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Potential Mid to Long Term Strategy for Pradaxa in SPAF

We have learned some important lessons since the launch of Pradaxa in the SPAF indication: (1) patients on older oral anticoagulants (OACs) are accustomed to and a significant proportion appear to like and expect frequent interactions with the Health Care system and its staff; (2) switches from older OACs to new OACs are uncommon in the marketplace; (3) most newly diagnosed AF patients still are prescribed an older OAC; (4) prescribers often want to know the extent of anticoagulation each patient is receiving via their current anticoagulant; (5) external experts and the media have expressed concerns about a "one size fits all" OAC, since dose adjusted OACs may have optimized outcomes; (6) Xarelto (rivaroxaban) competes effectively against Pradaxa despite inferior ROCKET data; (7) Eliquis (apixaban) is perceived to have the best outcomes data of all NOACs especially with regard to bleeding events; the latter two points suggesting that a unique selling point other than ischemic stroke reduction may be required for Pradaxa to effectively compete in the Marketplace.

A team in Medicine therefore explored whether data can be generated to support a strategy of a one time initial measurement (perhaps repeated annually and in some instances such as moderate renal impairment in shorter intervals) and titration of the Pradaxa dose to achieve an exposure in an individual patient that has been demonstrated in RE-LY to provide the best benefit risk ratio of preventing ischemic strokes with as little increase in bleeding risk as possible. An intense effort by Pharmacometrics and Statistics (data simulations plus selected data from RE-LY) has provided data that suggest that such a strategy could preserve the effect on ischemic stroke prevention but with a reduction of major bleeding events compared to well controlled warfarin of perhaps up to 30-40%. Interestingly, the data also suggest lower GI bleeds with Pradaxa compared to warfarin in such a setting.

A strategy of individualized dosing could be a unique selling point for Pradaxa in the Marketplace. In addition, FDA has indicated that such modeling data, together with clinical data (e.g. a PK/PD study) on a titration strategy, may be the only way forward to an approval of the 110 mg dose in the US. If a way forward could be found with FDA and other regulators, a re-launch of such a titration strategy needs to be timed to coincide with the availability of (1) a certified lab test to measure Pradaxa exposure and (2) potentially a point of care testing device. Finally, the availability of a dabigatran antidote at the same time would also be beneficial. For all three topics, projects are currently running at BI.

Interestingly, after this potential strategy was developed at BI, BI was contacted by Astra Zeneca with the proposal to co-develop their direct thrombin inhibitor which is about to enter Phase III with a very similar strategy. The AZ DTI appears to be a once daily compound with very little intra- and inter-individual variability of plasma concentrations. A high level meeting between AZ and BI to discuss a potential Co-Development and Co-Promotion model took place on 14-June.

There are currently several open questions: (1) should patients with low exposure to dabigatran 150 mg dose be excluded from treatment with Pradaxa? (2) If yes, what is the cut-off and how high would the percentage of such patients be of the overall AF population? (3) With a 30-45% intraindividual variability for dabigatran plasma concentrations, how many patients will need repeated assessments and/or require titrations up and down at yearly or more frequent intervals and will this negatively impact the product perception and will PCPs accept such a paradigm? Or reversely, would physicians monitor patients regularly, e.g. every quarter especially in elderly patients to adapt to renal function loss and other parameters or just to be on the safe side? (4) What is the extent of clinical data needed for such a strategy (PK/PD study only?

Electronic Health Record study, e.g. in the Kaiser Permanente setting? A clinical trial with bleeding events as primary endpoint? “RE-LY 2”?); (5) would such a strategy endanger the superiority label in the US? (6) what would be the implication of such a strategy for indications other than SPAF? (7) How expensive will testing be (under different frequency assumptions) and would such an approach affect cost competitiveness vs. other NOACs from a payor perspective, esp., if testing would be used more frequently? (8) When will the necessary testing kits be broadly available? Would we become dependent on one test methodology and one supplier?

During the meeting, we would like to discuss some potential next steps with you.