

# Alzheimer's Disease Drug Development Targets Disease Modification

BY MITCHEL L. ZOLER

WASHINGTON — Finding a drug therapy for patients with Alzheimer's disease that not only improves symptoms but also slows or stops the underlying disease process and results in disease modification will be a major challenge.

Disease modification “indicates the drug is attacking the underlying biology of the disease. The medications we have now affect only symptoms and are palliative,” David S. Knopman, MD, said in an interview during the Alzheimer's Association International Conference 2015.

Designing trials capable of identifying disease-modifying drugs “turns out to be very challenging. In principle, a drug with disease-modifying effects would have bigger and more enduring effects, could be started earlier in the disease, and would ultimately be

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of greater benefit to patients and to society,” said Dr. Knopman, a professor of neurology at the Mayo Clinic in Rochester, MN. He participated in a session at the meeting focused on the potential design of trials that could test a drug's disease-modifying effect.

## Delayed Start

The most likely design that researchers seem ready to use is a “delayed-start” trial, in which placebo-treated patients who serve as controls in the initial, blinded, and randomized phase of an efficacy trial then cross over to open-label treatment once the first segment primary-endpoint stage is finished. In most trials “the open-label, long-term extension will occur anyway,” so adding a delayed-start element following the end of an efficacy trial “does not add a lot of complication to the design,” he said.

Two factors make a delayed-start analysis challenging. First, the drug needs to show efficacy during the initial, double-blinded phase. “Only if you see both a cognitive and some sort of functional-outcome benefit can you engage in the delayed-start analysis, to see if the effect is enduring,” Dr. Knopman said. The second limitation is patient dropout. “An open-label, long-term extension over another 1, 2, or 3 years will invariably lead to subjects dropping out because of health issues or social matters and that makes the statistical analysis more

complicated.” During one trial that was discussed in depth at the session, about 40% of patients who entered the delayed-start phase had left the study by the time this stage finished 2 years later.

## FDA Support

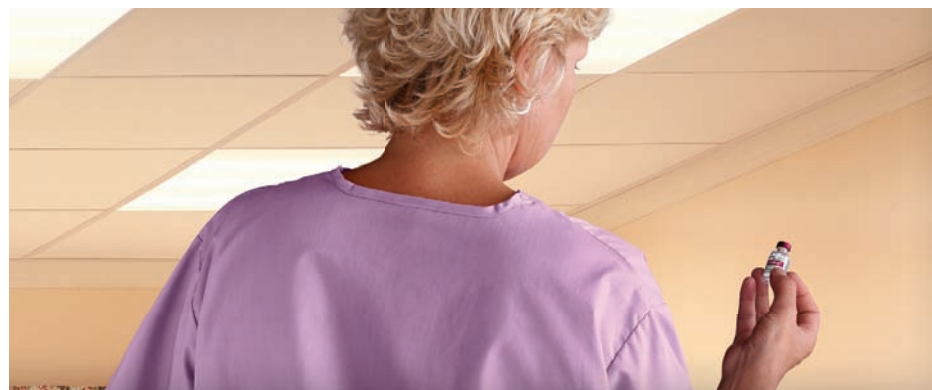
Despite these issues, adding a delayed-start phase to drug trials likely will become increasingly common, Dr. Knopman predicted. Drug developers “will probably include this as a secondary analysis

because it doesn't add much expense or added burden on participants, so it seems like a win-win.” Plus, representatives from the Food and Drug Administration who participated in the session seemed to endorse the general concept, he noted. But the most important caveat remains, he stressed. “You have to first show primary-outcome results. Only then you can talk about disease modification.”

The delayed-start trial design was developed by Eli Lilly. Dr. Knopman

received an honorarium from Lilly for chairing the data and safety-monitoring committee for two of their trials through 2012, but since then he has not had a financial relationship with the company. He currently is an investigator in a trial sponsored by Lilly. He said he has no other disclosures.

MITCHEL L. ZOLER is with the Philadelphia bureau of Frontline Medical News.



**Humalog small vials sized for individual patient care.\***

### Indication for Humalog

- Humalog is an insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus.

### Important Safety Information for Humalog

#### Contraindications

- Humalog is contraindicated during episodes of hypoglycemia and in patients who are hypersensitive to Humalog or any of its excipients.

#### Warnings and Precautions

- **Never Share a Humalog KwikPen, Cartridge, Reusable Pen Compatible with Lilly 3 mL Cartridges, or Syringe Between Patients:** Humalog KwikPens, cartridges, and reusable pens compatible with Lilly 3 mL cartridges must never be shared between patients, even if the needle is changed. Patients using Humalog vials must never share needles or syringes with another person. Sharing poses a risk for transmission of blood-borne pathogens.
- **Dose Adjustment and Monitoring:** Closely monitor blood glucose in all patients treated with insulin. Change insulin regimens cautiously. Concomitant oral antidiabetic treatment may need to be adjusted. The time course of action for Humalog may vary in different individuals or at different times in the same individual and is dependent on many conditions, including delivery site, local blood supply, or local temperature. Patients who change their level of physical activity or meal plan may require insulin dose adjustment.
- **Hypoglycemia:** Hypoglycemia is the most common adverse effect of Humalog. The risk of hypoglycemia increases with tighter glycemic control. Educate patients to recognize and manage hypoglycemia. Hypoglycemia can happen suddenly and symptoms may vary for each person and may change over time. Early warning symptoms of hypoglycemia may be different or less pronounced under conditions such as long-standing diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control. These situations may result in severe hypoglycemia and possibly loss of consciousness prior to the patient's awareness of hypoglycemia. Severe hypoglycemia may be life threatening and can cause seizures or death.

Use caution in patients with hypoglycemia unawareness and who may be predisposed to hypoglycemia. The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. Rapid changes in serum glucose levels may induce symptoms similar to hypoglycemia in persons with diabetes, regardless of the glucose value.

Timing of hypoglycemia usually reflects the time-action profile of administered insulins. Other factors such as changes in food intake, injection site, exercise, and concomitant medications may alter the risk of hypoglycemia.

- **Allergic Reactions:** Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with Humalog.
- **Hypokalemia:** Humalog can cause hypokalemia, which, if untreated, may result in respiratory paralysis, ventricular arrhythmia, and death. Use caution in patients who may be at risk for hypokalemia (eg, patients using potassium-lowering medications or medications sensitive to serum potassium concentrations).
- **Renal or Hepatic Impairment:** Frequent glucose monitoring and insulin dose reduction may be required in patients with renal or hepatic impairment.

### Important Safety Information for Humalog, continued

#### Warnings and Precautions, continued

- **Mixing of Insulins:** Humalog for subcutaneous injection should not be mixed with insulins other than NPH insulin. If Humalog is mixed with NPH insulin, Humalog should be drawn into the syringe first. Injection should occur immediately after mixing.
- **Subcutaneous Insulin Infusion Pump:** Humalog should not be diluted or mixed when used in an external insulin pump. Change Humalog in the reservoir at least every 7 days. Change the infusion set and insertion site at least every 3 days. Malfunction of the insulin pump or infusion set or insulin degradation can rapidly lead to hyperglycemia and ketosis. Prompt correction of the cause of hyperglycemia or ketosis is necessary. Interim subcutaneous injections with Humalog may be required. Train patients using an insulin pump to administer insulin by injection and to have alternate insulin therapy available in case of pump failure.
- **Drug Interactions:** Some medications may alter glucose metabolism, insulin requirements, and the risk for hypoglycemia or hyperglycemia. Signs of hypoglycemia may be reduced or absent in patients taking anti-adrenergic drugs. Particularly close monitoring may be required.
- **Fluid Retention and Heart Failure with Concomitant Use of PPAR-gamma Agonists:** Thiazolidinediones (TZDs), which are PPAR-gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin, including Humalog. This may lead to or exacerbate heart failure. Observe patients for signs and symptoms of heart failure and consider discontinuation or dose reduction of the PPAR-gamma agonist.

#### Adverse Reactions

- Adverse reactions associated with Humalog include hypoglycemia, hypokalemia, allergic reactions, injection-site reactions, lipodystrophy, pruritus, rash, weight gain, and peripheral edema.

#### Use in Specific Populations

- **Pediatrics:** Humalog has not been studied in children with type 1 diabetes less than 3 years of age or in children with type 2 diabetes.

#### Dosage and Administration

- Humalog should be given within 15 minutes before or immediately after a meal.

Please see accompanying Full Prescribing Information. Please see Instructions for Use included with the pen.

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\*Smaller vials contain 3 mL of insulin in a 5 mL vial.

*Humalog*

insulin lispro injection, USP (rDNA origin)  
100 units/mL

*Lilly*