

THE NEW BATTLEGROUND FOR NOVEL DIABETIC AGENTS: INCREMENTAL COST-EFFECTIVENESS RATIO

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Diabetes remains one of the hottest R&D areas for the pharmaceutical industry. Physicians now have numerous therapeutic options, beyond insulin and glucagon, to choose from and the research pipeline suggests that the selection may become more diverse. Nine classes of therapeutics are available on the market including insulins, secretagogues, biguanides, insulin sensitizers, carbohydrate blockers, incretin mimetics, neuroendocrine hormones, DPP-IV inhibitors, and dopamine agonists. There is also a seemingly endless pipeline of novel mechanisms of action (MOAs) attempting to provide better HbA1c control and preserve β -cell functioning. As more novel therapeutics and me-too competitors enter the diabetes market, the treatment algorithm will become even more inundated, which will pressure pharmaceutical players to develop marketing strategies and clinical programs that will highlight the unique value of their branded therapeutic. Over the next decade, clinical trials will increasingly focus on the superiority of competing medication regimens, and on the fact that the patient population will likely become more segmented as different MOAs demonstrate unique advantages for different patient sub-types. Additionally, the current market dynamics require new therapeutics to demonstrate cost effectiveness. Cost effectiveness, or more specifically [incremental cost-effectiveness ratio](#)

(ICER), is creating a higher hurdle for new therapeutics, especially new biologic agents. The efficacy and safety requirements for new agents are higher than for cheaper small molecules, and the only way a biologic agent will have a place in the treatment algorithm is if they demonstrate a dramatic improvement in long-term outcomes, while also demonstrating an acceptable ICER.

Cost effectiveness has changed the value proposition of agents in development

The pharmaceutical industry is investing heavily in diabetic therapies despite the general rule that therapeutics must be extremely affordable given the success of metformin, an inexpensive first-line diabetic drug. The market is likely to become even

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more price sensitive as thiazolidinediones (TZDs) head toward patent expiry and cheap generics flood the market. In fact, it will be interesting to see if DPP-IV inhibitors, the current gold-standard second-line therapeutic, are pressured into more third-line utilization as

payors favor cheaper therapeutic options. There is already a precedent for payors requiring physicians to utilize less effective and safe drugs due to cost effectiveness, namely in the case of sulfonylureas. Given this cost pressure dynamic, it is a calculated risk for companies to invest in the development of expensive biological agents. On the one hand, if short-term use of a biologic agent significantly

delays the onset of disease progression or provides a significant remission, then the cost justification is easy. On the other hand, a trend toward multimodal treatment is developing, which involves the combination of *good-enough* (cheap) drug therapy, plus incentives for diabetes education and behavioral change (i.e., improving dietary and exercise habits). If this multimodal regimen fails, then more expensive, newer therapies may be considered. If this multimodal approach to diabetic care ([see our blog post on the decentralization of diabetes care](#)) takes root, then drug developers need to reevaluate the market interest and ICER for new expensive drug therapies.

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Potential clinical value of immunomodulators


Two upcoming market events could eventually help determine how viable new expensive therapies are for the diabetes market. First, [genotyping and phenotyping diabetes may lead to sub-types of diabetes beyond type 1 and type 2, and may allow for identifying more rigid criteria for metabolic syndrome or pre-diabetes](#). Second, new clinical data on immunomodulators suggest biological agents could have a significant impact on the diabetes space, particularly if the benefits of these therapies provide significant leaps with regard to the time-to-diabetic-complication. Several novel immunomodulating MOAs have been developed to treat type 1 diabetes; however, there have been several notable failures. For example, the attempts by GSK and Tolerx to develop oteelixumab, a humanized anti-CD3 monoclonal antibody, failed in a large Phase III trial earlier this year. While GSK and Tolerx have not publicly announced the termination of the oteelixumab program and plan to analyze the results of a second suspended Phase III trial, uncertainty about this class of drug exists.

Teplizumab, a similar agent co-developed by Lilly and MacroGenics, also failed to meet its primary endpoints and was terminated in 2010. However, despite these two notable failures, there remain promising agents, such as DiaPep277, Kineret, and anti-CD40s targeted drugs, among others. In addition, one of the more reassuring signs

demonstrating the potential clinical value of immunomodulators for type 1 diabetes came from [a National Institutes of Health \(NIH\)-funded study of abatacept](#) (brand name [Orencia](#)). The initial results from the abatacept trial suggest that preserving endogenous beta-cell function and delaying the onset of diabetes can

significantly delay complications and lead to less hyperglycemia. Specifically, [fewer patients on abatacept \(32%\) had C-peptide levels, a protein that shows how much insulin the body is producing, below 0.2nmol/L at 24 months than patients receiving placebo infusions \(43%\)](#). Hemoglobin A1c remained under better control at 24 months with abatacept despite similar insulin doses. The proportion under an A1c of 7% was 47% compared with 26% for patients receiving placebo infusions (P=0.0071 over 24 months). While researchers have remained skeptical about the cost effectiveness of abatacept as a therapy for type 1 diabetes, the cost effectiveness bar which abatacept has to overcome may be facilitated with the recent FDA approval of the subcutaneous formulation on August 2, 2011. The ICER for abatacept is still unclear for diabetes; however, the ICER in rheumatology became notorious when the National Institute for Health and Clinical Excellence (NICE) rejected Orencia. [NICE reported the ICER for Orencia plus methotrexate \(i.e., the standard therapeutic regimen\), compared with conventional DMARDs, represented a gain of \\$47,878 per quality-adjusted life year \(QALY\)](#).

While further research is needed to determine if there are safe and effective therapies for preserving endogenous beta-cell functioning, other hurdles exist for new therapeutics. Demonstrating a clinically meaningful impact on preservation of endogenous beta-cells is an important advancement for diabetes; however, the field has moved beyond merely accepting scientifically important advances as the gateway for viable therapeutics. Diabetes is equally driven by

economic dynamics. New agents will have to demonstrate acceptable ICER versus the standard of care and superiority to other new therapeutic regimens. ICER evaluations are becoming a central battleground not only between new branded drugs and generic alternatives, but [also among new branded therapeutics.](#) 

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