and the other question. Since there are factors that can influence someone's subjective feelings of sleepiness, do you have any objective measures that support the indication of daytime sleepiness? Specifically, the one trial that I am aware of that had an MSLT and did daytime sleepiness as a primary outcome measure, in fact, appears to be not supportive of the indication.

DR. HOUGHTON: Yes, in the Scrima trial he used the MSLT measure and that was not statistically significant, as shown. The objective data that we propose supports very strongly the effect of adequate dosing of GHB was the SXB-20 trial that Dr. Black discussed. That is not only a profound improvement in the MWT at the 9 g dose but a defined dose response across all doses. That is very positive data.

DR. KAWAS: In ten patients, it appears.

DR. HOUGHTON: Twenty-one.

DR. MANI: May I also add that that was an open-label, non-randomized study?

DR. HOUGHTON: Sure, but using an objective measure.

DR. RISTANOVIC: I am I am Ruzica Ristanovic, medical director of Sleep Disorders

Center, in Evanston, Illinois. I would like to comment on add-on Xyrem in the presence of other stimulants. Other studies attempt to try to document the effectiveness of other stimulants in narcolepsy-related sleepiness documents, including the most rigorous trial of modafinil in double-blind, placebo-controlled studies. They document that these drugs improve sleepiness but very seldom outside of the range of pathological sleepiness as measured by Multiple Sleep Latency Test and Maintenance Wakefulness Test. So, the patients remain sleepy. That is the message. Add-on treatments are approved for other indications in other neurological diseases, such as epilepsy. So, I assume that this application for that particular indication is not for monotherapy but as an add-on to concurrent use of stimulants. I would like to bring this to your attention. So, patients do remain sleepy on stimulants and they need additional treatments.

DR. KAWAS: Dr. Temple?

DR. TEMPLE: Dr. Houghton also seemed to be distinguishing between monotherapy and add-on therapy. That is not the problem. The problem is whether there is adequate support for use as an

addition for whatever else the patient is on, and whether there are well-controlled studies that support that. So, add-on would be perfectly fine. That is usually true in a lot of conditions, not just neurological ones, where you continue to give standard therapy and try to improve it.

I just want to make one observation about the evidence. We do expect to see replicated or reproduced findings. Some of the issues here are whether the fact that the endpoints are secondary and need some correction means that there isn't adequate support. A lot of these things are matters of judgment that the committee can weigh in on. Not everything is, you know, a yes/no. Some of the things are moderately subtle and that is why this is being brought to you for judgment. There is one study that is obviously stronger than the rest but the others can be considered, and you sort of have to think about how many real endpoints there really are; how much of a correction is needed. Those are difficult discussions but worth considering.

DR. KAWAS: Dr. Katz?

DR. KATZ: I agree, but I think we would still have to have the application meet the

standard of independent replication, in other words two trials. You can decide that one of the other trials actually does meet the usual standard, again, taking into consideration the multiplicity and that sort of thing. All I am saying is that I don't think we can say we have one study that looks good. If you believe that GHB looks good and the others sort of contribute to a feeling that it probably is okay, I mean, we really need two independent sources that you believe demonstrate the effectiveness.

The only other point I wanted to add is to something, Claudia, you said which has to do with Dr. Houghton's view that they are not going for a claim of daytime sleepiness; they just want, I guess, to have language in the labeling that says that it improves that symptom. Most of the drugs we approve are for symptomatic claims, so there is no question that the inclusion of this language in the indication is a claim as we always understand that term.

DR. KAWAS: Dr. Guilleminault, followed by Dr. Wolinsky, please.

DR. GUILLEMINAULT: If you look at all the published data on modafinil, on amphetamine, on

methylphenidate, none of these drugs ever normalized all the objective tests on alertness and daytime sleepiness. None of them, including the modafinil data which were approved by the FDA. The MSLT and MWT for all these drugs are pitiful. The only data which shows significance was the Epworth Sleepiness Scale, which is a subjective scale, in all these trials. So, we cannot expect to have any positive result with subjective tests in any of these drugs. We will always have to rely on subjective tests even if the subjective test is not great. Everybody in the field agrees that the Epworth Sleepiness Scale is the most used scale despite the fact that it has a lot of downfall, and we have to remember that when we look at what has been approved and what is being used.

DR. KAWAS: Thank you, Dr. Guilleminault. I think that many people would agree with those comments, but my question to you would be not whether or not the Epworth Scale subjective measurements are good but do we have two randomized, controlled trials that show an improvement in subjective sleepiness.

DR. GUILLEMINAULT: That was my initial question because my understanding is, when the

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