Trampraprosate Falls Short in Phase III Alzheimer’s Trial

Unusually large placebo effect could be a recurring problem in studies that allow concomitant medications.

By Michele G. Sullivan
Mid-Atlantic Bureau

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rampraprosate, the first antiamyloid drug to enter a phase III trial, was not signif-
ically better than placebo in improving cognitive function in patients with Alzheimer’s
disease, according to officials of Neurochem Inc., manufacturer of the investigational agent and
sponsor of the North American trial.

The negative results are a blow to Alz-
heimer’s disease (AD) researchers and patient
advocacy groups, said Dr. Richard J. Caselli,
chair of neurology at the Mayo Clinic, Scopes-
dale. Caselli was the first anti-
amyloid drug to reach this point, and as such,
was widely watched by the Alzheimer’s dis-
ease community.” Dr. Caselli said in an inter-
view. “It’s failure to achieve its therapeutic
outcomes is therefore very disappointing.”

The question now is whether this failure pos-
es a serious challenge to the amyloid hypothesis of AD pathogenesis, he said. “Possibly not. Findings from a newly
released study suggest that in addition to its an-
tiamydloid effects, trampraprosate may have a competing effect favoring tau aggregation. It
remains too early to heavily discount the amy-
lid hypothesis, and other trials in progress will be watched expectantly.”

The North American Phase III study includ-
ed 1,102 patients with mild to moderate AD, re-
cruited from 67 sites in Canada and the United
States. Patients were randomized to placebo or
100 mg or 150 mg twice daily of trampraprosate.
They continued all their concomitant AD drugs
during the 18-month study period.

Although there were numerical differences in favor of trampraprosate, those differences failed to reach statistical significance in any of the three primary end points: the Alzheimer’s Disease Assessment Scale (ADAS-Cog), the Dementia Rating–Sum of Boxes rating scale (CDR-SB), or magnetic resonance imaging.

Dr. Margaritology’s Dr. Denis Garceau said the
company delayed the release of its findings,
which were to have been presented publicly in
June. In the meantime, Neurochem reworked
the statistical analysis and sought advice from the
Food and Drug Administration, said Dr. Garceau, who is senior vice president of drug
development. “While recognizing the chal-
nel of a trial at this magnitude, the FDA ad-
vised that neither the proposed adjusted mod-
elns nor any further adjustments could be used for this trial to support a positive effect of
trampraprosate,” Dr. Garceau said.

The data may, however, be used to modify the
primary analysis plan for the ongoing Eu-
ropean phase III trial, which includes 966 pa-
tients in 10 countries. Recruitment for that tri-
ial has completed, and new changes are possible, including changes to the study cohort,
duration of treatment, and the statistical analy-
sis, Dr. Garceau said. A company-appointed
independent advisor group, which reviewed the North American trial data, suggest any changes to the European trial, and ultimately recommend to Neurochem the fate of trampraprosate.

IEED: Uncertainty Reigns
In Diagnosis and Treatment

By Kerri Wachter
Senior Writer

Baltimore — The lack of diag-
nostic criteria has hamstrung at-
ttempts to diagnose involuntary emotional expression disorder. Dr. Sharon Handel said at a meeting on Alzheimer’s disease and related dis-
orders sponsored by Johns Hopkins University.

Even when they make the diag-
nosis with certainty, physicians have little to offer by way of Food and Drug Administra-
tion-approved therapy, said Dr. Handel, of the department of psychiatry and be-
havioral sciences at Johns Hopkins Uni-
versity, Baltimore. Part of the problem with identifying this condition has been
the numerous names under which it is known, she noted.

Involuntary emotional expres-
sion disorder (IEED) is also known as pseudobulbar affect and pathologic laughing or crying disorder. It’s estimated that more than 1 million people in the United States have IEED. The disorder has been associated with cerebrovascular ac-
cident, Alzheimer’s disease, multiple sclerosis, amyotrophic lateral scle-
rosis, and traumatic brain injury.

The hallmark of IEED is episodes of crying or laughing that are unre-
lated to or out of proportion with the ecciting stimulus. There is a dis-
connection between emotional ex-
pression and expersion. Emotional outbursts in IEED are involuntary, episodic, and incon-
gruent with baseline mood. The outbursts are intense, but are fol-
lowed by a return to baseline.

Dr. Handel said.

The differential diagnosis should in-
clude affective liability, emotional expression disorder, and witzelsucht. With affective liability, the subjective experience of an outburst of effect are not dissociated. Essential crying is a hereditary and lifelong tendency to cry easily. Witzelsucht is an ad-
duction to trivial joking, which can take the form of an inappropriate giddy affect and irritability or ag-
gressiveness.

In terms of clinical course, IEED frequently remains spontaneously within 6 months. Others may have remission with treatment within 3 months. Resolution of IEED can be independent of the resolution of depression. However, in some cases the disorder is chronic and persistent without treatment.

Treatment of IEED is still evolv-
ing. At present, there is no FDA-ap-
poved treatment for IEED. “What
are typically used—at least up to this point—are SSRIs. They tend to work quite quickly,” said Dr. Handel, who has no disclosures.

Dextromethorphan, in combina-
tion with quinidine, is being stud-
ied to treat patients who have IEED. Dextromethorphan is a nonopioid antisuasive, but it also has a number of other neuroph-
macologic properties. It is a potent in-
hibitor of this isozyme, thereby increasing and sustaining dex-
tromethorphan levels.