From: REDACTED lake/pprd/abbott;nsl REDACTED @abbott.com;smtp
To: REDACTED lake/pprd/abbott@abbott; REDACTED REDACTED
Bcc: lake/ppd/abbott@abbott
Cc:

Subject: more background on elderly agitation
Date: Wed Jul 09 2003 08:26:42 EDT

Another piece of background material. This is a little more along the lines of water under the bridge. Last year, marketing felt very strongly that an elderly agitation study should be monotherapy. In the email below, REDACTED was providing justification for adjunctive treatment instead of monotherapy. The email contains, however, several points related to reasons for failure of past studies and more detail on what a next study in elderly agitation should look like.

----- Forwarded by REDACTED LAKE/PPRD/ABBOTT on 07/09/2003 07:21 AM -----

REDACTED
07/08/2003 09:49 AM

To: REDACTED LAKE/PPRD/ABBOTT@ABBOTT
cc:
Subject:Re: elderly agitation

REDACTED

Copy of an email I found from one year ago which also touches on some of the questions you asked me about yesterday concerning an LTC Depakote elderly agitation proposal. I'll give a hard copy to REDACTED as well.

REDACTED

REDACTED
Associate Medical Director
Neuroscience Development
Abbott Laboratories
REDACTED
200 Abbott Park Road
Abbott Park, Illinois 60064-6148

Phone: REDACTED-REDACTED
Fax: REDACTED REDACTED
E Mail: REDACTED @abbott.com

----- Forwarded by REDACTED LAKE/PPRD/ABBOTT on 07/08/2003 09:48 AM -----

REDACTED
07/24/2002 05:11 PM

To: REDACTED LAKE/PPRD/ABBOTT@ABBOTT
cc:
Subject:Re: elderly agitation

To;

Hi REDACTED. Here are my responses. Yesterday, I started to write down the "arguments" you discussed for the three studies that I am working on...So many of my bullet points are a "cut and paste" of that information, plus additional comments. Sorry if long and redundant, but figured I'd give you all that I had already done.. We certainly "could" do a monotherapy trial--that is no problem to design--, ,,, However, most feel that with Abbott's past experience in this area, as well as some other issues I mention, that concept would be less favorable. I understand your situation in dealing with commercial. We are doing our best to come up with studies we feel would be good science, but also viable, and could be done in a timely fashion.

RED ACT-

Because commercial keeps hitting me on this point, and I keep forgetting our conversations (I also need to start capturing this info for August presentations), could you send me an email with the following related to the reasons we plan to do add-on treatment with depakote in the elderly vs. monotherapy:

1.The specific experiences we have had with depakote monotherapy trials in elderly agitation and the reasons, directly attributable to the fact that the studies were of monotherapy, that these studies failed (ie carefully explain the link between monotherapy and failure).

Depakote as monotherapy has two past Abbott trials (738 and 082) that failed to “hit” on their primary efficacy measure, and both were stopped prematurely. One due to high number of AE’s, and the other due to slow enrollment. In 738, the titration of Depakote was too rapid and doses escalated too high, leading to excessive somnolence. Also the primary endpoint was focused on mania (Bech Rafaelson Mania Rating Scale)—which was a mistake. Nonetheless, a pretty decent publication was produced by Tariot et al , since the secondary measure , the Cohen-Mansfield Agitation Inventory showed a statistically significant separation from placebo. Yet, I still suspect the somnolence was the true "treatment" effect for many-- just my opinion. In 082, because of safety concerns from 738, the inclusion/exclusion criteria were overly restrictive, and at least one of the two Depakote arms (500mg) was too low a dose to expect a difference. Also, because of the low number of patients (121, but study was powered for 396) and the three arms, the results were not good due to the trial being underpowered --as well as a very big PBO response. This doesn't really address why the trials failed specifically due to monotherapy, but we have been down this road several times now, and the factors that lead to failure were multiple. Another failed monotherapy trial would really hurt us, and possibly take us out of this clinical arena. An add-on trial, even if it is not all that successful, does not negate our current position in this population
Recruitment is difficult in this population when a "true" placebo group is involved (or I should say, a "no treatment" group is involved). Families don't like it.
Combination therapy is becoming the focus in geriatric psychiatry, as a large percentage of patients are

unresponsive or partially responsive to the first line treatment. I think this is the most compelling argument for investigating Depakote ER as an "add-on" strategy. Lamotrigine has made a nice "niche" for itself in bipolar disorder doing exactly that.
Risperdal and Zyprexa are the two most common atypical antipsychotic first line treatments (some different class agents, Desyrel and Ativan still get a lot of use also). I wish I had some great market research data about actual numbers, but even looking at out own sales data, it appears Zyprexa gets about 38% and Risperdal about 28% market share (however this is market share by sales $$, and with these meds being so much more expensive it is difficult to assess true use patterns -- plus Depakote has multiple uses, so it is hard to figure how much of our 12% is for agitation, as opposed to anti-seizure ...) Depakote gets "some" use first line, but still is mainly a second line monotherapy treatment for longer term management of this clinical problem. From the speaker's bureau data upon which I used to speak, that is generally what was felt-- with some minor exceptions. It is unlikely that we will gain on those particular atypicals as a first line treatment—they cover a larger spectrum of symptoms (psychosis, more acute agitation/aggression) in this population, and have much more clinical data to support their use. Being a special “niche” type first line (i.e., for patients with mild/moderate agitation without psychosis or thought disorder), and a solid second line monotherapy treatment is “not bad” for Depakote in this population. But frankly and we should focus on combination therapy—that is clearly where the future lies.
There is another Depakote monotherapy study (Tariot's NIA-funded ADCS study) still to be completed -- Depakote 750mg sprinkles versus placebo. It is to conclude soon –this fall sometime, and that is more data for us with respect to monotherapy with DR. However recruitment was very difficult for them as well, and they will likely finish with about 70 patients per arm (less than targeted) – not really enough to likely show anything meaningful, and at 750 mg, this is probably just a bit too low a dose for most effective treatment-- from what we know now. So, I am not entirely optimistic that we’ll find something big. Perhaps we’ll get lucky though. I have broken down all the data from 738 and 082 and have done numerous analyses. It seems that the most likely “effective” dose range is 10 to 20mg/kg/day. Doses below that-- and above that-- have response curves similar to placebo, and over 20mg/kg/day, the SEs seem to significantly increase.
Combination therapy is where this field is going. Physicians want—and need—this type of study data. If established as a viable “add-on” strategy to the most common atypicals (Risperdal and Zyprexa) this would give us an even bigger place in this market—as a solid add-on, and continue as a monotherapy treatment in certain patients. Also, if we establish value as an “add-on”, you could do a follow-up trial, looking at how patients do if you eventually withdraw the atypical (an idea??).

2.If we were to do a monotherapy trial, but with a design similar to the one you have currently, what would be your new probability of success? Also, would recruitment rate change (if so, what would the recruitment rate be for a similarly designed trial, but with monotherapy rather than add on)?

In a monotherapy study (which would be easy to construct), the chances of “hitting" statistical significant against placebo would be a challenge. This is why our design –however we choose to do it—should have a placebo lead-in. Nonetheless, I would say probability of success--if were could completely enroll and finish the study --would be about 50%.
Whereas I can't really give numbers, I would think that the add-on trial would be easier to recruit as opposed to monotherapy. We know the recruitment rate for monotherapy is about 0.5 patients/site/month (that was from 738). I believe 082 was lower than that (around 0.25/site/month- we just calculated). We don't have any add-on trials to use as a reference, but our team estimated a recruitment rate for our current add-on protocol to be about 0.75/site/month.
Recruitment for a monotherapy could not really allow for subjects taking other psychotropics, which would also slow recruitment and make the add-on design more attractive. In this "add-on" protocol we allow for all other psychotropics taken prior to enrollment to continue (with very limited exceptions). Families don't like the idea that grandmother could be assigned to the "no treatment" placebo group in a monotherapy study

3.Which specific advisors did you discuss this protocol with and what were the specific opinions expressed by each opinion leader on the question of whether the trial should be monotherapy or add-

on?

Advisors – REDACTED, REDACTED and REDACTED
We didn't poll them specifically about monotherapy VERSUS combination therapy. However, REDACTED and REDACTED (especially REDACTED) felt it was a good idea to explore combination therapy, since they see it as a very common --and growing--practice. REDACTED wasn't as sure about the frequency of combination therapy being practiced. All felt that a monotherapy trial would need very strong Abbott commitment to the investment, and that it would need be powered for any chance of success, and would have to be completed--not stopped short like 082. Otherwise, don't expect good results.
REDACTED and REDACTED were less apt to commit to any "definites" about the favorability of one design over another.
REDACTED, in particular, felt this add-on study would be easier to recruit, and could get completed in a much shorter timeline. He would actually be a good person to have at the head of such a study. He's a big name, was very enthusiastic about the idea, and could get this published in a good journal.
We should show safety and possible advantages of ER in this population
We need get our name out there in this population – for future –this is a growing population and an extraordinarily common clinical problem for which physicians currently have no "great" primary treatment. They are willing to use whatever works, as long as some data is out there, and the drug shown to be safe. There are lots of partial or inadequate responders to Risperdal and Zyprexa.
Availability of the ER 250mg tab should certainly expand use of Depakote ER in this population and we need a study to follow the release of that preparation

4.What did each opinion leader (include yourself and your experience) say about the current frequency of combination (depakote + atypical) vs. monotherapy (depakote alone) in the nursing home elderly agitation population?

REDACTED said approximately 60-70% of their patients in South Carolina receive combination therapy for this purpose.
REDACTED said he feels at Rochester it is about 50% or more. He also said he recently reviewed some large scale data that suggests that up to 60-70% of such patients receive combination therapy (this includes various combinations, atypical + benzo, atypical + SSRI, SSRI + Depakote, acetylcholinesterase inhibitor + atypical, etc., etc, etc)
Personally, I was a bit more conservative than these guys, and when in practice in South Bend, and more recently at The Univ. of Chicago, I would say my use of any combination therapy for this purpose was about 33%--but I treated a lot of outpatients as well as NH patients, probably bringing that number down a bit. In a controlled environment like a NH, I was more apt to use combo therapy
REDACTED didn't give an estimate, but I don't really think REDACTED treats many patients anymore. I could be wrong though
Combination therapy is a common practice which is growing, but with no great published data as to exact frequency-- nor what specific med combinations are most commonly used. Another thing that I would love some good market research on. .

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5.What specific statistical issues make add-on design preferable to monotherapy?

The add-on protocol as written is not powered – more of a pilot (40 patients per arm, two arms, N=80). This is because of recruitment concerns, and need to generate data in the not too distant future (DNSI criteria). We are writing the protocol to use the Neuropsychiatric Inventory –Nursing Home Version, which is an interesting scale in which key "target symptoms" can be identified as those most pertinent to study, and a "core total" of those specific items are summed as the primary endpoint. It was developed by REDACTED This is advantageous since it much more closely reflects real clinical practice in this population, and you can hone in on specific med effects you want to test. This is the scale REDACTED used in its nursing home Zyprexa trials with this population (Street et al), and it is valid. However, I don't necessarily think that scale favors "add-on" versus monotherapy in any way. But, in an add-on concept (as opposed to monotherapy), we are making the endpoint only a 30% reduction in

the NPI-NH score, which would be clinically defensible since we are looking for "additional" improvement, which has meaning in this population

If we did a monotherapy study, you really couldn't accept patients who are taking other psychotropics, which is one issue that would affect enrollment.

In an add-on study we are already working with patients who are "partial responders" to atypicals, so the likelihood of placebo effect (the major problem with 082) should be less an issue. However, you can make the converse argument they may also be "harder" subjects to get any treatment effect with.

Feel free to just type in your answers below the above questions. Thanks!