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ORIGINAL ARTICLE

Current progress with basal insulin analogues

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***Abstract:** In spite of its availability since 1921 and its current usage for last 90 years, insulin still continues to inspire molecular innovations primarily motivated by growing unmet needs. Although initial preparations of insulin from animal sources were successful, animal insulin were fairly crude, had highly variable efficacy, caused allergy, abscess formation at injection site, immune-mediated lipoatrophy at the injection site and antibody-mediated insulin resistance. It also caused significant hyperglycaemia and hypoglycaemia due to unpredictable dissociation of insulin from antibodies. This unpredictable variability between batches of animal-based formulations led to difficulty in determining proper doses and achieving good glycaemic control.[1-3] Subsequently, synthetic and recombinant human insulin were developed to enhance insulin purity as well as reproducibility of response. The production of this insulin, along with advances in animal insulin purification, significantly decreased allergy and lipoatrophy associated with the older preparations. However, these preparations also did not fully mimic endogenous insulin secretion, and hypoglycaemia remained a common adverse effect.[4]*

Long-acting (basal) insulin analogues were developed to provide a more physiologic pharmacokinetic/ pharmacodynamic (PK/PD) profile with longer duration of action, less intra-patient variability, less pronounced peak in time-action profiles, and decreased hypoglycaemic risk compared with human insulin.[5] However, clinical challenges regarding the management of diabetes with insulin still exist.Insulin detemir and insulin glargine both have a longer duration of action and a flatter profile than NPH. Both have less intra-patient variability, less pronounced peak in time-action profiles and decreased hypoglycaemic risk than NPH but even these insulin analogues do not last for 24 hours in some patients requiring up to two injections to achieve glycaemic control.[6-11]. It is estimated that approximately 40% of type 1 patient still require twice daily injections of long-acting insulin analogues like glargine and detemir and these patients in particular could benefit from newer basal insulin options with longer time-action profiles.[12, 13]

It would be worthwhile to note that just prolonging the half life of basal insulin may not merely yield a clinical benefit. These lessons can be learnt from the studies with bovine-NPH and ultra-lente insulin. Though both had much longer half life of approximately 36 hours, bovine-NPH had very poor bio-availability requiring very high doses and ultra-lente had a very peculiar property of erratic absorption leading to labile blood glucose swings. Both are no longer available for clinical use and hence it may be concluded that longer acting basal insulin may not necessarily be better. Therefore, the need of hour is to have long acting insulin (with duration of action of at least 24 hours) with good biological properties.[14]Newer basal insulin analogues like degludec, PEG-lispro and glargine U300, have longer, flatter time-action profiles with lesser variability and thus expected to have lesser hypoglycaemia (particularly nocturnal). This mini review will critically analyse the progress with these three newer basal insulin analogues and will attempt to

understand whether this advancement actually translated in any clinical benefits.

Insulin Degludec

Insulin degludec is a neutral, soluble, ultra-long-acting basal insulin analogue that has the same amino acid sequence as human insulin, with the following structural modification: deletion of the threonine amino acid residue at B30 and the addition of a fatty acid (hexadecanedioic acid) to the lysine at B29 via a glutamic acid spacer. In the presence of phenol and zinc (i.e. in its pharmaceutical formulation), insulin degludec has a soluble, stable dihexamer structure. Following subcutaneous injection, the phenol dissipates and insulin degludec forms a depot of multihexamer chains. As the zinc diffuses, these multi-hexamers gradually disassemble into biologically active monomers that are slowly absorbed into the circulation.[15] Thus, there is prolonged, stable release of insulin degludec from the subcutaneous depot, resulting in a glucose-lowering profile that is ultra-long and flat.[16] The duration of action of insulin degludec was found to be >42 hour in patients with type 1 diabetes. Insulin degludec has a mean elimination half-life of ~ 25 hour. In patients with type 2 diabetes, steady state was reached in 2–3 days with subcutaneous administration of once-daily insulin degludec. At steady state, there was no day-to-day change in overall exposure for insulin degludec.[16, 17] Within-subject variability of insulin degludec is four times less compared to glargine and in fact least compared to all available basal insulins.[17, 18] The degradation of insulin degludec is similar to that of human insulin, with all metabolites being inactive. The primary route of elimination of insulin degludec is via degradation at the insulin receptor independent of dose.[17]

Seven randomised, controlled, open label, phase 3a treat-to-target trials (26 or 52 week)typically named BEGIN trial compared degludec versus glargine (2 trials in type 1 diabetes and 5 trials in type 2 diabetes).[19-25] One randomised, open label, phase 3a treat-to-target trials (26 week) of degludec were also compared with insulin detemir (type 1 diabetes).[26] All these trials compared degludec once daily either in fixed or flexible dose.[34]

Results from all the eight head-to-head trials showed non-inferiority of degludec over glargine or detemir. There was no difference in A1c primarily as these were treat-to-target trials, however degludec consistently lowered FPG more than glargine and detemir in many of the trials (4 trial).[21,24-26] The mean total daily insulin dose was also consistently lower with degludec across majority of the studies (6 trials).[19-21,23,25,26] A very recent post-hoc patient-level meta-analysis (all the five phase 3a trials of type 2 diabetes) compared the within-subject variability in mean blood glucose assessed via 9-point self-measured blood glucose (9P-SMBG) profiles.[27] Interestingly, within-subject variability in mean 9P-SMBG was significantly lower for degludec over glargine thereby reinforcing the finding seenwith PK studies.[27] Additionally, a pooled analysis conducted from four phase 3a studies of basal-oral therapy (BOT, type 2 diabetes), revealed that, degludec has 82% higher likelihood ($p<0.05$) for achieving FPG without causing hypoglycaemia compared to glargine.[28]

A patient-level meta-analysis (all seven trials in type 1 and type 2 diabetes) compared the hypoglycaemic events of two insulin (degludec versus glargine) analysed by negative binomial regression model.[29] Nocturnal hypoglycaemia were significantly lower (-26%) with degludec over glargine in combined population (- 32% in type 2 diabetes and -17% in type 1 diabetes). Overall hypoglycaemia was only marginally lower with degludec (-9%) over glargine.[29] The cost-effectiveness of degludec versus glargine has also been evaluated in adults with type 2 diabetes mellitus using a short-term economic model. This analysis demonstrates that degludec is a cost-effective treatment option compared to glargine and offers additional benefits to patients suffering from recurrent hypoglycaemia.[30]

Interestingly, the criteria used to define hypoglycaemia and nocturnal timings in these head-to-head studies, received criticism from USFDA. Notably, ADA defines hypoglycaemia as blood sugar < 70 mg/dl and none of these degludec studies followed this ADA principle but in reality neither of the earlier basal insulin studies done so far with glargine and detemir used these ADA criteria in their pre-approval studies when compared to NPH (possibly because these definitions emerged later). However, when this ADA criterion of hypoglycaemia was applied to these degludec head-to-head studies against glargine, the margin of benefits lowered by approximately 7-8%, nonetheless remain significant in quite a few studies. When nocturnal timings were changed by 2 hours on either side of Novo-Nordisk timings (as stated by FDA), the margin of benefit alsoreduced to some extent but nevertheless persisted in some studies.[31,32]Although FDA review board have not yet approved degludec based upon their updated data which showed increase in major adverse cardiac events (MACE) by 33% when unstable angina were excluded from original dataset, other regulators like European agency (EMA), Japan FDA and many other countries including Mexico and India have already given their approval to degludec based on the same original data. FDA will likely reconsider for its approval once further updated data in this regard is placed. Nevertheless, it is evident that when unstable angina was not excluded from the original data set of the pre-approved protocol, MACE events were not found to be raised with degludec. It is also unclear as to why FDA decided to exclude unstable angina from MACE.[31, 32]

However, an area which probably needs further clarification about degludec is the effect of over-insulinization and its consequences on CV effect and mitogenecity in long term. Generally, in insulin-treated persons with type 2 diabetes, it is usual to recommend that plasma insulin concentrations

remain within a 50–200 pmol/L range in order to avoid over-insulinization. Such concentrations are achieved when daily doses of insulin glargine or NPH insulin approximate 0.4 units per kg. However, the total plasma insulin concentrations are much greater in persons treated with insulin degludec. As these insulin derive their protracted action from the insertion of a long chain fatty acid moiety, stable total plasma concentrations as high as 6000 pmol/L are observed for insulin degludec.[33]The consequences of such high insulin concentration is not yet known. Moreover, as the free to bound ratio of plasma insulin concentrations remains unknown, we need to fully understand as to how this insulin are eliminated or degraded.A prospective CV studies with degludec which is already in progress will expectedly throw some lights on these issues.

Pegylated Lispro Insulin (PEG-LISPRO)

Since theperipheral administration of insulin does not replicatethe physiological two- to threefold higher portal versus systemiccirculating insulin levelsand makesan imbalance betweenhepatic and peripheral metabolic actions, anbasal insulin analogue with predominant hepatic selectivity were developed.

Poly-ethylene-glycol (PEG) is a non-toxic neutral polyether which can be conjugated to proteins. Each monomer can bind three molecules of water allowing it to become highly hydrated. Insulin lispro has been PEGylated at lysine B28, via a urethane bond. PEGylation of proteins increases the hydrodynamic size of the molecule to which it is appended.[35] PEG-lispro has a hydrodynamic diameter of 7.8 ± 0.4 nm, which is four times larger than lispro and analogues to a globular protein of size approximately 75 kDa.[36]When administered to the subcutaneous tissue, this increase in hydrodynamic size serves to delay the absorption ofPEGylated proteins by slowing their diffusion rate. Moreover, glomerular filtration of such proteins is also reduced since the increase in molecular size supersedes the renal ultra-filtration cut-off. These factors are important considerations with respect to protracting the half-life of PEGylated proteins. Phase 1 studies in healthy volunteers demonstrated that serum concentrations of PEG-lispro were relatively flat for approximately 48 h post-dose, with t1/2 values ranging from 24 to 48 h, and a duration of action of at least 36 h, reflective of the prolonged serum concentration-time profile. PEG-lispro also demonstrates low intra-subject variability following single subcutaneous doses: < 18% for pharmacokinetic and < 32% for glucodynamic profile.

The binding affinity of PEG-lispro to the insulin receptoris 17 times less than insulin lispro (about 6%), and the affinity for insulin-like growth factor 1 receptor ismore than 32 times less than insulin lispro, which may indicate lesser mitogenic potential.[37,38]The reducedbinding capacity to the receptor may alsoin part explain that the molar quantities required toachieve half-maximal response are greater with PEG-lispro than lispro. Other possibilities could be increasednonreceptor-mediated clearance or less bioavailabilityafter administration subcutaneously.[43]The fateof PEG-lispro after receptor binding is unknown.

Until now, few clinical data on PEG-lispro have been published. An open-label, randomized, Phase II, 12-week trial in type 2 diabetes (n = 288) compared the efficacy and safety of once-daily PEG-lispro versus glargine in combination with metformin and/or sulfonylurea.[39] At equivalent glycemic control, PEG-lispro was associated with a 48% reduction in nocturnal hypoglycemia after correcting for baseline pre-randomization rate, and with weight loss (-0.58 kg versus + 0.31 kg , p = 0.001). Data from a subset of patients from this study (51 with PEG-lispro and 25 with glargine) who underwent continuous glucose monitoring (CGM on three consecutive days) suggested that PEG-lispro is associated with reduced blood glucose variability versus insulin glargine.[40]

The incidence of total and nocturnal hypoglycaemia didnot differ between the two groups, although PEG-lispro treated patients had a 48% reduction innocturnal hypoglycaemia after adjusting for run-in periodof hypoglycaemia. At week 12, mean insulin dose/kg was 1.5-fold greater with PEG-lispro than with insulin glargine treatment. The finding of weight loss associated with PEG-lispro was quite unexpected, but was also found in a small, crossover study comparing once-daily PEG-lispro with insulin glargine (each given with prandial insulin) in 137 patients with type 1 diabetes.[41]Although the risk of nocturnal hypoglycaemia was 25% lower with PEG-lispro, total hypoglycaemia rates were higher and severe hypoglycaemia did not differ between the two treatments. A weight loss of 1.2 kg was reported during PEG-lispro treatment versus 0.7 kg gain with glargine.[41]A pooled analysis of the two trials suggests that weight loss with PEG-lispro was not dependent on baseline body mass index, hypoglycemia, or gastrointestinal adverse events.[42, 43]The weight-sparing effect is probably a result of thehepato-selectivity of PEG-lispro leading to less lipogenesisand increased lipid oxidation compared with insulinglargine.[43] Liver transaminase levels rose significantly across patients treated with PEG-lispro, although the mean values remained within normal limits; moreover, PEG-lispro was associated with lower high density lipotrotein (HDL)-cholesterol, higher low density lipoprotein (LDL)-cholesterol, and higher triglyceride concentrations when compared to glargine.[39, 41]

Currently, eight phase III trials have been planned and recruiting patients on PEG-lispro, these are typically named IMAGINE trials of which, three(IMAGINE - 1, 3 and IMAGINE- 7) is being conducted in type 1 and five with type 2 diabetics (IMAGINE – 2, 4, 5, 6 and IMAGINE – Asian).[44]The results from clinical trials of longer duration in relation tohepatic fat content, risk of hypoglycaemia, weight regulation,lipoprotein subclass distribution and

concentration,and other cardiovascular disease risk factors incomparison with not only insulin glargine but also insulindegludec are of fundamental interest. Furtherclinical data will reveal whether a basal insulin analogue with preferential liver specific action results in therapeuticadvantages.

Glargine U300

This is a newer high-strength glargine formulation containing glargine at a concentration of 300 U/ml rather than the usually available glargine 100 U/ml. Although the mechanism of protraction of this product is essentially the same as for the U100 strength formulation, U300 forms a compact subcutaneous depot with a smaller surface area to produce a more gradual and prolonged release compared to glargine. Consequently, glargine U300 has a flatter PK/PD profile, with a prolonged duration of action compared to glargine U100.[45]Five phase III studies with glargine U300 have been planned of which three is being conducted in type 2 diabetics (EDITION-I,II,III, JP II) and two is being conducted in type 1 (EDITION-IV, JP I). Currently the clinical evidence for the supposed clinical benefits of this new glargine formulation is limited to two Phase III (EDITION-I and EDITION-II), which are available but still to be published as full reports. Also, some early top-line results of other U300 trials, EDITION-III (insulin naive type 2 diabetes) and EDITION-IV, EDITION-JP I (type 1 diabetes) have been made available on sponsored website and sooner expected to declare.

In EDITION-Itrial, 807 patients on basal-bolus insulin plus oral diabetes drugs were randomized to receive glargine U300 or glargine U100 once-daily for 6 months in combination with prandial insulin, while continuing on oral drugs. As these are treat-to-target trial there were similar reductions in HbA1c from baseline to 6 months and similar proportions of patients achieving an HbA1c < 7%. However, there was a 21% reduction in severe or confirmed nocturnal hypoglycemia (<70 mg/ml) and a lower occurrence of any nocturnal hypoglycemic event with glargine U300.[46] There were no differences in other adverse events. In EDITION-II trial, 811 patients on basal insulin plus oral diabetes drugs were randomized to glargine U300 or glargine U100. Although both insulin achieved a similar HbA1c reduction,there was 23% less severe or confirmed (plasma glucose <70 mg/dl) nocturnal hypoglycaemia with U300 (p=0.036). Incidence of any nocturnal hypoglycaemia was 27% lower with U300.[47]Surprisingly, the doses of glargine U300 were approximately 10% higher than U100 at the end of both the study.

EDITION-III compared U300 with U100 in 878 people with type 2 diabetes not previously treated with insulin and uncontrolled on oral medication. Although the rates of severe or nocturnal confirmed hypoglycaemia in EDITION-III were lower with U300 but unlike EDITION-I and II, the reduction was not statistically significant.

EDITION-IV enrolled 549 type 1 patients internationally, while EDITION-JP I was conducted in 243 type Japanese patients. The primary endpoint was met in both studies which showed similar reductions in HbA1c at 6 months but confirmed and severe nocturnal hypoglycaemia from month 3 to 6 was not pre-specified as a main secondary endpoint per study protocol.[47] Analyses of several hypoglycaemia categories are underway and will be presented soon.

Conclusion

The quest to find the ideal basal insulin continues. Glargine is a an improvement over NPH, being longer acting, used once daily, with much lesser variability and lesser nocturnal hypoglycaemia compared to NPH. Detemir is even more improvised technically with lesser variability; lesser nocturnal hypoglycaemia and lesser weight gain compared to glargine but often needs twice daily injection and relatively larger doses. Both glargine and detemir cannot be mixed with other insulin. Degludec currently seems to be most improvised with a flatter profile, least variability, and a truly once daily with the advantage of flexible timing of administration, lesser nocturnal hypoglycaemia (compared to glargine and detemir) with additional ability to be mixed with other insulin as well as GLP- 1agonist.

Glargine U300 seems to have some advantage of lesser nocturnal hypoglycaemia when compared to U100 but more data from further studies is currently required to substantiateit's conceivableadvantage. PEG-lispro seems to possess a hepatic selectivity with unique advantage of weight loss and a better PK-PD profile compared to glargine U100 along with the suggestion of lesser nocturnal hypoglycaemia but it still has to go a long way from the safety perspective. Results from its phase III trials will shed further light on these issues and clarify their advantage over existing basal analogues. Finally, cost should also be considered by decision makers, as most health providers have limited budgets and hard choices have to be made on cost-effectiveness.

References

1. Deckert T, Andersen OO, Poulsen JE. The clinical significance of highly purified pig-insulin preparations. Diabetologia. 1974;10:703–8.
2. Borgono CA, Zinman B. Insulins: Past, present, and future. EndocrinolMetabClin North Am. 2012;41:1–24
3. Tibaldi JM. Evolution of insulin development: focus on key parameters. AdvTher 2012;29:590–619
4. Shah V N, Moser E G, BA et al. The future of basal insulin. Diabetes Technology & Therapeutics 2013; 15,:727-32
5. Pieber TR, Treichel HC, Hompesch B et al. Comparison of insulin detemir and insulin glargine in subjects with type 1 diabetes using intensive insulin therapy. Diabet Med. 2007;24:635–42.
6. Rosenstock J, Davies M, Home PD, Larsen J, Koenen C, Schernthaner G. A randomised, 52-week, treat-to-target

trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. Diabetologia 2008; 51: 408–416.
7. Le Floch JP, Levy M, Mosnier-Pudar H, Nobels F, Laroche S, Gonbert S et al. Comparison of once- versus twice-daily administration of insulin detemir, used with mealtime insulin aspart, in basal-bolus therapy for type 1 diabetes: assessment of detemir administration in a progressive treat-to-target trial (ADAPT). Diabetes Care 2009; 32: 32–37.
8. Robertson KJ, Schoenle E, Gucev Z, Mordhorst L, Gall MA, Ludvigsson J. Insulin detemir compared with NPH insulin in children and adolescents with Type 1 diabetes. Diabet Med 2007; 24: 27–34.
9. Garg SK, Gottlieb PA, Hisatomi ME, et al. Improved glycemic control without an increase in severe hypoglycemic episodes in intensively treated patients with type 1 diabetes receiving morning, evening, or split dose insulin glargine. Diabetes Res ClinPract 2004; 66: 49–56.
10. Peterson G E. Intermediate and long-acting insulins: a review of NPH insulin, insulin glargine and insulin detemir. Current Medical Research and Opinion 2006, 22; (12): 2613–2619
11. Heise T, Pieber TR. Towards peakless, reproducible and long-acting insulins. An assessment of the basal analogues based on isoglycaemic clamp studies. Diabetes ObesMetab 2007; 9:648–59
12. Evans M, Schumm-Draeger PM, Vora J, et al. A review of modern insulin analogue pharmacokinetic and pharmacodynamic profiles in type 2 diabetes: improvements and limitations. Diabetes ObesMetab 2011; 13:677–84
13. Ashwell SG, Gebbie J, Home PD. Optimal timing of injection of once-daily insulin glargine in people with Type 1 diabetes using insulin lispro at meal-times. Diabet Med 2006; 23: 46–52.
14. Kalra S, Unnikrishnan AG, Baruah M, et al. Degludec insulin: A novel basal insulin. Indian J EndocrinolMetab 2011; 15(suppl 1):S12-S16
15. Jonassen I. Design of the Novel Protraction Mechanism of Insulin Degludec, an Ultra-long-Acting Basal Insulin. Pharm Res DOI 10.1007/s11095-012-0739-z
16. Heise T, Nosek L, Bøttcher SG, et al. Ultra-long-acting insulin degludec has a flat and stable glucose-lowering effect in type 2 diabetes. Diabetes ObesMetab 2012;14(10):944–50.
17. Keating GM. Insulin Degludec and Insulin Degludec/Insulin Aspart: A Review of Their Use in the Management of Diabetes Mellitus. DOI 10.1007/s40265-013-0051-1.
18. Heise T, Hermanski L, Nosek L, et al. Insulin degludec: four times lower pharmacodynamic variability than insulin glargine under steady-state conditions in type 1 diabetes. Diabetes, Obesity and Metabolism 2012; 14: 859–864.
19. Heller S, Buse J, Fisher M, et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. Lancet 2012; 379(9825): 1489-1497.
20. Mathieu C, Hollander P, Miranda-Palma B, et al. Efficacy and safety of insulin degludec in a flexible dosing regimen vs insulin glargine in patients with type 1 diabetes (BEGIN: Flex T1): A 26-week randomized, treat-to-target trial with a 26-week extension. J ClinEndocrinolMetab2013; 98(3): 1154-1162.
21. Zinman B, Philis-Tsimikas A, Cariou B, et al. Insulin degludec versus insulin glargine in insulin-naive patients with type 2 diabetes: A 1-year, randomized, treat-to-target trial (BEGIN Once Long). Diabetes Care 2012; 35(12): 2464-2471.
22. Garber AJ, King AB, Del Prato S, et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. Lancet 2012; 379(9825): 1498-1507.
23. Onishi Y, Park SW, Yoo SJ, et al. Insulin degludec improves glycemic control in insulinnaive patients with type 2 diabetes: Results of a randomized pan-Asian trial (Abstract 1059-P). Diabetes 2012; 61(Suppl 1): A272.
24. Meneghini L, Atkin SL, Gough SC, et al. The efficacy and safety of insulin degludec given in variable once-daily dosing intervals compared with insulin glargine and insulin degludec dosed at the same time daily: A 26-week, randomized, open-label, parallel-group, treat-to-target trial in individuals with type 2 diabetes. Diabetes Care 2013; 36(4): 858-864.
25. Gough SC, Bhargava A, Jain R, et al. Low-volume insulin degludec 200 units/mL once daily improves glycemic control similar to insulin glargine with a low risk of hypoglycaemia in insulin-naive patients with type 2 diabetes: A 26-week, randomized, controlled, multinational, treat-to-target trial: The BEGIN LOW VOLUME trial. Diabetes Care 2013; May 28. [Epub ahead of print].
26. Novo Nordisk. Insulin degludec and insulin degludec/insulin aspart treatment to improve glycemic control in patients with diabetes mellitus.Briefing Information for the November 8, 2012 Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee. Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/En docrinologicandMetabolicDrugsAdvisoryCommittee/UCM327017.pdf
27. Meneghini L F, Harris S B, Evans M, et al., Diabetologia 2013, 56; S 419: P-1043. 49th Annual Meeting of the European Association for the Study of Diabetes, Barcelona, Spain.
28. Zinman B, Vora J, Niemeyer M, et al. Diabetologia 2013,56;S 422: P-1051. 49th Annual Meeting of the European Association for the Study of Diabetes, Barcelona, Spain.
29. Ratner RE, Gough SC, Mathieu C, et al. Hypoglycaemia risk with insulin degludec compared with insulin glargine in type 2 and type 1 diabetes: a pre-planned meta-analysis of phase 3 trials. Diabetes ObesMetab2013; 15(2): 175-184
30. Evans M, Wolden M, Gundgaard J, et al. Cost-effectiveness of insulin degludec compared with insulin glargine for patients with type 2 diabetes treated with basal insulin - from the UK Health care cost perspective. Diabetes ObesMetab 2014 Apr;16(4):366-75
31. Owen D R, Metfin G, Monnier L. Basal insulin analogues in the management of diabetes mellitus: What progress have we made? Diabetes Metab Res Rev 2014;30(2):104-19.
32. U.S. Food and Drug Administration - FDA Briefing Information, Insulin Degludec and Insulin Degludec/Aspart, for the November 8, 2012 Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee. Available from: http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm327015.pdf
33. Monnier L, Colette C, Owens D. Basal insulin analogs: from pathophysiology to therapy. What we see, know, and try to comprehend?Diabetes Metab. 2013 Dec; 39(6):468-76.
34. Singh AK, Sinha B. Basal insulin analogues – lesson learnt from current evidences. JIMA. Nov 2013, 111;11:735-742.

35. Caparrotta TM, Evans M. PEGylated insulin Lispro, (LY2605541)-a new basal insulin analogue. Diabetes ObesMetab 2014 May;16(5):388-95.
36. Hansen RJ, Cutler GB, Vick A, et al. LY2605541: leveraging hydrodynamic size to develop a novel basal insulin. Diabetes 2012;61(Suppl 1):A228
37. Beals JM, Cutler GB, Vick A, et al. LY2605541: leveraging hydrodynamic size to develop a novel basal insulin (Conference Abstract). Diabetologia 2012;55(Suppl 1):S23
38. Sinha VP, Choi SL, Soon DK, et al. Single-dose pharmacokinetics and glucodynamics of the novel long-acting basal insulin LY2605541 in healthy subjects. J ClinPharmacol 2014, doi:10.1002/jcph.276
39. Bergenstal RM, Rosenstock J, Arakaki RF, et al. A randomized, controlled study of once-daily LY2605541, a novel long-acting basal insulin, vs. insulin glargine in basal insulin-treated patients with type 2 diabetes. Diabetes Care 2012;35:2140-7.
40. Bergenstal RM, Rosenstock J, Bastyr EJ III, et al. Lower glucose variability and hypoglycemia measured by continuous glucose monitoring with novel long-acting insulin LY2605541 versus insulin glargine. Diabetes Care 2013, doi:10.2337/dc12-2621
41. Rosenstock J, Bergenstal RM, Blevins TC, et al. Better glycemic control and weight loss with the novel long acting basal insulin LY2605541 compared with insulin glargine in type 1 diabetes a randomized, crossover study. Diabetes Care 2012;36:522-8
42. Jacober SJ, Rosenstock J, Bergenstal RMContrasting weight changes with LY2605541, a novel long-acting insulin, and insulin glargine despite similar improved glycaemic control in T1DM and T2DM.Diabetes ObesMetab. 2014 Apr;16(4):351-6.
43. StenMadsbad. LY2605541- A Preferential Hepato-Specific Insulin Analogue. Diabetes 2014;63:390–392
44. http://clinicaltrials.gov/ct2/results?term=LY2605541+IMAGINE+trial&Search=Search
45. Tillner J, Bergmann K, Teichert L, et al. Euglycemic clamp profile of new insulin glargine U300 formulation in patients with Type 1 Diabetes (T1DM) is different from glargine U100 (Abstract 920-P). Diabetes 2013;62(Suppl 1):A234
46. Riddle MC, Bolli GB, Ziemen M, et al. New insulin glargine formulation: glucose control and hypoglycemia in people with type 2 diabetes using basal and mealtime insulin (EDITION I) (Abstract 43-LB). Diabetes 2013;62(Suppl 1A):LB12
47. Sanofi. Sanofi announces positive Phase 3 results for investigational new insulin U300. Press release, 22 June 2013. Available from: http://en.sanofi.com/Images/33225_20130622_EDITION-I-and-II-ADA_en.pdf