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Principia Biopharma Inc. (PRNB)

Hype Over Multiple Sclerosis "Data" Is Overblown

We are short shares of Principia Biopharma. Last week, Sanofi, the large pharma company that has licensed Principia's BTK inhibitor SAR442168 for use in multiple sclerosis, announced that the drug met the primary endpoint of its Phase 2 trial. In our original report on Principia, we noted the severe flaws in the design of this clinical trial and predicted that "[a]ny data are bound to be noisy and inconclusive." But Sanofi circumvented this problem by simply not providing any granular data at all: its press release and subsequent management commentary contained no numbers or other specifics, deferring such details to "an upcoming medical meeting" in the second quarter. (In a striking contrast, Sanofi's press release just a week earlier about clinical-trial results for a different drug included many concrete figures, including quantification of statistical significance.) For now, all we have to go on is Sanofi's enthusiasm – yet the market has viewed this big-pharma thumbs-up as strong enough evidence of long-term efficacy to drive Principia's stock price even higher.

We think this blind faith is a mistake. Here we explain further why the Phase 2 trial – which stands out from other recent multiple-sclerosis Phase 2 trials by being unusually brief, small, and uninformative – seems almost engineered to shed no real light on how well (or poorly) SAR442168 works. In particular, while Sanofi has claimed success on the basis of "reduction of new active gadolinium (Gd)-enhancing T1-hyperintense brain lesions after 12 weeks of treatment," such lesions counts often drop significantly during clinical trials *even in patients on placebo,* as initially intense disease activity (perhaps what drove patients to enroll in the trials in the first place) naturally subsides and fluctuates. In other words, a decrease in lesion counts is unsurprising even on an ineffective drug – underscoring the importance of a true control group, which Sanofi's trial lacked. Nonetheless, at a time when Sanofi's new CEO is reportedly eager to regain the company's "lost…mojo," act less "defensive," and "play to win," Sanofi has rushed forward on the basis of this flimsy and unreliable evidence into Phase 3 trials that we expect to fail.

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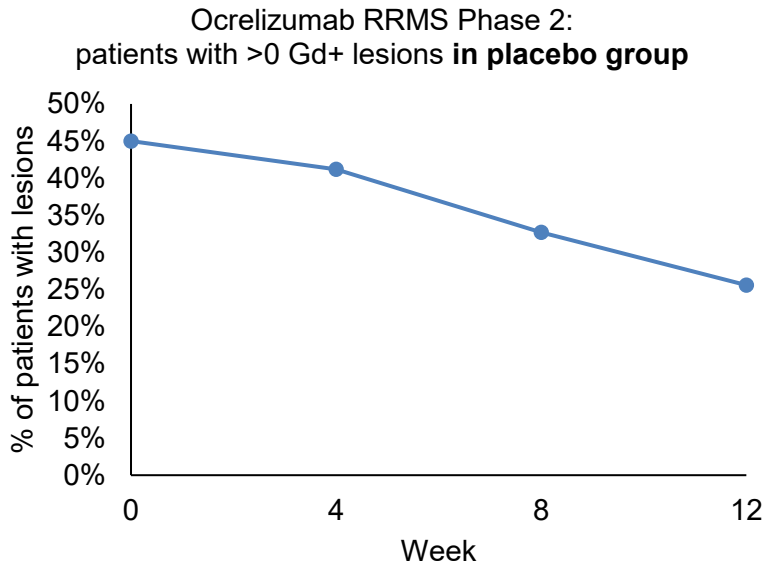
The MS Phase 2 Trial Design Was Deeply Flawed

Even Patients on Placebo Often See Lesion Reductions

Despite the fact that Sanofi headlined its press release "Sanofi brain-penetrant BTK inhibitor **meets primary endpoint** of Phase 2 trial in relapsing multiple sclerosis" (emphasis added), it remains difficult to say with any confidence what precisely that primary endpoint was. Sanofi said that SAR442168 "significantly reduced disease activity associated with multiple sclerosis as measured by [MRI]," and the company's head of R&D repeated during its earnings call that "the primary endpoint…was a reduction in the number of new gadolinium-enhancing hypersensitive [*sic* – he likely meant "hyperintense"] lesions at 12 weeks as detected by MRI." But "reduction" implies a comparison: what was reduced relative to what? Since there was no true control group (all patients on the trial received 12 weeks of daily SAR442168 treatment), the most natural reading is that the reduction measured was from baseline to week 12 across all patients; in this interpretation, the average number of new Gd+ lesions identified on the week-12 scans was lower, to a statistically significant degree, than the average number of such lesions identified on the week-zero scans.

But there's a big problem with the achievement of this endpoint: it wouldn't be surprising or impressive even if the drug did nothing. Consider, for instance, the Phase 2 results in relapsing-remitting MS of the anti-CD20 antibody ocrelizumab. A recent publication has supplemented the original study to provide greater detail on the time course of lesion reduction during the trial. The graph below shows the percentage of patients in one arm of the trial who had one or more Gd+ lesions over time. Strikingly, with each successive scan over the course of 12 weeks, fewer and fewer of these patients (falling from 45% to 26%) had any lesions – the drug must be working! *But these patients weren't taking a drug.* They were in the placebo group.



Source: Kappos et al. 2011, Barkhof et al. 2019, Kerrisdale analysis

This apparent improvement in the ocrelizumab Phase 2 placebo group was not just a one-off fluke. Another striking example comes from a study of Avonex (interferon beta-1a) relative to placebo. While patients with no MRI lesions at baseline tended to continue to exhibit low activity, those starting out *with* lesions saw their lesion count sharply decline on average – *even when they were only taking placebo* (represented by the solid line in the upper portion of the graph below, showing a declining from a mean of ~4 lesions at baseline down to ~2 by year 1).

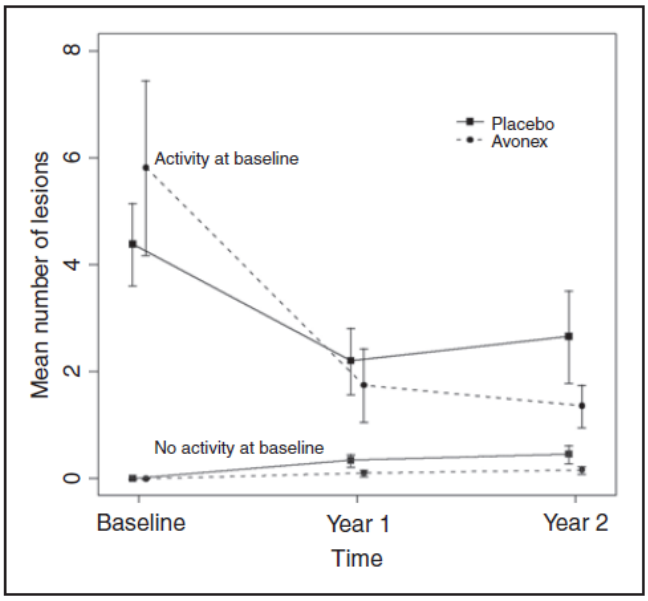
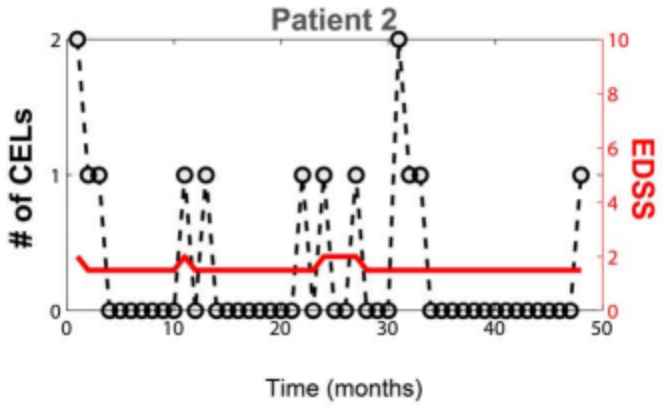


Figure 5. Mean lesion count (with standard error bars) by time, treatment, and baseline activity.

Source: Morgan et al. 2010

What's going on here – why are patients seemingly getting better on placebo? To begin with, the data are inherently quite volatile. According to one of several studies of the difficulty of modeling individual MS lesion counts over time, "CEL [contrast-enhancing lesion] dynamics are considered unpredictable and are characterized by high intra- and interpatient variability…The natural history of a CEL is highly variable both within and between patients." Consider the lesion history of this MS patient, who was not taking any immunosuppressive drugs during the period shown:



Source: Velez de Mendizabal et al. 2013
Note: the red line indicates score on Expanded Disability Status Scale (EDSS), a standard metric of physical disability in MS.

The patient happened to enter the study with two active Gd+ lesions. Within three months, however, the patient was lesion-free – without taking any medication. (A 100% decline in lesion count within ~12 weeks – how can Principia and Sanofi compete with this "no treatment" treatment?) In most months, the patient's MRI scans showed no lesions, yet occasionally one or two would appear, then vanish. This pattern is not unusual. Depending on when such a patient entered a trial and how long he or she was tracked, he or she might appear to get greatly improving or greatly deteriorating – all because of chance. Similar results have appeared in other observational studies of patients not taking disease-modifying therapy. As the plots below show, not only do patient-level lesion counts fluctuate significantly even from week to week; they also exhibit a tendency to decline over time, even without treatment ("For example, the patient with the highest number of lesions early in the study has a large decrease in the number of lesions by the end of the study"):

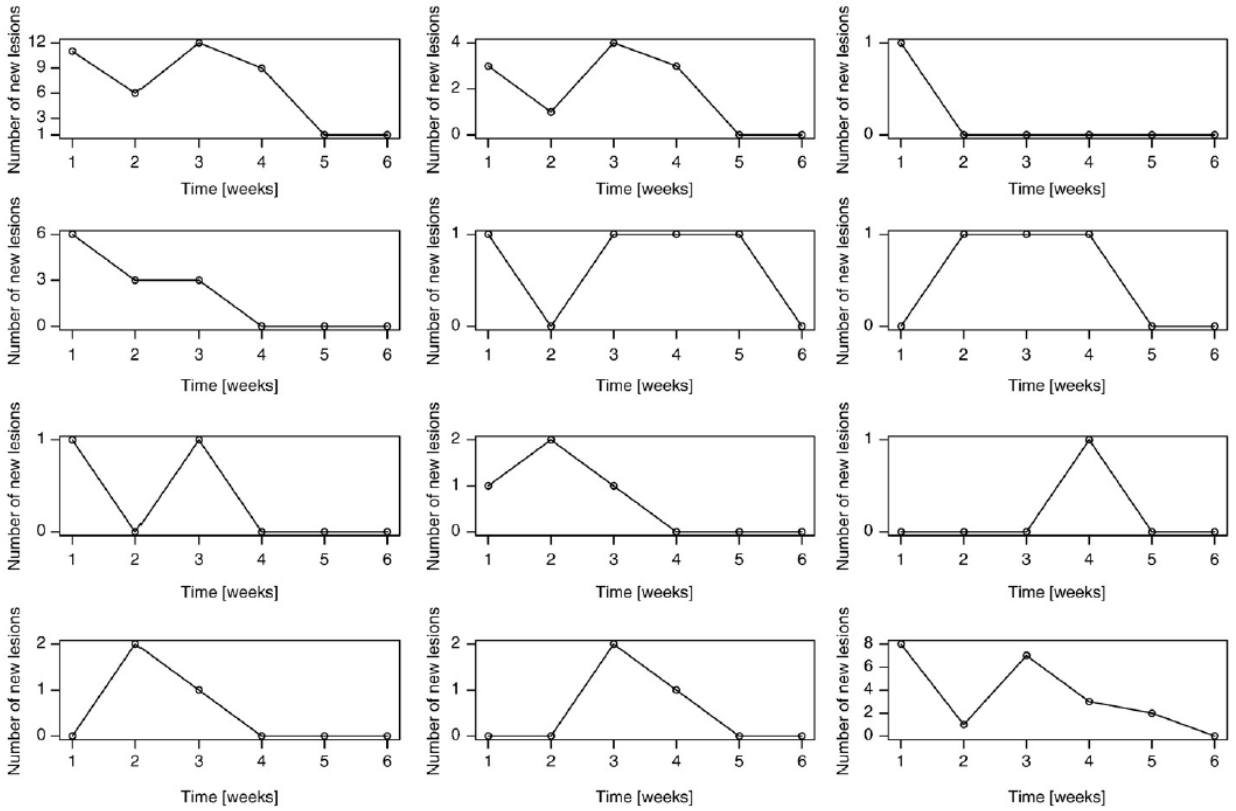


Fig. 1. Number of new gadolinium-enhancing brain lesions observed in an observational study of patients with multiple sclerosis [17]. Each plot represents a different patient. The number of new lesions changes over the course of the study for many patients. For example, the patient with the highest number of lesions early in the study has a large decrease in the number of lesions by the end of the study.

Source: Healy et al. 2009

As various researchers have discussed (in e.g. Zhao et al. 2008, Healy et al. 2009, Barkhof et al. 2011, and Stellmann et al. 2015), one force driving the "mysterious" improvements witnessed in untreated patients is regression to the mean: patients may tend to enroll in studies at a time when their condition has randomly gotten worse; when their luck returns to normal, they will appear to "get better" irrespective of treatment. Another complementary force is the very nature of the most common – "relapsing-remitting" – form of MS, characterized by alternation between periods of high and low disease activity. Clinical trials often explicitly *select* for patients experiencing relatively high disease activity. The Sanofi Phase 2 trial, for instance, required the following:

> Participant must have at least 1 documented relapse within the previous year, ≥2 documented relapses within the previous 2 years, or ≥1 active Gadolinium (Gd)-enhancing brain lesion on a magnetic resonance imaging (MRI) scan in the past 6 months and prior to screening.

But, given the inherent tendency of relapsing-remitting MS to relapse and remit, patients selected for active disease will tend to shift toward inactive disease, even if they're receiving ineffective treatment or no treatment.

In light of this well-documented pattern of illusory improvement on placebo, Sanofi's proud claim that SAR442168 "significantly reduced disease activity associated with multiple sclerosis as measured by [MRI]" rings hollow. The company failed to heed the warnings issued by researchers more than a decade ago: "the natural disease process in RRMS can profoundly impact the estimated treatment effect on gadolinium-enhancing lesions from one-arm clinical trials with enriched enrollment selection based on active disease… In all cases [of simulated lesion data], conventional comparison of pretreatment to on-treatment measurements overestimated the treatment effect." (Healy et al. 2009). There's an easy fix to all these concerns: use a legitimate control group. Of course, if one's goal were to drum up excitement about a drug of dubious efficacy, a trial design that inherently "overestimated the treatment effect" would be just what the doctor ordered.

Sanofi's Secondary-Endpoint Results Were Likely Shaky

Beyond its claims about the primary endpoint, Sanofi has also said that "SAR442168 demonstrated a dose-response relationship in the reduction of new active gadolinium (Gd)-enhancing T1-hyperintense brain lesions after 12 weeks of treatment." In other words, some group of patients on a higher dose experienced a larger reduction (whether in terms of percentage decline in lesion count, absolute decline in lesion count, or something else is unclear) than some group of patients on a lower dose – a pattern depicted as a signal of drug efficacy.

But there are is a major caveat. Conspicuously absent from the phrase "demonstrated a dose-response relationship" is the modifier "*statistically significant.*" Was the difference between the high-dose and low-dose results large enough to rise above the high background variability in individual patient lesion counts? Sanofi has not said so. Indeed, given that the trial included eight different groups (four dose levels administered in two different crossover structures (12 weeks of drug then 4 weeks of placebo vs. the reverse sequence)), with only 15 patients in each group, Sanofi has many degrees of freedom to decide what particular dose-response relationship it wants to highlight. For instance, it could pool the results across the two crossover sequences, or it could separately highlight whichever individual 15-patient subgroups looked the best after the fact.

Aside from the primary endpoint tied to new Gd+ lesions, the SAR442168 trial also, according to information on ClinicalTrials.gov, tracked two additional MRI-based secondary endoints:

- Number of new or enlarging T2 lesions
- Total number of Gd-enhancing T1 hyperintense lesions [*as opposed to the **new** Gd+ lesions required by the primary endpoint, though, since such lesions usually only persist for about a month, the difference between "new" and "total" is usually minor*]

On Sanofi's earnings call, management said that "secondary brain imaging studies also show promising results. The caveat, of course is that these imaging end points are surrogate markers"

– meaning that they don't directly measure patient health or well-being – "but the results give us the confidence to go forward." But an additional caveat lies again in the choice of wording: while the secondary-endpoint results are said to be "promising," no mention is made of their statistical significance – often a sign that it was absent.

The Phase 2 Trial Appears Unusually Perfunctory and Rushed

Sanofi's admission that its Phase 2 results only measure "surrogate markers," not standard clinical outcomes like annualized relapse rate or disability progression/change in EDSS score, raises an obvious question: why didn't it measure those clinical outcomes? To be fair, it's unlikely that such metrics would move enough over a 12-week period to clearly distinguish an effective drug from an ineffective one, but that in turn raises another question: why treat patients for only 12 weeks? Indeed, looking more broadly at key characteristics of the trial relative to those of other major recent RRMS Phase 2s, we see that the Sanofi/Principia trial is a clear outlier: brief, small in terms of patient count, stingy in eschewing multiple repeated MRI scans to average out some of measurement noise and volatility, and uninformative in its omission of clean control groups and clinical (as opposed to MRI-based) outcomes:

Drug	SAR-442168	evo-brutinib	ocrel-izumab	ofatu-mumab	dacli-zumab + IFN beta	dimethyl fumarate	teri-flunomide
Sponsor	Sanofi	Merck KGaA	Roche	Novartis	Biogen/ Facet (now AbbVie)	Biogen	Sanofi
Phase	2b	2	2	2b	2	2b	2
Patients	120	267	220	232	230	257	179
Weeks on treatment (primary endpoint)	12	24*	24*	24	24	24	36
Number of monthly MRI scans included in primary endpoint	1	4	4	3	5	4	6
Pure control group(s)	none	placebo dimethyl fumarate	placebo IFN β-1a	placebo	IFN β + placebo	placebo	placebo
Clinical metrics	none	relapses, EDSS	relapses, EDSS	relapses, EDSS	relapses, EDSS	relapses, EDSS	relapses, EDSS

Source: Sanofi press release, Montalban et al. 2019, Kappos et al. 2011, Bar-Or et al. 2018, Wynn et al. 2010, Kappos et al. 2008, O'Connor et al. 2006, Kerrisdale analysis
** Some results also disclosed for week 48.*

Across several dimensions, the SAR442168 trial looks rushed and perfunctory, as if it were less a genuine attempt to asses the efficacy of the drug than an exercise in going through the motions before Phase 3. Indeed, when, at its Capital Markets Day in December, Sanofi management first began to talk up the drug in earnest and strongly hint that it would be moving

into Phase 3, there were still 23 days left before the final trial results could be compiled, let alone analyzed (source: "actual study completion date" on ClinicalTrials.gov).

Rushing Ahead on the Basis of Weak Evidence Tends to Fail

When a drug developer believes in a certain mechanism of action and sees what look like promising early results, it's always tempting to rush ahead – especially with competition waiting in the wings. In the case of SAR442168 (formerly PRN2246), the timeline is striking. At the same medical meeting in October 2017, both Principia and Merck KGaA (1, 2) presented preclinical data on the use of BTK inhibitors in mouse models of multiple sclerosis. Within a few days, Principia and Sanofi announced their licensing deal. But, by this point, Merck's Phase 2 trial was already heading towards completion; Sanofi and Principia were lagging. However, Merck's own issues with questionable Phase 2 data (gathered in Bulgaria, Czechia, Poland, Russia, Serbia, Slovakia, Spain, and Ukraine) appear to have slowed it down, giving Sanofi a chance to catch up. Merck has already initiated Phase 3 trials and expects to be done in 2023 – but, by conducting an abbreviated Phase 2 and moving forward aggressively, Sanofi is not far behind, targeting submission for regulatory approval in 2024-25 (source: Q4 2019 presentation, slide 20).

Of course, that's far down the road. Before it can hope to achieve regulatory approval, Sanofi has to show that SAR442168 can significantly improve patient health (not just MRI metrics) in large trials with real control groups. The overall picture is reminiscent of recent big-pharma maneuvering in the asthma market. There, Sanofi has gained market share with its new treatment Dupixent, putting pressure on competitors to gamble on their own drug pipelines. Novartis pushed forward with a DP2 antagonist despite questions about the quality of its Phase 2b data and a history of past failures in similar drugs from other companies, but ultimately Novartis had to admit defeat: its drug failed repeatedly in Phase 3, leading the company to pull the plug.

Such failure is hardly unknown in multiple sclerosis. Consider laquinimod. In the early 2000s, a 24-week, 209-patient Phase 2 study seemed to show that laquinimod, an immunomodulatory drug that appeared to work animal models of MS and other autoimmune disorders, significantly outperformed placebo in terms of active-lesion reduction and exhibited a "dose response relationship," albeit one that was not statistically significant on most metrics. Also, "[n]o differences with respect to clinical variables (relapses, disability) were found." Nonetheless, the drug, developed by the small Swedish firm Active Biotech, was licensed to Teva, the maker of the once dominant MS treatment Copaxone, in 2004, and was reportedly "seen as a potential blockbuster heir to Copaxone…capable of generating up to $4 billion a year. [But it]…would go on to see a series of disappointing efficacy results in later-phase trials, in both relapsing-remitting and primary progressive MS," leading Teva to finally give up and return the rights to laquinimod to Active in 2018, having wasted 14 years and untold dollars. Over the same period, Active's stock price has fallen about 90%.

More recently, a similar story has played out with minocycline, an antibiotic thought to inhibit the activation of microglia (currently the hot new target once again now that Sanofi has claimed that SAR442168's "success" stems in part from influence on microglia, a topic to which we will return). Beginning in the late 1990s, minocycline became the darling of a group of Canadian MS researchers, who became convinced it would be an effective treatment. After demonstrating benefits in a common mouse model of MS, they published a paper in 2004 showing that, in a 10-patient single-arm trial with no control group, the mean number of Gd+ lesions per MRI scan declined *84%* when comparing a three-month pre-treatment period to a six-month post-treatment period (similar to Sanofi's use of a four-week placebo period and a twelve-week treatment period). Seemingly convinced that this 84% decline could not have been the product of chance, regression to the mean, or the relapsing/remitting nature of the form of MS they were studying, they conducted a larger Phase 2 trial with funding from Teva. Published in 2009, the trial compared minocycline plus Copaxone to placebo plus Copaxone. While the researchers found that Gd+ lesions were lower by 63% in the minocycline add-on group, this difference was not statistically significant, and they admitted indirectly that regression to the mean might have contributed to the apparent efficacy of minocycline: the baseline number of Gd+ lesions in the minocycline group was higher than in the placebo group, perhaps accounting for much or all of the subsequent decrease and "mak[ing] interpretation of the data more challenging." Sure enough, a second Phase 2 trial, sponsored by Merck KGaA and enrolling more than 300 patients (another case of big-pharma competitors rushing ahead to pursue new drug categories on the basis of flimsy evidence), was terminated early in 2013; the results, published in 2016, showed "no statistically significant differences" between minocycline plus interferon β-1a (a common MS treatment) and placebo plus interferon β-1a, whether on clinical or MRI-based outcomes. With two controlled trials showing no significant value-add in MS, minocycline now seems to be abandoned.[1]

The minocycline story has almost everything it needs to serve as a template for SAR442168: an intriguing and novel mechanism of action (microglia and all), early alleged success in an animal model, clinical data showing "impressive" reductions in lesion activity amid unreliable and flawed trial design, big-pharma titans falling over themselves to capture the opportunity first, and finally – we expect – ultimate failure in larger, well-controlled studies, leading everyone to wonder why they ever believed in the drug in the first place.

[1] The same Canadian researchers continue to believe in minocycline and now claim it can delay progression from a pre-MS condition called clinically isolated syndrome to full-blown MS, though their results appear weak (no difference between minocycline and placebo after 24 months) and have been challenged by other researchers ("too early to tell," "may not be entirely well founded").

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