Spotlight on BTK inhibitors in MS

In recent years, interest in BTK inhibitors (BTKi) for MS has surged, with hopes that they could offer a new way to tackle the underlying drivers of the disease. But the journey, so far, has been a rollercoaster, and the delayed FDA decision on tolebrutinib marks the latest twist and turn. For now, the gates remain closed to this long-awaited generation of disease-modifying therapies in the MS fairground.

Why the hype with BTKi?

The buzz around BTK inhibitors comes down to two standout features:

Impact independent of relapse:
BTK inhibitors are a new kind of ride - designed to do more than simply control relapses. Their CNS-penetrant mechanism targets immune cells in the brain and spinal cord, addressing progression that many current therapies cannot.

Potential across multiple forms of MS:
MS is diverse, and BTK inhibitors could appeal to populations with few options - such as non-relapsing secondary progressive MS (nrSPMS). Early data also suggest promise across other forms of MS, giving them a shot at being a main attraction in a crowded therapeutic fairground.

The journey so far: a bumpy ride for BTKi

Despite a few bumps - anticipation for BTKi keeps growing

Early excitement over CNS-penetrant BTK inhibitors was met with scepticism. Safety jolts, including liver toxicity that temporarily halted tolebrutinib's trials, added to the ride's bumps. And, trial outcomes haven't always followed a straight track either - evobrutinib's EVOLUTION and tolebrutinib's GEMINI 1/2 trials in relapsing MS missed primary endpoints, leaving **crowds questioning if the new attractions could truly deliver**.

Despite the hurdles, **momentum has held**. Positive Phase 3 data for tolebrutinib, indicating potential in nrSPMS, and Phase 2 data for fenebrutinib has kept the BTKi carousel turning and the class in the spotlight.

Tolebrutinib: a highly anticipated attraction for MS care

The eagerly watched tolebrutinib has generated months of buzz

Fast-tracked for priority review and widely featured in lists of the "most anticipated launches of 2025", the buzz surrounding this therapy has been loud - and for good reason. Positive Phase 3 HERCULES data in nrSPMS positioned it as the first BTKi poised to deliver a meaningful impact in a population with no approved therapies.

Expectations for the first-in-class FDA approval were building. But the **delayed FDA decision** is the latest turn of events in this rollercoaster journey, keeping the gates closed for now. The big question is whether this long-awaited attraction will be able to open its gates at the end of the year and deliver a smooth ride.

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Safety: the key twist on the tolebrutinib ride

With safety checks in place, can the ride still deliver? And thrill?

Efficacy data for tolebrutinib has thrilled the crowds in the MS fairground, but the FDA delay underscores that **safety remains the central twist**. Early liver toxicity signals which prompted trial delays and enhanced monitoring requirements have likely contributed to the hold-up.

If approved, tolebrutinib will **likely carry a black box warning**, requiring regular lab checks. For neurologists, these safety considerations will shape how quickly and confidently they climb aboard, influencing adoption if, and when, the gates finally open. There is potential to thrill the crowds, but the ride must remain safe for all on board.

What's next for the BTKi ride?

The coming year will set the pace for the BTKi race

With the FDA decision now expected in December, the **tolebrutinib ride opening is temporarily paused**. But, it's PERSEUS trial in Primary Progressive Multiple Sclerosis (PPMS), reporting later this year, could provide the next big twist, offering more data to guide regulators and neurologists - but for now, the gates stay closed.

Meanwhile, **fenebrutinib is lining up on the next track**. Targeting a larger relapsing MS population, it's expected to report FENhance 1 & 2 later this year. Without the same safety concerns, it has a chance to gather real-world momentum and keep the race for best-in-class alive.

Even as tolebrutinib waits in the wings, the **BTKi carousel keeps spinning** - with multiple players racing for position, the MS fairground is far from quiet.

What the future holds for BTK inhibitors remains an unanswered question; **can BTK inhibitors move from theoretical promise to tangible impact in MS care?** Following yet another bump in its journey, Pharma will be watching every twist and turn with each trial readout and clinical insight at the centre of attention over the coming months. Anticipation continues to grow amongst the crowds in the MS fairground, on what they hope will be the final stretch before the long-awaited next chapter.

Our neurology team is always up for a conversation on the latest clinical developments and what they mean for pharma strategy. If you'd like to discuss we'd love to hear from you. **Get in touch.**

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