Message

From: Smith Lewis GBAP [/O=NOVARTIS-AG/OU=GBRGCP01P/CN=RECIPIENTS/CN=802825]
Sent: 4/21/2005 4:46:59 PM
To: Travis Kim GBAP [/O=NOVARTIS-AG/OU=GBRGCP01P/CN=RECIPIENTS/CN=803810]
Subject: RE: HPPD inhibitors and Parkinson's Disease

Sensitivity: Company Confidential

Kim

Please send me a copy.

Thanks.

Lewis

-----Original Message-----
From: Travis Kim GBAP
Sent: 21 April 2005 17:32
To: Smith Lewis GBAP
Subject: RE: HPPD inhibitors and Parkinson's Disease
Sensitivity: Confidential

A copy of this 2 page document was found recently in an old filing cabinet in RITS, so you can call off the search. Whilst the results are interesting, and encouraging, I am following your advice at our meeting that this letter should remain very low profile,

Kim

-----Original Message-----
From: Smith Lewis GBAP
Sent: 21 April 2005 16:37
To: Travis Kim GBAP
Subject: RE: HPPD inhibitors and Parkinson's Disease

Kim
We were concerned about this some years ago and we did work at Wilmington. I have asked for an archive search to try to locate the two page letter report we got on this. The scientist is no longer with AZ.

Lewis

-----Original Message-----
From: Travis Kim GBAP
Sent: 21 April 2005 15:01
To: Smith Lewis GBAP
Subject: RE: HPPD inhibitors and Parkinson's Disease

Just a quick note to point out that 5HT is a product of tryptophan metabolism, not tyrosine metabolism. It is possible that tyrosinaemia could affect levels of tyrptohan and other aromatic amino acides, by competition effects at the transporter they share at the blood-brain barrier. Studying this is included in the project plan,

Thanks,

Kim

-----Original Message-----
From: Smith Lewis GBAP
Sent: 15 October 2004 17:14
To: Travis Kim GBAP
Subject: RE: HPPD inhibitors and Parkinson's Disease

Kim

Thanks for sending this to me. I had heard of this on the grapevine and will look forward to our chat on Friday. However, I would like to emphasise that under no circumstances will mesotrione be used in these studies. There are a number of other HPPD inhibitors which can be used and I am sure we retained sole use of 0735 for Syngenta, with the exception of control of tyrosinaemia and other in-borne erros of metabolism, which are related. On a second point you

may wish to think of how the increase of 5HT in the brain, which will result from a tyrosinaemia can be selectively targeted to these substantia nigra. Increasing 5HT in all areas of the brain may not have a desired effect.

Lewis

-----Original Message-----
From: Travis Kim GBAP
Sent: Dienstag, 12. Oktober 2004 09:59
To: Smith Lewis GBAP
Subject: HPPD inhibitors and Parkinson's Disease

I've come up with a Biopharma product idea, and because it impinges to some extent on CPD I want to make sure you hear about this idea directly rather than through the grapevine.

I'm on the mesotrione and PQ-Parkinson's HATTs, and in August I put the two together in my mind and realised that HPPD inhibitors might be a good treatment for Parkinson's Disease. The more I dug into the literature, the better the idea looked, so I presented it to the Biopharma business team. On Friday I will present a costed proposal for work to prove the concept in an animal model (an MPTP mouse model), and if sanctioned a new project will be born. I will lead it for this proof of concept phase.

I am conscious of the need to actively manage this project with respect to the money we make from mesotrione and paraquat. Jane Botham is on the project team to represent the interests of mesotrione, as well as for her HPPD toxicology experience, and Nick Sturgess is also on the team. Mesotrione is far too weak to be a good drug candidate, and in any event we will make a point of not doing any of the work using mesotrione. NTBC is a much better bet for many reasons, though we've got lawyers examining the small print of whether AZ have any rights to NTBC for this application. With this potential exception of NTBC it is likely that Syngenta could stitch up the IP for the whole area once we have the proof of concept data.

The proof of concept phase will end next summer, at which point the project will either die or expand enormously. If the latter, then there will have to be detailed discussions about how to take this forwards, including how we manage the impact of having a blockbusting HPPD-inhibiting Parkinson's drug on our books as well as mesotrione and paraquat. Clearly this possibility re-inforces the need to build a cast-iron defence case for PQ with respect to Parkinson's: I personally think we'll have an excellent case in good time.

I've attached a brief slideset describing how HPPD inhibitors might work to treat Parkinson's (it is light on science - there is a lot more science behind the idea if needed). I'm genuinely excited that this idea has a good chance of
•radically improving treatment for Parkinson's patients
•dominating the market for Parkinson's treatment, creating a billion dollar product

I hope you agree that the project can have an amber light in respect of impact on CPD at this stage. I've put a meeting in the diary for Friday week so that we can discuss this,

Regards,

Kim
<< File: HPPD inhibitors for Parkinson's Disease - for LLS.ppt >>