Berlin Cures' Failed Long COVID Clinical Trial Yields Lessons on Study Design

BC 007, a German infusion drug that targets autoantibodies, is heading for new study.

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Key points you should know:

- After advertising a potential long COVID "cure" in its novel drug, called BC 007 (rovunaptabin), the German start-up Berlin Cures abruptly concluded its phase 2 clinical trial with a brief press release in November 2024 announcing the study was unsuccessful.
- The Sick Times spoke with study participants and outside experts and found that, while some participants did see improvement in their symptoms following BC 007 infusions, the study's design was not set up to fully capture those changes.
- The trial may have also cast too wide a net in selecting participants, failing to focus on people who were most likely to benefit from BC 007 — exemplifying a common challenge in testing treatments for the highly complex disease that is long COVID.
- Another, smaller trial of BC 007, at University Hospital Erlangen, did find that the drug alleviated long COVID symptoms, according to a preprint shared in December. This trial was better designed to capture improvement, experts said.
- A new start-up called APTA Therapeutics, led by former Berlin Cures CEO Oliver von Stein, has acquired BC 007 and plans to continue research with future studies that learn from the prior trial's shortcomings.
- For other clinical trials going forward, long COVID and related disease researchers and advocates recommend carefully selecting participants who may benefit most from a given drug

and designing studies in collaboration with people who have lived experience.

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The clinical trial changed Shayna Bhalla's life.

After years with long COVID — debilitated by fatigue, headaches, and neurological issues — her symptoms dramatically receded. While not fully back to her pre-COVID-19 baseline, she was able to resume university classes and other daily activities.

"In the last few months, I have literally regained life," Bhalla said in an interview last year, in November.

Bhalla posted on social media about her experience, garnering attention from other people with long COVID who hoped they could benefit from the same drug: an infusion called BC 007 (or rovunaptabin). Berlin Cures, the company that developed this drug, had repurposed it from heart disease research, hypothesizing that it could alleviate symptoms by reducing autoantibodies — immune system components that mistakenly attack the body as if it is an outside invader.

Thanks to posts like Bhalla's and coverage in German media, the international long COVID community closely followed Berlin Cures' trial, with many people expressing high hopes for its results in patient support groups and forums. The trial was a rare double-blind study of a novel drug, at a time when most long COVID research is still observational. Even the U.S. National Institutes of Health's $1.6 billion RECOVER initiative has primarily tested behavioral changes in its trials so far rather than pharmaceuticals.

But then, in November 2024, Berlin Cures posted a press release saying the phase 2 clinical trial had been unsuccessful. Furthermore, Berlin Cures was out of funding and would not conduct additional research, the company said.

Bhalla was devastated: "I feel like I'm back at zero," she said. She and other trial participants who spoke to The Sick Times expressed disappointment that such a highly anticipated study had ended so abruptly. BC 007 was a rare compound that had led to clear symptom improvements for some participants — and it was suddenly unavailable for patients or future research.

The BC 007 trial exemplifies the challenges of developing long COVID treatments. A review of the trial by The Sick Times shows that from the start, the study failed to account for the vast complexity of long COVID. Rather than testing the infusion on a specific group of patients who were likely to benefit, the Berlin Cures researchers used an unreliable blood test to select participants and failed to rigorously measure symptom changes, among other potential study design issues, experts said.

Long COVID, which has affected around 6% to 7% of adults globally, is an umbrella term for a cluster of diseases with different patterns of symptoms. Scientists agree that no treatment will be a universal cure.

Berlin Cures' drug might be a promising treatment for some people with long COVID and related chronic diseases, said Dr. Artur Fedorowski, a cardiologist at the Karolinska Institute in Stockholm who specializes in dysautonomia and has researched similar interventions. But the company's recent trial was not set up properly to capture that promise, he said.

For more accurate results, experts like Fedorowski say trials must carefully choose their participants, match potential interventions to symptoms and biological measurements, and monitor outcomes in close collaboration with the people participating. Indeed, another study also looking at BC 007 utilized more suitable selection criteria and outcomes measures — and those researchers did find the infusion helped alleviate participants' symptoms.

The Sick Times has learned that BC 007 may yet have a future. In an interview this summer, sharing the first news about this drug since late 2024, former Berlin Cures CEO Oliver von Stein said he is leading a new start-up, called APTA Therapeutics, that has acquired the prior company's assets and is planning further research in collaboration with long COVID and related disease experts.

"We do want to give patients hope that this drug will continue in its clinical development path," von Stein said. He acknowledged that Berlin Cures' phase 2 trial was "not an optimum study in design" and said that future research will learn from its shortcomings.

Selecting patients with an unreliable biomarker

Berlin Cures, a biotech company based in Germany, spent over two decades focused on developing treatments for autoantibodies. Its scientists designed the drug BC 007 to treat chronic heart failure; a clinical trial completed in 2018 found the infusion safe and capable of neutralizing a specific type of autoantibody that blocks G-protein coupled receptors (GPCRs).

GPCRs are important molecules involved with many different functions in the body, explained Bornali Bhattacharjee, who has studied how long COVID impacts the immune system as associate director of Yale University's Center for Infection & Immunity. These receptors act as signals in many different biological pathways; if those pathways are interrupted by rogue autoantibodies, it can lead to malfunctioning circulatory and nervous systems.

Prior research from Bhattacharjee and her colleagues at Yale has found that some people with long COVID have malfunctioning GPCRs. Before the pandemic, researchers found similar GPCR issues in people with postural orthostatic tachycardia syndrome (POTS), a dysfunction of the autonomic nervous system that many have developed following COVID-19.

Federowski said the trial should have homed in on participants with post-COVID POTS, given the prior research showing the connections between this condition and GPCR autoantibodies.

Berlin Cures became interested in long COVID as patient numbers quickly grew. In fall 2021, researchers from Berlin Cures and the University Hospital Erlangen published a case report about one individual with long COVID who was "healed" by a single infusion of BC 007. The patient's

fatigue and other symptoms improved significantly, according to that paper.

Following more successful case studies at University Hospital Erlangen, the medical institution and Berlin Cures each embarked on phase 2 clinical trials starting in summer 2023. To select participants with GPCR autoantibodies, both studies used a test looking at circulatory system cells called cardiomyocytes, which was performed by Berlin Cures. Then, the researchers used that same test to examine how well the BC 007 infusion worked in neutralizing autoantibodies. But this test may have been unreliable.

“There are no good studies demonstrating that there’s a difference between patients and healthy controls in how the plasma makes cardiomyocytes respond,” Fedorowski said. He would have liked to see the scientists use blood cell tests that have been validated by other research groups.

Study participants also noticed inconsistencies in the test. “Multiple people got screened at multiple screening sites multiple times,” said Claudia, another participant in the Berlin Cures trial. (Besides Bhalla, this story uses pseudonyms for other trial participants to preserve their privacy.)

People with long COVID went to different trial sites “until they finally got a positive result” so that they could participate, she said. “Which means that the [autoantibodies] are either not always present in the blood, or the test is flawed and can’t always measure them.”

Failing to measure success

Outside of the autoantibody test, the Berlin Cures study did not focus on specific symptoms or characteristics within long COVID’s broad definition. According to the study’s listing on ClinicalTrials.gov, any adult who reported “chronic fatigue” and “at least one additional symptom” following a documented SARS-CoV-2 infection was eligible to participate. The study initially focused on people who had long COVID for less than a year, then expanded to include those who had been sick for longer.

To identify people with chronic fatigue and later track potential improvements, the trial used fatigue questions from a symptom survey called the Functional Assessment of Chronic Illness Therapy (FACIT). While fatigue is a common long COVID symptom, for many people with the disease, it’s not actually the best factor to track: rather, researchers recommend evaluating post-exertional malaise, or PEM, which is a state of new or worsened symptoms following activity.

PEM can include many symptoms and signs — not just fatigue but also pain, sleep problems, cognitive issues, muscle weakness, flu-like symptoms, and more. It’s a cardinal feature of myalgic encephalomyelitis (ME), a chronic disease for which many people with long COVID meet the diagnostic criteria. ME researchers have identified surveys and tests that accurately track PEM, but FACIT is not one of them.

Not only does the FACIT survey fail to capture PEM, it can’t determine differences in severity, said Chloé de Canson, a patient-researcher with long COVID who closely follows clinical trials. A participant could regain the ability to cook for themselves or work part-time, but “not see

improvement on this outcome measure" if they still feel "tired," de Canson said.

Indeed, this was the case for Bhalla, the Berlin Cures trial participant who experienced dramatic improvement following the infusion. Participant Emma, too, reported that her symptoms improved somewhat following the infusions but that it was "challenging" for her to answer the survey questions accurately because they didn't match her experience with PEM.

Presenting additional challenges for participants, the Berlin Cures trial required long, in-depth visits to medical institutions without protection from potential infection with SARS-CoV-2 or other pathogens. People with long COVID often request that medical centers take safety measures such as requiring high-quality masks, as reinfection can worsen their symptoms.

Emma didn't see any staff masking during her visits, she said: "Honestly, I felt that there were zero precautions made and no consciousness present." Another participant, Lisa, said the nurses "generally did not wear masks."

Furthermore, in-person visits to medical centers can themselves cause post-exertional malaise, potentially interfering with the effects of a treatment. Multiple participants noted that the Berlin Cures study required long hours for every appointment, on top of travel.

"There are so many things that went wrong in this trial that it's not surprising to us that it failed," said Claudia.

Von Stein, appointed as Berlin Cures' CEO in June 2023 after years of experience in developing nucleic acid-based drugs like BC 007, agreed that the trial likely included too broad a group of patients and did not use the best endpoints to capture symptom improvement. The trial didn't fail because the drug "doesn't perform" for some people with long COVID, he said. Rather, "we had a disappointing outcome, I would like to believe, most likely [because] we did not have an optimum patient selection program in place."

This is a common challenge for phase 2 trials, particularly for complex diseases like long COVID, von Stein said. "Going forward now, the lessons learned here must be that we must pay great attention to the patient selection, really try to specify who we think is best to enter these trials, so that we can really come to a meaningful clinical endpoint," he said.

More promising results in a separate study, plans to move forward

In contrast to the Berlin Cures study, a second trial at University Hospital Erlangen did find that BC 007 alleviated symptoms. Researchers reported their results in a preprint posted to medRxiv in December 2024: Participants found "significant improvement" for fatigue and PEM following infusions.

While it was a smaller study — comprising 30 people, compared to 119 in Berlin Cures' trial — the Erlangen trial was more effective in selecting a subset of participants likely to benefit from the drug and tracking their outcomes, outside experts said. (The study has not been peer-reviewed as

of July.)

The Erlangen researchers sought to test BC 007's safety among an "autoimmune subgroup" of people with long COVID. Alongside a positive test for GPCR autoantibodies, the criteria included a past confirmed SARS-CoV-2 infection, a score in the moderate to severe range on an ME scale, and at least three out of a longer list of common symptoms. The researchers also excluded people with documented organ damage from COVID-19, which some studies suggest may represent a different subset of people with long COVID from those who meet the criteria for ME.

In addition to the more specific selection criteria, the Erlangen trial used several different symptom surveys to capture outcomes, including some designed and validated for people with ME. Results using these ME surveys showed that BC 007 led to significant improvements.

"We don't have any long COVID–specific validated instruments," Bhattacharjee said, so it's best to use multiple tests together and capture a range of data.

Another advantage for participants in the Erlangen study was that the trial utilized a crossover design: all 30 patients received BC 007. One group received first the drug, then a placebo, while the other received first the placebo, then the drug. In their preprint, the researchers wrote that their results suggest BC 007 should be tested in a larger group of patients who meet similar criteria.

Von Stein said the Erlangen study has "promising signals" for future research. He also noted this study's selection criteria and endpoints as potential reasons why it reported different outcomes from Berlin Cures' trial.

With Berlin Cures' assets transferred to the new company, APTA Therapeutics, von Stein plans to commission a more complete analysis of the phase 2 trial's data, hopefully later published in a scientific paper. "I think we have an obligation to tell the world, what was the output from the [trial]?" he said.

Along with that analysis, APTA will work with the Erlangen researchers and other specialist university clinics in the EU focused on long COVID and related diseases to further study BC 007 in small cohorts, eventually compiling enough data for a larger trial with a more robust design.

"The hope is maybe within 18 months … to have enough robust data that could form the basis of a registration study [phase 3 trial], where we've teased out a lot of these unknowns and thereby really maximize the chance of getting this drug to market," von Stein said.

In addition to designing studies themselves, finding funding for these trials has been a challenge, von Stein added. "I think in light of the impact that COVID has had globally, it's quite disappointing to see that the level of financial support has been quite minimal" from governments like Germany's, he said.

Better trials need more rigorous selection, stratification

The challenges that Berlin Cures faced in testing BC 007 among people with long COVID are familiar to researchers and patient-advocates who studied ME, POTS, and other similar complex chronic diseases before COVID-19 emerged. These researchers offer solutions: Clinical trials should carefully stratify their participants, and designing trials in collaboration with people who have lived experience is key.

Helen Brownlie, a patient-researcher with ME in the U.K. who has followed clinical trials for decades, said the Berlin Cures saga reminded her of past ME trials. While ME has been researched in some form for nearly a century, the disease is under-prioritized by governments compared to its burden on patients. There is no accepted biomarker or diagnostic test, and some researchers and advocates disagree about how to define it, especially when including people diagnosed with the older and broader term "chronic fatigue syndrome."

Randomized controlled trials, the gold standard in medical evidence, are designed for "when you have a well-delineated disorder, a well-established protocol for treating that disorder with a robust evidence base, and then a new drug that you want to compare" to the existing paradigm, Brownlie said. For ME, all of this is "nonexistent."

And the challenge only intensifies with long COVID: people with the disease are generally unified in that all can trace their symptoms back to a SARS-CoV-2 infection, but beyond that, symptoms and potential biological mechanisms vary widely. Subgroups under the long COVID umbrella aren't yet clearly defined, and long COVID also lacks a diagnostic test or biomarker.

But clinical trials are crucial, because millions of people are dealing with debilitating symptoms. For now, experts like Brownlie recommend smaller trials that match patients who meet a specific biological profile with treatments that are likely to help in their specific case. Rather than "take a broad brush," researchers should "differentiate," she said.

The Patient-Led Research Collaborative (PLRC), a group of scientists who live with long COVID and have led foundational research into the disease, makes similar recommendations. In a brief of clinical trial guidelines submitted in response to a request for information from the RECOVER-Treating Long COVID initiative, the group recommended "starting with smaller signal-finding trials" that can inform larger studies. Other leading Long COVID researchers are thinking this way, too, as shown by recent talks at symposia led by PLRC and the PolyBio Research Foundation.

The collaborative also urges researchers to guard against post-exertional malaise. "All tests of all types should be considered that they may induce PEM, and methods to care for patients in the aftermath should be implemented," PLRC recommended in their brief.

Additionally, given how severe long COVID can be for some people, patient-advocates have called for decentralized study methods, in which medications and other supplies are mailed to participants, or where researchers travel to participants, rather than participants being made to come to them.

Above all, people with long COVID say that including their feedback in all stages of the scientific

process will make for more effective studies. “I think that involving people with long COVID and ME/CFS directly in the planning stages would help ensure that the tools and methods used truly reflect our real-life experiences and challenges,” Berlin Cures participant Emma said.

Despite all the challenges and disappointments of the Berlin Cures trial, participant Jakob said he “would do it again,” because taking part in trials “is the only way we can defeat this disease with new medication.”

This story is the first in a series about promising Long COVID treatment trials and how they are designed. To share tips or feedback for the series, reach out to us at editors@thesicktimes.org.

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