Message

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Sent: 12/20/2002 6:30:12 PM
To: Santos, Ivan [/O=MERCK/OU=NORTHAMERICA/CN=RECIPIENTS/CN=SANTOSIV]; Wenslow, Robert M. [/O=MERCK/OU=NORTHAMERICA/CN=RECIPIENTS/CN=WENSLOW]; Egan, Richard S. [/O=MERCK/OU=NORTHAMERICA/CN=RECIPIENTS/CN=EGANR]; Dowling, Thomas M. MRL-Rahway [/O=MERCK/OU=NORTHAMERICA/CN=RECIPIENTS/CN=DOWLINGT]; Wyvratt, Jean M [/O=MERCK/OU=NORTHAMERICA/CN=RECIPIENTS/CN=WYVRATT]; Davidson, Omar A. [/O=MERCK/OU=NORTHAMERICA/CN=RECIPIENTS/CN=DAVIDSOO]; Tom, Jean W [/O=MERCK/OU=NORTHAMERICA/CN=RECIPIENTS/CN=TOMJEAN]; Kaba, Mahmoud [/O=MERCK/OU=NORTHAMERICA/CN=RECIPIENTS/CN=KABAMAH]
Subject: FW: Summary of 9 December DPIV PDT Meeting

See Trish's detailed update below. The highlights of the meeting were:
•confirmation that Proof of Concept was established in the Phase IB study for L715, based on interim analysis of 18 patients in a crossover study comparing placebo, 25 mg and 200 mg
•the primary endpoint of the Phase IB trial was glucose lowering following an oral glucose tolerance test (OGTT), although plasma DP-IV, GLP-I levels, plasma glucagon levels and C-peptide levels were also measured
•a discussion of BID vs QD dosing strategy for Phase II (not yet resolved, but BID is definitely on the table) based upon the thoery that 200mg QD was not sufficient for maximal DPIV inhibition over 24 hours. Note that DP-IV inhibition is an elusive target as the marker being measured is DP-IV in plasma while the actual target endothelial-anchored DP-IV enzyme
•a discussion of the consultant's meeting where consultants noted all of the following:
•L715 is the "safest" DP-IV under development (in their estimation)
•Efficacy in moderate vs severe diabetics should be compared. The L715 Phase IB data were sorted based on hemoglobin A1c levels and this comparison made, noting a much strong response in "mild to moderate" diabetics with a hemoglobin A1c < 7.5
•Efficacy at 24 hours has been an elusive target for our competitors
•Off target activity and related safety effects is beginning to be recognized by other pharmaceutical companies.
•a detailed discussion of Phase II plans (Phase IIA vs Phase IIB, etc). Plans to be presented at RMC on 8 Jan.
•the "go ahead" to Biopharmaceutical Chemistry group (G. Kwei) to do regional adsorption studies of L715 to probe the feasibility of controlled release

-----Original Message-----
From: Hurter, Patricia N
Sent: Tuesday, December 10, 2002 3:55 PM
To: Ip, Dominic P.; McClintock, Sam; McLaughlin, Patrick E; Mendenhall, Douglas W.; Reynolds, Scott D.; Storey, David Edward; zzKaufman, Michael J. 12/4/02 KMS; Allain, Leonardo R.; Chamberlin, Steven D; Galbier, Linda; Gandek, Thomas P.; Givand, Jeffrey C.; Godbole, Pradyumna P; Hossain Jahansouz (E-mail); Hurter, Patricia N; John, Christopher T.; Kube, Kenneth P; Kwei, Gloria Y.; Lees, Anna T; Liu, Yun; Luna, Ernestina A.; Lynn, Kari J; Mayr, Suzanne M.; Ney, James R.; Nissley, Becky P.; Ostovic, Drazen; Palkar, Saurabh Arvind; Qin, Xue-Zhi; Rhodes, Timothy; Shelukar, Suhas D.; Shultz, Leigh; Sidhu, Parminder; Thompson, Karen C.; Tsai, Eric W.; Ulmer, Craig R.; Wall, Rebecca; Wang, Lei; Zhang, Dina
Cc: Moonis, Mona; DiCesare, Elizabeth A.; Magyar, Ildiko J; Armstrong, Joe D; Starbuck, Cindy; Thornberry, Nancy A
Subject: Summary of 9 December DPIV PDT Meeting

Summary
The interim analysis of the Phase IB SD study in diabetics is complete. Following an OGTT, the reduction in incremental glucose AUC compared to placebo was 19% for a 25mg dose, and 32% for a 200mg dose. Proof of concept has thus been established for this compound. Since the DPIV inhibition at trough with the 200mg dose is similar to the 25mg dose at peak (80%), the thought is that 200mg QD is not sufficient for maximal DPIV inhibition over 24 hours, and the team is considering higher doses for Phase IIB (i.e. 400mg QD or 200mg BID). Efficacy appears to be higher in mild to moderate diabetics, compared to severe diabetics, which may drive the clinical development strategy.
The consultants meeting was held on Dec 6th, the consultants were enthusiastic about the target and claimed that '715 has the cleanest safety profile of the DPIV inhibitors being studied. The consultants recommended that we get sufficient clinical data in mild to moderate patients to demonstrate efficacy.
Clinical/Clin Pharm are finalizing the Phase II development strategy, and are currently considering a number of options, including going directly to Phase IIB, versus doing a Phase IIA study prior to Phase IIB to clarify whether QD or BID dosing is needed. The recommended strategy will be presented to RMC on Jan 8th.
Since it is almost certain that BID will be investigated in Phase II, the PDT has asked that PR&D investigate the feasibility of a controlled release formulation, via a regional absorption study.
A backup compound, L441565, will likely be brought forward as a PCC in Feb 03. This compound has improved potency

and selectivity, and is structurally diverse.
The dates for the proposed IIB study have been clarified, the first patient screened will be no earlier than March 15th, with clinical supplies required at the site by April 1st.

Phase IB Interim Analysis Results
Gary Herman reviewed the available data from the interim analysis of the 1B SD study in diabetic patients. The patient population for the entire study will be 36-48 Type 2 diabetics, the interim analysis was done on 18 patients. This was a three period cross over study with patients being dosed placebo, 25mg L-224715, and 200mg L-224715. DPIV inhibition at peak and trough was 80% and 55% respectively with 25mg, versus 95% and 80% with the 200mg dose. It would thus be expected that the 200mg dose at trough would provide similar effectiveness in glucose lowering as the 25mg dose at peak. Following an OGTT (oral glucose tolerance test) at 2 hours post dose, the 25mg dose resulted in a 19% reduction in incremental glucose AUC compared to placebo, and the 200mg dose resulted in a 32% decrease. This data was thus considered to establish proof of concept for this compound (the target was a 20% reduction). Since the OGTT at 2 hours showed a difference between the 25mg and 200mg dose, this suggests that >80% inhibition is needed for maximal effectiveness, and the 200mg dose at 24 hours is thus not sufficient to provide maximal effectiveness over 24 hours. For this reason, the PDT is now considering either going to a 400mg QD dose, or 200mg BID. The reduction in glucose AUC following meals at 6 hours and 24 hours post dose was considered uninterpretable, the 6 hour post-dose meal was too soon after the OGTT, and the variability in the 24 hour data made drawing conclusions difficult. There did appear to be a decrease in incremental glucose AUC following a meal with active versus placebo, but the confidence interval for the geometric ratio in glucose AUC in active vs placebo included 1. One important finding was that the post-OGTT glucose lowering was greater in mild patients than in severe (measured by baseline HbA1c values, arbitrarily cut off at <7.5 being defined as mild). Even though glucose lowering was not as large for some of the more severe diabetics, there was still a measurable increase in active GLP-1 levels, which means that longer term dosing with L-224715 may prove to be effective, even though a SD was not effective for some of the severe patients.

PK projections of BID and QD regimens were shown, which illustrate that 200mg BID will provide much better coverage than 400mg QD, without a huge spike at Tmax. It is not known which of these regimens would be safer however, this would depend on whether the peak concentration causes adverse effects, or whether having 24 hour DPIV inhibition (which would prevent clearance of other incretins that are cleaved by DPIV) might lead to longer term safety problems. Preclinical data in rats (with Fering's compound) showed that a BID regimen provided effective glucose lowering long term, whereas a QD regimen became ineffective after 25 days. However the BID regimen was the same dose as the QD, with twice the frequency, i.e. double the dose per day.

Overview of Dec 6th Consultants Meeting
The IB interim data was presented at the Consultants' meeting on Dec 6th. There was enthusiasm for the mechanism, and L-224715 is the safest of the DPIV inhibitors out there, according to the consultants. There are quite a few other companies working on this apart from Novartis, e.g. BMS and Fering. Novartis is not the only one in the clinic, others have apparently done (or are in the process of doing) Phase II studies. None of the drugs has achieved maximal DPIV inhibition for 24 hours. We are not considered (by the consultants) to be significantly behind. Apparently Novartis is experiencing some delay with LAF237, and may have to repeat the Phase IIA study.

From the consultants experience with our competitors' drugs, they believe this mechanism is not likely to work in more severe diabetics. This is line with the preliminary data we have seen from the IB study, however the experiment has not been done with maximal inhibition for 24 hours, over the long term. It is also not known whether more severe patients could be "rescued" with some other agent (e.g .metformin), then put onto DPIV once their HbA1c levels are under control. The consultants recommended that Merck focus their studies on mild to moderate patients, to ensure that we demonstrate efficacy.

Since it is almost certain that BID will be investigated in Phase II, the PDT has asked that PR&D investigate the feasibility of a controlled release formulation, via a regional absorption study. We have also been asked to determine what the development strategy/timelines/bulk drug requirement would be, if we had to develop a controlled release formulation.

A meeting was planned for yesterday afternoon with Clinical/Clin Pharm senior management, to discuss the issues raised by the IB data and consultants meeting, i.e. BID vs QD dosing, the effectiveness of the target in mild/moderate vs severe diabetics, and the clinical development strategy through Phase II given these issues. The proposals on the table include going direct to IIB, with either a choice between QD or BID, or possibly a hybrid approach with both BID and QD panels, doing a limited Phase IIA study prior to IIB to study BID vs QD prior to the IIB DRF study, or possibly doing an expanded IIA study (increased patient population, BID and QD dosing) followed by a hybrid IIB/III study. The main disadvantage of the 2nd two options is extending the time to WMA filing, the disadvantage of the first option is the increased risk of not getting the dose/regimen right, and having a larger study with higher risk early on.

Basic Research Update

Ann Weber presented some information on the lead backup, L-441565. This has increased potency over '715, is more selective, and is structurally diverse (has the same LHS, totally different RHS), however it does not have an improved half life or address the renal/hepatic elimination balance. It is likely that this compound will be brought forward as a PCC in February 2003.

Other

Since most of the meeting was spent discussing the Phase IB results and the implications, the rest of the agenda was not covered. Peter Stein did confirm the Phase IIB timing (assuming we still go that route), the first patient screened will be March 15th, which means that the earliest administration of placebo tablets will be April 7th, and earliest administration of active tablets April 21st. PR&D will thus plan to supply both active and placebo tablets at the clinical site on April 1st.

Other functional updates will be sent out as an annotated agenda sometime in the near future. The RMC review of the Phase II CDS is on Jan 8th.