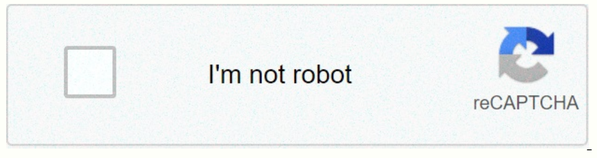

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Hope was here pdf

Welcome to Review & Preview, a new daily email from Barron's. Every night we will review the news that markets have moved during the day and look ahead to what it means for your portfolio in the morning. We'd like to know what you think. Give us your feedback by replying to this email or by filling out a short survey. TGIF. Welcome to a 65.5-hour break. After another 1,000-point swing in the Dow Jones Industrial Average today, tomorrow is guaranteed to be calm — at least on Wall Street. The bad news is that we still don't know what Monday will bring. However, there was a glimmer of hope this afternoon that the market may have found a bottom. Around 1:30 p.m..m S&P futures touched their lowest point of the week -- matching the low set late Monday night. (S& P futures trade through the night so they offer a better sense of real-time sentiment.) But rather than falling through that low point, the future bounced right from the bottom, along with the rest of the market. The Dow ended the day down to 330 points, or 1.4%. That means something for a technical analyst who studies stock cards for a living. We can't predict whether the low blows are Monday, but it's a decent place to start the week. Maps may not be all that interesting to you and me, but the machines are now tracking these trends. And they are the ones who perform most of the trades. All told, it was the market's worst week in two years. The Dow has 5.2%, - 1,330 points - this week - for most of us, it feels a lot worse. DJIA: +1.38% to 24,190.90 S& P 500: +1.49% to 2619.55 Nasdaq: +1.44% to 6874.49 The hot stock: Mattel +7.9% The Biggest Loser: Expedia -15.5% Best Sector: Real Estate +2.5% Worst Sector: Energy -0.3% The New Amazon Threat? Another day is another industry under pressure from Amazon.com. Today, it's the logistics and delivery business dominated by UPS and FedEx.The Wall Street Journal, reports that Amazon will launch a business to pick up packages from businesses and bring them to consumers. The service called Shipping with Amazon can all start in a few weeks. All things considered, ups and FedEx shares held pretty well on the news, down 2.6% and 1.7% respectively. Similar Amazon threats to the grocery business and the health care industry have caused much bigger selling to those stocks. My colleague Avi Salzman argued that ups and FedEx might actually have the most to fear. Amazon makes up about 5% to 10% of UPS's business, according to estimates, and less than 3% at FedEx. But Avi wrote today, those numbers can't fully quantify the potential threat because Amazon's delivery service could peel off even more business from sellers who aren't already tied to Amazon. This weekend's cover we read • Brace more sexual harassment allegations in the C-SuiteBarron's • Exit Interview: Mark Mobius at 30 years Budding MarketsBarron's • Equifax Hack Could Be Worse Than You Think WSJ • Within the Sudden End of Silicon Valley's Biggest Trial Bloomberg The Calendar With 68% of Companies in the S& P 500 after reported fourth-quarter earnings, there was more than the usual case of upside surprises - 78% reported earnings beating analysts' expectations, while 14% missed estimates, according to Thomson Reuters I/B/E/S. In a typical quarter, going back to 1994, 64% of companies beat and 21% misses. Have a great weekend. Be sure to make sure to take advantage of the rest - the clock is already ticking on that 65-hour market break. Give in honor & Memorial for Email Cancer A-Z Remains Healthy Treatment & Support News Our Research Gets Involved with our partners about our search features left to right: Genetic Counselor Emily Brown, neurologist Michael Polydefkis and nurse practitioner Kathleen Burks On a recent fall day, 80-year-old Gail Delente rolled her motorized scooter through the door of the retirement home Liquidating through the kitchen to the living room, she took her 7-foot Steinway Model B grand piano—one of the most beautiful pianos there ever was, she says. It is a memento for the long career she has held as a university professor and concert pianist. She has performed widely in the United States and France, where she established a piano festival to promote the authentic performance of French piano music worldwide. In recognition of her efforts, the French government knighted Delente in 2000. But nowadays, playing the piano is a distly memory. Six years ago, Delente noticed a troublesome tingling in her fingers, which gradually stopped working as she always expected them and began throwing with pain. A crippling numbness began to spread from her toes to just above the knee, making it impossible for her to walk. Desperate for a diagnosis, Delente saw a string of specialists before landing at Johns Hopkins and undergoing numerous tests. In February 2017, she got a long-awaited answer: She told transthyretin amyloidosis, also known as hATTR amyloidosis, a disease in which abnormal protein deposits build up in the nerves, heart or both. When they gave me test results, the first thing they said was that they finally had a diagnosis, she recalled. They then added that it's fatal. Indeed, until recently, patients like Delente with hATTR amyloidosis had few options to treat this progressively deactivation and deadly condition. But two clinical trials, both of which recently took place at Johns Hopkins, give new hope for patients. These drugs provide not only the potential to save lives, but to possibly reverse the course of this devastating disease – something that patients and doctors have long thought to be an impossible feat. A Dreaded Feared Johns Hopkins neurologist Michael Polydefkis is one of the few neurologists in the United States who specializes in treating hATTR amyloidosis. This disease, caused by one of 120 different point mutations—a one-letter exchange in a person's genetic code—affects a protein known as transthyretin (TTR). His job is to ferry thyroid hormone and vitamin A into the body. TTR usually exists as a tetramer, explains Polydefkis, a form like a four-leaf claver. But it can also separate into individual leaves. For people with an amyloidosis-causing TTR mutation, these leaves can fold incorrectly and aggregated, form amyloid, which accumulates in tissues and ultimately causes dysfunction. Amyloid is a generic term for proteins that fold and clump together abnormally, causing diseases to vary as widely as Alzheimer's disease or other conditions that affect the child or liver. In the case of hATTR amyloidosis, Polydefkis adds, these protein aggregates can accumulate in the heart, making it too tight to beat effectively, eventually leading to heart failure. Sometimes amyloid acryroid accumulates in peripheral nerves, affecting sensational and motor capabilities or causing diarrhea or constipation when acting on nerves in the gasintestinal tract. Most patients have components of both heart and neurological manifestations. Although the exact appearance of this condition is unknown, estimates suggest about 50,000 people worldwide are affected, with about 5,000 in the United States. The median age of onset is about 39, but some patients begin to show symptoms as early as their 20s. Once the process begins, it's a progressive decline, which translates into increasing disability and ultimately death, Polydefkis explains. [Until recently], I feared delivering these diagnoses because I knew what was in store for these patients. Because this condition could be genetic, Polydefkis adds, many patients he saw also knew what would come once they received their diagnosis. They saw their older, aunt, cousin or other family members slowly degenerate, trapped in a dysfunctional body wrecked with pain. Because this condition could be genetic, many patients knew what would come once they received their diagnosis. They saw their older, aunt, cousin or other family members slowly degenerate, trapped in a dysfunctional body wrecked with pain. [Until recently], I feared delivering these diagnoses because I knew what was in store for these patients. -Michael Polydefkis Until recently, patients with this diagnosis were relatively rare in Polydefkis' practice, he says. That's because many already knew there was relatively little to offer. For those who saw him anyway, there were only a handful of options he and his Practitioner, Kathleen Burks, could propose. One potential way to treat hATTR amyloidosis is through a liver transplant, says Burks, Burks, this is the main source of TTR. However, depending on the mutation that causes a patient's condition, TTR produced by the new liver can also fold incorrectly and continue the disease's progression. A drug called tafamidis, which stabilizes the tetramer form of the protein and prevents it from separating and wrongly, has been approved in Europe after testing on several clinical trial sites, including Johns Hopkins—but it is not approved in the U.S. because it has only slightly improved outcomes. Researchers found that a generic nonsteroidal anti-inflammatory drug called diflunisal had similar characteristics. It is often used in the US to slow disease progression, but it can cause serious side effects, such as kidney toxicity, and this can complicate the management of heart conditions. It was depressing for patients to hear that there are no real options for treatment, that we cannot undo what happened and that we cannot stop it from progressing, says genetic counsellor Emily Brown, who works in the Division of Cardiology to detect and advise patients with heart or combined manifestations of this disease. Patients are often referred to Polydefkis' practice from cardiology based on their symptoms. While we could treat the symptoms, Brown adds, we previously couldn't treat the underlying disease. Consequently, many of our patients felt hopeless. 'Unprecedented' improvement But those talks began to take a turn a few years ago, polydefkis says. That's when two clinical trials launched at Johns Hopkins and selected sites around the world for new drugs to treat hATTR amyloidosis. The trials, run by two different drug companies, offered separate strategies for those whose condition manifested neurologically. One trial, administered by Boston-based Alnylam Pharmaceuticals, tested a drug called patisiran. Delivered by infusion every three weeks, Patisiran uses a phenomenon called RNA to limit interference cells' ability to make TTR. The drug binds to messenger RNA instructions that make the cell prints of DNA proteins—and mark it for deterioration. The other trial, by Carlsbad, California-based Ionis Pharmaceuticals, tested a drug called inotersen. This drug, which falls into a category known as antisense oligonucleotide therapeutics, takes a different but related pak to inhibit TTR production. An injection that patients self-administer once a week, inotersen binds to messenger RNA to make it ineffective at producing proteins. Preclinical testing in animal models showed that both of these drugs can significantly reduce the amount of TTR circulating in the blood, which in turn has reduced the ability of misfolded proteins to total and form. But until the clinical trials, no one knew exactly what would happen when patients with hATTR amyloidosis took these drugs. For both Burks says, study volunteers are split 2-to-1—for every two patients who receive the actual drug, one has a placebo. Neither the medical team that administered the drugs and cared for these patients or the patients themselves knew who was regimen. I've worked on many clinical trials, and it's almost impossible to tell who's on the drug and who's on the placebo. Clinical trials only rarely succeed, so you don't often see patients improving, Burks says. You're not supposed to guess, but here we started to see some differences among patients. Some patients continued the precipitous drop characteristic of this disease over the next few months, she says. But other patients gradually stalled in their illness. Rather than progressively developing more sensory and motor dysfunction, their progress has stopped. A few on patisiran, she says, even slightly improved the longer they were on the drug. For this disease, says Polydefkis, it is unprecedented. We didn't think of hATTR amyloidosis in terms of improvement. Never. The trials were so successful that after two years of an investigation phase, both drug companies switched to an extensive access program where newly diagnosed patients could receive the drug instead of the placebo. Pham Hung, a 68-year-old physics professor at the University of Virginia, joined the expanded access program in January 2018. Hung's hATTR amyloidosis involves combined heart and neurological symptoms. Nearly three years ago, progressive problems in walking and then an irregular heartbeat brought him to a series of specialists, seeking an answer. A genetic test confirmed his diagnosis in 2017. After that, Hung had surgery to receive an implanted cardioverter defibrillator. It also collects data, downloadable by doctors, on heart rate rhythm patterns. As walking grew harder and harder, Hung started using a set of hiking sticks instead of a cane. After six months on patisiran, he improved enough to stop using his walking sticks altogether. Data from its implantable cardioverter defibrillator shows that episodes of irregular heart rate have reduced from about 200 over three months to just five. Gastroinenterinal problems that have plagued him for years have disappeared. A blood test showed that the amount of TTR protein circulating in its bloodstream has decreased from a range of 18 to 38 milligrams per deciliter-typical for healthy patients and those with hATTR amyloidosis equal—to less than 3. I'm a physicist, so it usually takes a few numbers before I believe in something, Hung. To me, it's like science fiction that this drug has caused so many measurable improvements. I'm a physicist, so it usually takes a few numbers before I believe in something, Hung. Tells me it's like science fiction this drug drug causes so many measurable improvements. -Patient Pham Hong One of Polydefkis' research areas uses punched skin biopsies – clinical tests in which small skin samples can shed light on various factors of patients' health – to detect different forms of neuropathy. Its lab has a way of detecting amyloid in the skin's nerves as a way to follow the progression of hATTR amyloids. He recorded these biopsies in Johns Hopkins' clinical trials. These tests showed us what patients have already told us, polydefkis says. We could physically see that amyloid congestion has stopped. And in some patients it reversed. More in the Works Patisiran was approved by the FDA in August 2018. Inotersen was approved in October 2018. As trials continued for both drugs, word spread like wildfire among the hATTR amyloid community. Near Hagerstown, Maryland, is a hotspot for this disease, polydefkis explains. Many members of the same family passed on their mutant gene to descendants. As patients told their relatives about the two trials, Polydefkis and his colleagues began to see an influx of new patients, all with new hope about what could be done for their condition. There were so many that he set up a register of local patients —many of whom were related to each other, and others who were non—who now have totaled 100 individuals who track Polydefkis and often treat. Delente, who is on Polydefkis' register but not related to the Hagerstown clan, also made modest gains on patisiran. Although she still can't walk distances more than 5 to 10 feet and struggles to use her hands, her car disapproving has stopped. Gastroinenterinal symptoms that have long bothered her have disappeared. Now that the trial is over, Delente is nearing the end of her free doses — a time that she's feared since her first infusion in early 2017. The estimated price for a year of patisiran is $450,000, an amount that is untenable for almost all of the patients who need it. Since the drug has only recently gained FDA approval, most insurance companies still don't automatically cover it, and it's unclear how and when insurance approvals will come through. Burks and her colleagues are currently working the 40 patients currently using this drug or inotersen at Johns Hopkins to find options to continue the medication once they leave these trials. Meanwhile, Polydefkis says, more pharmaceuticals for the treatment of hATTR amyloidosis are in the works. Although the patisiran and inoters and trials focused on the neurological manifestations of this disease, other trials currently running use variations of these drugs to treat the heart manifestations of hATTR, as well as a mechanically identical TTR amyloidosis that is not inherited, called wildlife type TTR amyloidosis. I got in gone because it contains so much difficult that we are just beginning to understand from a mechanistic standpoint, polydefkis says. I see this dramatic change for the first time in my career. It transformed those difficult conversations with these patients into optimistic people.

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