DIABETES/METABOLISM RESEARCH AND REVIEWS
*Diabetes Metab Res Rev* 2002; **18**: S57–S63.
Published online in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/dmrr.317

# An overview of insulin glargine

Philip D. Home*
Simon G. Ashwell

*Department of Diabetes and Metabolism, University of Newcastle upon Tyne, UK*

*Correspondence to: Professor P. D. Home, Department of Diabetes and Metabolism, Medical School, Framlington Place, Newcastle upon Tyne, NE2 4HH, UK.
E-mail: philip.home@ncl.ac.uk

## Summary

Insulin glargine is an innovative, long-acting human insulin analogue, whose prolonged mean activity profile has no pronounced peak. Accordingly, it mimics more closely the natural physiological profile of basal endogenous insulin secretion than do traditional extended-acting insulins such as NPH insulin. As would be expected for a more satisfactory basal insulin, clinical trials comparing insulin glargine with NPH insulin show less nocturnal hypoglycaemia, improved pre-breakfast blood glucose levels, or both. Furthermore, no substantive safety concerns have emerged for insulin glargine. Thus, insulin glargine represents the first major advance in the provision of basal insulin injection therapy for people with type 1 and type 2 diabetes for over 50 years. Copyright © 2002 John Wiley & Sons, Ltd.

**Keywords** basal insulin; diabetes; hypoglycaemia; insulin glargine; NPH insulin

## Introduction

The earliest experiences of injecting pancreatic extracts containing insulin found that a single subcutaneous dose was unable to control blood glucose concentrations for more than a few hours. Subsequently, reports of modifications to prolong the absorption of subcutaneously injected insulin were published [1]. The material chosen at that time to retard the absorption of insulin was the basic protein protamine, which became the foundation of the stable pharmaceutical preparation NPH insulin, introduced in the 1940s [2]. The current formulation of NPH insulin is essentially unchanged from that time, differing only by the use of enhanced purification techniques and by a change in the species origin of the insulin. Very few other pharmaceutical preparations have survived largely unchanged as a therapeutic mainstay from the 1940s.

Advances in the understanding of insulin physiology, including the development of insulin and C-peptide assays, highlighted the crucial importance of a basal insulin supply to control blood glucose concentrations in patients with the hormone (insulin) deficiency disease that is type 1 diabetes. It has subsequently been shown that basal insulin secretion accounts for approximately 50% of the total insulin secreted each day [3]. Since basal insulin secretion regulates blood glucose concentrations during the night and between meals, it is necessary to ensure adequate basal insulin levels within a narrow range, as well as appropriate meal-time boosts of insulin supply, in order to prevent acute metabolic deterioration whether of hyper- or hypoglycaemia. NPH insulin and other protracted-acting insulins fail to provide adequate overnight physiological insulin replacement, because of a pronounced peak of action at around 5 h after injection. This limits the dose that can be administered without inducing hypoglycaemia, and this inadequate dose then results in a duration of absorption that is often too short. Furthermore, erratic absorption of NPH insulin leads to further risk of

hypoglycaemia, further reduction of insulin dosage, and thus further shortening of the action profile.

An alternative approach to providing basal insulin supply is continuous subcutaneous insulin infusion of unmodified insulin [4]. While now accepted as a successful means of therapy, this is achieved at a cost well beyond that affordable by many health-care systems, and is found cumbersome and more difficult to manage than pen-injectors by some people with diabetes.

From a therapeutic perspective, the failure of currently available preparations to achieve basal insulin replacement resembling physiological production is most apparent during the night. In people with type 1 diabetes, nocturnal hypoglycaemia is common when using NPH insulin. This is then followed by hyperglycaemia in the morning hours before and after breakfast at a time when the absorption and thus activity of the NPH insulin has fallen to inadequate levels. Given these shortcomings of NPH insulin, many attempts have been made to produce basal insulins with better activity profiles. Candidates have included the insulin–zinc suspensions of the 1950s (including lente and ultralente insulins), as well as other subsequent preparations many of which have failed to reach formal clinical trials [5,6]. However, the objective of more optimal basal insulin therapy now appears to have been met with the development of insulin glargine.

## The development of insulin glargine

Insulin glargine is a long-acting human insulin analogue in which the addition of two arginine residues to the *C*-terminus of the insulin B chain results in a change in the net charge of the molecule and, thus, a shift in its isoelectric point. The result is an insulin that is soluble in a mildly acidic injection medium of pH 4.0–5.0, but precipitates after injection at the physiological pH (7.4) of subcutaneous tissue.

Although diarginyl insulin is a natural by-product of physiological insulin production (and is normally present in the circulation at very low concentrations), its low solubility makes it unsuitable as a therapeutic preparation because it remains in the subcutaneous depot as a microprecipitate and is largely degraded before absorption. This failure to achieve adequate solubility has been a recurring fault of new basal insulins. It is not difficult to retard the absorption of insulin from subcutaneous tissue, but if the preparation remains at the injection site for too long a period, degradation may occur. In order to stabilize both the acid-soluble and precipitated forms of the modified insulin, a second modification was made to the diarginyl insulin by substituting glycine for arginine at position A21 (Figure 1). This results in stabilization of the insulin glargine hexamer relative to diarginyl insulin and an increased number of inter-hexamer interactions relative to human insulin. These properties enhance physical and chemical stability in the pharmaceutical preparation, and further retard absorption after injection.

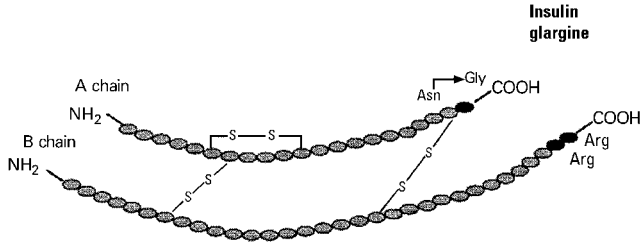


**Figure 1. The amino acid substitutions of insulin glargine compared with human insulin. Note the addition of two arginine residues to the *C*-terminus of the B chain, and substitution of the A21 arginine with glycine**

Substitution with glycine and arginine residues gave rise to the name insulin 'glargine'.

## Pharmacokinetics and pharmacodynamics of insulin glargine

Early studies of the subcutaneous pharmacokinetics of a new insulin usually begin with radioactive disappearance studies, monitoring residual radioactivity after injection. An important assumption is that the measured radioactivity is remaining in the insulin molecule, an assumption which is probably increasingly inaccurate with time from injection. Nevertheless, the technique has a long record of giving meaningful comparative, but not absolute data. The pharmacokinetic properties of insulin glargine (formerly HOE 901) were assessed initially by this technique, showing that, compared with NPH insulin, insulin glargine was absorbed more slowly from the injection site, as demonstrated by the difference in the disappearance curves [7,8]. While quantitative interpretation should be treated with caution for the reasons given above, as an approximation, insulin glargine was absorbed at about half the rate of absorption of NPH. Interestingly, there is some suggestion of a difference in shape of the absorption curves, albeit subtly so [7]. The NPH curve is a gentle arc, consistent with absorption declining in proportion to the preparation remaining at the injection site, while the insulin glargine curves are indistinguishable from straight lines. This would imply constant absorption of insulin glargine over the time of the study, which would be ideal for generating a flat, steady insulin supply.

The pharmacodynamic properties of insulin glargine have been investigated by means of glucose clamp studies, which assess the glucose infusion rate required to maintain constant blood glucose levels after a subcutaneous injection of insulin in people kept fasting [9–11]. In healthy subjects, the glucose infusion rate after an injection of NPH insulin reaches a peak between 4 and 8 h, and then falls off rapidly, with a duration of effect of 12–14 h [9,10]. In contrast, insulin glargine has a much slower onset of action, followed by a relatively steady activity plateau [9]. These studies have consistently

shown that, in healthy subjects and in people with type 1 diabetes, insulin glargine has a much longer and flatter time–activity profile compared with NPH insulin. Thus, in a glucose clamp study in people with type 1 diabetes, the administration of insulin glargine required a constant mean glucose infusion rate to maintain blood glucose levels during 24 h [11].

These studies are not easy to perform, because basal insulin therapy cannot be withdrawn from people with the absolute insulin deficiency of type 1 diabetes, resulting in protocol design and interpretation difficulties from the necessary overlap between pre-study basal insulin and study basal insulin. Additionally, it is important not to interpret the mean curve as applying to every patient with type 1 diabetes, a point emphasized by the need to stop this study, in line with the protocol, before 24 h in four of the 20 subjects studied on insulin glargine, due to hyperglycaemia. This was, however, true for all the NPH insulin studies, and the curves for NPH insulin fit in well with our clinical perceptions, with its peak effect matching the peak time of hypoglycaemia at night in people on insulin injections [11]. The conclusion would appear to be that insulin glargine should be a 24 h insulin in many, but perhaps not all, people with type 1 diabetes.

Early studies on the pharmacokinetic properties of insulin glargine were performed with different concentrations of zinc (15, 30 or 80 mg/l), which acts as a stabilizer and is present in all insulin preparations. All of these studies demonstrated no meaningful differences among preparations with varying concentrations of zinc [7]. The commercial preparation of insulin glargine contains 30 mg/l of zinc.

Another aspect of insulin absorption, particularly important for basal insulins, is the importance of variability of absorption. This is difficult to measure formally in clinical laboratory experiments, because the insulin absorption action profile in the glucose clamp of any one individual on one day is quite erratic; thus, there is no easily measured variable which can be used to compare an individual's profile on one day with that on a second or subsequent days. Such data that do exist for insulin glargine show a variability, on visual inspection of glucose clamp profiles, very much less than for human ultralente insulin, but similar to NPH insulin [12]. Similar variability in an insulin with longer duration of action is a major advance in insulin therapy, as it is variability of absorption, and thus erratic occurrence of hypoglycaemia, which limits the increase in the NPH insulin dose necessary to control pre- and post-breakfast hyperglycaemia.

## Insulin and IGF-1 receptor interactions

The binding characteristics of insulin glargine and human insulin to human insulin receptors, either expressed on rat fibroblasts, or solubilized after expression in animal tissues, have been compared in two studies [13,14]. Berti and colleagues report receptor association as equal for the two insulins, but precise figures cannot be derived from the paper [13]. Kurtzhals and colleagues suggested that insulin glargine has somewhat lower affinity for the receptor than human insulin, and similarly in terms of metabolic effects in an *in vitro* tissue assay [15]. It is important to realise that such differences are not clinically relevant, and will not be reflected in *in vivo* potency, because decreased clearance through the insulin receptor results in higher plasma concentrations which compensate exactly for changes in affinity.

Dissociation characteristics of new insulin analogues are usually studied with some interest, due to experience with Asp(B10)-insulin. This human insulin analogue caused mammary tumours in susceptible animals, and was subsequently shown to have somewhat unusual, prolonged binding characteristics to the insulin receptor. In this respect, Berti and colleagues found no difference for insulin glargine compared with human insulin, and indeed reported that insulin glargine dissociated from the receptor rather more quickly than did human insulin [13].

That paper went on to look at autophosphorylation and dephosphorylation of the insulin receptor, and also phosphorylation of the cellular intermediate IRS-1. The findings were that human insulin and insulin glargine were similar in these respects, and markedly different from Asp(B10)-insulin [13]. Both insulin glargine and human insulin strongly stimulate autophosphorylation of the insulin receptor, with a response that fades during prolonged stimulation. As might be expected, insulin glargine is also able to stimulate a range of metabolic activities (including lipogenesis, glucose transport, GLUT-4 translocation, and glycogen synthase) through the insulin receptor signalling pathway — although with 38%–65% less potency compared with human insulin [14; personal communication, Aventis Pharma]. Again, such differences will not be clinically evident in the *in vivo* situation after injection.

In addition to binding to the insulin receptor, human insulin also binds to the IGF-1 receptor, although with many-fold lower affinity than IGF-1 binds to its own receptor. When comparing estimates of the IGF-1 receptor binding affinity of insulin glargine to that of human insulin, estimates range from 1.4 times (using rat myoblasts with 7000 IGF-1 receptors per cell) to 6.5 times higher (using solubilized receptor previously expressed in animal tissues) [15,16]. Similar figures are reported in these papers for studies of DNA synthesis in cultured cell lines (often termed 'mitogenicity', but measuring thymidine incorporation into DNA). The difference between the papers may result from differences in methodology (these are not easy studies to perform) including differences in cell line, and the relevance of some of these models to human pathogenesis is difficult to assess. Furthermore, Asp(B10)-insulin was found to be 'supermitogenic' in mouse T lymphoma cells, yet these do not express any IGF-1 receptors [17]. Asp(B10)-insulin also showed a

significantly greater binding affinity than insulin glargine and human insulin for the IGF-1 receptor of rat heart cardiomyoblasts. This was associated with increased proliferative activity for Asp(B10)-insulin, comparable to that of IGF-1, while insulin glargine showed significantly less proliferative activity, comparable to that of human insulin [16].

There are other reasons to be cautious about over-interpreting the IGF-1 receptor binding data. Not least, human insulin and animal insulin have been injected at very high concentrations into subcutaneous tissue for around 80 years, without a single recorded example of tumour induction, despite repeated injection (often into a single site) year after year by many patients. Circulating IGF-1 concentrations are, anyway, orders of magnitude higher than circulating insulin concentrations, and IGF-1 affinity for its own receptors is orders higher than that for insulin. Thus, the effects of any insulin are likely to be swamped at any tissue site. However, quantitative calculations are not easy to make — the dynamics of the various IGF-1 binding proteins are ill understood and make the tissue concentrations of free IGF-1 somewhat uncertain.

It appears, therefore, that insulin receptor binding affinity and activation characteristics of insulin glargine are similar to those of human insulin and different from those of the oncogenic Asp(B10)-insulin analogue.

## Clinical studies

The aim of improving basal insulin therapy is to reduce the incidence of nocturnal hypoglycaemia and improve pre- and post-breakfast blood glucose levels, which, on average, are the highest of the day [18]. In addition, improving basal insulin therapy would prevent the deterioration of late postprandial blood glucose levels in patients who use pre-prandial rapid-acting insulin analogues with long intervals between meals, and thus between injections [19].

Nocturnal hypoglycaemia and pre-breakfast hyperglycaemia can be considered manifestations of the same problem. As previously discussed, it is the development of nocturnal hypoglycaemia that limits the possibility of increasing the night-time basal insulin dose of NPH insulin to the amounts necessary to control overnight blood glucose levels through to the next morning. This can present a problem in clinical trials and in clinical practice, since some physicians and people with diabetes will adjust basal insulin doses to reduce nocturnal hypoglycaemia (depending on its frequency and their tolerance of it), while others will adjust basal insulin doses to improve overnight blood glucose control through to breakfast. This therapeutic dichotomy (with some people trying to achieve both options to different degrees) in effect gives many insulin trials dual objectives, thereby decreasing their power. It is useful, therefore, to examine clinical study results with the combined goals in mind, rather than considering nocturnal hypoglycaemia and pre-breakfast blood glucose levels as separate outcomes.

A European phase 2 study of insulin glargine in people with type 1 diabetes reported that clinic fasting blood glucose concentrations (recorded during morning clinical trial attendances) were significantly reduced by about 2.0 mmol/l (36.0 mg/dl) compared with baseline, while no change from baseline was seen with NPH insulin [20]. However, clinic fasting blood glucose concentrations may overemphasize the benefit of a true long-acting insulin compared with NPH insulin, because the measurements are generally performed much later than the person's usual pre-breakfast glucose test at home, and at a time when blood glucose levels are rising. Indeed, in the same study, self-monitored pre-breakfast blood glucose concentrations were improved to a lesser extent than fasting blood glucose levels measured at the clinic visit. In this study, there was also a small, but statistically significant, improvement in glycated haemoglobin ($HbA_{1c}$), an index of overall blood glucose control.

Similar results were reported from the equivalent North American phase 2 study [21]. Of particular interest are the blood glucose profiles measured overnight in this study. These profiles showed the effect of waning insulin supply from the NPH insulin injection resulting in rising glucose concentrations toward morning, whereas glucose concentrations remained stable, or even fell slowly, with insulin glargine at the end of the night. Adequacy of the insulin supply in the people using insulin glargine thus resulted in the absence of dawn hyperglycaemia, consistent with findings in healthy individuals [22]. These results also indicate that insulin glargine may be more effective when given earlier in the evening rather than at bedtime, as has been used in the clinical studies. This hypothesis is currently under investigation. It is also important to determine whether it is possible for reasons of convenience to use insulin glargine at the same time as a rapidly acting insulin analogue (although it should be remembered that insulin glargine must not be mixed with any other insulin prior to injection, because of the difference in carrier pH).

To understand the results of the phase 3 clinical trials of insulin glargine in people with type 1 diabetes, it is useful to combine data from the pivotal US phase 3 study with those from the similar European study [23–25]. These studies have very similar protocols, and in particular inclusion criteria and endpoints. However, caution is advised when interpreting findings from studies of any new insulin because of inherent bias against the new formulation. Thus, all of the insulin glargine studies involved clinicians and patients with experience of using NPH insulin, but without experience of using insulin glargine. Indeed, the study designs, which used large numbers of centres with small numbers of patients from each centre, may have precluded the possibility of investigators gaining useful experience with the new insulin within the time span of the study. Against this, the necessarily open design might lead to new product bias, though this is limited by external laboratory analysis of

the biochemical endpoints (though not of course hypoglycaemia), and by the 6-month duration of the studies. Accordingly, more experience with different study designs is needed before it is possible to determine the magnitude of advantage provided by insulin glargine for overall blood glucose control.

The combined data from the phase 3 studies in people with type 1 diabetes indicate that the changes in $HbA_{1c}$ values from baseline, as well as in pre-breakfast blood glucose concentrations, with insulin glargine did not quite reach statistical significance compared with NPH insulin (Figure 2a). However, the reduction in frequency of nocturnal hypoglycaemia of approximately 22% with insulin glargine compared with NPH insulin did reach statistical significance (Figure 2b). Thus, both the combined data presented here and data from the individual studies [23,24] showed that insulin glargine is associated with a reduction in nocturnal hypoglycaemia, and has an advantageous effect on fasting blood glucose levels in some people.

Evidence that insulin glargine either reduces nocturnal hypoglycaemia or improves morning blood glucose levels is also provided in the results of a large study of insulin glargine compared with NPH insulin in people with type 1 diabetes receiving insulin lispro [26]. In that study, there was no difference between the insulin glargine and NPH insulin groups with regard to the rates of nocturnal hypoglycaemia. However, the advantage of insulin glargine was confirmed by the reduction in pre-breakfast blood glucose levels, with a statistically significant difference of about 1.0 mmol/l (18 mg/dl) between insulin glargine and NPH insulin. This finding is in accord with the phase 2 data from the European study discussed above [20].

The results of studies in people with type 2 diabetes are similar to those in people with type 1 diabetes. Two studies are available: one conducted in Europe and South Africa, which compared insulin glargine or NPH insulin in combination with oral glucose-lowering agents for one year [27], and one carried out in the United States, which compared insulin glargine or NPH insulin in combination with pre-meal insulin for 28 weeks [28]. No statistically significant differences between the effects of insulin glargine and NPH insulin on $HbA_{1c}$ or overall symptomatic hypoglycaemia were found in the two studies. However, nocturnal hypoglycaemia was significantly less frequent (by approximately 60%) during treatment with insulin glargine, in the European study.

Lastly, in children with type 1 diabetes, insulin glargine has been shown to lower fasting blood glucose concentrations without increasing the risk of hypoglycaemia [29]. Indeed, children given insulin glargine experienced fewer severe and severe nocturnal episodes of hypoglycaemia than did children given NPH insulin. Thus, it seems that the ability of insulin glargine to reduce nocturnal hypoglycaemia and/or improve fasting blood glucose concentrations is consistent not only across continents and between studies, but also in both type 1 and type 2 diabetes.

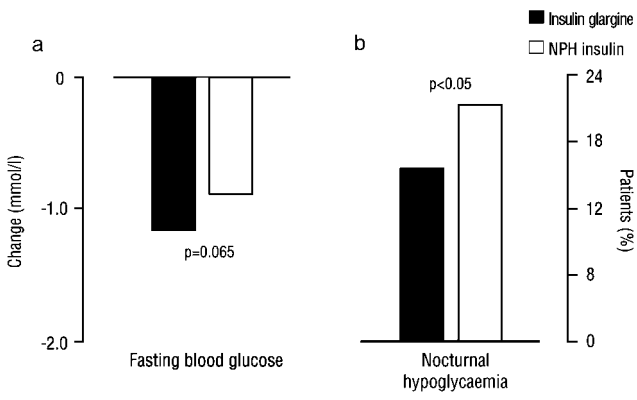


**Figure 2. Change in 'clinic' fasting blood glucose concentrations (a) and nocturnal hypoglycaemia (b) based on combined data from the 6-month European and North American phase 3 studies comparing insulin glargine (filled bars) with NPH insulin (open bars) in people with type 1 diabetes [23,24]. Combined numbers randomized to insulin glargine were 556 and to NPH insulin, 263**

## Safety

A detailed examination of phase 3 study data raises no significant safety concerns for insulin glargine. An isolated finding of retinopathy progression was noted in one study, however, the overall incidence of this isolated finding cannot be determined because of the small number of patients involved, the short follow-up period, and the fact that this finding was not observed in other clinical studies. In this context, an independent panel of ophthalmologists and physicians reviewed all the trial data and concluded that the data did not support the view that there was evidence of progression of any form of retinopathy in people with either type 1 or type 2 diabetes [30,31]. Additional studies are underway to confirm this. Other adverse events were reported in similar numbers for the insulin glargine and NPH insulin study populations.

## Cost-effectiveness issues

Pharmacoeconomic issues are also important. As a new insulin, insulin glargine has inevitably incurred development costs which no longer apply to NPH insulin, and it is therefore more expensive on the market. However, the potential market for a new basal insulin is large, and these costs are therefore widely spread. Formal economic analyses of the incremental cost–benefit gain for insulin glargine have not been published, but very small gains in health utility (QALY, quality adjusted life year) would be needed to bring the incremental cost effectiveness ratio within conventional health-care thresholds (perhaps US$30 000 per QALY gained) for acceptance of a new pharmaceutical preparation.

QALY improvements could be expected with insulin glargine treatment, as a result of reduction in hypoglycaemia (hypoglycaemic episodes can be unpleasant and frightening for the individual and a major concern for the treating physician). Further, hypoglycaemia is known to be a major barrier to glycaemic control [32] and therefore effects long-term clinical outcomes. By removing this barrier, insulin glargine will be likely to improve glycaemic control in the longer term, thereby reducing the risk of late tissue damage, and potentially translating into additional health-care cost benefits.

# Conclusion

The pharmacodynamic properties of insulin glargine and NPH insulin are very different, with the former having an activity profile much closer to that of normal physiologic basal insulin. In nearly all people using insulin glargine, it provides a long duration of action, but more importantly, the insulin activity does not peak inappropriately during the night. In a clinical setting, these characteristics are translated into less nocturnal hypoglycaemia and/or lower blood glucose levels in the morning.

Appropriate applications of this new insulin and its novel pharmacodynamic properties are, however, still under investigation. With further understanding and clinical experience, it is likely that these new properties may be used to the significant long-term advantage of people with diabetes. Further studies examining new treatment algorithms and different timing of injections are under way, and the results are awaited with considerable interest.

## Acknowledgements

The author is grateful to the investigators of studies as yet unpublished or available only in abstract form for permission to refer to their data. PDH has received, on behalf of the University of Newcastle upon Tyne, consultation and lecture fees, and research support from Hoechst AG and Aventis Pharma in connection with the development of insulin glargine. SGA is supported by those research funds.

# References

1. Scott DA, Fisher AM. Studies on insulin with protamine. *J Pharmacol Exp Ther* 1936; **58**: 78–92.
2. Krayenbühl C, Rosenberg T. Crystalline protamine insulin. *Rep Steno Hosp* 1946; **1**: 60–73.
3. Kruszynska YT, Home PD, Hanning I, Alberti KGMM. Basal and 24-h C-peptide and insulin secretion in normal man. *Diabetologia* 1987; **30**: 16–21.
4. Pickup JC, Keen H, Parsons JA, Alberti KGMM. Continuous subcutaneous insulin infusion: an approach to achieving normoglycaemia. *Br Med J* 1978; **i**: 204–207.
5. Hallas-Møller K, Petersen K, Schlichtkrull J. Crystalline and amorphous insulin-zinc compounds with prolonged action. *Science* 1952; **116**: 394–399.
6. Holman RR, Steemson J. OPID 174: a novel long-acting insulin preparation. *Diabet Med* 1989; **6**(suppl 1): A41 (Abstract).
7. Owens DR, Coates PA, Luzio SD, Tinbergen JP, Kurzhals R. Pharmacokinetics of $^{125}$I-labeled insulin glargine (HOE 901) in healthy men. *Diabetes Care* 2000; **23**: 813–819.
8. Luzio SD, Owens D, Evans M, Ogunku A, Beck P, Kurzhals R. Comparison of the sc absorption of HOE 901 and NPH human insulin in type 2 diabetic subjects. *Diabetes* 1999; **48**(suppl 1): 111 (Abstract).
9. Dreyer M, Pein M, Schmidt C, Heidtmann B, Schlünzen M, Roßkamp D. Comparison of the pharmacokinetics/dynamics of GLY(A21) ARG(B31,B32) human insulin (HOE71GT) with NPH insulin following subcutaneous injection by using euglycaemic clamp technique. *Diabetologia* 1994; **37**(suppl 1): A78 (Abstract).
10. Heinemann L, Linkeschova R, Rave K, Hompesch B, Sedlak M, Heise T. Time-action profile of the long-acting insulin analog insulin glargine (HOE 901) in comparison with those of NPH insulin and placebo. *Diabetes Care* 2000; **23**: 644–649.
11. Lepore M, Pampanelli S, Fanelli C, *et al*. Pharmacokinetics and pharmacodynamics of subcutaneous injection of long acting human insulin analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. *Diabetes* 2000; **49**: 2142–2148.
12. Scholtz HE, van Nieker N, Meyer BH, Rosenkranz B. An assessment of the variability in the pharmacodynamics (glucose lowering effect) of HOE901 compared to NPH and ultralente human insulins using the euglycaemic clamp technique. *Diabetologia* 1999; **42**(suppl 1): A234 (Abstract).
13. Berti L, Kellerer M, Bossenmaier B, Seffer E, Seipke G, Häring HU. The long acting human insulin analog HOE 901: characteristics of insulin signalling in comparison to Asp(B10) and regular insulin. *Horm Metab Res* 1998; **30**: 123–129.
14. Seipke G, Sandow J. Effects of insulin glargine, human insulin, and the insulin analog Asp(B10) on the insulin receptor cascade. *Diabetes* 2001; **24** (suppl 1): Abstract 525-P.
15. Kurtzhals P, Schäffer L, Sørensen A, *et al*. Correlations of receptor binding and metabolic and mitogenic potencies of insulin analogs designed for clinical use. *Diabetes* 2000; **49**: 999–1005.
16. Bähr M, Kolter T, Seipke G, Eckel J. Growth promoting and metabolic activity of the human insulin analogue [GlyA21,ArgB31,ArgB32] insulin (HOE 901) in muscle cells. *Eur J Pharmacol* 1997; **320**: 259–265.
17. De Meyts P. The structural basis of insulin and insulin-like growth factor-I receptor binding and negative co-operativity, and its relevance to mitogenic versus metabolic signalling. *Diabetologia* 1994; **37**(suppl 2): S135–S148.
18. Francis AJ, Home PD, Walford S, Alberti KGMM, Mann N, Reeves WG. Prevalence of morning hyperglycaemia: determinants of fasting blood glucose concentrations in insulin-treated diabetics. *Diabet Med* 1985; **2**: 89–96.
19. Ahmed ABE, Home PD. Optimal provision of daytime NPH insulin in patients using the insulin analog lispro. *Diabetes Care* 1998; **21**: 1707–1713.
20. Pieber TR, Eugène-Jolchine I, Derobert E, for the European Study Group of HOE 901 in Type 1 Diabetes. Efficacy and safety of HOE 901 versus NPH insulin in patients with type 1 diabetes. *Diabetes Care* 2000; **23**: 157–162.
21. Rosenstock J, Park G, Zimmerman J, for the US Insulin Glargine (HOE 901) Type 1 Diabetes Investigator Group. Basal insulin glargine (HOE 901) versus NPH insulin in patients with type 1 diabetes on multiple daily insulin regimens. *Diabetes Care* 2000; **23**: 1137–1142.
22. Kruszynska YT, Home PD. Night-time metabolic changes in normal subjects in the absence of the dawn phenomenon. *Diabet Metab* 1988; **14**: 437–442.
23. Ratner RE, Hirsch IB, Neifing JL, Garg SK, Mecca TE, Wilson CA, for the US Study Group of Insulin Glargine in Type 1 Diabetes. Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. *Diabetes Care* 2000; **23**: 639–643.
24. Home PD, for the European Insulin Glargine Study Group. A randomized, multicentre trial of insulin glargine versus NPH insulin in people with Type 1 diabetes (Abstract). *Diabetologia* 2002; **44**: Abstract 800.
25. Standl E. Results of an international, multicentre, randomized 28-week study for the comparison of insulin glargine (HOE 901) and NPH insulin in the intensified treatment (ICT) of Type 1 diabetics. *Exp Clin Endocrinol Diabetes* 2000; **108**(suppl 1): 159 (Abstract pFr107).
26. Raskin P, Klaff L, Bergenstal R, Halle JP, Donley D, Mecca T. A

 

16-week comparison of the novel insulin analog insulin glargine (HOE 901) and NPH human insulin used with insulin lispro in patients with type 1 diabetes. *Diabetes Care* 2000; **23**: 1666–1671.
27. Yki-Jarvinen H, Dressler A, Ziemen M, for the HOE 901/3002 Study Group. Less nocturnal hypoglycemia and better post-dinner glucose control with bedtime insulin glargine compared with bedtime NPH insulin during insulin combination therapy in type 2 diabetes. *Diabetes Care* 2000; **23**: 1130–1136.
28. Rosenstock J, Schwartz S, Clark CM, Park GD, Donley DW, Edwards MB. Basal insulin therapy in Type 2 diabetes. *Diabetes Care* 2001; **24**: 631–636.
29. Schober E. Insulin glargine, a new long-acting insulin, compared to NPH insulin in Type 1 diabetic children and adolescents. *Diabetes Care* 2001; **24**: 2005–2006.
30. Forjanic-Klapproth J, Home PD. Progression of retinopathy with insulin glargine or NPH insulin — a multi-trial analysis. *Diabetologia* 2001; **44** (suppl 1): 1103 (Abstract).
31. Bolli GB, Owens DR. Insulin glargine. *Lancet* 2000; **356**: 443–445.
32. Cryer PE. Hypoglycemia is the limiting factor in management of diabetes. *Diabetes Metab Res Rev* 1999; **15**: 42–46.