Evaluate Vantage

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# German Merck boosts autoimmune BTK inhibitor chase

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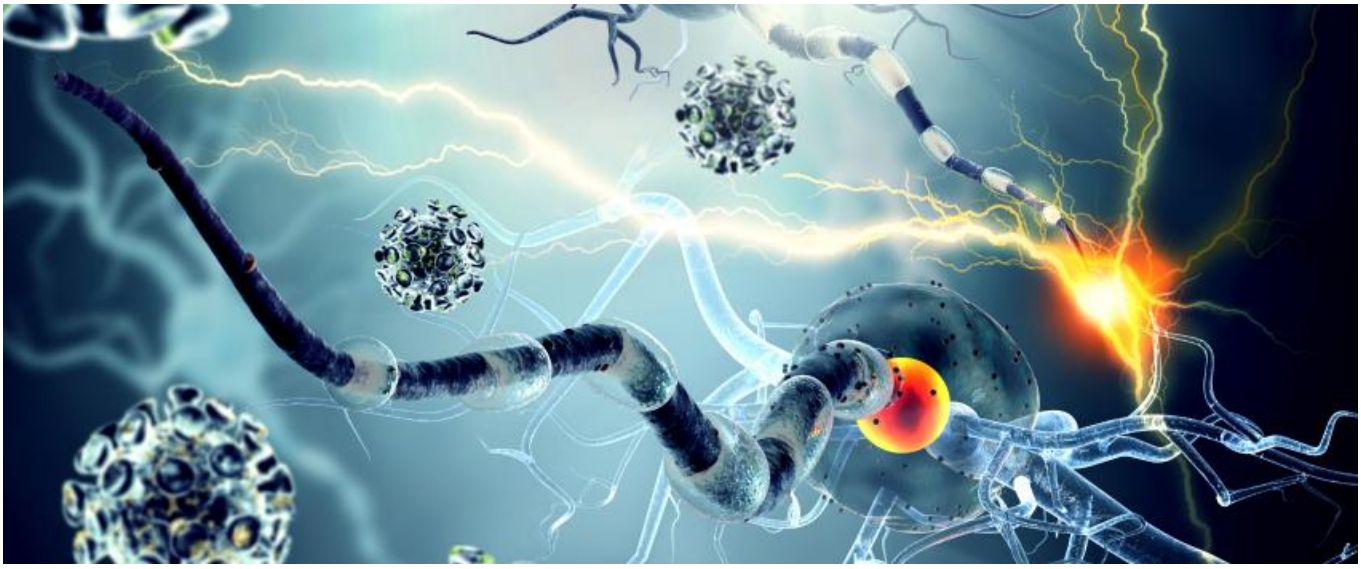

**Promising mid-stage data with Merck KGaA's evobrutinib in multiple sclerosis could help the German group carve out a niche for its BTK inhibitor – unless bigger players decide to muscle in.**

BTK inhibitors such as Abbvie and Johnson & Johnson's Imbruvica are currently used as therapies for cancer rather than autoimmune diseases. But phase II data presented last week with Merck KGaA's contender evobrutinib suggest that the class could also have promise in multiple sclerosis.

Merck is currently leading the chase in MS. But if the bigger groups decided to get involved in this indication they could presumably carry out the trials needed to add a new use to Imbruvica's label fairly quickly – and perhaps even wipe out the German group's head start.

Whether they will choose to do this is another matter: J&J told *Vantage* it had no plans to study Imbruvica in autoimmune diseases. Interestingly, the other approved BTK inhibitor, Astrazeneca's Calquence, has been evaluated in a different autoimmune disease, rheumatoid arthritis. A phase II study in this indication was completed in 2016, though it is unclear whether any more work is planned.

At present, RA is a more popular indication than MS for companies looking outside BTK inhibitors' approved uses of haematological cancer. This strategy fell flat in February when Lilly dumped Hanmi's poseltinib after disappointing data in the joint disease.

In MS, meanwhile, the most advanced BTK inhibitors after evobrutinib are Sanofi and Principia Biopharma's SAR442168, which is in a phase I trial in healthy volunteers. Biogen's BIIB068 completed a healthy volunteer study in 2016 but the company has not clarified whether the drug is still in active development.

| Blood cancers or autoimmune disease: the BTK inhibitor landscape | | | |
|---|---|---|---|
| **Product** | **Company** | **Lead indication(s)** | **Autoimmune trial(s)** |
| ***Approved*** | | | |
| Imbruvica | Abbvie/Johnson & Johnson | Leukaemia, lymphoma | - |

| Blood cancers or autoimmune disease: the BTK inhibitor landscape | | | |
|---|---|---|---|
| Calquence | AstraZeneca | Lymphoma | RA (NCT03777762*) |
| ***Filed*** | | | |
| Zanubrutinib | Beigene | Leukaemia, lymphoma | - |
| ***Phase II*** | | | |
| Evobrutinib | Merck KGaA | MS, lupus, RA | MS (NCT02975349); lupus (NCT02975336); RA (NCT03233230) |
| BTK Inhibitor Program/BMS-986142 | Bristol-Myers Squibb | RA | RA (NCT02638948) |
| RG7845/fenebrutinib | Roche/Chugai Pharmaceutical | RA, lupus, urticaria | RA (NCT02983227); lupus (NCT02908100, NCT03407482) |
| PRN1008 | Principia Biopharma | Pemphigus vulgaris, ITP | Pemphigus vulgaris (NCT02704429), ITP (NCT03395210) |
| Tirabrutinib | Ono Pharmaceutical/Gilead Sciences | Leukaemia, lymphoma | Sjögren's syndrome (NCT03100942) |
| Vecabrutinib | Biogen/Sunesis Pharmaceuticals | Leukaemia, lymphoma | - |
| M7583 | Merck KGaA | Lymphoma | - |
| LOU064 | Novartis | Urticaria | - |
| ***Phase I*** | | | |
| BIIB068 | Biogen | Lupus, MS | NCT02829541* |
| SAR442168/PRN2246 | Sanofi/Principia Biopharma | MS | Phase I healthy volunteers trial (no ID) |
| AC0058 | Acea Biosciences | RA, lupus | NCT02847325 |
| ARQ 531 | Arqule | Leukaemia, lymphoma | - |
| DTRMWXHS-12 | DTRM Biopharma | Leukaemia, lymphoma | - |
| DTRM-505 | DTRM Biopharma | Leukaemia, lymphoma | - |
| DTRM-555 | DTRM Biopharma | Leukaemia, lymphoma | - |
| TG-1701 | TG Therapeutics | Leukaemia, lymphoma | - |

**Inactive trial. ITP: idiopathic thrombocytopenic purpura; MS: multiple sclerosis; RA: rheumatoid arthritis. Source: EvaluatePharma, clinicaltrials.gov.*

The rationale behind using BTK inhibitors in autoimmune diseases is that they deplete B cells, which are implicated in these disorders.

There is a precedent for a similar approach in MS: Roche's Ocrevus, an anti-CD20 MAb, also targets B cells and has the same mechanism of action as the Swiss company's lymphoma and leukaemia therapy Rituxan, which is also used for RA.

Still, Merck should not start celebrating just yet: its data, from the phase II study of evobrutinib, presented at the Ectrims meeting in Berlin last week, were promising but not emphatic. The study in relapsing disease hit its primary endpoint, with the two higher doses of evobrutinib, 75mg given either once and twice daily, reducing the number of gadolinium-enhancing T1 lesions versus placebo.

Evobrutinib also outperformed Biogen's Tecfidera on this measure, but Merck played this down, saying the latter had been included as an open-label reference and that no formal statistical comparisons had been made. Indeed, Tecfidera looked worse than placebo on lesion number, though there was a high level of variability in this arm of the trial.

**Relapse miss**

Evobrutinib missed a secondary endpoint, annualised relapse rate. Merck claimed that the declines in relapse rate seen at 48 weeks with the 75mg once and twice-daily doses were clinically relevant, but they did not hit significance. This could be a red flag for phase III trials of Merck's project. In contrast, Ocrevus showed a highly significant benefit on annualised relapse rate, the primary endpoint of its two phase III trials.

However, the Ocrevus studies spanned 96 weeks, and relapsing MS can progress slowly and unpredictably. The UK's Multiple Sclerosis Trust notes that, on average, patients have around one relapse every two years. Some might have several relapses in one year and others can go for several years without experiencing one.

A pooled analysis of disability progression from the pivotal Ocrevus trials only showed a separation from placebo after around a year of therapy, so it might simply be that the evobrutinib study was too short to show an effect.

Merck will presumably have to run longer phase III studies if it wants to show a benefit on relapse. At the moment, time is on the German company's side – but this could change if Abbvie, J&J or Astra decide they want in on the MS space.

*This story has been updated to include J&J's response to the question of whether it planned to study Imbruvica in autoimmune diseases.*