retinopathy, impaired hepatic/renal function, recurrent major hypoglycemia, uncontrolled HTN, severe cardiac problems, insulin allergy, pregnancy/ breastfeeding	**Detemir morning and bedtime + regular vs. NPH morning and bedtime + regular** starting detemir dose- 50% of basal dose pretrial dose Starting dose of NPH not discussed Starting dose of regular insulin not discussed During 1st 2 weeks, the dose of basal insulin was optimized based on results of SMBG. Thereafter, basal or bolus may be adjusted Target glucose levels: • Fasting and nocturnal (2-4am) 72-126mg/dl • 90-min postprandial ≤ 180mg/dl	**Values for detemir / NPH** **age (years):** 40.7 ± 13.4 / 42.5 ± 12.3 **% males:** 62% / 66% **DM duration (years):** 16.1 ±9.1 / 16.0 ± 10.6 **HbA1c (%):** 7.72 ± 1.26 / 7.66 ± 1.2 **FPG (mg/dl):** 196.2 ± 85.5 / 195.8 ± 91.1 **weight (kg):** 76.9 ± 11.8 / 75.9 ± 13.1 **BMI (kg/m²):** 25.2 ± 3.0 / 25.6 ± 3.3 **total basal insulin dose (units/day):** 26.8 ± 11.7; 27.1 ± 12 **total bolus insulin dose (units//day):** 28.7 ± 13.8 / 26 ± 9.5 mean ± SD	(see table below)

	Detemir + HSI	NPH + HSI
completed trial		
• 6-months	212/237 (89.5%)	209/224 (93.3%)
• 12-months	134/154 (87%)	118/135 (87.4%)
HbA1c (%)^	7.88 ± 0.082	7.78 ± 0.088
FPG (mg/dl)^	181.8 ± 8.1	177.12± 8.64
9-pt. SMBG^	only 90-min post lunch and 90-min post dinner values were significantly lower with detemir	
Weight (kg)		
• 6-months	-0.4kg*	+0.9kg
• 12-months	-0.3*	+1.4
basal/bolus dose (units/day)^	23.3/ 33.4	29.8/ 29.2
Hypoglycemia (# events/ # pts./ events per pt-month)		
All events	4096/ 135/ 2.45	5129/ 113/ 3.48
All major events	35/ 18/ 0.02	20/ 14/ 0.01
All nocturnal	757/ 102/ 0.45	934/ 94/ 0.63
Major nocturnal	9/ 5/ 0.005	5/ 5/ 0.003
symptoms only (all)	1981/ 106/ 1.18	2470/ 94/ 1.68
symptoms only (nocturnal)	329/68/0.2	390/67/0.26

Mean ± SE
*Significant vs. NPH
^values are for 12-months; 6-month values not shown

De Leeuw 2005 R, OL, PR, MC Europe 6-month extension of study by Vague N=315 (n=216 detemir, n= 99 NPH) ITT Non-inferiority design	Type 1 DM ≥1 year ≥ 18 years old Used basal/bolus insulin therapy for ≥2 months BMI ≤ 35 kg/m² HbA1c ≤12% Total basal insulin dose ≤ 100 units/day Exclusions: proliferative retinopathy,	**Detemir before breakfast and bedtime + mealtime aspart vs. NPH before breakfast and bedtime + mealtime aspart** starting detemir dose- 50% of basal dose pretrial dose NPH dose – pretrial basal insulin dose (if previously on once daily NPH, the dose was divided equally between morning and evening)	**Values for detemir / NPH** **age (years):** 40.1 ± 12.8 / 40.8 ± 13.2 **% males:** 53.7% / 52.5% **DM duration (years):** 17.8 ± 9.7 / 16.6 ± 10.2 **HbA1c (%):** 8.18 ± 1.14 / 8.03 ± 1.11 **FPG (mg/dl):** 213.3 ± 95 / 207.2 ± 92.9 **weight (kg):** 71.3 ± 10.7 / 71.7 ±	(see table below)

	Detemir + aspart	NPH + aspart
completed trial	97%	97%
d/c due to AE (n)	2	0
HbA1c (%)	-0.64	-0.56
HbA1c (%) ± SE	7.53 ± 0.1	7.59 ± 0.13
FPG (mg/dl)	-10.44	-7.56
FPG (mg/dl)	192.6	194.4
9-pt BG profile	overall shape similar for both groups	
basal insulin dose	30.4 ± 15.6	33.6 ± 15.3

	impaired hepatic/renal function, recurrent major hypoglycemia, uncontrolled HTN, severe cardiac problems, insulin allergy, pregnancy/breastfeeding	During first 2-weeks only basal was adjusted. In subsequent weeks, basal or bolus doses can be adjusted For extension phase, patients maintained regimen they were taking at 6 months. Dosage adjustments were allowed Target glucose levels: • Fasting, preprandial, and nocturnal (2-4am) 72-126mg/dl • postprandial < 180mg/dl	12.4 **BMI (kg/m²):** 24.4 ± 2.9 / 24.6 ± 3.5 **total basal insulin dose at end of parent trial (units/day):** 29.2 ± 15; 32.6 ± 14.9 **total bolus insulin dose at end of parent trial (units//day):** 30.2 ± 15.3 / 27.1 ± 13.6 mean ± SD	

(units/day)		
bolus insulin dose (units/day)	31.7 ± 15.3	27.3 ± 13
Weight (kg)	-0.1kg	+1.2kg
Weight (detemir-NPH) [95%CI]	1.34kg [-2.12, -0.56]*	
Hypoglycemia		
≥ 1 event	96%	96%
major	14%	21%
nocturnal	180 (83%) / 1378*	87 (88%)/ 926
major nocturnal	5.1% / 20	9.1% / 14

Mean ± SD unless otherwise indicated
*Significant vs. NPH

Hermansen 2004 R, OL, PR, MC Europe 6-week titration period 12-week maintenance period N=595 (n=298 detemir,; 297 NPH) ITT	Type 1 DM ≥ 1 year ≥ 18 years old Used basal/bolus or premixed insulin therapy for ≥ 6 months BMI ≤ 35 kg/m² HbA1c ≤ 12% Total daily insulin dose ≤ 1.4 units/kg/day Exclusions: proliferative retinopathy requiring acute treatment, impaired hepatic/renal function, recurrent major hypoglycemia, uncontrolled HTN, severe cardiac problems, h/o drug or alcohol dependence, insulin allergy, pregnancy/ breastfeeding	**Detemir morning and evening + mealtime insulin aspart vs. NPH morning and evening + mealtime regular insulin** Insulin detemir or NPH was started at 70% of the patients prior basal insulin dose (if previously on once daily NPH, the dose was divided so that 25-30% was administered in the morning and 70-75% in the evening) initial dosing of NPH, aspart/regular insulin was not described During 6-week titration period, basal insulin dose was adjusted to achieve pre-breakfast and dinner glucose 102-6 - 131.4mg/dl. Thereafter, the dose ratio between basal/bolus could be adjusted to achieve fasting/ preprandial glucose 102.6-131.4mg/dl and 90-min postprandial of 153-182mg/dl	**Values for detemir / NPH** **age (years):** 38.8 ± 13.5 / 39.3 ± 12.9 **% males:** 61.4% / 65% **DM duration (years):** 15.4 ± 10.1 / 15.1 ± 10.4 **HbA1c (%):** 8.48 ± 1.12 / 8.29 ± 1.19 **FPG (mg/dl):** 158.9 ± 77.6 / 165.1 ± 73.3 **weight (kg):** 73.5 ± 11.4 / 74.2 ± 12.2 **BMI (kg/m²):** 24.8 ± 3.0 / 24.9 ± 3.2 **total basal insulin dose (units/day):** 24.2 ± 11.0; 24.5 ± 11.3 **total bolus insulin dose (units/day):** 28.5 ± 12.3 / 27.8 ± 13.3 **% of patients with > 1 basal injection/day:** 56.7% / 60.3% mean ± SD	

	Detemir + aspart	NPH + regular
completed trial	97%	95.3%
d/c due to AE (n)	5	1
HbA1c (%)	-0.5	-0.28
HbA1c (%)	7.88 ± 0.05	8.11 ± 0.05
HbA1c (detemir-NPH) [95%CI]	-0.22% [-0.34, -0.10]*	
FPG (mg/dl)	136.4 ± 3.42	145.8 ± 3.6
8-pt SMBG	smoother and more stable profile and lower PPG with detemir/aspart*	
basal insulin dose (units/day)	32.1	28.2
bolus insulin dose (units/day)	26.4	26.3
Weight (kg)	73 ± 0.14*	74.1 ± 0.14
Weight (kg)	-0.95 ± 0.14	+0.07 ± 0.14
Weight (detemir-NPH) [95%CI]	-1.01kg [-1.37, -0.66]*	
Hypoglycemia (# patients (%)/# events)^		
All	219 (75%) / 2497/37.1*	238 (82.9) / 3192/ 48.2
all (major)	19 (6.5%) / 40	18 (6.3%) / 45
nocturnal	113 (38.7%) / 271/ 4.0*	173 (60.3%) / 608/ 9.2
major nocturnal	3 (1%) / 4*	12 (4.2%) / 24
symptoms only (all)	121 (41.4%)/677	148 (51.6%)/865
symptoms only (nocturnal)	41 (14%)/71*	72 (25.1%)/157

Mean ± SE
*Significant vs. NPH
^for all hypoglycemia and nocturnal hypoglycemia, events/pt-year are

				also shown			
Pieber 2005 R, OL, PR, MC Europe N=400 n=139 detemir am/ dinner n=132 detemir am/hs n= 129 NPH 16-weeks ITT Subgroup of patients (n=191) underwent CGMS after 12 weeks of treatment	Type 1 DM ≥1 year ≥ 18 years old Used basal/bolus insulin therapy for ≥2 months BMI ≤ 35 kg/m^2 HbA1c ≤12% Total basal insulin dose ≤ 100 units/day Exclusions: significant medical disorders hypoglycemia unawareness recurrent major hypoglycemia, pregnancy, using medications that interfere with glucose metabolism	**Detemir twice daily (morning and pre-dinner) + aspart** **Detemir twice daily (morning and bedtime) + aspart** **NPH twice daily (morning and bedtime) + aspart** Starting dose of basal insulin was 70% of prestudy NPH dose. Those previously using once daily basal insulin split their basal dose to 20-30% in the morning and 70-75% at dinner/bedtime Dosing of aspart was not described Basal dose was optimized first. Thereafter dose ratio of basal/bolus was adjusted based on SMBG Target glucose levels: • Pre-breakfast, dinner, and night 72-126mg/dl • Postprandial ≤ 180mg/dl	**Values for detemir (am/dinner)/ detemir (am/hs)/ NPH** **% males:** 56.1/ 68.2/ 56.6 **Age (years):** 39 ± 12.4/ 40.4 ± 11.4/ 41.1 ± 11.9 **Duration of DM (years):** 14.4 ± 10.8/ 15.9 ± 10.3/ 14.4 ± 9.2 **Weight (kg):** 75.6 ± 15/ 77 ± 13.7/ 74.8 ± 13.1 **BMI (kg/m2):** 25 ± 3.7/ 25.4 ± 3.2/ 25.2 ± 3.1 **HbA1c (%):** 8.01 ± 1.24/ 8.13 ± 1.37/ 8.08 ± 1.15 **FPG (mg/dl):** 180 ± 86.2/ 191.3 ± 82.4/ 191.7 ± 78.7 **Basal insulin dose (units/kg/day):** 0.35 ± 0.14/ 0.34 ± 0.13/ 0.32 ± 0.13 **Bolus insulin dose (units/kg/day):** 0.39 ± 0.17/ 0.39 ± 0.17/ 0.37 ± 0.14 **% receiving once daily basal insulin:** 30% Mean ± SD			

	Detemir (am/dinner)	Detemir (am/hs)	NPH (am/hs)
completed trial	95%	92%	97%
HbA1c (%)	-0.43	-0.49	-0.39
HbA1c (%)	7.67 ± 0.07	7.65 ± 0.07	7.73 ± 0.07
FPG- lab (mg/dl)	178 ± 6.3*	165 ± 6.5*	200 ± 6.3
FP - SMBG (mg/dl)	148 ± 3.2	144 ± 3.2	150 ± 3.2
FPG within-person variability [SD (CV%)]	44.82mg/dl* (31.1%)	46.98mg/dl* (33.3%)	55.62mg/dl (37.8%)
Weight (kg)	-0.6*^	+0.1*	+0.7
basal insulin dose(units/kg/day)	0.45 ± 0.21	0.41 ± 0.15	0.38 ± 0.14
bolus insulin dose(units/kg/day)	0.38 ± 0.18	0.39 ± 0.17	0.34 ± 0.12
10-pt SMBG profile	Overall shape of curves similar. Glucose was higher between dinner and bedtime and lower between 2am and breakfast with detemir (am/dinner) than detemir (am/hs)		
CGMS (mmol/l•h) ¶ • >24h • overnight	43.21 ± 4.93* 10.47 ± 1.45	48.85± 4.65* 12.68 ± 1.41	54.02 ± 4.64 12.67 ± 1.37
Hypoglycemia (# episodes/ # patients/ events per person)			
all	876/ 100/ 6.4	1005/92/ 7.9	842/ 100/ 6.7
all major	12/5	6/5	5/4
nocturnal	184/ 60/ 1.3	142/ 51/ 1.1	167/ 60/ 1.3
major nocturnal	4/3	2/1	2/2

*Significant vs. NPH
^Significant vs. detemir (am/hs)
mean ± SE
¶deviation from the individual mean

Appendix 2: Clinical trials in type 2 diabetes (see p. 19 for list of abbreviations)

Trial	Inclusion/exclusion	Treatment regimen	Baseline information	Results
Raslova 2004 R, OL, PR, MC Europe, Argentina n=394 (n=195 detemir; n=199 NPH) 6-weeks titration period, 16-weeks maintenance period ITT	Type 2 DM $\geq$ 1 year $\geq$ 18 years old BMI $\leq$ 40 kg/m^2 HbA1c < 12% Total daily insulin dose $\leq$ 1.4 units/kg/day treated with insulin $\pm$ oral agents Exclusions: significant medical disorders hypoglycemia unawareness recurrent major hypoglycemia, pregnancy	**Detemir + aspart vs. NPH + regular** Basal insulin was administered once or twice daily based on pretrial tx. Starting basal insulin dose for both groups- 70% of pretrial basal dose. If glycemic target not reached with once daily basal, pt. was switched to a twice daily regimen starting dose for bolus insulin was not described oral hypoglycemic agents were discontinued During 1st 6 weeks, the dose of basal insulin was optimized based on results of SMBG. Thereafter, dose ratio for basal and bolus may be adjusted. Target glucose levels: • Fasting <108mg/dl • Preprandial 90-126mg/dl • postprandial $\leq$ 162mg/dl	**Values for Detemir / NPH** **age (years):** 58.3 $\pm$ 9.4 / 58.2 $\pm$ 9.2 **% males:** 40% / 44.2% **DM duration (years):** 13.7 $\pm$ 7.5 / 14.5 $\pm$ 8.1 **HbA1c (%):** 8.16 $\pm$ 1.28 / 8.08 $\pm$ 1.23 **weight (kg):** 82.0$\pm$ 13.3 / 79.6 $\pm$ 12.1 **BMI (kg/m^2):** 29.8 $\pm$ 4.6 / 28.7 $\pm$ 4.3 **% of patients with 2 basal injections/day:** 54.9 / 53.8 **% of patients on basal/bolus insulin:** 45.1/ 46.2 **% of patients on biphasic insulin:** 21.5/ 22.1 **% of patients on insulin + OHA:** 33.3/ 30.7 mean $\pm$ SD	(see results table below)

Results (Raslova 2004):

	Detemir + aspart	NPH + regular
completed trial	94.9%	97%
d/c due to AE (n)	5	2
HbA1c (%)	-0.65	-0.58
HbA1c (%)	7.46	7.52
diff in HbA1c	-0.062% [95%CI -0.249, 0.125]	
FPG (mg/dl)	131 $\pm$ 2.3	131. 8 $\pm$ 2.2
FPG within-person variability (SD)	21.6mg/dl*	27.7mg/dl
8-pt SMBG profile	Parallel between both tx's. comparable mean plasma glucose at all time points	
basal insulin dose (units/kg/day)	0.58	0.46
bolus insulin dose (units/kg/day)	0.37	0.33
% using once daily basal insulin	31%	36%
Weight (kg)	+0.51 $\pm$ 0.22*	+1.13 $\pm$ 0.21
Hypoglycemia n (%) / E		
all	65 (34.6%) / 269	70 (36.1%) / 317
all major	2 (1.1%) / 2	1 (0.5%) / 1
nocturnal	28 (14.9%) / 49	34 (17.5%) / 82
major nocturnal	0	1 (0.5%) / 1

mean values
*significant vs. comparator

Trial	Inclusion/exclusion	Treatment regimen	Baseline information	Results
Haak 2004 R, OL, PR, MC Europe n=505 (n=341 detemir; n=164 NPH) 26-weeks non-inferiority trial ITT	Type 2 DM $\geq$ 1 year $\geq$ 35 years old HbA1c $\leq$ 12% insulin tx for $\geq$ 2 months Exclusions: use of oral hypoglycemics within 2 months of trial; proliferative retinopathy, impaired hepatic/renal function, recurrent major hypoglycemia, uncontrolled HTN, cardiac problems, pregnancy, total daily basal insulin dose > 100 units/d	**Detemir + aspart vs. NPH + aspart** Basal insulin was administered once or twice daily based on pretrial tx. Starting detemir dose- 50% of basal pretrial dose NPH dose – pretrial basal insulin dose Starting dose for bolus insulin was not described If glycemic target not reached with once daily basal, pt. was switched to a twice daily regimen Target glucose levels:	**Values for Detemir / NPH** **age (years):** 60.6 $\pm$ 8.7 / 60.0 $\pm$ 8.4 **% males:** 48.4% / 56.7% **DM duration (years):** 12.9 $\pm$ 7.4 / 13.7 $\pm$ 8.0 **HbA1c (%):**7.9$\pm$ 1.3 / 7.8 $\pm$ 1.3 **FPG (mg/dl):** 181.8 $\pm$ 59.8 / 187.2 $\pm$ 61.6 **weight (kg):** 85.7$\pm$ 14.9 / 89.3 $\pm$ 17.5 **BMI (kg/m^2):** 30.1 $\pm$ 5.0 / 31.1 $\pm$ 5.8 **% of patients on basal/bolus insulin:** 86/ 88 **% of patients on biphasic insulin:** 14/ 12 **total basal insulin dose (units/day):** 27.8 $\pm$ 14.7 / 28.0 $\pm$ 15.4 **total bolus insulin dose (units/day):** 33.6 $\pm$ 19.2 / 34.8 $\pm$ 19.9	(see results table below)

Results (Haak 2004):

	Detemir + aspart	NPH + aspart
completed trial	92.4%	95.1%
HbA1c (%)	-0.2	-0.4
diff in HbA1c	0.16 [95%CI 0.003, 0.312]	
HbA1c (%)	7.6 $\pm$ 0.1	7.5 $\pm$ 0.1
FPG (mg/dl)	174.6 $\pm$ 3.6	172.8 $\pm$ 5.4
FPG within-person variability [SD (CV%)]	23.4 mg/dl (17.6%)*	25.2mg/dl (18.5%)
9-pt SMBG profile	no difference in overall shape of profile	
basal insulin dose (units/day)	36.4	35.3
bolus insulin dose (units/day)	40.2	35.8
% using twice daily basal insulin	61%	59%
weight (kg)	+1	+1.8

	• Fasting, and nocturnal (2-4am) 72-126mg/dl • 90-min postprandial < 180mg/dl	mean ± SD	Weight (detemir-NPH)	-0.79kg [95%CI -1.44, -0.14]*

Hypoglycemia n (%) / E		
All	152 (46.2%) / 1218	80 (49.7%) / 708
nocturnal	52 (15.8%) / 166	38 (23.6%) / 80
All major	< 2%	< 2%

mean ± SE
*significant difference

Appendix 3: Abstracts/posters (see p. 19 for list of abbreviations)

Trial	Inclusion/exclusion	Treatment regimen	Baseline information	Results
Study 1372 R, OL, PR, MC Australia, Germany, S. Africa n=320 (n=161 detemir; n=159 glargine) 26-weeks	Type 1 DM≥ 1 year ≥ 18 years old HbA1c 7.5-12% BMI ≤ 35 kg/m² using basal/bolus or premix insulin total insulin dose ≤ 1.4units/kg/day	**Detemir twice daily + aspart before each meal** **Glargine once daily at bedtime + aspart before each meal**	51% males **Age (years):** 40.2 ± 13.6 **Duration of DM (years):** 16.7 ± 10.5 **HbA1c (%):** 8.84 ± 0.98 **Weight (kg):** 76.3 ± 14.2 **BMI (kg/m2):** 25.5 ± 3.6	(see table below)
Study 1373 R, OL, PR, MC Europe, USA n=582 (n=291 detemir; n=291 glargine) 52-weeks non-inferiority design	Type 2 DM ≥ 1 year ≥ 18 years old HbA1c 7.5-10% insulin naïve Tx with 1 or 2 OHAs (excluding TZDs) for ≥ 4 months BMI ≤ 40 kg/m²	**Detemir once or twice daily + pre-study OHAs** **Glargine once daily + pre-study OHAs** All patients in the detemir group began with once daily dose. Dose may be increased to bid if necessary	58% males **mean age:** 58.9 years (range 27-82 years) **FPG:** 194mg/dL **HbA1c:** 8.6%	(see table below)

Study 1372 Results:

	Detemir + aspart	Glargine + aspart
HbA1c	8.165	8.195
change in HbA1c	-0.6%	-0.6%
FPG (mg/dL)	139*	126
9-point blood glucose profile	comparable between groups	
overall hypoglycem	similar with both groups	
nocturnal hypoglyc	77 patients 4.3 episodes/pt/ yr*	81 patients 6.6 episodes/pt/yr
major hypoglycemia	3 patients 0.1 episode/pt/yr*	12 patients 0.3 episodes/pt/yr
weight (kg)	+0.52	+0.96
daily dose of basal insulin	0.47 units/kg	0.35 units/kg
daily dose of aspart	0.36 units/kg	0.39 units/kg

*significant difference

Study 1373 Results:

	Detemir + OHA (QD +BID)	Glargine +OHA
completed study	79.5%	86.6%
HbA1c (%)	7.16%	7.12%
change in HbA1c	-1.45%	-1.45%
% pts. achieving HbA1c ≤ 7%	~ 50%	~ 50%
% pts. achieving HbA1c ≤ 7% in the absence of hypoglyc	~ 30%	~ 30%
FPG (mg/dl)	128.5	125.6
FPG within-person variability	no difference between all detemir patients and glargine patients	
FPG variability (qd determir vs glargine)	CV=15%*	CV= 17.1%
pre-dinner glucose	CV=19.8*	CV=22.1%

variability (qd detemir vs. glargine)		
10-point blood glucose profile	comparable between groups	
Hypoglycemia minor/ major/ nocturnal (%)	46.4/ 1.7/ 32.6	51.9/ 2.7/ 32
Weight (kg)	3.02	3.93
insulin-analog specific antibodies	yes	no

*significant vs. comparator

	Detemir QD + OHA n=104)^	Detemir BID + OHA (n=127)^	Glargine + OHA (n=291)
HbA1c (%)	7.12	7.06	7.12
FPG (mg/dl)	130.9	121.1	125.6
Hypoglycemia minor/ major/ nocturnal (%)	51.9/ 1/ 31.7	52/ 0.8/ 38.6	51.9/ 2.7/ 32
Weight (kg)	2.25	3.71	3.93
daily insulin dose (units/kg)	0.52	0.85	0.44

^per-protocol population; data on file NovoNordisk

| Study 1337 R, OL, PR USA, Puerto Rico

n=467 (n=309 detemir; n=158 NPH)

6-months

non-inferiority design | Type 2 DM $\geq$ 1 year $\geq$ 35 years old BMI $\leq$ 40 kg/m^2 inadequate control on OHAs HbA1c 8-12% (on < 3 OHAs) HbA1c 8-10% (on $\geq$ 3 OHAs) | **2:1 randomization** **Detemir once daily in the evening + metformin** **NPH once daily evening + metformin**

Metformin 500mg or 850mg taken with meals (to maximum tolerated dose). Other baseline OHAs were discontinued

mean metformin dose: 2200mg

Insulin was initiated at 0.1U/kg for FBG < 180mg.dl or 0.2U/kg for FBG > 180mg/dl. Dose was increased every 3 days to achieve FBG goal of 126mg/dl | 54% males **mean age** 55.8 years (range 34-87 years) **HbA1c:** 9.5% (detemir); 9.4% (NPH) **FPG (mg/dL):** 246.8 (detemir); 246.2 (NPH) **duration of DM:** 6 years **mean weight:** 90kg **mean BMI:** 31.5kg/m^2 **metformin alone:** 19% **metformin +TZD:** 37% **metformin combination + TZD:** 44% |

	Detemir + metformin	NPH + metformin
completed study	86%	88%
HbA1c	-0.9%	-1.5%
HbA1c	8.5%	8.0%
HbA1c difference [95%CI]	0.56% [0.326 -0.784%]*	
FPG (mg/dL)	153	154.1
9-point blood glucose profile	significantly different between groups favoring NPH (data not shown)	
FPG within-person variability	similar between groups (data not shown)	
Hypoglycemia	RR of hypoglycemia (esp. nocturnal) ~ half of that in the NPH group (data not shown)	
Weight	maintained with detemir and slightly increased with NPH (data not shown)	
Insulin dose	0.56 U/kg	0.45U/kg

*criterion for non-inferiority was not fulfilled

Study 1530 Hermansen (poster) R, OL, PR, MC Europe n= 475 (n=237 detemir; n=238 NPH) 24-weeks ITT	Type 2 DM ≥1 year ≥ 18 years old HbA1c 7.5-10% insulin naïve Tx with 1 or 2 OHAs (excluding TZDs) for ≥ 4 months BMI ≤ 35 kg/m²	**Detemir morning and evening + prestudy OADs** **NPH morning and evening + prestudy OADs** Starting dose of either insulin 10 units in the morning and evening. Dose titrated to pre-breakfast and pre-dinner glucose targets < 108mg/dl	**Values for Detemir / NPH** **% males:** 49%/ 57% **Age (years):** 61.3 ± 9.1/ 60.4 ± 9.3 **Duration of DM (years):** 9.6 ± 6.6/ 9.8 ± 6.2 **HbA1c (%):** 8.61 ± 0.78/ 8.51 ± 0.76 **FPG (mg/dl):** 200.5/ 193.7 **BMI (kg/m²):** 28.9 ± 3.6/ 29 ± 3.6 **OHA monotherapy:** 34.6%/ 34.9% **OHA combination therapy:** 65.4%/ 65.1% Mean ± SD	(see table below)

	Detemir + OHA	NPH + OHA
Completed study	95%	95%
HbA1c	6.6%	6.5%
change in HbA1c [95%CI]	-1.8 [-1.97 to -1.71]	-1.9 [-2.0 to -1.78]
% pts. achieving HbA1c ≤ 7%	70%	73.8%
% pts. achieving HbA1c ≤ 7% in the absence of hypoglyc	25.7%*	15.5%
FPG (mg/dL)	119	113
FPG within-person variability (SD)	23.76mg/dl*	25.92 mg/dl
10-point blood glucose profile	comparable between treatments	
overall hypoglyc (events/pt-year)	8.6*	15.9
nocturnal hypoglyc (events/pt-year)	1.5*	3.3
major hypoglycemia	1 episode	8 episodes
Weight (kg)	1.2*	2.8
insulin dose	0.77 units/kg*	0.52 units/kg
*Significant vs. NPH		

Abbreviations: AE=adverse event; BG=blood glucose; BMI=body mass index; CGMS=continuous glucose monitoring; CV=coefficient of variation; DM=diabetes mellitus; FPG=fasting plasma glucose; HTN=hypertension; ITT=intent-to-treat; MC=multicenter; OHA=oral hypoglycemic agent; OL=open label; PR=parallel; R=randomized; TZD=thiazolidinedione