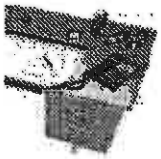

Stephen Brannan /AM/LLY
10/23/2002 11:22 AM

To David G Perahia/EMA/LLY@Lilly
cc
bcc
Subject Re: HMBU : Taper period

Thanks for the quick, thourough incorporation of comments into the new taper period!

In regard to #4 below, though it may cause some increased risk, i don't think the one wk taper from 150 mg will be much of a problem; this is fairly std for most meds and I don't think will cause ERB difficulties (at least no more than usual!); there probably will be more risk for complaints that this taper may not be "ideal"; however, we can defend this fairly easily, especially by noting Cymbalta is not treated any differently and that the taper period is longer for higher doses.

Also agree with checking out the poss of DESS via telephone

Stephen Brannan, M.D.
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David G Perahia

David G Perahia
10/22/2002 01:21 PM

To: Kimberly Spencer/AM/LLY@Lilly
cc: Apurva Prakash/AM/LLY@Lilly, Cherri Miner/AM/LLY@Lilly, Christopher J Nosek/AM/LLY@Lilly, Debbie Patterson/EMA/LLY@Lilly, Janet Ford/AM/LLY@Lilly, Joel Raskin/AM/LLY@Lilly, Kimberly Spencer/AM/LLY@Lilly, Michael Detke/AM/LLY@Lilly, Pierre V Tran/AM/LLY@Lilly, Stephen Brannan/AM/LLY@Lilly, Yili Lu/AM/LLY@Lilly
Subject: Re: HMBU : Taper period

All,

Many thanks for your thoughts and comments on the HMBU taper period (Study Period IV) design.

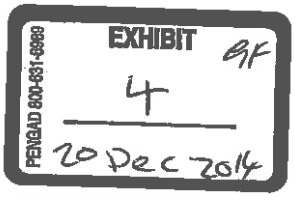
My responses +/- design changes, in no particular order, are as follows :

1. Cymbalta downward titration schedule changed from 120 - 90 - 60 to **120mg - 60mg - 30mg** as suggested.

2. All completers should enter Study Period IV prior to entry into compassionate use programme.

3. All patients discontinuing study from Visit 3 onwards for reasons other than withdrawal of consent should enter Study Period IV if possible.

4. I agree that we should try to titrate Effexor down as per the SmPC/US PI. If we didn't, any data we generated showing a difference in discontinuation profile would be strongly criticised and treated with scepticism. It's also putting patients at increased risk. I'm therefore inclined to increase the visit intervals between taper visits (and hence downward titrations) from 3 days to 7 days to bring us nearer to PI/SmPC recommendations. The literature seems to suggest that the emergence of DESS is significantly less likely following dose reduction than on stopping the drug anyway, and that we are therefore more likely to see the emergence of DESS during the third week of the taper where patients are off drug altogether. We shall



see.

Regarding SmPC's and P.I.'s, the new proposal will mean that patients ending the flexible dosing period on 150mg Efexor will only actually withdraw over 1 week (i.e. reduction to 75mg for 7 days, then placebo for 7 days, then off drug for 7 days). This is in compliance with the E.U. SmPC BUT not in the U.S. where patients receiving drug for more than 6 weeks should be tapered over 2 weeks or more. I'd be interested in your views on how much of a problem this would be in the U.S., both for ERB's and when we come to defend our data. Comments please.

5. Agree that the proposed visit schedule (even allowing for an increased visit interval as above) is potentially burdensome to patients and investigators BUT if we want to gather clinically meaningful data with the potential to differentiate between treatments, relatively frequent collection of data is necessary. Kim, you suggested the possibility of gathering data for DESS via telephone to make life easier - can we look into the logistics of this ?

6. Patients discontinuing during the taper period due to an adverse event will be logged as such, and no specific "rescue" package will be offered.

Let me know if you have further comments, otherwise we'll go with the above. Revised Study Period IV diagram attached below.

Cheers,

D.

Kimberly Spencer

Kimberly Spencer
17/10/2002 19:04

To: David G Perahia/EMA/LLY@Lilly
cc: Stephen Brannan/AM/LLY@Lilly, Michael Detke/AM/LLY@Lilly, Janet Ford/AM/LLY@Lilly, Yili Lu/AM/LLY@Lilly, Cherri Miner/AM/LLY@Lilly, Christopher J Nosek/AM/LLY@Lilly, Debbie Patterson/EMA/LLY@Lilly, Apurva Prakash/AM/LLY@Lilly, Joel Raskin/AM/LLY@Lilly, Kimberly Spencer/AM/LLY@Lilly, Pierre V Tran/AM/LLY@Lilly
Subject: Re: HMBU : Taper period

david et al, please see my comments below in RED
kim

Kim Spencer
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Joint Antidepressant Group
317-277-1858
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David G Perahia

David G Perahia
10/17/2002 05:52 AM

To: Stephen Brannan/AM/LLY@Lilly, Yili Lu/AM/LLY@Lilly, Christopher J Nosek/AM/LLY@Lilly, Debbie Patterson/EMA/LLY@Lilly, Joel Raskin/AM/LLY@Lilly, Kimberly Spencer/AM/LLY@Lilly, Pierre V Tran/AM/LLY@Lilly
cc: Michael Detke/AM/LLY@Lilly, Cherri Miner/AM/LLY@Lilly
Subject: HMBU : Taper period

Colleagues,

I've attached a Powerpoint slide of my proposed design for the taper period (Study Period IV) in HMBU/CQ and would greatly appreciate your brief review and comments.

For those that don't know the study design well, patients will arrive at Visit 14 after 12 weeks of active drug treatment and will be receiving Cymbalta 60-120mg or Effexor XL/XR150-225mg at that point. What I envisage is that at Visit 14, study subjects will then either :

1. Enter the compassionate use programme (under construction), or
2. Enter the taper period (Study Period IV)

I see a number of reasons for having a study period IV, most importantly :

- patients will potentially be taking the highest licensed doses of Cymbalta or Effexor at the end of study period III (flexible dosing phase) and ERB's will take a dim view of those patients who don't enter the compassionate use programme being cut free at the end without some form of taper, not to mention the unpleasant effects that will be experienced by some of the subjects themselves.
- Individuals both inside and outside Lilly have suggested that DESS might provide a significant area of difference between the drugs favouring Cymbalta, so an appropriately-designed taper period may yield valuable data

In summary, I am proposing we titrate down in three steps. The titration is deliberately rapid - if we do it too slowly we obviously reduce our chances of showing a difference in DESS. As an example, a patient on 225mg Effexor at Visit 14 (end of flexible dose phase III) would have their dose reduced to 150mg for 3 days, then 75mg for 3 days, then stop drug completely and be reviewed after a further 7 days. We'd assess DESS each time the dose is reduced (taper visits 1,2 and 3). At this point, subjects would go on their own merry way. Patients on 150mg Effexor at Visit 14 would go to 75mg for 3 days, placebo for a further 3 days and then stop drug. I think you get the idea. We'd maintain the blind by giving patients on lower doses placebo once their active drug had been titrated down to zero.

Additional issues and questions :

(a) Is it likely that so few patients will enter study period IV (because the majority choose to enter the compassionate use programme) that we will not be able to collect sufficient data to do a valid comparison of DESS between the drugs ? In which case, should **all** subjects enter study period IV, after which they will then be eligible to enter the compassionate use programme

I recommend that all subjects must enter SP IV to be eligible for the compassionate use program. While this may initially seem self-serving, it specifically states in the SmPC and the US PI for Effexor XL that withdrawl reactions have not been systematicfly evaluated in depression in controlled clinical trials (they only have data from retrospective survey for depression, however they do have clinical trials evaluating withdrawl for GAD). Also we don't yet have clinical trial data specifically for withdrawl symptoms for Cymbalta (although I think HMBC has a taper period)

(b) Should patients discontinuing at any point during the study be entered into study phase IV ?

In the SmPC and the US PI for Effexor XL it recommends that tapering is warrented if the patient has been on drug for more than 1 week. My recommendation would be to allow the taper period at Visit 3 and beyond (see additional information below). Also, in the Cymbalta draft label I have (which is somewhat dated) tapering is also recommended if the patient has been on drug for 1 week or more.

(c) Is 3 days at each stage of the down titration too short (or even too long ?!), and is the resulting proposed visit schedule (4 visits in the space of 2 weeks) just too onerous ?

4 visits in 2 weeks will be very burdensome for both patients and physicians. Are you proposing only to collect the DESS at these visits? If so, would there be a possibility that this could be done via phone interview? Although this could be a headache in and of itself and a potential training/compliance

nightmare it might be a reasonable alternative.

(d) Does this design go against any specific instructions in the US/OUS Effexor SPC regarding how to discontinue the drug ? (apologies - I am working remotely and don't have access to these documents at present). If it does, could we still reasonably proceed regardless on the premise that the design offers a compromise between the 'ideal' of the Effexor label and the reality that patients often abruptly discontinue their antidepressant without consulting their physician ?
down titration in US PI : when discontinuing aftermore than 1 week of therapy it is generally recommended that the dose be tapered to minimize the risk of discontinuation symptoms. Patients who have received effexor XL for 6 weeks or more should have their dose tapered over at least a 2-week period. In clinical trials with effexor XL (I assume GAD trials) tapering was achieved by reducing the daily dose by 75 mg at 1 week intervals.

down titration in SmPC : ...recommended that when discontinuing effexor XL after more than one week's therapy, the dose should be gradually reduced over at least one week and the patient monitored in order to minimise the risk fo withdrawl reactions.

(e) Should we consider some specific 'rescue'package for patients who experience intolerable symptoms during this phase, or should they just be logged as study discontinuations due to A.E.'s and be treated as per investigators discretion/compassionate use etc.

SmPC: retrospective survey of events occuring during taper or following discontinuation of Effexor XL revealed the following events that occured with an incidence of at least 3% and at least twice the placebo incidence: dizziness, dry mouth, insomnia, nausea, nervousness and sweating.
US PI: no data on incidence, but a much larger listing of symptoms.

Does a 3% incidence warrent a rescue package? David, what would you envision the rescue package to look like? Recommend the patients must enter SP IV but not require that they complete the entire 2 weeks (they could d/c if they have intolerable symptoms and immediately enter the compassionate use program or receive other alternative therapy). Those that d/c due to AE during this period would make an interesting endpoint.

Also, of note, not all countries allow compassionate use programs , perhaps not all physicians may want to participate in the program as we are not planning on providing funding for visits , just study drug (the CRF is very small). Somehow, we need to write the protocol so that the compassionate use program may not be an option for all patients (yuck!)

just my two cents, hope the additional information is helpful in decision making.
kim

Proposed design attached below - comments please ASAP !

Chris, please could you also comment on the feasibility of the proposal from a CT materials perspective ?

Mike, Cherri, I know neither of you are directly involved in this project and are both very busy, but if you have time to review and comment then all the better.

Many thanks,

David.

[attachment "HMBU Taper.ppt" has been removed by David G Perahia/EMA/LLY]

[attachment "HMBU Taper V.2.ppt" has been removed by Stephen Brannan/AM/LLY]