

Alzheimer's

April 2019



It has never been more disheartening to win on a short.

Biogen's stock collapsed on the announcement of the failure of the latest Alzheimer's trial. By some counts, this was the latest failure in over a hundred clinical trials based on the amyloid-beta ($A\beta$) hypothesis. Biogen deserves full credit for taking such a bold financial risk, but something has clearly gone very wrong. The hypothesis has been around since the 1980s, yet every $A\beta$ treatment has failed its patients, not to mention investors.

We may well be observing a multi-decade correlation/causation error. Everyone with Alzheimer's has $A\beta$, but not everyone with $A\beta$ has Alzheimer's. Biogen's drug aducanemab, as others have in the past, helped clear the $A\beta$ plaques, but offered no benefit to patients.

This latest failure could be taken as evidence of the opposite hypothesis: that plaques are a symptom, and not a cause.

Many more qualified have made these points better, before. A scientific review is available [here](#), and there is an excellent (more readable) set of articles [here](#).

With such widespread dissent, why are the decision-makers in academia and industry devoting so much capital attention towards $A\beta$?

The answer goes to the core of how science is done. Everyone from an aspiring PhD student, to Biogen management themselves, has to pitch for funding. This is no easy task in any field, and $A\beta$ has been taught for decades. It's forged a large number of PhDs and careers. As the leading theory, grants are seen through the $A\beta$ lens.

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The hypothesis has a clear mechanism with well-characterised targets, making it all the more attractive to researchers. Dominant paradigms are hard to displace, and so they should be. But each failure suggests more slow, non-financially rewarding, basic research needs to be done.

Biogen's trial shows other interesting features of biotech.

Firstly, in small Phase 1 and Phase 2 trials, there will often be a segment of the population that does better than others. Survival might be higher in the younger, or those with a particular medical history. Perhaps the dose was wrong, and can be corrected in Phase 3. Natural randomness ensures there's hope that a different design would yield a different result.

Scientists and executives tend to do their best to rescue a drug and find a clinical path forward. No-one wants to halt a drug program with billions of dollars of investment behind it. In this case, Biogen's drug had already failed its main trial, a tell-tale sign of a clinical program in trouble. Experimental design is best done at the start, not the end.

[If unfamiliar with the process, Phase 1 trials generally test safety, by escalating small doses in small numbers of healthy people. Phase 2 tests different doses and ideally yields the first efficacy data, but the main task is to get more data to design a Phase 3 trial. Phase 3 is the one that counts. We only invest in biotech companies with strong efficacy data - ie data that shows the drug cures symptoms - before Phase 3 trials, such as our [genetic engineering investments](#). Many drugs go to Phase 3 without clear evidence they work in people, for the reasons above.]

Secondly, from an investing perspective, you're often better off going short than going long. Typically a number of companies target the same disease, with only one possible winner. Sometimes a whole class of drugs fails, and no-one wins. If a drug does succeed, the market may turn out to be smaller than hoped for, or the drug may face new competition. Cynics would find rich pickings in biotech.

Shorts are a small part of what we do, and we don't like to talk about them. In this case, a long-held view became an actionable trading idea, but we would really just prefer the scientific community tried different approaches.

Thirdly, the nature of some diseases makes it very hard to prove anything. Imagine testing the impact of diet on aging. You'd have to track people from youth to old age, and control everything they ate. It's just not practical, and one of the reasons dietary advice is so inconclusive.

Alzheimer's is similarly tough. Symptoms occur late, so there's no way to disprove a drug. The case can always be made that it just needed to be tried in younger patients. Still, one might expect one of these drugs to show *some* measurable Phase 3 benefit, but none have.

Animal trials may also be part of the problem. The evidence for some of these candidates comes from mice engineered to produce human A β . The human brain is different to that of animals, to put it mildly, and may have even less to do with an engineered chimera.

Due to the length of time taken to develop a drug, and the rate of progression of current patients, those suffering from later stage Alzheimer's now have no late stage trial results to look forward to.

The rewards for success would be immense. Alzheimer's strikes down a sixth of us, and causes immeasurable loss to society by removing years of life from large numbers of the elderly at the peak of their wisdom. A cure would catapult the corporate sponsor into the ranks of the world's most valuable companies.

There are many alternative avenues of research. Alzheimer's has the hallmarks of an auto-immune disease. And in Taiwan, there's new evidence A β may be the brain's own defence against infection. A study covering 34,000 patients showed that those with herpes HSV-1 were 2.6x more likely to get dementia. Treating the herpes virus lowered the risk of Alzheimer's by over 80%. Early work, sure, but the team should be commended for pursuing a different approach.

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The original data presented by Biogen, which caused the spike in the share price that allowed us to enter our position, and some investment banks to assume a 50% chance of success, stands in stark contrast to what we prefer to see in our pharmaceutical investments:

1. Evidence in early phase trials that the drug works, not just that it's safe, or reaches the right part of the body.
2. Consistency in trial methods. It's a bad sign when a pharmaceutical company changes the parameters of their phase 3 trial. Often failed drugs are sold to new biotech startups, who raise money, and test it all over again (see [Axovant](#).) This is not something we would invest in, though we wish those companies well and are glad some are taking those risks.
3. Detailed data released periodically. If a drug is working convincingly, the information may become available before the end of the trial. No news means the trial hasn't yet been successful enough to justify giving the drug to patients on placebos. Biogen's opacity was quite different to [bluebird bio's](#) steady release of successful patient outcomes.

You don't need to take my word on all this. Just keep an eye out for the next set of Alzheimer's headlines. A number of companies are progressing A β antibodies and vaccines that have successfully cleared the plaques in mouse models. What was it they say about trying the same thing again and again and expecting different results?

Michael

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