Closer Look

MEMORANDUM

Article in Nature Reviews Endocrinology questions cost-effectiveness of long-acting insulin analogs for type 1 diabetes - January 18, 2013

Executive Highlights

- In a recent "News and Views" piece in *Nature Reviews Endocrinology*, Dr. David Nathan questions whether long-acting insulin analogs are cost-effective in type 1 diabetes.

In a "News and Views" article recently published in Nature Reviews Endocrinology, Dr. David Nathan (Harvard Medical School, Boston, MA) questions whether what he characterizes as the "modest" benefits of long-acting insulin analogs in type 1 diabetes justify their added cost. The full article can be found at http://www.nature.com/nrendo/journal/v8/n12/full/nrendo.2012.208.html. Dr. Nathan argues that, while novel insulin treatments have been developed to reduce hypoglycemia and provide flexibility, the new basal analog insulin degludec (Novo Nordisk's Tresiba), may not offer a significant advantage over traditional analog options like insulin detemir (Novo Nordisk's Levemir) and insulin glargine (Sanofi's Lantus), or even NPH in terms of A1c-lowering efficacy or severe hypoglycemia. While we agree that the cost-effectiveness of insulin analogs deserves study given their costs (though the daily cost of insulin for type 1 diabetes is still lower than many oral drugs for type 2 diabetes), we also believe that the physiological benefits are clear to many patients who have switched from NPH to a basal analog. The increased stability associated with better insulins is very important from our view as is the greater flexibility in terms of dosing; we also believe that the benefits of degludec will be more apparent when combined with ultra rapid acting analogs still in development. From our view, the importance of increased quality of life may not be seen in A1c, but it may be more clear through looking at the impact of "time in zone"; it is hard to put a value on this, but to suggest that such products not be approved or reimbursed might change the pace of innovation ahead. Finally, we are surprised and disappointed to see an A1c comparison to the DCCT and disparagement that degludec does not provide an A1c drop as large as DCCT did. The trials were not designed the same way, DCCT was an extremely long trial in which patients started with very high A1cs (which makes it easier to show a bigger drop), and most importantly, the treatment arm in DCCT had three times the number of severe hypoglycemic events as did the placebo arm. We want patients to move forwards, not backwards, and though DCCT was a landmark trial in terms of the importance of showing the very very great importance of tight glycemic control, we hope patients never again return to severe hypoglycemic levels shown in that trial. To discuss the A1c drop without noting the downside of severe hypoglycemia seems like a sub-optimal way to characterize that trial. While degludec offers, in our view, incremental change compared to the changes made moving from NPH to the first-gen basal insulin analogs, the change is nonetheless real. We note in closing that pricing has not been established for degludec; other leading diabetes companies (albeit smaller) like Dexcom and Insulet have announced pricing will be the same for their next gen products (the widely praised G4 and the advanced, smaller pod) as for previous generation products. Both companies are setting a very important example in the diabetes field and we hope that Novo Nordisk takes on similar pricing leadership as well, particularly given the extreme cost pressures seen in diabetes of late that are being incorrectly associated with therapies and technologies rather than much larger cost buckets of preventable complications.

- **Dr. Nathan first draws into question whether the ultra-long acting insulin degludec (Novo Nordisk's Tresiba) represents a step forward for insulin analogs, with the underlying assumption that degludec will cost more than existing basal analogs.** We would point out that pricing has not yet been established; there are multiple products that are "more" innovative where pricing has not increased, and we hope Novo Nordisk offers degludec at

the same price as Levemir to maximize accessibility to patients. While degludec was developed with the goal of reducing hypoglycemia and increasing dosing flexibility, Dr. Nathan emphasizes that clinical evidence does not support the use of premixed degludec/aspart (Ryzodeg) over current insulin options. A treat-to-target trial comparing premixed degludec/aspart (taken once daily with two daily aspart injections) to basal-bolus therapy with insulin detemir (Novo Nordisk's Levemir; one daily detemir injection plus three daily aspart injections) found no difference in A1c reductions, rate of hypoglycemia, or quality of life (Hirsch et al., *Diabetes Care* 2012). We would wonder if the "time in zone" would be different; we do not think A1c comparison is the "end-all, be-all" and are very curious to know what CGM comparisons will show. Other type 1 studies comparing degludec with glargine have found similar results, with degludec providing no benefit in the rate of severe hypoglycemic events although we believe that CGM "time in zone" analyses may show something different. More importantly, we wonder what the combination of improved rapid acting insulins compared with degludec will show; we believe the potential is high.

- **Dr. Nathan points out that the non-analog insulins used in DCCT allowed patients to reach a mean A1c target of 7% for several years (from a baseline of 8.8-9.0%) which is lower than the A1c levels obtained with degludec** (from 8.3% at baseline to 7.6% at 26 weeks in a 2012 study [Hirsch et al., *Diabetes Care* 2012]; from 7.7% to 7.3% in a one-year study comparing degludec with glargine). While degludec and other basal insulin analogs appear to reduce the risk of severe hypoglycemia, whether this advantage persists in patients actually achieving an A1c of 7% is not clear.
- **To us, this thought-provoking article underscores the need to better study and characterize the advantages of newer therapies. This is very important. In our view, the paper also fails to address some important points.**
    - We wonder whether degludec and glargine lead to more "time in zone" compared to NPH, as glycemic variability is receiving increasing attention as a potential contributor to risk of complications.
    - Additionally, Dr. Nathan does not discuss mild to moderate hypoglycemia, or nocturnal hypoglycemia, which patients deal with on a more frequent basis than severe hypoglycemia. For reference, members of the FDA's EMDAC appeared to believe that degludec represents an improvement over current insulin options, voting 8-4 in favor of the drug's approval largely due to the ability to maintain glycemic control with flexible dosing and true 24-hour coverage (see our report at http://www.closeconcerns.com/knowledgebase/r/c53dd554).
    - Finally, Dr. Nathan also acknowledges that, if he is to make a cost-effectiveness argument, the larger type 2 diabetes population is much more significant for cost savings, but he does not discuss type 2 data, which is odd from our perspective since plenty of patients took degludec in trials.
- **We believe that study of insulin analogs' cost-effectiveness is warranted due to their very high prices, but in our view, the physiological benefits are clear - the question isn't whether these analogs improve quality of life for patients (as Dr. Nathan seems to suggest) but whether the costs are justified.** For an in-depth debate on this topic between Dr. Irl Hirsch (University of Washington, Seattle, WA) and the NICE's Dr. Amanda Adler(Adenbrooke's Hospital, Cambridge, UK), see page 9 of our Keystone 2012 full report here (http://www.closeconcerns.com/knowledgebase/r/02a4e396).

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