

1 and the other question. Since there are factors
2 that can influence someone's subjective feelings of
3 sleepiness, do you have any objective measures that
4 support the indication of daytime sleepiness?

5 Specifically, the one trial that I am aware of that
6 had an MSLT and did daytime sleepiness as a primary
7 outcome measure, in fact, appears to be not
8 supportive of the indication.

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

18 DR. KAWAS: In ten patients, it appears.

19 DR. HOUGHTON: Twenty-one.

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

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

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

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

21 DR. KAWAS: Dr. Temple?

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

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

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

23 DR. KAWAS: Dr. Katz?

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

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

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

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

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

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

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

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

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