U.S. FOOD & DRUG ADMINISTRATION

22 CASE STUDIES WHERE PHASE 2 AND PHASE 3 TRIALS HAD DIVERGENT RESULTS

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Table of Contents

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I. Overview

Pre-market clinical testing usually progresses in phases, with increasingly rigorous methods at each phase. Product candidates that appear insufficiently safe or effective at one phase may not proceed to the next phase. Roughly 9 in 10 drugs/biologics that are tested in humans are never submitted to FDA for approval.[1] Typically, a candidate drug is submitted to the FDA for marketing approval after phase 3 testing. In recent years, there has been growing interest in exploring alternatives to requiring phase 3 testing before product approval, such as relying on different types of data and unvalidated surrogate endpoints.

To better understand the nature of the evidence obtained from many phase 2 trials and the contributions of phase 3 trials, we identified, based on publicly available information, 22 case studies of drugs, vaccines and medical devices since 1999 in which promising phase 2 clinical trial results were not confirmed in phase 3 clinical testing.[*] Phase 3 studies did not confirm phase 2 findings of effectiveness in 14 cases, safety in 1 case, and both safety and effectiveness in 7 cases. These unexpected results could occur even when the phase 2 study was relatively large and even when the phase 2 trials assessed clinical outcomes. In two cases, the phase 3 studies showed that the experimental product increased the frequency of the problem it was intended to prevent.

This paper is not intended to assess why each of these unexpected results occurred or why further product development was not pursued. Rather, these cases, chosen from a large pool of similar examples, illustrate the ways in which controlled trials of appropriate size and duration contribute to the scientific understanding of medical products.

II. Clinical Trials: Understanding Medical Product Testing

In the classical drug development paradigm, pre-market clinical trials for drugs are conducted in three phases. The trials at each phase have a different purpose and help scientists answer different questions.

- *Phase 1 Trials.* In phase 1, researchers test the potential product in humans for the first time, to identify rudimentary product characteristics, such as how the body metabolizes a drug and how long it stays in the body, and to provide evidence that the product is not too toxic for further human testing. The treatment group is small (typically 20 – 80 healthy volunteers), but allows researchers to begin to evaluate the treatment's safety, adjust dosing schemes, and start to identify side effects. This information guides the design of phase 2 studies.

- *Phase 2 Trials.* Phase 2 studies are intended to explore the effectiveness of the product for a particular indication over a range of doses, and to assess short-term side effects. These studies typically involve a few hundred patients who have the target condition, but do not generally have other diseases that might obscure the effect of the drug on the target condition. Phase 2 trials may be randomized and/or controlled, but often measure laboratory values or other biomarkers rather than clinical outcomes (i.e., effects on how a patient feels, functions, or survives). When a phase

[*] For the purposes of this analysis, the terms "trial" and "study" are used interchangeably.

2 study does assess clinical outcomes, it is usually for relatively short periods of time and in a relatively small number of people. Sponsors assess phase 2 results to determine if the preliminary results are sufficiently promising to justify a phase 3 study.

- *Phase 3 Trials*. Compared to phase 2 trials, the goal of phase 3 trials is to test the experimental product in larger groups of people (typically 300 – 3000), in people who are more similar to those likely to use the product once marketed, and for longer periods of time. Phase 3 studies generally assess clinical outcomes, and are designed to determine whether the demonstrated benefits of the product outweigh its risks.

As discussed in Section III, below, the appropriate size and duration of clinical trials varies significantly from condition to condition, and product to product.[†]

For most approved drug products, clinical evaluation may be continued even after a product is on the market. These studies are termed phase 4 trials, and can be helpful to uncover information on new uses that can be shared with health care providers to refine prescribing advice or can indicate that new warnings should be added to the product's label.

III. Flexibility in Clinical Trial Design

In practice, clinical testing progression and design has become increasingly flexible as the science of clinical trials has evolved. Phase 1 might be combined with phase 2 if the drug is expected to have toxicity unacceptable for healthy volunteers. If the product's mechanism of action and safety profile are well characterized, phase 2 testing may be shortened or skipped altogether. When there is sufficient evidence that a change in a biomarker reliably predicts a clinical benefit, the biomarker can serve as a surrogate measure for that clinical benefit in a trial, and the effect of the product on the surrogate measure can be a basis for product approval. Surrogate measures are often biomarkers that help diagnose or monitor a disease, such as blood pressure to predict stroke risk or the amount of human immunodeficiency virus in the blood to predict the development of acquired immunodeficiency syndrome.

The nature of definitive trials also varies. Larger and longer trials may be needed if, for example, the condition to be treated is chronic or if the event the drug is intended to prevent occurs infrequently. Smaller or shorter trials may be needed where, for example, the drug produces a dramatic improvement in patients, or is intended for short-term conditions like many infections. Other factors, such as whether the condition is widespread or rare, whether it is life-threatening, and whether there are other effective treatments for the condition are also important in determining what kind of clinical testing is appropriate.

Where a drug or biologic is intended to treat a serious condition for which there are limited available alternative therapies, FDA has implemented four separate expedited development and review programs.[2] For example, when there is evidence that a biomarker is "reasonably likely to predict"

[†] Medical device testing often does not follow this "phase 1 - 3" paradigm or use the same "phase 1 – 3" vocabulary. In some cases, practical limitations related to the device or disease condition may limit the feasibility of a large randomized, controlled trial design. But the need, in certain circumstances, for one or more large well controlled studies to determine whether a device actually improves clinical outcomes can be equally applicable. Such trials serve a purpose similar to phase 3 drug and biologic trials. For editorial convenience, we use the phrase "phase 3" throughout the document to refer to both phase 3 drug and biologics trials, as well as "pivotal" and similar trials for devices.

clinical benefit, that biomarker can be a basis for approval under FDA's accelerated approval authority. In these situations, sponsors have been required to conduct post-market confirmatory studies to further define the clinical benefit of the drug.

While clinical testing progression and design has become increasingly flexible, and advances in biomedical science and statistics have enabled introduction of non-traditional study designs and data sources into phase 3 testing, a randomized, controlled, clinical trial (RCT) of a size and duration that reflect the product and target condition remains the gold standard for determining whether there is an acceptable benefit/risk profile for drugs and biologics. For more discussion on clinical trial design, including the unique features of RCTs that make such trials more likely to be definitive, see Appendix A.

IV. Case Studies

The methods underlying case selection, as well as a discussion of the limitations of this study, are described in Appendix B.

A. Phase 3 Trials Demonstrating Lack of Efficacy in a Promising Experimental Therapy

1. Bitopertin

Product	Bitopertin
Sponsor	Roche
Purpose	Add-on treatment of schizophrenia
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite statistically significant results in reducing the symptoms of schizophrenia in phase 2, in phase 3 trials Bitopertin failed to improve the negative symptoms of schizophrenia.

Schizophrenia is a chronic brain disorder in which people abnormally interpret reality and features three symptom categories: positive, negative and cognitive. Positive symptoms include hallucinations and delusions, while negative symptoms may include social withdrawal, lack of motivation, and reduced emotional reactivity. Cognitive symptoms include problems with memory and concentration.

Schizophrenia typically requires lifelong treatment with antipsychotic medications, which come in two types: typical and atypical. Both types block the brain's dopamine pathway, but atypical antipsychotics are less likely to cause certain undesired side effects (e.g., movement problems), making them useful for long-term management of patients with schizophrenia. However, atypical antipsychotics are still associated with undesirable side effects such as weight gain, increased cholesterol, and movement disruption.

Like dopamine, glycine is a neurotransmitter that has been implicated in the schizophrenia disease process. Over the past years, researchers have noted that people with schizophrenia have a decreased level of glycine in their blood and cerebrospinal fluid.[3] Bitopertin increases the availability of glycine in the synapse (the connection between nerve cells), suggesting a novel approach in the treatment of schizophrenia. A placebo-controlled, double-blind, eight week study randomized over 320 patients across 66 sites worldwide. The study found a statistically significant 25% reduction in negative symptoms among those patients who received the drug compared to those who received placebo.[4]

Three subsequent double-blind, placebo-controlled phase 3 studies evaluated the efficacy and safety of bitopertin when added to conventional drugs in patients with negative symptoms of schizophrenia. These studies together followed over 1800 patients for one year or more, and measured improvement in a patient's negative symptoms compared to symptoms before treatment began. However, results from two of these phase 3 studies found no evidence of a statistically significant improvement in negative symptoms over baseline in patients who received bitopertin add-on therapy compared to those who received placebo.[5, 6]

2. Brivanib

Product	Brivanib
Sponsor	Bristol-Myers Squibb
Purpose	Treatment of hepatocellular cancer
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite promising anti-tumor activity in phase 2 trials, in phase 3 trials Brivanib failed to improve overall survival of patients compared to approved treatment, and demonstrated identified unexpected toxicities.

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, occurring in four out of five cancers that start in the liver.[7] Treatment options for liver cancer, depending on the stage and severity of cirrhosis, include surgery to remove the tumor, embolization to block blood supply to the tumor, radiation, and transplantation.[8, 9]

The only FDA-approved drug is sorafenib, which delays tumor growth and improves survival by inhibiting certain signals used in cell growth or function.[10, 11] Generally, sorafenib is administered to patients who are not candidates for local-directed therapies. To treat those patients who do not respond to sorafenib or who have severe side effects related to the drug, brivanib was developed. Brivanib inhibits a novel growth factor, in addition to those growth factors targeted by sorafenib.

A phase 2 trial was conducted in which 55 patients with advanced HCC received a daily dose of brivanib in the first-line setting.[12] According to the published report, using computed tomography (CT)/magnetic resonance imaging (MRI) measurements of tumor volume, one patient had a complete response, three had a partial response, and 24 had stable disease following exposure to brivanib. A second cohort of 46 patients received brivanib after failing sorafenib therapy or discontinuing sorafenib due to intolerable side effects.[13] Using the same CT/MRI tumor measurement criteria, according to the published report, two patients had a partial response and 19 had stable disease following treatment. Together the studies showed that brivanib showed antitumor activity, with almost half of participants being classified as having stable disease following treatment. The investigators also reported a manageable safety profile for patients with advanced HCC.

Several phase 3 RCTs designed to isolate the effects of brivanib, confirmed statistically significant antitumor activity, but found no evidence that treatment with brivanib improves the overall survival of patients with HCC. One phase 3 study, designed to compare brivanib to sorafenib, randomized over 1,100 patients with advanced HCC who had no prior drug treatment to receive either brivanib or sorafenib.[14] The median overall survival was 9.5 months in the brivanib group and 9.9 months in the sorafenib group, and the primary objective (i.e., non-inferiority of survival) of the study was not met. The authors concluded that brivanib was “less well-tolerated” than sorafenib, as patients receiving brivanib had significantly higher rates of decreased appetite, fatigue, hypertension, nausea, and low blood sodium levels. The authors also stated that patients who received brivanib had a more pronounced decline in physical function and in role function.

Another phase 3 study randomized 395 patients with advanced HCC in patients who previously received sorafenib to receive either brivanib or placebo.[15] This study did not demonstrate a statistically significant improvement in overall survival in patients who received brivanib as compared to placebo.

A third phase 3 study investigated whether brivanib could increase survival compared to placebo in Asian patients with advanced hepatocellular carcinoma who failed prior treatment with sorafenib; however, this study was discontinued by its sponsors and no results are available.[16]

A fourth phase 3 study compared brivanib as an additional treatment to chemoembolization with those receiving only chemoembolization in patients with HCC.[17] However, this trial was terminated early after the two other phase 3 studies mentioned above failed to show improvement in overall survival of patients with HCC. At termination, this study showed that brivanib had not improved overall survival (26.4 vs. 26.1 months).

3. Capsaicin Topical Patch (Qutenza) ‡

Product	Capsaicin topical patch (Qutenza)
Sponsor	NeurogesX
Purpose	Treatment of HIV-associated nerve pain
FDA-approved for any indication at time of initiation of phase 3 trial	Yes, treatment of shingles-associated nerve pain.
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite demonstrated efficacy in a related condition and positive clinical results in a proof of concept study, in an RCT pain control was similar in the Qutenza and control groups.

Many HIV patients experience a burning-type of pain, often in the feet or hands, as a result of nerve damage. Called HIV-associated distal symmetric polyneuropathy (HIV-DSP), it is the most common nerve complication of HIV infection, affecting over 50% of patients.[18-20]

Qutenza is made from capsaicin, the pungent component that makes chili peppers hot. Capsaicin acts on certain pain receptors in the skin by desensitizing nerve endings, resulting in analgesia and pain relief. In 2009, FDA approved Qutenza (8% patch) as a medicated skin patch for pain relief in patients with post-herpetic neuralgia, a painful complication following shingles.[21]

Researchers also studied the efficacy of capsaicin in a related intended use, painful HIV-DSP. An open-label pilot study assessed the efficacy and safety of NGX-4010 (capsaicin 8% patch) in twelve patients with HSV-DSP.[22] Following a single 60-minute NGX-4010 application, these patients were followed up for 12 weeks. The majority of these patients reported a significant reduction in pain, prompting the researchers to proceed to a large, controlled clinical trial.

In two similarly designed RCTs, 800 patients with HIV-DSP were randomized to receive NGX-4010 or a 0.04% concentration control patch. This low concentration control patch was considered too weak to actually treat HIV-DSP, but strong enough to cause the localized skin reactions that are common with capsaicin so that patients would not know to which group they had been assigned. While the initial study found significant pain relief with NGX-4010 over 12 weeks of treatment compared to controls, these findings were not replicated in the second study.[22, 23]

In 2012, a FDA Advisory Committee analyzed the two controlled trials and agreed that there was no substantial evidence of effectiveness for Qutenza in treating HIV-DSP.[24] The Advisory Committee did not recommend the approval of Qutenza, and FDA did not approve the drug.[25]

‡ Product names in parentheses are brand names.

4. Darapladib

Product	Darapladib
Sponsor	GlaxoSmithKline
Purpose	Add-on to a statin for prevention of cardiovascular disease complications in patients with prior heart attack
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite exciting biomarker evidence in phase 2, in phase 3 trials darapladib failed to reduce the risk of heart attack or cardiac death compared with placebo in patients with chronic cardio vascular disease.

Cholesterol builds up in blood vessels of patients with cardiovascular disease, hardening the arteries in an inflammatory process called atherosclerosis.[26] Atherosclerosis restricts blood flow to the heart muscle, causing heart attacks.

Atherosclerosis is thought to be driven by inflammation. Lp-PLA2 is a protein produced by inflammatory cells, and blood levels of Lp-PLA2 are thought to predict heart attack risk.[27] A phase 2 study found both impressively reduced blood levels of Lp-PLA2 and stabilized atherosclerotic plaques in patients administered darapladib in addition to a statin (a cholesterol-reducing medication), compared to placebo plus a statin.[28] Another phase 2 study indicated that darapladib significantly reduced interleukin-6, another cardiovascular inflammatory marker.[29] Mechanistically, then, darapladib seemed promising. Human Genome Science CEO Tom Watkins predicted that darapladib was a "blockbuster in the making."[30]

The phase 3 STABILITY trial randomized over 15,000 patients with chronic, stable heart disease to take darapladib and a statin or a placebo and a statin, and monitored their cardiovascular outcomes over a median of 3.7 years.[31] The STABILITY trial's primary outcome measures were cardiovascular death, heart attack, and hospitalization for acute cardiac events. An additional phase 3 trial, the SOLID-TIMI 52 trial, randomized over 13,000 patients to receive either darapladib or a placebo within 30 days of a heart attack and followed their cardiovascular outcomes over a median of 2.5 years.[32] The study's primary outcome measures were cardiovascular death, nonfatal heart attack, and nonfatal stroke.

Neither study demonstrated benefit. Primary outcome event rates were 10.4% on placebo and 9.7% on darapladib in STABILITY, a difference that was not statistically significant. Primary outcome event rates in SOLID-TIMI 52 were 15.6% on placebo and 16.3% on darapladib, a lean in the opposite direction that was also not statistically significant.[33]

5. Dexmecamylamine

Product	Dexmecamylamine
Sponsor	Targacept/AstraZeneca
Purpose	Add-on treatment of depression
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite statistically significant results on measures of depression in phase 2, in the phase 3 trial dexmecamylamine proved no more effective than a placebo as add-on treatment for depression.

First-line therapies for depression include selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). These drugs increase the amount of serotonin and norepinephrine in the brain − neurotransmitters known to have a role in mood.[34]

Researchers have also hypothesized that drugs that activate certain other receptors called nicotinic neural receptors, such as the drug dexmecamylamine, could normalize the activity in these receptors and potentially be a treatment for depression.[35] In 2009, a phase 2 trial randomized 270 participants on SSRIs to receive either dexmecamylamine or placebo over a course of eight weeks. The study found that those who took dexmecamylamine improved more on a standard depression scale compared to placebo.[36]

With these promising phase 2 results, dexmecamylamine underwent four phase 3 studies in which a total of 614 study participants whose depression did not improve with standard SSRI or SNRI therapies were randomized to receive dexmecamylamine or placebo while continuing their SSRI or SNRI therapy. After eight weeks of add-on treatment, these studies found no difference between the treatment effects of dexmecamylamine and placebo in treating depression on standard depression scales in any of the phase 3 studies.[37-39]

6. Exhale Drug-Eluting Stent

Product	Exhale Drug-Eluting Stent
Sponsor	Broncus Technologies
Purpose	Reduction of shortness of breath in patients with emphysema
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy
Divergent result in phase 3 trial	Despite statistically significant results on measures of lung function and symptoms in phase 2, in the phase 3 trial the Exhale Stent failed to improve lung function or symptoms in patients with emphysema.

Emphysema is a disease in which air sacs in the lungs called alveoli are gradually destroyed. Alveoli inflate and deflate with breathing, allowing inhaled oxygen to enter the blood and carbon dioxide to be exhaled. In emphysema, the alveoli hyperinflate and eventually rupture, trapping air in the lungs. As a result, fresh, oxygen-rich air cannot enter the lungs properly, causing progressive shortness of breath. It is frequently caused by many years of smoking and has no cure. Treatment for emphysema is intended to relieve symptoms, prevent complications, and slow disease progression. Therapies may involve smoking cessation, oxygen supplementation, medications such as bronchodilators (drugs that widen airway passages), surgery to reduce lung volume, and lung transplantation.[40]

A new bronchoscopic procedure was designed to reduce hyperinflation and improve airflow in emphysema. Called airway bypass, the procedure involves insertion of a flexible tube called a bronchoscope through the mouth so that the airways can be visualized. Once a diseased site is identified, a needle pierces the airway wall to create a new passage so that trapped air can escape.[41] A device smaller than a pencil eraser called the Exhale Drug-Eluting Stent is then placed in the newly created passageway to keep it open. A drug is included in the stent to prevent tissue growth in the new passage. A phase 2 study assessed the effects of the Exhale stents in 35 patients with severe emphysema by measuring how well their lungs took in and released air and whether their symptoms improved.[42] At the 6-month follow-up, there were statistically significant improvements in symptoms and various indices of lung function, as compared to baseline, leading researchers to conclude that the stents reduce hyperinflation and provide clinical improvement.

A phase 3 study further investigated whether these Exhale airway stents could improve lung function and reduce breathlessness in severely affected emphysema patients.[43] More than 300 patients were randomized to undergo either the airway bypass with Exhale stent placement or a sham procedure (a fake procedure in which bronchoscopes were used, but no airway walls were pierced and no stents were placed).[44] At 6 months, there were no differences in lung volume or shortness of breath between the two groups. The study thus concluded that Exhale airway stents provide no sustained benefit in patients with emphysema.

7. Experimental HSV-2 Vaccine

Product	Experimental HSV-2 Vaccine
Sponsor	Chiron (now Novartis Vaccines & Diagnostics)
Purpose	Prevention of genital herpes
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite positive biomarker results in phase 2, in the phase 3 trials the vaccine did not prevent genital herpes.

Genital herpes is a common sexually transmitted disease caused by herpes simplex virus type 1 (HSV-1) or the generally more serious type 2 (HSV-2). Most people with herpes have no symptoms, but others may have painful genital sores that tend to recur. People with weakened immune systems, including individuals with HIV/AIDS, organ transplants, and cancer, are at increased risk for severe herpes infections. Pregnant women can also pass the infection to newborns, causing neonatal herpes, a rare but potentially life-threatening disease.[45] There is no cure for herpes, but there are medicines to prevent recurrences or shorten the duration of those recurrences.

An HSV-2 vaccine was developed by Chiron. Two phase 2 studies randomized over a hundred persons with no antibodies to HSV-2 in their blood to receive one of three different doses of the vaccine. The studies showed that the vaccine induced an antibody response similar to persons who had a naturally-acquired HSV-2 infection.[46]

Two phase 3 RCTs followed, involving almost 2,400 persons with no detectable antibodies for HSV-2 who were followed for one year after their final immunization.[47] These studies, however, showed that despite producing an antibody response similar to natural HSV-2 infection, vaccine recipients acquired HSV-2 infection at a rate similar to placebo (4.6% of placebo group versus 4.2% of vaccine group). Researchers concluded that the vaccine produced only a partial and transient protection against HSV-2 infection.[48]

8. Glutamic Acid Decarboxylase Vaccine

Product	Glutamic Acid Decarboxylase (GAD) Vaccine
Sponsor	Diamyd Medical
Purpose	Preservation of insulin secretion for patients with recent-onset type 1 diabetes
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite promising biomarker results in phase 2, in the phase 3 study treatment with GAD vaccine did not improve pancreatic function or clinical outcomes.

Type 1 diabetes is an autoimmune disease in which a person's pancreas stops producing insulin. It affects adults and children and occurs when the body's immune system attacks and destroys the insulin-producing cells in the pancreas, called beta-cells. While intensive insulin therapy can delay the onset and slow progression of kidney failure, blindness, and nerve damage, these complications continue to cause high rates of morbidity and mortality.[49]

Vaccination with Glutamic Acid Decarboxylase (GAD) to control the abnormal immune response was proposed as a strategy to prevent or delay loss of beta-cell function. Although intensive insulin therapy improves glycemic control and is the therapeutic gold standard, insulin itself does not treat the underlying disease process. Treatment with therapies that down-regulate other parts of the immune system, including specific antibodies targeting important mediators of the immune response, have been tried but to date have not proved effective and have caused serious adverse reactions.[50]

In a phase 2 study, 70 patients recruited within 18 months of their type 1 diabetes diagnosis were randomly assigned to receive injections of GAD or placebo.[51] The primary endpoint was the change from baseline to month 15 in C-peptide levels, a measure of beta-cell function that drops as beta cell function declines. The C-peptide levels gradually decreased in both study groups, but patients receiving GAD injections showed significantly less decline in C-peptide levels than the patients receiving a placebo injection. This suggested that vaccination with GAD could potentially preserve the insulin-producing function of beta cells. The researchers claimed that the results provided a preliminary proof of concept.

In the phase 3 trial, 334 patients were randomly assigned to one of three study treatments and followed for 15 months: four doses of GAD, two doses of GAD followed by two doses of placebo, or four doses of placebo. The same time points from the phase 2 trial were used to measure C-peptide levels and other clinical outcomes such as insulin requirement, plasma glucose, glycosylated hemoglobin levels and rate of hypoglycemia.[52] The primary outcome was the change in C-peptide levels between the baseline visit and the 15-month visit. The phase 3 trial did not confirm the preliminary results and concluded that treatment with GAD did not significantly reduce the loss of C-peptide or improve any important clinical outcomes over a 15-month period.

9. Imiquimod (Aldara 5% Cream)

Product	Imiquimod (Aldara 5% Cream)
Sponsor	3M
Purpose	Treatment of molluscum contagiosum (MC) lesions in children
FDA-approved for any indication at time of initiation of phase 3 trial	Yes, treatment of external anogenital warts.
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite demonstrated efficacy in another viral skin infection and promising phase 2 results on clearance of MC lesions, in the phase 3 trial treatment with imiquimod cream was no more likely to clear MC lesions than treatment with placebo.

Molluscum contagiosum (MC) is a relatively common viral skin infection that primarily affects children. It is characterized by clusters of pearly, flesh-colored, dome-shaped bumps on the skin surface. These lesions are usually painless, but may be itchy and inflamed. If scratched, the lesions can spread to other areas of the body or to other persons, and can become infected with bacteria. MC disappears spontaneously, typically after 6 to 12 months, but some bumps can last up to four years.[53]

Common treatments for MC include cryotherapy (freezing with liquid nitrogen), curettage (scraping), topical agents, and lasers.[54] These treatment modalities can be effective but uncomfortable, especially for children. There are no FDA-approved drug treatments for MC.[55]

Imiquimod is a topical drug that is FDA-approved to treat external genital and perianal warts, which are caused by a different skin virus.[56] The drug works by stimulating the immune system's reaction to the virus, thereby strengthening the body's ability to fight off the infection. Researchers hypothesized that because imiquimod was effective for one viral skin infection, it might also be effective for others, leading researchers to investigate imiquimod's efficacy in MC.

A randomized, single blinded phase 2 clinical trial compared weekly cryotherapy to daily topical imiquimod in 74 children over 16 weeks. This study suggested impressive drug efficacy, with over 90% of those receiving imiquimod experiencing complete clearance of MC lesions at 12 weeks.[57] In the cryotherapy group, all lesions were cleared.[57] However, pain, blistering, and scarring were significantly more common in the cryotherapy group, making imiquimod look promising as a better tolerated, effective treatment for MC.[57]

Imiquimod cream was then evaluated in two double-blind phase 3 RCTs involving a total of 702 pediatric MC patients aged 2-12.[58] These children received imiquimod cream or placebo cream three times per week for up to 16 weeks and were assessed at week 18 for complete clearance of MC lesions. In the first study, the complete clearance rate was 24% in the imiquimod group compared with 26% in the vehicle group. In the second study, the clearance rate was 24% in the imiquimod group compared with 28% in the vehicle group. These studies thus failed to demonstrate any efficacy against MC. In addition, children who received imiquimod were more likely to experience application site reactions, conjunctivitis, low white blood cell counts, and inflamed lymph nodes.[58]

10. Iniparib

Product	Iniparib
Sponsor	Sanofi
Purpose	Add-on treatment of "triple negative" breast cancers
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite promising phase 2 results on both tumor response and survival, in the phase 3 trial adding iniparib to an established chemotherapy regimen did not improve survival.

Breast cancer is the most common cancer in women.[59] Triple-negative breast cancer is a subtype of breast cancer that is aggressive and difficult to treat. It is called triple-negative because the cancer cells do not over-express three different receptors; the cancer could otherwise be treated by chemotherapies and/or agents targeted to the receptors.

Iniparib showed strong activity in preclinical testing, enhancing the effects of standard chemotherapy on triple-negative metastatic breast cancer cells.[60, 61] In phase 2 testing, 123 patients with metastatic triple-negative breast cancer were randomized to receive either standard chemotherapy or standard chemotherapy plus iniparib. Adding iniparib to a standard chemotherapy regimen significantly improved tumor response and overall survival, without increasing toxicity.[62]

Despite promising phase 2 results, iniparib was not shown to be effective in phase 3 testing. Five hundred nineteen patients with metastatic triple-negative breast cancer were randomly assigned to receive either standard chemotherapy regimen or the standard regimen plus iniparib. The phase 3 trial did not identify any significant safety concerns, but the addition of iniparib to the standard regimen did not demonstrate any improvement in overall or progression-free survival.[63] Overall survival of the patients receiving standard chemotherapy was 11.1 months, versus 11.8 months for those also receiving iniparib.[63]

11. Lithium

Product	Lithium
Sponsor	King's College London (UK)
Purpose	Add-on treatment to delay disease progression of amyotrophic lateral sclerosis
FDA-approved for any indication at time of initiation of phase 3 trial	Yes, treatment of bipolar disorder.
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite positive effects on disease progression and survival in a phase 2 trial, in the phase 3 trial treatment with lithium did not improve survival, health status or quality of life.

Amyotrophic lateral sclerosis (ALS), sometimes called Lou Gehrig's disease (after the famous baseball player who was diagnosed with it), is a nervous system disease that causes muscle weakness. In ALS, the nerve cells that control the movement of muscles gradually die, leading to progressive weakness. Affected patients gradually lose ability to move their arms and legs, speak, eat, and breathe. Most ALS patients die within 2 to 5 years of diagnosis.[64]

Most cases of ALS have an unknown cause, but scientists believe that there is a genetic mutation in up to 10% of cases.[64-66] There is no cure for ALS, and riluzole is the only FDA-approved drug for the treatment of ALS.[67, 68] This drug extends patient survival by two to three months.[67, 69],

A proof of concept study randomized 44 ALS patients to receive daily doses of either riluzole or riluzole plus lithium.[70] Over a 15-month period, the study compared the survival rate and disease progression between the two groups. For disease progression, the study measured muscle strength and lung function (volume of air expired after a full inspiration) every three months. At the end of the study, all patients treated with lithium and riluzole were alive while 30% of patients who received riluzole alone had died. The study also showed that patients who received lithium had a slower disease progression compared to those who did not. The researchers thus concluded that lithium delays ALS progression.

A phase 3 placebo-controlled study followed and randomized over 200 ALS patients.[71] This study evaluated the safety and efficacy of lithium combined with riluzole, compared to placebo combined with riluzole. Over an 18-month period, the study compared (1) the overall survival of patients, and (2) health outcomes such as mobility, self-care, usual activities, pain or discomfort, anxiety, and depression. At the end of the study, the number of patients alive was similar between the treatment groups (50% in the lithium group versus 59% in the placebo group).[72] As for health outcomes, there was a marked deterioration in functional health status and quality of life in patients assigned to both groups with no difference between groups in their rates of decline. The study thus concluded that, while there was no safety concern, lithium has no evidence of benefit in patients with ALS.

12. MAGE-A3 vaccine

Product	MAGE-A3 vaccine
Sponsor	GlaxoSmithKline
Purpose	Treatment of patients with non-small cell lung cancer (NSCLC) following surgery
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite a promising proof of concept trial of this targeted immune therapy, in the phase 3 trial the MAGE-A3 vaccine conferred no clinical benefit when compared to a placebo.

Broadly, lung cancer comes in two forms: small cell and NSCLC. Current therapies for treatment of NSCLC include surgical removal of the cancer, chemotherapy, and radiation therapy, yet long-term survival rates remain low.[73]

Recent advances in cancer research indicate the potential for treating NSCLC by harnessing the body's immune system. Certain tumor cells exhibit surface molecules (antigens) that can be targeted by therapeutic cancer vaccines, potentially preserving healthy cells.[74] One example of these cell surface antigens is MAGE-A3, a tumor-specific antigen present on the surface of certain tumor cells. Approximately 33% of NSCLCs express MAGE-A3, which is not seen in normal lung cells, thus making it a potential target for NSCLC therapies.

A phase 2 study evaluated a MAGE-A3 vaccine as a treatment for patients with MAGE-A3-positive NSCLC. Following surgery to remove as much of the tumor as possible, 182 patients were randomized to receive either the MAGE-A3 vaccine or placebo 13 times over 27 months. The results showed a non-statistically significant improvement in disease-free survival and overall survival among patients receiving this cancer vaccine.[75] The study was only large enough only to provide proof of concept. The sponsor determined that the results were promising enough to propel the vaccine to the largest phase 3 trial of a NSCLC therapy ever undertaken.[76]

In the phase 3 MAGRIT trial, investigators randomized 2,272 patients with completely resected MAGE-A3-positive NSCLC to receive 13 intramuscular injections of either the vaccine or placebo using the same schedule as the phase 2 trial.[77] The study, however, did not demonstrate that treatment with MAGE-A3 cancer vaccine increased patients' disease-free survival (60.5 months vs. 57.9 months, a statistically non-significant difference).[77] The results of the study led the researchers to conclude that this cancer vaccine offers no clinical benefit in patients with NSCLC.[77]

13. NicVAX Vaccine

Product	NicVAX vaccine
Sponsor	Nabi Biopharmaceuticals
Purpose	Smoking cessation
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy
Divergent results of phase 3 trial	Despite phase 2 evidence suggesting positive biomarker and clinical results, in the phase 3 trials the abstinence rate in the NicVAX group was similar to that in the placebo group.

Nicotine is the primary addictive agent in tobacco. Nicotine vaccines aim to stimulate the immune system to produce nicotine-specific antibodies, which would bind with the nicotine in the bloodstream and prevent or slow the rate at which the nicotine reaches the brain.[78] This, in turn, might reduce the urge to smoke, leading to cessation.

One phase 1/2 and four phase 2 trials of one such vaccine, NicVAX, were conducted by Nabi Biopharmaceuticals.[79] All of these trials, which enrolled between 11 and 301 patients, focused on the safety and immunogenicity of NicVAX, and identifying the best dosing regimen. The phase 2b placebo-controlled trial with 301 patients also assessed efficacy of NicVAX for smoking cessation in smokers who wanted to quit.[80] In this study, those smokers who developed the highest concentrations of anti-nicotine antibodies in response to the vaccine were significantly more likely to maintain abstinence for 8 weeks than smokers receiving placebo. Collectively, these trials identified a 6-injection, high-dose regimen as the most likely to be effective, based on the anti-nicotine antibodies measured.[81]

Two phase 3 RCTs were conducted in which about 2,000 patients were given 6 vaccinations of NicVAX or placebo.[81] The last vaccination was at week 26, and the primary endpoint was the number of patients who remained abstinent for 16 weeks. This timeframe corresponded to the peak anti-nicotine antibody levels observed in the phase 2 trials. Despite the suggestions of efficacy in the phase 2b trial, one of phase 3 trials reported similar abstinence rates of approximately 11% in the NicVAX and placebo groups, failing to demonstrate efficacy.[81] The other phase 3 trial also failed to demonstrate efficacy.[§][81]

[§] Data for the second phase 3 trial were not reported in the paper.

14. Velimogene Aliplasmid (Allovectin-7)

Product	Velimogene Aliplasmid (Allovectin-7)
Sponsor	Vical
Purpose	Treatment of metastatic melanoma
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite evidence of tumor shrinkage in phase 2, in the phase 3 trial Allovectin-7 reduced tumor size in significantly fewer patients than two marketed therapies in late-stage melanoma patients.

A largely curable disease if detected early and surgically removed, melanoma is relatively resistant to treatment and generally deadly in its advanced stages. Melanoma has been shown to respond to therapies that stimulate the immune system to recognize and target melanoma cells.

In early phase 1 studies in advanced melanoma patients, one such therapy−Allovectin-7, a gene transfer therapy directly injected into melanoma tumors–was able to shrink tumors, including those distant from injected tumors.[82] Additional apparent evidence of effectiveness was generated in subsequent studies, most notably in an uncontrolled phase 2 study revealing complete or partial tumor shrinkage in 11.8% of late-stage melanoma patients who had previously failed on or could not tolerate conventional chemotherapy who were injected with Allovectin-7. Tissue examinations from two patients revealed no evidence of melanoma.[83] Based on the results of this study, the drug advanced to a phase 3 multinational clinical trial.

That trial featured 390 patients with stage III and IV melanoma who were randomly assigned to receive Allovectin-7 or one of two marketed therapies used to treat advanced melanoma.[84] Allovectin-7 failed to meet its endpoints. Allovectin-7 proved significantly less effective than these therapies, registering a favorable tumor response rate in 4.6% of patients receiving it for at least 24 months compared to 12.3% of patients on the other treatments.

B. Phase 3 Trials Demonstrating Lack of Safety in a Promising Experimental Therapy

15. Olanzapine Pamoate (Zyprexa Relprevv)

Product	Olanzapine Pamoate (Zyprexa Relprevv)
Sponsor	Eli Lilly
Purpose	Long-acting injection treatment for schizophrenia
FDA-approved for any indication at time of initiation of phase 3 trial	Yes, in oral short-acting formulation for treatment of schizophrenia
Problem identified in phase 3 trial	Lack of safety
Divergent result in phase 3 trials	Although a different formulation of this drug was already approved, the phase 3 studies identified a serious safety risk of the long-acting formulation, requiring safety monitoring.

Schizophrenia is a chronic brain disorder characterized by an altered perception of reality. Symptoms may include hallucinations, delusions, and disordered thinking and behavior.[85, 86] Medication compliance in schizophrenia is a challenge, as roughly half of the patients with the disease have difficulty adhering to medical treatment.[87] A useful option is to inject patients with a long-acting formulation of the desired drug to ensure sustained treatment without the need for daily oral doses or daily injections.

Eli Lilly thus developed a long-acting, injectable formulation of its atypical antipsychotic olanzapine for use in patients with schizophrenia. Early phase studies showed evidence of non-inferiority to oral olanzapine, and did not identify new safety concerns.[88]

A subsequent phase 3 trial evaluated the efficacy of long-acting olanzapine injectable compared to placebo, and another phase 3 trial compared its efficacy with oral olanzapine. Both studies confirmed that the new long-acting formulation was effective in reducing the severity and frequency of schizophrenia symptoms.[88] However, early in these trials, two episodes of profound sedation occurred in the first hour after injection. These episodes triggered a review of all adverse events reported in trials of the injection formulation, as well as ongoing surveillance. Other incidents of sedation, dizziness, confusion and/or loss of consciousness in the immediate post-injection period were reported,** some occurring as late as three hours after injection.[88] This phenomenon became known as post-injection delirium sedation syndrome (PDSS).

In 2008, an FDA Advisory Committee reviewed the compiled evidence, which showed clear efficacy along with sometimes profound PDSS in 0.07% of injections and about 1.2% of patients.[89] The Advisory Committee determined that it would be worth trying to manage the risks of the injectable formulation in order to make the product available for patients with a history of non-adherence. It recommended approval, but with the imposition of a mandatory post-injection period of observation.[90] The FDA went on to approve the long-acting drug with a Risk Evaluation and Mitigation Strategy, which requires that all patients be observed by healthcare professionals for three hours after injection to ensure medical care is available if needed.[91]

** PDSS mimics olanzapine overdose, leading investigators to hypothesize that the injected olanzapine may have entered a blood vessel, leading to rapidly rising blood levels instead of the planned gradual release of the drug. Citrome L. Olanzapine pamoate: A stick in time. International Journal of Clinical Practice. 2009;63:140–50.

C. Phase 3 Trials Demonstrating Lack of Efficacy and Lack of Safety in a Promising Experimental Therapy

16. Aliskiren (Rasilez, Tekturna)

Product	Aliskiren (Rasilez, Tekturna)
Sponsor	Novartis
Purpose	Add-on treatment for prevention of congestive heart failure (CHF) complications
FDA-approved for any indication at time of initiation of phase 3 trial	Yes, treatment of hypertension.
Problem identified in phase 3 trial	Lack of efficacy
Divergent results in phase 3 trial	Despite approval of the drug for a related indication and positive biomarker effects in a proof of concept study, in the phase 3 trial adding aliskiren to standard therapy did not reduce cardiovascular-related death or CHF re-hospitalization after discharge, and increased the incidence of kidney failure and low blood pressure.

Congestive heart failure (CHF) occurs when the heart fails to pump enough blood to meet the needs of the body. When the heart fails to pump effectively, the amount of a hormone called renin rises in the bloodstream, causing fluid to build up in the body. Fluid overload can be quantified using a lab test called brain natriuretic peptide (BNP); an elevated BNP is associated with greater fluid overload and is indicative of a CHF exacerbation.[92]

It is well established that drugs that block the effects of renin can improve heart failure, but they also raise renin levels, thereby limiting the effectiveness of the medication. Pharmaceutical companies have developed drugs called direct renin inhibitors in hopes of improving treatment for CHF and high blood pressure. One such drug is aliskiren, which significantly reduced plasma BNP and renin activity compared to placebo in a proof of concept trial.[93]

Investigators evaluated aliskiren's clinical efficacy in the 2013 ASTRONAUT trial by randomizing over 1,600 patients hospitalized for CHF to take aliskiren or placebo for a year, in additional to standard therapy. The primary outcome measure was a composite including cardiovascular-related death or CHF-related rehospitalization. While BNP levels decreased, adding aliskiren to standard therapy did not reduce cardiovascular-related death or CHF rehospitalization after discharge compared to placebo: 10% of the patients receiving aliskiren and 11% of the patients receiving placebo died, indicating no significant mortality benefit to taking the drug. Moreover, patients receiving aliskiren had significantly higher rates of kidney failure and low blood pressure, as well as elevated potassium levels (not statistically significant), compared with patients who received placebo.[94]

17. CoStar Drug-Eluting Stent

Product	CoStar Drug-Eluting Stent
Sponsor	Conor Medsystems
Purpose	Reduction of heart attack risk in patients with coronary artery disease
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy, lack of safety
Divergent results in phase 3 trial	Despite approval in the European Union and positive results in a small trial, in an RCT patients who received a CoStar stent had worse outcomes than those who received a different stent.

The heart's main blood supply comes from the coronary arteries. Coronary artery disease (CAD) results in a narrowing of these arteries, which restricts blood flow to the heart. Poor blood flow to the heart can lead to heart attacks and poor cardiac function. Coronary stents are wire-mesh tubes implanted in narrowed heart arteries to prop open the vessels, thereby preventing serious cardiac events. Drug-eluting stents are coated with a drug intended to augment the device's mechanical effects to help keep the artery open, and have gained popularity in recent years.

One such stent was the CoStar, which was coated with paclitaxel, an anti-cancer drug that inhibits scar formation around a stent, thus preventing re-narrowing of the artery. A small clinical study of the CoStar stent conducted outside the U.S. suggested that this stent performed as well as other marketed stents.[95] On this basis, the stent received European Union approval and was widely used in Europe.[96] Before approval in the U.S., however, the FDA insisted upon a large, double-blind, controlled study to demonstrate the CoStar stent's safety and comparability to available products.

Investigators conducted a clinical trial of 1,700 patients in the U.S. to support an application for FDA approval. The CoSTAR II trial was a RCT comparing the CoStar stent with the Boston Scientific Taxus Express2™ paclitaxel-eluting stent in the treatment of CAD. The primary outcome measure was major adverse cardiac events (MACE) at eight months, defined as a composite of target vessel re-narrowing, heart attack, and cardiac-related death. In the study, the CoStar stent showed a significantly higher MACE rate (11%) than the Taxus stent (6.9%).[97] Vessels in which the CoStar stent had been placed were significantly more likely to re-narrow (32%) than those in the comparison group (24%) and patients treated with the CoStar stent had a nearly 2-fold higher rate of needing a repeat coronary artery procedure to treat a recurrent blockage. The heart attack and stent thrombosis rates were numerically higher in patients treated with the CoStar stent, though the difference was not statistically significant.

18. Figitumumab

Product	Figitumumab
Sponsor	Pfizer
Purpose	Add-on treatment of advanced non-small cell lung cancer (NSCLC)
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy, lack of safety
Divergent results in phase 3 trial	Despite positive clinical results in phase 2 for this targeted therapy, adding figitumumab to established chemotherapy regimens in phase 3 failed to improve survival, and in combination with one regimen increased serious adverse events and deaths.

Broadly, lung cancer comes in two forms: small cell and NSCLC. Current therapies for treatment of NSCLC include surgical removal of the cancer, chemotherapy, and radiation therapy, yet long-term survival rates remain low.[73]

Figitumumab was developed to inhibit a specific growth factor (IGF-1R) thought to contribute to the development and progression of NSCLC, among other cancers.[98, 99] In animal testing, it enhanced the anti-tumor effects of standard chemotherapies, and in phase 1 testing figitumumab appeared to inhibit the target pathway and showed signs of antitumor activity against several types of cancers, including NSCLC.[98] In a phase 2 study, NSCLC patients receiving figitumumab in combination with a standard chemotherapy regimen (carboplatin and paclitaxel) appeared to show a higher response rate than patients receiving carboplatin and paclitaxel alone.[98, 100]

Based on these results, two phase 3 trials were conducted comparing figitumumab plus various standard therapies to the standard therapies alone, in a total of 1264 patients with NSCLC.[101, 102] Both studies were halted early because figitumumab failed to improve overall survival. Further, combining figitumumab with one of these standard regimens showed a trend toward decreased overall survival and increased the incidence of treatment-related serious adverse events (SAEs) and deaths, with 21% of patients receiving figitumumab experiencing SAEs, compared with 12% of patients receiving the standard chemotherapy regimen alone.[102] The rate of treatment-related-death in patients receiving figitumumab was 5%, versus 1% in the standard regimen patients.[102]

After the phase 3 trials were terminated early for lack of efficacy and safety concerns, Pfizer retracted the article describing the phase 2 data.[103] The company discovered that tumor shrinkage had not been confirmed in all responding patients, deviating from Pfizer's standard operating procedures. The corrected data showed a lower response rate.

19. Recombinant Factor VIIa (NovoSeven)

Product	Recombinant Factor VIIa (NovoSeven)
Sponsor	Novo Nordisk
Purpose	Reduction of intracerebral bleeding and hematoma size in patients with stroke
FDA-approved for any indication at time of initiation of phase 3 trial	Yes, treatment of hemophilia.
Problem identified in phase 3 trial	Lack of efficacy, lack of safety
Divergent results in Phase 3 Trial	Despite positive clinical results in phase 2, in the phase 3 trials patients with intracerebral bleeding who received recombinant factor VIIa experienced no clinical benefits and an increased incidence of serious adverse events compared to patients who received placebo.

A stroke is a disruption of the brain's blood supply, leading to brain cell death. There are two kinds of stroke: ischemic and hemorrhagic. Ischemic stroke accounts for over 85% of all strokes, and occurs when blood flow to the brain is blocked by a blood clot. Hemorrhagic stroke is less common than ischemic stroke, and occurs when blood flow to the brain is disrupted by a bleed in the brain. Hemorrhagic stroke is often devastating because there is no effective treatment to stop the bleeding.

Factor VIIa is an essential protein in the body's clot-forming pathway. Recombinant factor VIIa (rFVIIa) is a product that has been used for a number of years to treat individuals with hemophilia who do not respond to conventional treatment. Researchers hypothesized that giving rFVIIa to patients experiencing an acute hemorrhagic stroke could reduce bleeding, and thus reduce the severity of bleeding and disability. In a placebo-controlled, double-blinded trial with 399 patients, researchers were heartened to find that treatment with rFVIIa within four hours after the onset of a hemorrhagic stroke reduced the amount of bleeding in the brain, reduced mortality, and improved patients' functional outcomes at 90 days.[104]

Subsequently, in order to further evaluate the efficacy of rFVIIa in improving survival and functional outcomes among patients, investigators randomized nearly 850 patients with acute hemorrhagic stroke to either placebo, 20 micrograms per kilogram rFVIIa, or 80 micrograms per kilogram of rFVIIa in the phase 3 FAST trial. The primary outcome measure was severe disability or death 90 days after the stroke. Although patients who received either dose of the study drug did have smaller bleeding volumes than those in the placebo group, they experienced no clinical benefit; approximately 20% of patients died no matter what they received, and rates of significant disability were comparable between the three groups.[105] Patients who received rFVIIa also experienced a statistically significant increase in thromboembolic events compared to those who received placebo.

20. Semagacestat

Product	Semagacestat
Sponsor	Eli Lilly
Purpose	Improvement of cognitive and functional status in persons with Alzheimer's Disease
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy, lack of safety
Divergent results in Phase 3 Trial	Despite promising biomarker results in phase 2, the phase 3 trial was terminated early because patients who received semagacestat had worsened cognitive and functional status and an increased risk of skin cancer compared to patients who received placebo.

Alzheimer's Disease (AD) is chronic and progressive; survival after diagnosis can range from four to 20 years, depending on the individual and other coexisting health conditions.[106] Currently, there are several FDA-approved medications for the condition – three cholinesterase inhibitors (Aricept/donepezil, Exelon/rivastigmine, Razadyne/galantamine) and one N-methyl-D-aspartate receptor antagonist (Namenda/memantine) – but their efficacy is limited and they do not slow disease progression.

AD is associated with a buildup of amyloid-beta protein in the brain, and that protein is thought by many to play an important role in the disease process. Brain amyloid has been considered a biomarker with potential clinical meaning, and researchers have hypothesized that reducing amyloid-beta may improve disease symptoms. Semagacestat blocks gamma-secretase, an enzyme involved in the creation of amyloid-beta, and thus is intended to prevent the buildup of amyloid-beta in the brain; semagacestat was also expected to reduce blood concentrations of amyloid-beta protein.[107] A phase 2 trial that examined the effect of semagacestat in AD did show a reduction in blood levels of amyloid-beta among patients receiving the drug daily for 14 weeks.[108] Investigators were hopeful that semagacestat's effect on the levels of this [peptide] in blood would translate into clinically meaningful improvements in the disease.

A phase 3 trial randomized over 1,500 patients to receive placebo or semagacestat for 18 months.[109] The primary outcomes were the change in cognition from baseline to month 18 in the ADAS-cog and ADCS-ADL, which are measures of cognition and function, respectively. The trial was terminated before completion because patients taking semagacestat experienced worse cognitive and overall functioning over the course of the trial compared to those taking a placebo.[109] Treatment with semagacestat was associated with decreases in blood concentrations of amyloid-beta, but was also associated with a statistically significant dose-related decline in primary outcomes including activities of daily living, global functioning, cognitive functioning, and quality of life, compared to placebo. Patients taking semagacestat had more adverse events – including infections, skin cancers, and total cancers – compared to placebo. In fact, patients receiving semagacestat had at least double the risk of developing skin cancer compared to patients receiving placebo.

21. Torcetrapib

Product	Torcetrapib
Sponsor	Pfizer
Purpose	Prevention of cardiovascular events in patients with a history of cardiovascular disease or type 2 diabetes
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy, lack of safety
Divergent results of phase 3 trial	Even though torcetrapib improved biomarker (cholesterol) levels in phase 2 testing, in the phase 3 trial it increased mortality and cardiac events compared with placebo in patients at high cardiovascular risk.

Having high cholesterol puts patients at risk of developing heart disease, the leading cause of death among Americans. Cholesterol is carried in the blood stream in different ways. HDL-cholesterol (HDL-C) is sometimes referred to as "good" cholesterol because higher levels of HDL-C are associated with a lower risk of cardiovascular disease; conversely, LDL-cholesterol (LDL-C) is sometimes referred to as "bad" cholesterol because higher levels of LDL-C are associated with an increased risk of adverse cardiovascular events.[110] Consequently, clinicians often aim to raise HDL-C and to reduce LDL-C in an attempt to reduce a patient's cardiovascular risk.

Cholesteryl ester transfer protein (CETP) is an enzyme that transfers cholesterol molecules from HDL to LDL. Torcetrapib blocks CETP, thereby simultaneously raising HDL-C and lowering LDL-C. The drug performed well on measures of LDL-C and HDL-C in phase 2 trials, although small increases in blood pressure were sometimes observed with torcetrapib treatment.[111, 112] Pfizer executive Jeff Kindler said that torcetrapib might be "one of the most important developments in our generation."[113] Pfizer reportedly spent over $800 million to develop and test torcetrapib.[114]

A phase 3 study randomized over 15,000 participants with coronary artery disease, history of stroke, diabetes, or peripheral artery disease to receive either torcetrapib or placebo in addition to a statin. The primary outcome measure was the time to first occurrence of a major cardiovascular disease event (e.g., heart attack, stroke); other outcomes measures included cholesterol levels and blood pressure. Although HDL-C increased and LDL-C decreased significantly among those receiving torcetrapib compared with those receiving placebo, the drug was not shown to be effective and proved to be dangerous. Patients who received torcetrapib were 25% more likely to suffer a major adverse cardiac event, and were 58% more likely to die from any cause, than those taking the placebo (both results were statistically significant).[115] The torcetrapib group also showed a significant increase in blood pressure.[115] The trial was halted three years earlier than expected because of these compelling and unexpected safety concerns.[113]

22. V710 vaccine

Product	V710 vaccine
Sponsor	Intercell (nowValneva) / Merck
Purpose	Vaccine to prevent Staphylococcus aureus infection
FDA-approved for any indication at time of initiation of phase 3 trial	No
Problem identified in phase 3 trial	Lack of efficacy, lack of safety
Divergent results in Phase 3 trial	Despite promising biomarker results in phase 2, a phase 3 study of V710 vaccine was terminated due to lack of efficacy and with potential risk for serious adverse events and death.

Staphylococcus aureus, called "staph" for short, is one of the most common bacteria found on the skin and nose of even healthy persons. It does not usually cause any harm other than skin infections like infected pimples and boils. However, staph can cause serious and life-threatening infections if it enters the bloodstream. Between 10% and 30% of patients with staph in their blood will die from this infection.[116] Staph infection can be prevented by good hygiene especially hand-washing, sterile wound dressings, and antibiotics prior to certain medical procedures. An effective staph vaccine has not been made.[117]

V710 is an investigational staph vaccine that elicited a good immune response in early studies.[118] A phase 2 study randomized 206 chronic hemodialysis patients (who are at high risk for staph) to receive either V710 or placebo on days 1, 28, and 180. The study results indicated that V710 produced an antibody response evident by day 28 and which was sustained for up to one year after initial vaccination.[119] There were no serious adverse effects attributed to the vaccine.

A phase 3 study followed, involving almost 8000 patients from 26 countries.[120] These patients, scheduled to have cardiothoracic surgery, were randomized to receive a single injection of either V710 or placebo. This study was designed to determine whether the vaccine could prevent staph infection in the blood and/or chest wound infection for up to 90 days following the surgery. However, this study was terminated early because of safety concerns and low efficacy. The study showed that V710 did not prevent staph infection any better than placebo (2.6 v. 3.2 infections per 100 person-years). There were also more cases of multi-organ failure and death among those who acquired staph infection in the V710 group compared to placebo. The researchers concluded that, in addition to the identified safety concerns, V710 was unlikely to yield a significant clinical benefit.[121]

V. Discussion

The following summarizes the wide range of circumstances in which phase 2 findings did not accurately predict safety and/or efficacy and provides some additional observations stemming from these case studies.

A. Large RCTs Can Produce Unexpected Results Across all Types of Products, Patients, and Conditions

These case studies demonstrate that large phase 3 RCTs can generate critical evidence across all types of products, patients, and diseases. Both safety and efficacy failures occurred even when the phase 2 studies were relatively large (e.g., recombinant VIIa), and even when the product was already approved for another condition (e.g., aliskiren). In some cases, the phase 3 study revealed that short-term results found in the phase 2 study were not associated with a long-term benefit (e.g., bitopertin) or that the product had toxicity that was not uncovered in the phase 2 study (e.g., semagacestat). Unexpected evidence from a phase 3 trial does not always result in non-approval -- in one case, the evidence led to the addition of a safety monitoring requirement (long-acting formulation of olanzapine pamoate). The Summary Table in Appendix C provides an overview of the type of unexpected results in the phase 3 studies presented here.

We identified unexpected results in phase 3 trials whether the underlying disease was acute (e.g., V710 vaccine) or chronic (e.g., Qutenza); common (e.g., CoStar drug-eluting stent) or rare (e.g., lithium); and preventative (e.g., HSV-2 vaccine) or intended to treat symptoms (e.g., dexmecamylamine). Similarly, unexpected results occurred whether the experimental product targeted early disease (e.g., GAD vaccine) or later stages (e.g., figitumumab), and whether the product targeted adults (e.g., darapladib) or children (imiquimod). There were unexpected failures in phase 3 trials whether the promise in phase 2 was a positive response on a potential surrogate endpoint (e.g., torcetrapib) or on clinical outcomes (e.g., iniparib). Unexpected failures in phase 3 occurred with all types of medical products – drugs, vaccines and other biologics, and devices.

In several cases where more limited data from phase 2 studies seemed to show a benefit, the more conclusive phase 3 evidence revealed that the experimental product actually increased the frequency of the problem it was intended to prevent. For example, torcetrapib, which was intended to reduce heart attacks by increasing “good” cholesterol (HDL) and lowering “bad” cholesterol (LDL), showed in phase 2 trials that the drug did in fact increase HDL and lower LDL. Yet, the phase 3 trial, which examined whether the drug actually reduced heart attacks, showed that patients taking the drug were actually 25% more likely to suffer a major cardiac event than those in the control group.

B. An Experimental Product’s Presumed Mechanism of Action Does Not Automatically Predict Clinical Effects

As these case studies show, a medical product’s apparent mechanism of action does not automatically predict clinical outcomes.[122] There was a plausible mechanism of action associated with most products in these case studies, but that often did not translate into clinical benefit. Down-regulating specific immune functions associated with diabetes did not delay progression of the disease (GAD vaccine). A vaccine targeting proteins present on certain tumor cells but not on normal lung cells was not effective against lung cancer (MAGE-A3 vaccine). A compound that inhibited growth factors associated with lung and other cancers (figitumumab) was not proven effective.

These cases also show that phase 2 data do not necessarily predict the product's safety and efficacy, even where the product is already approved for a related condition and phase 2 data seem promising for the second condition. In several of the cases reviewed here, the experimental product was already approved for one condition and seemed promising for a different but related condition, but full testing failed to show that the drug was effective and/or demonstrated that the drug was dangerous for the related condition. Imiquimod turned out to be effective against some skin viruses but not others. Qutenza proved effective against nerve pain associated with shingles, but not nerve pain associated with HIV. Recombinant Factor VIIa was shown to stimulate blood clotting in a way that helps those with hemophilia but not patients with hemorrhagic stroke. Safety failures occurred even where the phase 3 trial tested a new formulation of an already-approved product (olanzapine pamoate in a long-acting formulation to treat schizophrenia).

Many medical conditions are complex; targeting a single component of a condition cannot be presumed to have a positive effect on the patient unless there is objective clinical evidence. This array of unexpected results from phase 3 studies demonstrates the complexity of the interaction between a medical product and the patient, and how logical presumptions without corroborating clinical evidence can be unreliable.

C. Many Biomarkers Do Not Reliably Predict Clinical Outcomes[††]

While biomarkers have many important uses in clinical practice and product testing, most have not been shown to reliably predict clinical outcomes. As several of these case studies illustrate, promising biomarker data in phase 2 do not necessarily translate into effective product performance. Biomarker data were promising in phase 2 testing in products targeting conditions ranging from heart disease (aliskiren, darapladib, torcetrapib) to Staph infection (V710 vaccine), and from AD (semagacestat) to herpes infection (HSV-2 vaccine). These experimental products were not proven effective when tested in phase 3 trials.

VI. Conclusions

Rapid advances in biomedical sciences are now helping researchers improve the predictive capacity of phase 1 and phase 2 trials in certain circumstances. Improved molecular understanding of cancer, for instance, is already helping us design phase 1 and phase 2 trials that can demonstrate clinical benefits persuasively, by matching the patient to a specific experimental drug based on molecular mutations rather than tumor type.

At the same time, the 22 cases explored in this paper demonstrate that phase 2 results can inaccurately predict safety and/or effectiveness for medical products in a wide range of diseases and patient populations. These cases also help illustrate the potential public health implications of undue reliance on phase 2 studies and the benefits of conducting Phase III studies. As a result of the Phase III studies discussed in this paper, patients outside of clinical trials were not subjected to drugs that would not benefit them or to the risk of unnecessary serious toxicities, and did not suffer unnecessary financial expenditures. Where effective alternative therapies existed, they were not diverted from proven

[††] For a review of the array of uses of biomarkers, from use in disease monitoring to use as surrogates for clinical outcomes, see U.S. Food and Drug Administration-National Institutes of Health Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource [Internet]. Silver Spring (MD): Food and Drug Administration (US); 2016-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK326791/ Co-published by National Institutes of Health (US), Bethesda (MD).

treatments; where an implanted medical device was at issue, patients were spared unnecessary surgical procedures.

Phase 3 trials help care providers understand when a medical product provides clinical benefit to patients that outweigh the risks. They also help researchers understand when a purported mechanism of action is credible and merits further development, allowing researchers to avoid investing substantial time and resources going in the wrong direction, resources that could be deployed to identify a truly effective product. As we continue to explore alternatives to requiring phase 3 testing, it is important to keep in mind the benefits they provide to both patients and to the medical research enterprise.

Appendix A: RCTs and Clinical Trial Design Considerations

In many cases, demonstration of an acceptable benefit/risk profile requires a randomized, controlled, clinical trial, of a size and duration that reflect the product and target condition. Since the 1940s, when the first RCTs were done, the practice of medicine has greatly benefited from the availability of the unbiased, evidence-based information they produce.[123] Three crucial elements of the RCT that make it more likely to be definitive are: comparing the product to a control; randomizing patients between the control and treatment groups; and, where possible and appropriate, blinding the patients and clinicians as to whether patients are receiving the product being studied or the control.

Control: The control group is a group of patients that is as close to the treated group as possible in all relevant characteristics, other than whether they receive the medical product being tested. The purpose of the control group is to ensure that any improvement in the treated group is above and beyond that resulting from the natural course of the disease, supportive medical care received as part of the trial, or a placebo effect. The control need not be a placebo; the experimental product may be tested against one or more known effective therapies.

Randomization: Randomizing patients between the control and treatment groups helps ensure that any difference observed between the treated and controlled groups is likely caused by the product being studied. It does so by ensuring that factors that might affect the outcome, such as age, gender, and other medical conditions, are approximately equally distributed between the treated and control groups.

Blinding: Blinding means not allowing various parties to the trial to know who has been assigned to the treated or control groups. Blinding is intended to reduce the possibility that unconscious bias, rather than the medical product, caused any difference between the treatment and control groups.

Together, these features of RCTs make it possible to separate the effects of the product being tested from other influences. Advances in biomedical science and statistics, however, can also enable a more flexible approach to determining which trial designs can be considered "adequate and well controlled." The agency has issued an array of draft and final guidances describing circumstances under which trial designs that do not follow the typical paradigms may provide reliable evidence, including:

Use of adaptive designs, potentially allowing changes in trial protocol based on interim trial results. This can allow enrollment of fewer patients and potentially shorter trial duration, but requires significant safeguards to avoid introduction of bias.[124]

Use of enrichment designs, potentially allowing highly targeted selection of trial patients. This can allow enrollment of fewer patients and those who are more likely to respond to the test product, but may present challenges with regard to the interpretability and generalizability of the trial results.[125]

Use of historical controls instead of a classically controlled trial, potentially allowing patients outside the trial to serve as the control. This may allow enrollment of fewer patients and allow all patients in the trial to receive the test product, but sacrifices randomization and blinding.[126] Historical control designs are usually reserved for circumstances where the natural history of the disease is very well characterized and relatively uniform.[127]

Appendix B: Methods

We present a set of 22 phase 3 RCTs published or otherwise publicly reported in sufficient detail since 1999, in which the study produced unexpected evidence despite phase 2 results suggesting that the product could be safe and effective. The intent of these case studies is to shed light on the kinds of medical insights Phase 3 trials can generate, and illustrate the ways that the results of phase 2 trials, alone, can be misleading. We selected examples from among numerous additional candidates, to represent as wide an array of conditions, types of patients, and types and formulations of prescription medical products as possible.

A. Sources

We identified candidate case studies through expert elicitation, and review of published scientific articles and the trade press.

- Expert elicitation. We engaged FDA medical product reviewers and scientists in the following Offices. These experts identified examples of phase 3 RCTs that had produced unexpected results, and provided insights into ways that the information from phase 3 trials is used, beyond the approval decision (see discussion in section VI).

    - Office of the Commissioner: Deputy Commissioner for Medical Products and Tobacco; Office of Pediatric Therapeutics; the Office of Orphan Products Development.
    - Center for Drug Evaluation and Research (CDER): the Deputy Center Director for Clinical Science
    - CDER, Office of New Drugs, Office of Drug Evaluation: the Division of Cardiovascular and Renal Products; the Office of Antimicrobial Products; the Office of Hematology and Oncology Products; the Division of Neurology Products; the Division of Psychiatry Products; the Division of Pediatric and Maternal Health; the Division of Metabolism and Endocrinology Products; and the Division of Anesthesia, Analgesia, and Addiction Products.
    - Center for Biologics Evaluation and Research: the Center Director, Deputy Director, and the Office of Cellular, Tissue, and Gene Therapy.
    - Center for Devices and Radiologic Health: the Deputy Center Director for Science.

- Review of published, peer-reviewed, literature. The scientific information on the phase 2 and 3 trials examined in these case studies was obtained from PubMed and ClinicalTrials.gov. The Centers for Disease Control and Prevention and National Institute of Health websites provided additional epidemiologic information.

- Trade press and other public/online sources. We reviewed trade press and annual compilations of pipeline failures published by FierceBioTech and Genengnews.com to identify candidates for review and possible analysis. While we relied primarily on peer-reviewed literature for the actual analyses, in a few cases, where the failed phase 3 trial was not published, we used company press releases where these were sufficiently detailed. For some case studies, an Advisory Committee transcript provided additional information on the phase 3 trial results.

B. Limitations

This is not an analysis of "success rates" or the predictive accuracy of phase 2 data broadly. A rigorous study involving all or a random sample of all medical products that enter phase 3 is not possible. Many phase 3 trials are never published and are otherwise not in the public domain; cases that could not be

presented using only public sources could not be included. Even FDA may be unaware of certain phase 3 trials, if they are conducted abroad and not under an Investigational New Drug Application.[‡‡] Reporting of results to Clinicaltrials.gov was not required by statute until 2008; further, during the time of this study, summary results were only required for approved, licensed, or cleared products. The bias toward publishing only successful trials has been well documented.[128] When product development is halted, the sponsor often releases only a press announcement, or makes no announcement at all, and the scientific issues behind the termination of product development are not available.[129]

Rather, we attempted to identify cases that could be illustrative across different types of products, conditions, and patients. Further, we focused on the medical information produced in phase 3 trials, not business or other non-scientific reasons for halting product development.

[‡‡] When a drug sponsor wants to test its potential drug in humans for the first time, the sponsor must submit an Investigational New Drug Application to the FDA providing, among other things, the preclinical data that shows that the drug is reasonably safe for initial testing in humans, and the sponsor's protocols for proposed clinical studies. The sponsor may proceed after 30 days, unless FDA objects.

Appendix C: Summary Table

Summary Table: An overview of the types of divergent results observed in the phase 3 studies

Product	Purpose	Lack of			Approved for Any Indication at Time of Phase 3 Trial	Page
		Efficacy	**Safety**	**Efficacy and Safety**		
Aliskiren (Rasilez, Tekturna)	Add-on treatment of prevention of congestive heart failure (CHF) complications	✓			✓	21
Bitopertin	Add-on treatment of schizophrenia	✓				5
Brivanib	Treatment of hepatocellular cancer	✓				6
Capsaicin Topical Patch (Qutenza)	Treatment of HIV-associated nerve pain	✓			✓	8
CoSTAR Drug-Eluting Stent	Reduction of heart attack risk in patients with coronary artery disease			✓		22
Darapladib	Prevention of cardiovascular disease complications in patients with prior heart attack	✓				9
Dexmecamylamine	Add-on treatment of depression	✓				10
Exhale Drug-Eluting Stent	Reduction of shortness of breath in patients with emphysema	✓				11
Experimental HSV-2 Vaccine	Prevention of genital herpes	✓				12
Figitumumab	Treatment of advanced non-small cell lung cancer			✓		23
Glutamic Acid Decarboxylase Vaccine	Preservation of insulin secretion in patients with recent-onset type 1 diabetes	✓				13
Imiquimod (Aldara)	Treatment of molluscum contagiosum lesions	✓			✓	14
Iniparib	Add-on treatment of “triple negative” breast cancers	✓				15
Lithium	Treatment to delay disease progression of amyotrophic lateral sclerosis	✓			✓	16
MAGE-A3 Vaccine	Treatment of patients with non-small cell lung cancer following surgery	✓				17
NicVAX Vaccine	Smoking cessation	✓				18
Olanzapine Pamoate (Zyprexa Relprevv)	Long-acting treatment for schizophrenia		✓		✓	20
Recombinant Factor VIIa (NovoSeven)	Reduction of intracerebral bleeding and hematoma size in patients with stroke			✓	✓	24

Semagacestat	Improvement of cognitive and functional status in Alzheimer's disease		✓	25
Torcetrapib	Prevention of cardiovascular disease events in patients with a history of cardiovascular disease or type 2 diabetes		✓	26
V710 Vaccine	Vaccine to prevent *Staphylococcus aureus* infection		✓	27
Velimogene Aliplasmid (Allovectin-7)	Treatment of metastatic melanoma	✓		19

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