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**From:** [Redacted] (ClinD&MedA) BIP-DE-I  
**Sent:** Tuesday, October 16, 2012 6:40 PM  
**To:** [Redacted] (ClinD&MedA) BIP-DE-I; [Redacted] (ClinD&MedA) BIP-DE-I; [Redacted] (ClinD&MedA) BIP-DE-I; Friedman,Dr.,Jeffrey (CR) BIP-US-R  
**Subject:** WG: Dabigatran Exposure-Response in AF Patients, a pharmacokinetic analysis of RE-LY  
**Attachments:** image001.png; image002.gif; image003.gif; image004.gif; Concentration response ver 8 Oct 2012 pr.docx

Please, find my comments embedded.

While I agree that some modifications were made I still do not understand the purpose of this paper...

The summary says it quite correctly...

.....

*Both doses of dabigatran etexilate in RE-LY were associated with a more than 5-fold variation of plasma concentrations, indicating a wide therapeutic range. Renal function was the predominant patient characteristic that determined exposure. Safety and efficacy outcomes were correlated with plasma concentrations of dabigatran, with age as the most important covariate. There is no single plasma concentration range that provides optimal benefit-risk for all patients. The balance between stroke risk and bleed risk varied with concentration, indicating that there is a subset of AF patients who may improve their benefit-risk balance with dabigatran by a tailoring of the dose in relation to patient characteristics.*

So what ? this publication will more harm than be useful for us, neither in the market but be especially harmful in the discussions with regulatory bodies.

Can't this be avoided ?

[Redacted]

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**Von:** [Redacted] (ClinD&MedA) BIP-DE-I  
**Gesendet:** Dienstag, 16. Oktober 2012 17:26  
**An:** [Redacted] (ClinD&MedA) BIP-DE-I; [Redacted] (ClinD&MedA) BIP-DE-I  
**Cc:** [Redacted] (ClinD&MedA) BIP-DE-I  
**Betreff:** WG: Dabigatran Exposure-Response in AF Patients, a pharmacokinetic analysis of RE-LY

FYI – we can comment on this version and send comments to Paul.

Kind regards

[Redacted]

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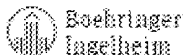
**Von:** Reilly,Dr.,Paul (CR) BIP-US-R  
**Gesendet:** Freitag, 12. Oktober 2012 21:04  
**An:** Friedman,Dr.,Jeffrey (CR) BIP-US-R; Haertter,Dr.,Sebastian (MED) BIP-US-R; [Redacted] (ClinD&MedA) BIP-DE-I  
**Cc:** [Redacted] (ClinD&MedA) BIP-DE-I; [Redacted] (ClinD&MedA) BIP-DE-I; [Redacted]  
**Betreff:** FW: Dabigatran Exposure-Response in AF Patients, a pharmacokinetic analysis of RE-LY

Dear All,

Here is a revised version of the exposure-response manuscript. I have tried to incorporate all changes suggested on the last version. It has been simultaneously sent to the RE-LY OC for review. I think it has significantly improved and would be grateful for your feedback.

(Thorsten, in the interests of space limitations, I simplified some of your changes but we can discuss)

Kind regards  
Paul



**Paul A. Reilly, PhD**  
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**From:** Reilly,Dr.,Paul (CR) BIP-US-R

**Sent:** Friday, October 12, 2012 2:58 PM

**To:** Redacted@ucr.uu.se'; Redacted; Redacted (ClinD&MedA) BIP-DE-I;  
Redacted@comcast.net; Redacted; Redacted (TransMed) BIP-DE-B; Redacted

**Cc:** Redacted@comcast.net'; Redacted@ucr.uu.se'; Redacted  
Redacted Redacted BIP-DE-I; Redacted

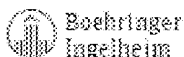
**Subject:** Dabigatran Exposure-Response in AF Patients, a pharmacokinetic analysis of RE-LY

Dear Group,

Please find attached a revised version of the exposure-response paper. I have incorporated almost all the comments that have been sent on the last version (Redacted), including BI internal comments in an attempt to satisfy all the different points of view. There are a couple of analyses that we will do in the background (demographic characteristics of sampled patients compared to RE-LY population, add amiodarone and verapamil to the regression model) but these are not expected to impact the text very much. At the same time I will get feedback from BI internal partners. From my point of view, the paper is improved again and ready for submission.

If we have time, perhaps we can discuss briefly on our next OC call on Wed Oct 17. The paper is currently formatted for submission to JACC.

Kind regards  
Paul



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**From:** [Redacted]@phri.ca]  
**Sent:** Friday, September 28, 2012 4:14 PM  
**To:** [Redacted]@ucr.uu.se; [Redacted] Reilly,Dr.,Paul (CR) BIP-US-R; [Redacted]; [Redacted] (ClinD&MedA) BIP-DE-I; [Redacted]@comcast.net  
**Cc:** [Redacted] [Redacted]@comcast.net; [Redacted]@ucr.uu.se; [Redacted] [Redacted] (ClinD&MedA) BIP-DE-I; [Redacted]  
**Subject:** RE: RELY Operations Committee Teleconference: October 1, 2012 9:00 am. - 10:00 am (EDT)  
**Importance:** High

Dear group:

Please find enclosed the preliminary agenda for Mondays update call. [Redacted] plans to circulate the updated RELY-ABLE manuscript by tomorrow for discussion on our call.

With kind regards,

[Redacted]

Dial in details are as follows:

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