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Interview – J&J needs fresh blood as Xarelto's star wanes

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If you can't beat them, join them. This appears to be the view of Johnson & Johnson, which is teaming up with its arch anticoagulant rival, Bristol-Myers Squibb, to develop a next-generation blood thinner.

J&J thinks there is plenty of life left in its stalwart Xarelto, but the Bristol deal means that it is already looking to the future, with two mid-stage projects that it believes could offer similar efficacy but better safety. The company needs to stay ahead of the game if it is to fill a looming Xarelto-shaped hole – the drug, which is set to come off patent in 2024, is forecast to breach the $9bn barrier by 2022 along with Bristol-Myers Squibb/Pfizer's rival Eliquis (see table below).

But any would-be Xarelto heirs will need to show more than just an incremental benefit if they are to justify a premium price, and the pressure is now on J&J to deliver (*Vantage Point – Solving the incremental innovation dilemma, March 15, 2018*).

Jim List, head of cardiovascular and metabolism in J&J's Janssen division, is adamant that there is no reason to panic, telling *EP Vantage*: "We're still investing very heavily in Xarelto, and we see great potential here – not only for the current indications, but also potential future indications. But we're also building for the future at the same time."

XI Factor

One of J&J's new bets, the oral factor XIa inhibitor BMS-986177, comes from this week's deal with Bristol. The compound is set to enter a phase II trial this year in secondary stroke prevention, joining several other mid-stage projects targeting targeting factor XI or XIa.

This is an area where Bayer – J&J's partner for Xarelto – is particularly well represented, boasting the monoclonal antibody BAY 1213790 and the antisense project IONIS-FXIRx, licensed from Ionis.

Factor XI(a) projects in active development				
Project	**Company**	**Description**	**Trial(s)**	**Primary completion**
Phase II				
BAY 1213790	Bayer	Anti-factor XIa MAb	Foxtrot, NCT03276143 (knee replacement)	Apr 2019
BAY 2306001/IONIS-FXIRx	Ionis/Bayer	Factor XI antisense	NCT03358030 (ESRD)	Jun 2019
MAA868	Novartis	Anti-factor XI MAb	NCT03398434 (atrial fib); NCT03393481 (knee replacement)	Jul 2019; Oct 2019
Phase I				
BMS-986177	Bristol-Myers Squibb/Johnson & Johnson	Oral factor XIa inhibitor	Phase II to begin 2018	-
EP-7041	Exithera Pharmaceuticals	IV factor XIa inhibitor	NCT02914353	Data presented Nov 2017
Preclinical				
IONIS-FXI-LRx	Ionis/Bayer	Factor XI ligand conjugated antisense	-	-
AB022	Aronora	Anti-factor XIa MAb	-	-
Status unknown				
BMS-262084	Bristol-Myers Squibb	IV/oral factor XIa Inhibitor	-	-
BMS-962212	Bristol-Myers Squibb	IV factor XIa inhibitor	-	-
ESRD: end-stage renal disease. Source: EvaluatePharma.				

J&J and Bristol did not give financial details of their collaboration, but a spokesperson for Bristol told *EP Vantage* that the companies would share development and commercialisation costs and any future profits, “roughly 50/50”, and that, if BMS-986177 is approved, Bristol would expect to book US sales and Janssen ex-US revenues.

While Bristol also has two other factor XIa projects in its pipeline, the company is currently prioritising BMS-986177, the spokesperson said, adding that it was not looking at other antithrombotic mechanisms outside factor XIa.

J&J is not putting all its eggs in one basket, though – it is also working on another next-gen anticoagulant, JNJ-9375, which it gained via its acquisition of XO1 in 2015. That project, a monoclonal antibody against exosite 1 thrombin, is already in a phase II trial in patients undergoing knee replacement surgery, due to be completed next year.

“We have two very good shots on goal; they’re very different,” says Mr List, pointing out that the oral BMS-986177 will likely be dosed daily, while JNJ-9375 will probably be a monthly injection.

The idea is that the next-generation approaches could give equivalent or better efficacy versus the likes of Xarelto, but with a lower risk of side effects, particularly bleeding events. Indeed, an increased incidence of bleeding took the edge off last year’s win in the Compass trial in coronary and peripheral artery disease.

Still, J&J hopes for an expanded label on the back of the Compass data, with a decision due by the end of the year. And Xarelto’s bleeding risk has not hindered a steady rise in analyst forecasts in the past year. While an *EP Vantage* analysis carried out in September had Bristol-Myers Squibb/Pfizer’s Eliquis overtaking Xarelto by

2022, sellside consensus now has Xarelto back in front (*Spotlight – Xarelto and Eliquis's blood feud, September 12, 2017*).

Xarelto vs Eliquis							
		Sales forecasts ($bn)					
Product	**Companies**	**2018**	**2019**	**2020**	**2021**	**2022**	**12-mth rise in 2022 forecast***
Xarelto	Bayer/Johnson & Johnson	6.5	7.4	8.3	9.1	9.9	11%
Eliquis	Bristol-Myers Squibb/Pfizer	6.1	7.1	7.9	8.7	9.2	40%
**Current 2022 vs consensus in April 2017; Source: EvaluatePharma.*							

But J&J's label-expansion efforts have not always gone smoothly: Navigate Esus, in secondary stroke prevention, was stopped for futility in October. J&J is to report three more key label-extension trials this year: Mariner, Commander and Cassini.

BMS-986177, meanwhile, will also be studied in indications outside secondary stroke prevention. Neither J&J nor Bristol is giving details for now, but Mr List hinted that this could be a large development programme: "We're not going to be shy in phase II or III."

J&J has ploughed a huge amount of cash into expanding Xarelto's reach, but sales cannot keep growing forever. The question now is whether BMS-986177 or JNJ-9375 can show a better safety profile – and, if they can, whether this will be enough to get payers to cough up once Xarelto goes generic.

Upcoming Xarelto label-expansion readouts			
Study	**Setting**	**Trial ID**	**Primary completion**
Mariner	Prevention of VTE in post-hospital discharge high-risk patients	NCT02111564	May 2018
Commander HF	Prevention of major cardiovascular events in heart failure patients	NCT01877915	May 2018
Cassini	Prevention of VTE in cancer patients	NCT02555878	July 2018

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