Evaluate Vantage

# JP Morgan 2022 Conference Article Pack

ARTICLE PACK

Evaluate Vantage

# Contents

# Biogen hints at jobs cuts unless government pays up

**BY JACOB PLIETH**

An analyst call over the Aduhelm coverage debacle sees Biogen threaten more cost cutting.

Biogen had already gone on the offensive against Tuesday's proposal by the US Centers for Medicare & Medicaid Services to curtail Aduhelm coverage, and today it directed more venom against what it called an "incomplete and sometimes inaccurate assessment".

An analyst call did lay out some of the company's plans, but perhaps its most extraordinary moment came when Biogen effectively threatened to cut more jobs unless the national coverage determination (NCD) was changed. "We need to be incentivised and rewarded," said the company's chief executive, Michel Vounatsos.

Biogen had already announced $500m of cost-cutting measures last month, alongside halving Aduhelm's annual cost to $28,000. The NCD is still at the draft stage, but "should we be in such a position in April [when the final guidance is due] there will be additional waves. We have to protect the bottom line," Mr Vounatsos said.

He called for interested parties to make their voices heard during the 30-day public comment period now starting. The draft NCD, proposing coverage with evidence development, means that Medicare would only cover patients given Aduhelm in randomised, controlled trials that are approved by the CMS, and in those backed by the NIH.

"I cannot believe that the final NCD position will be the same as the draft," Mr Vounatsos, who is seen by many as fighting for his job in light of the debacle, told analysts. "We don't want unfair treatment for the pioneer [of amyloid-beta research]."

## WITHDRAW?

Asked whether Biogen would consider pulling Aduhelm from the market if the final NCD was unchanged, he said the company would "follow the data and the science. But everything is on the table."

It is clear, therefore, what Biogen does not want to see. As for what it does want, the dream scenario would be open access, but it says coverage with restrictions, to reflect Aduhelm's clinical data, would be a more realistic outcome.

Alisha Alaimo, president of Biogen US, said that even a less onerous coverage with evidence development, involving a patient registry or more inclusive clinical trials, for example, would limit the number of patients on Aduhelm.

Another thread to Mr Vounatsos's argument was the stick and carrot. He claimed that since 1995 the industry had spent $40bn on Alzheimer's drug development "with the expectation that this would be rewarded", adding that the draft NCD, if implemented, could have a "chilling effect on future innovation".

## CMS VS FDA

In a separate statement Eisai, Biogen's amyloid-beta partner, today expressed concern that the guidance called into question the FDA's autonomy and undermined the accelerated approval pathway. But both companies largely avoided commenting on Aduhelm's questionable supporting dataset, which is at the root of a problem that has pitched the CMS against the FDA.

With Aduhelm famously selling just $300,000 in its first full quarter on the market, analyst attention has understandably turned to Biogen's next big Alzheimer's readout, that of lecanemab's phase 3 trial, due in the second half. An obvious question is what Biogen would do should this readout be positive.

It would seem logical then to pivot away from Aduhelm and switch to lecanemab, but on this point the company basically said it would wait and see.

*Published on January 13, 2022*

# Abbvie looks to crack the cystic fibrosis code

BY MADELEINE ARMSTRONG

Phase 2 data could indicate whether the big pharma has a chance of disrupting Vertex's monopoly.

When it comes to cystic fibrosis Vertex is the undisputed heavyweight, but this has not stopped other groups from taking it on. Abbvie is the latest challenger, and data due this quarter could give clues about whether the group was wise to go all in on projects originated by Galapagos.

Abbvie has two phase 2 trials under way, one of a doublet and one of a triplet. The big pharma reckons it can do better than Vertex's latest drug, the triplet Trikafta, in terms of efficacy – but an edge on tolerability could also be enough to justify moving forward, Abbvie execs hinted at the JP Morgan meeting this week.

Vertex is not standing still, and already has a next-generation triplet in phase 3; the Skyline 102 and Skyline 103 studies of VX-121, tezacaftor and VX-561 are set to complete next year. That group's chief executive, Reshma Kewalramani, talked up the high bar set by Trikafta, concluding that: "If it is possible to improve on Trikafta, we're determined to be the ones who do so."

| | |
|---|---|
| **Project** | CF doublet (ABBV-3067 + ABBV-2222); CF triplet (ABBV-3067 + ABBV-2222 + ABBV-119) |
| **Company** | Abbvie |
| **Event type** | Phase 2 data |
| **Indication** | Cystic fibrosis |
| **Date** | Q1 2022 |
| **Trial IDs** | NCT03969888 (doublet); NCT04853368 (triplet) |

Trikafta is a triplet comprising elexacaftor and tezacaftor, both CFTR correctors, plus ivacaftor, a potentiator. It was approved in 2019 for patients homozygous for the F508del mutation in the CFTR gene, and those with one copy of the F508del mutation and one minimal function mutation (known as F508del/Min) – thereby addressing 90% of the cystic fibrosis population (Vertex's double cystic fibrosis surprise, October 22, 2019).

Trikafta is forecast to be the biggest cystic fibrosis drug in 2026 with sales of $9bn, according to sellside consensus compiled by Evaluate Pharma.

No wonder Abbvie wants a piece of the action. The group has a triplet in development combining two correctors – ABBV-2222 (galicaftor) and ABBV-119 – with the potentiator ABBV-3067 (navocaftor). It is also evaluating a doublet comprising ABBV-2222 and ABBV-3067.

This quarter, the group is due to report topline data and make a decision on whether to take the programme forward, Abbvie's president, Michael Severino, said. When asked what the group would need to see versus Trikafta, he replied: "Our goal would be to be better from an efficacy perspective."

Abbvie believes that a marginal improvement could be enough, with execs previously saying the group was striving for an efficacy advantage of just a few percentage points on forced expiratory volume in 1 second (FEV1). But this would be on a cross-trial basis: Abbvie's studies are comparing its assets versus placebo.

The table below shows what Abbvie is up against, both in F508del homozygous and F508del/Min patients. Abbvie's doublet study is in homozygous patients only, while the triplet is being evaluated in both F508del homozygous and heterozygous subjects.

**Going up against Trikafta: what Abbvie will need to show**

| Population | F508del/Min | F508del homozygous |
|---|---|---|
| Trial ID | NCT03525444 | NCT03525548 |
| Change in ppFEV1 | 13.8* | 10.0** |
| Change in sweat chloride | 41.2* | 45.1** |

All efficacy figures given at 4 weeks. *Relative to placebo; **relative to Smydeko (tezacaftor plus ivacaftor). Source: Trikafta label.

However, efficacy is not the only consideration, according to Mr Severino: "There could be advantages, for example, on drug interactions or tolerability. We'll look at that entire package."

Trikafta's label carries warnings about liver injury and cataracts.

Still, improved tolerability might not count for much if Abbvie's triplet cannot at least equal Trikafta on efficacy.

## MIX 'N' MATCH

Despite Abbvie's bullishness about ABBV-2222, which it has described as a "best-in-class corrector", the group's progress in cystic fibrosis has been far from smooth. In 2018 it discontinued development of a triplet comprising ABBV-2222 and ABBV-3067 – then known as GLPG2222 and GLPG3067 – plus a different corrector, GLPG2737.

And yet another combo, GLPG2222 plus GLPG2451 and GLPG2737, disappointed in the Falcon trial. Despite this, Abbvie opted to take over the cystic fibrosis programme from its partner, Galapagos (Abbvie's low-risk bet could challenge Vertex on price, October 25, 2018).

That deal spurred hopes of cost competition in cystic fibrosis, where Vertex's monopoly has meant it has had the freedom to set high prices. But first, Abbvie needs to convince on efficacy.

*Published on January 13, 2022*

# Aduhelm verdict puts the heat on Biogen – and on the FDA

BY JACOB PLIETH

The US Centers for Medicare & Medicaid Services' national coverage determination for Biogen's Aduhelm makes for uncomfortable reading.

Yesterday's proposal to limit Medicare's obligation to pay for Biogen's Aduhelm could have been worse, but not by much. The draft guidance is so restrictive that, assuming it is implemented, it could result in Aduhelm recording virtually no revenue in the near term.

But it also comes as an apparent slap on the wrists of the FDA: not much reading between the lines is required to see the agency being told that it should never have approved the controversial Alzheimer's disease drug to begin with. The guidance's main thrust is that until Aduhelm shows a meaningful benefit on cognition and function it should not be paid for.

While Aduhelm's accelerated approval is already conditional on a confirmatory study, it seemed unlikely that the FDA would actually pull the drug should such a trial fail years down the line. But the guidance effectively puts pressure on the agency to stick to the conditions of the accelerated approval, as well as making it extremely hard for Biogen to sell any Aduhelm during its conditionally approved phase.

Aduhelm has hardly been prescribed since its approval in June, and Biogen had claimed that doctors were holding off until implementation of the guidance, a national coverage determination (NCD) spelling out the conditions under which all Medicare contractors would have to provide and pay for the drug.

## WHAT DOES IT MEAN?

Few had expected the worst-case scenario of blanket non-coverage, but coverage with evidence development, which the Centers for Medicare & Medicaid Services (CMS) is now proposing, represents a materially worse outcome than the middle ground many analysts had forecast.

In effect it means that Medicare would only cover patients given Aduhelm in randomised, controlled trials that are approved by the CMS, and in those backed by the NIH. Such trials must be conducted in a hospital-based outpatient setting, and meet other criteria.

This was viewed as sufficiently restrictive for Mizuho to remove nearly all Aduhelm sales from its Biogen model yesterday. In a statement Biogen said the draft NCD would almost completely remove Aduhelm coverage for Medicare beneficiaries, and duplicate efforts like Aduhelm's 1,696-patient Embark and 6,000-patient Icare-AD-US studies.

These two trials are of immediate relevance as more lenient coverage with evidence development might have encompassed them. But, as they have no control arms, if the NCD is enacted per the draft they will not qualify.

Indeed, on the question of available data so far the CMS is scathing, listing 21 phase 3 randomised controlled clinical trials of projects from bapineuzumab to crenezumab alongside those of Aduhelm, and casting doubt on Aduhelm's purportedly positive Emerge trial given its premature halting for futility.

"With conflicting results from Emerge and Engage, and a secondary analysis that did not resolve the difference, CMS believes that the available evidence is insufficient to establish that the treatment is reasonable and necessary," the draft NCD states.

## NO SURROGATE BIOMARKER

Further, the CMS appears to slam the FDA's view that brain amyloid-beta plaque reduction is a biomarker capable of backing accelerated approval. The draft instead calls for evidence of meaningful benefit on cognition and function, and says "no biomarker has achieved surrogate status in Alzheimer's".

Randomised Aduhelm data will emerge, eventually: Biogen vows to start screening for Aduhelm's confirmatory trial in May, with primary completion four years after initiation. At least the 1,300 patients expected to be enrolled here might qualify for coverage under the proposed NCD, as long as the study is approved by the CMS.

It must also be stressed that the guidance applies to all amyloid-beta MAbs, and likely raises the bar for what pivotal trials of Eisai/Biogen's lecanemab, Lilly's donanemab and Roche's gantenerumab must show when they yield data this year. Biogen today opened off 10%, but Lilly and Roche fell a more restrained 3% and 2% respectively.

Biogen's next key event is tomorrow's analyst call, at which it will presumably say what it plans to do next. It cannot be underestimated how much Aduhelm now reflects on the tenure of the group's chief executive, Michel Vounatsos.

Clearly, if halving Aduhelm's price was intended somehow to please the CMS it has not worked, though it might yet raise Biogen's standing with patient advocates. Yesterday the Alzheimer's Association called the draft NCD a "shocking discrimination" that proposed to restrict Aduhelm access to "a privileged few – those with access to research institutions".

Such views are relevant because there now follows a 30-day public comment period. The bull case is that pressure groups succeed in persuading the CMS to reverse or water down the draft guidance, with analysts citing the example of Car-T therapies, whose draft NCD was coverage with evidence development (specifically trials and a patient registry), but whose final determination was full coverage.

That said, Aduhelm's draft NCD is so negative that the CMS might already have painted itself into a corner.

*Published on January 12, 2022*

# Infinity beckons for Illumina

**BY ELIZABETH CAIRNS**

Illumina closed up 17% yesterday having released strong preliminary fourth quarter revenue of $1.2bn, a 25% increase year-on-year and an easy beat of consensus expectations, which had sat at around 15% growth.

The company expects to grow at this rate throughout the coming year, too, the regulatory uncertainty surrounding its decision to close the acquisition of Grail without approval from antitrust authorities notwithstanding. Perhaps more interesting for the long term is the news that the company, a specialist in sequencing short strands of DNA, is working on a new long-read technology. Codenamed Infinity, this runs on existing Illumina instruments and can provide sequences of around 10,000 bases in length. Early access for Infinity is to start in the second half of this year, Illumina said yesterday at the JP Morgan conference. Adding long-read tech to its core short-read offering was the thinking behind Illumina's attempted $1.2bn takeout of Pacbio, squashed on anticompetitive grounds in 2019. Now it seems to be attempting to build a short- and long-read empire from within, taking on Pacbio in the process. Pacbio's shares sank 11% yesterday, though this might also have been related to its preliminary fourth-quarter sales figures, which at $36m missed analyst expectations.

*Published on January 12, 2022*

# Sarepta gets another bite at the gene therapy cherry

BY MADELEINE ARMSTRONG

But unimpressive phase 2 results, plus a lack of a placebo control arm, raise questions.


A year ago Sarepta's Duchenne muscular dystrophy gene therapy SRP-9001 failed to beat placebo in a phase 2 trial. Now the company hopes that updated findings from the same study will support accelerated approval – but these compared SRP-9001-treated patients against external controls, rather than placebo.

It was these results, presented at the JP Morgan meeting yesterday, that sent Sarepta's stock down 11%, the main disappointment being the small benefit seen with SRP-9001. As such, it seems entirely possible that the FDA will want to wait for results from an ongoing pivotal trial before considering the project for approval.

Unlike with some of Sarepta's previous projects, placebo-controlled data should come soon enough: the phase 3 Embark study of SRP-9001 is set to complete enrolment in mid-2022 and read out next year.

## STUDY 102 TAKE TWO

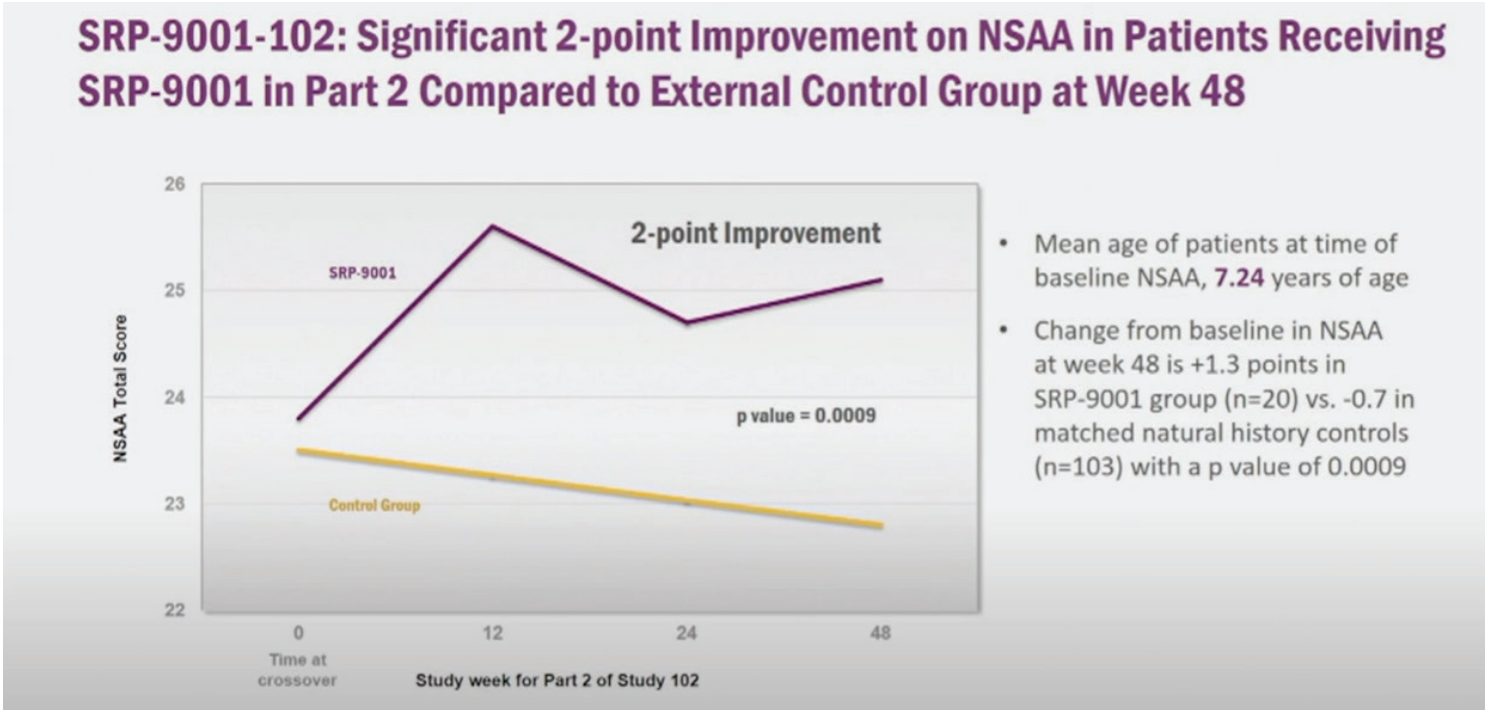
In the meantime, Sarepta hopes that a "totality of the evidence" argument might win out, especially considering the progressive and life-threatening nature of DMD.

A year ago the first part of the phase 2 trial in question, Study 102, failed to show a difference between SRP-9001 and placebo on the primary functional endpoint, North Star Ambulatory Assessment (NSAA) score at 48 weeks (Gene therapy trial fails to rectify Sarepta's sorry record, January 8, 2021).

Yesterday, Sarepta reported data from part two of the same trial, in which 21 patients originally randomised to placebo crossed over to SRP-9001. Results of this group were compared against an external control cohort, constructed from three separate studies.

The group's chief executive officer, Doug Ingram, was at pains to explain that the design of part 2 had been prospectively defined and submitted to the FDA, and that the external subjects had been "rigorously matched" with the Study 102 patients.

Sarepta's second attempt with Study 102 was better than its first: the crossover patients showed a 1.3-point improvement in the NSAA from baseline, versus a 0.7-point decline with the external controls. The company claimed statistical significance with a p value of 0.0009.




Source: JP Morgan presentation

Given the failure of part one of the study it is unclear whether this will be enough for regulators. The magnitude of benefit seen in part two could also raise questions: Leerink analysts had hoped for a 2.5-3.5-point difference between the crossover patients and external control.

### 4-5 YEAR OLDS

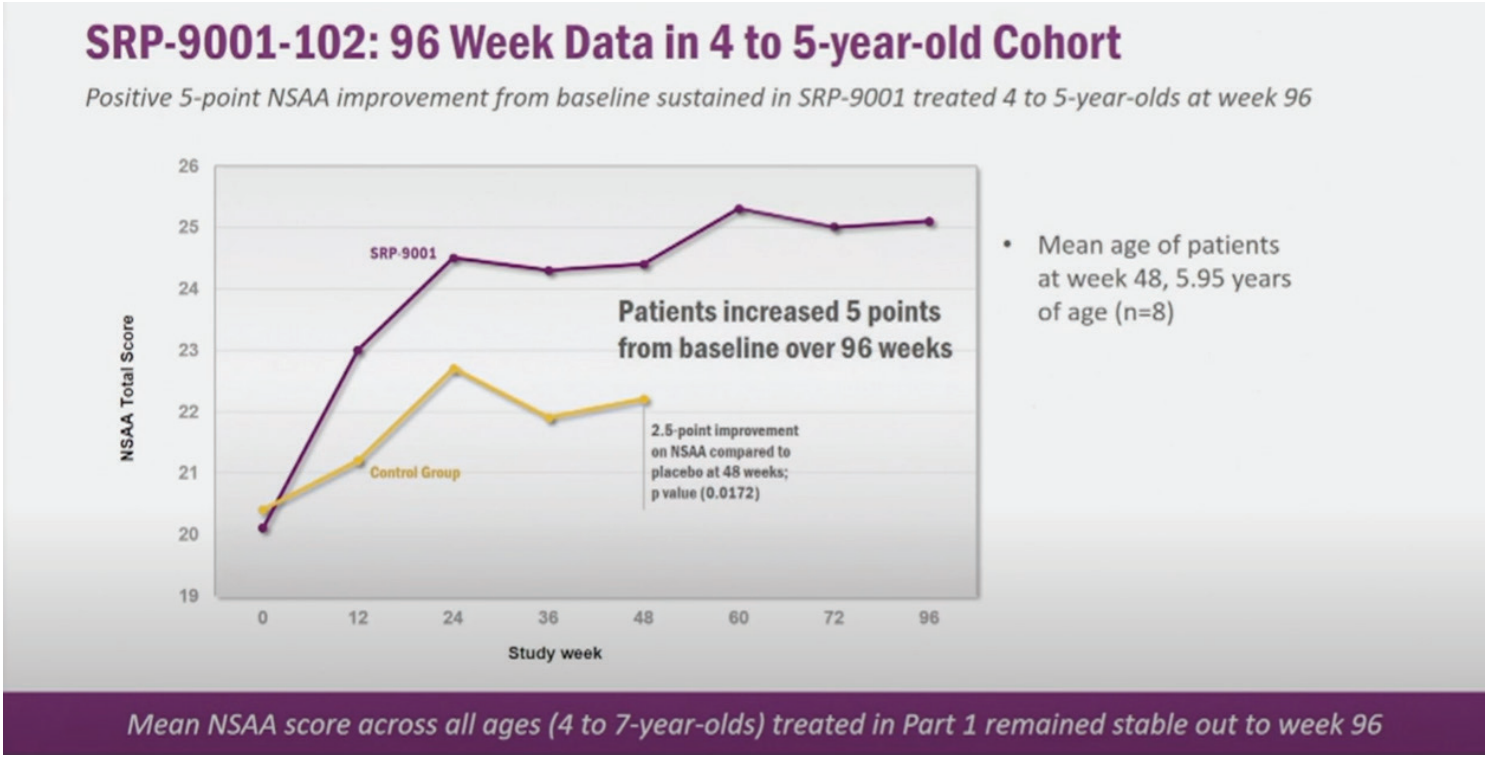
Sarepta had blamed the failure of part one of the trial on the fact that older patients, aged six or seven, had not been well matched in terms of baseline NSAA, leading to fitter patients in the placebo arm. It previously claimed a statistically significant benefit in patients aged four or five, but this can only be considered exploratory given the primary endpoint fail.

Yesterday, Sarepta presented two-year data on these younger part one subjects, which appeared to show ongoing benefit. Results from the older patients were conspicuous by their absence, with Sarepta disclosing only that NSAA scores across all patients "remained stable" at two years. Mr Ingram promised more data at an upcoming medical meeting.

All the updated Study 201 data, along with results from the four-patient Study 101 and six-month data from Study 103, of commercial-grade SRP-9001, are intended to support the accelerated approval.

But Embark will be the big test. Mr Ingram talked up the prospects of the pivotal study, saying the strict inclusion and exclusion criteria around both NSAA and another measure, time to rise, should reduce heterogeneity and increase chance of success.

Hopefully this means that the group will not have to resort to subgroups and external control cohorts to get a win here.




Source: JP Morgan presentation

*Published on January 11, 2022*

# JP Morgan 2022 roundup – Biogen in focus

**BY JACOB PLIETH AND MADELEINE ARMSTRONG**

Much of this week's business development might be done and dusted, but for Biogen things are just warming up.

With several companies timing deal announcements to coincide with the start of the JP Morgan healthcare conference yesterday, the meeting looks set to continue with a focus on smaller tie-ups and more subtle updates to development pipelines and filing plans.

Perhaps the biggest spotlight remains on Biogen, which cannot shake the stench of failure from its Alzheimer's drug, Aduhelm, and which will hope for a crucial US healthcare coverage decision, due tomorrow, to kick-start sales; its JP Morgan presentation yesterday gave some clues as to what it expects. Elsewhere, RNA-based therapeutics remain of interest, as does oncology.

Among company presentations taking place late yesterday, Mirati quietly revealed that it had filed its Kras G12C inhibitor adagrasib with the FDA at last – some 12 months after its rival sotorasib was filed by Amgen. The latter is, of course, already approved for NSCLC in the US as Lumakras, and got an EU nod (as Lumykras) yesterday.

Despite promise in colorectal cancer, Mirati's filing is also in NSCLC, where the phase 2 portion of the Krystal-1 trial has yielded a 43% overall response rate. A key update to this, including duration-of-response data, will not emerge until the first half of this year, possibly at Asco, and the FDA seems unlikely to rule on the filing until it has seen these.

Mirati told JP Morgan that the update would be "similar to what was presented last year by Amgen". As for colorectal cancer, where on a cross-trial basis adagrasib looks better than Lumakras, Mirati promised "additional clarity on a potential pathway for accelerated approval" within the next six months.

## RNA REMAINS HOT

For its part, Amgen today splashed a discovery deal with Arrakis that, while small, at $75m up front, concerned the hot area of target degradation. Unlike Bristol Myers Squibb's cereblons, however, Amgen and Arrakis aim to identify small molecules that degrade RNA, specifically the RNA that codes for "difficult-to-drug" targets.

RNA was also the subject of a tie-up between Allogene, which yesterday revealed the lifting of US clinical hold on its pipeline, and Antion. The goal here is to use microRNAs to silence multiple gene targets and develop a new generation of allogeneic Car-T therapies; terms were not disclosed.

RNA was also in focus recently when Pfizer and Biontech agreed to develop an mRNA-based shingles vaccine that could eventually threaten Glaxosmithkline's biggest growth driver, Shingrix.

Glaxo has long faced questions about its strategy, but its chief executive, Emma Walmsley, brushed off concerns about the potential rival today, pointing to Shingrix's 97% efficacy figure, as well as "eight years of sustained protection" – possibly a dig at the fading effect of mRNA-based Covid vaccines.

At JP Morgan yesterday Pfizer's chief exec, Albert Bourla, said mRNA vaccines could have a better tolerability profile, with similar efficacy. Of course, this still needs to be proved, and the group plans to start clinical trials of its shingles contender in the second half of this year, or perhaps even sooner.

## COVERAGE DECISION

But the spotlight was on Biogen, which this week expects a vital US national coverage determination (NCD) that will spell out the conditions under which all Medicare contractors will have to provide and pay for its controversial Alzheimer's disease drug Aduhelm.

A draft decision on the NCD is expected tomorrow, and Biogen has already convened an analyst call for Thursday before the markets open. Biogen told JP Morgan yesterday that it would first see the draft at the exact same time as everyone else, and that it had a team waiting for it to be posted.

Aduhelm polemics have centred on its ropey dataset and price, and Biogen last month caved in and halved the drug's wholesale acquisition cost to around $28,000 a year. Its chief executive, Michel Vounatsos, yesterday accepted that the outcry from doctors and patients had proved the initial pricing decision wrong, but characterised the cut as "courageous".

Still, the Centers for Medicare & Medicaid Services "doesn't take price into consideration when they consider the NCD", Alisha Alaimo, president of Biogen US, told JP Morgan. The wide-ranging process includes reviews of clinical data, consultations with professional societies, and external technology assessments.

While potential outcomes range from full Medicare coverage to non-coverage, Evercore ISI analysts expect a decision somewhere between full coverage and coverage with evidence development. Biogen would not speculate on which of the five possible scenarios it expected, but said there would be a 30-day public comment period, with a final NCD posted by April 12, stressing that final determination could look very different from the draft.

The group is advocating for coverage aligned to the clinical trial patient population, and "that is the outcome that we would like to see". Mr Vounatsos, whose reputation is in many ways riding on Aduhelm, said "anything that starts to provide access in [the US] is very good news. It means that the door is open."

## ADCOM APPROACHES

Meanwhile, in a curtain-raiser to tomorrow's JP Morgan presentation, Bluebird Bio revealed that a US adcom had been scheduled for March 9 for Lentiglobin in beta-thalassaemia, before a May 20 Pdufa date. The gene therapy is approved in the EU for this use as Zynteglo, but trials in sickle cell disease are subject to a partial US hold.

Bluebird recently spun its oncology business into a new company, 2Seventy Bio, which today announced the discontinuation of bb21217, an anti-BCMA Car-T therapy follow-up to Abecma. 2Seventy cited the strength of Abecma's dataset as a reason; bb21217 findings presented at Ash 2020 had suggested marginally better efficacy than Abecma, with meaningfully worse toxicity.

However, yesterday's slew of deals was not enough to lift sentiment around the biotech market; today's updates are unlikely to move the needle either.

*Published on January 11, 2022*

# JP Morgan 2022 – day one sees healthy deal flow from biopharma

BY AMY BROWN, JACOB PLIETH AND LISA URQUHART

But transactions are small, and mostly involve licensing rather than takeouts, with cancer and gene editing featuring heavily.

Over the years many large biopharma deals have been unveiled to coincide with the JP Morgan healthcare conference, a week when the eyes of the sector are squarely focused on San Francisco. Day one of this year's meeting certainly delivered plenty of transaction news, but the absence of any billion-dollar buyouts will disappoint those hoping for a big opener.

The meeting having gone virtual once again, the motivation to grab attendees' attention is understandably waning. Perhaps the flurry of bigger moves announced in late December would, in other years, have been held back. Instead, biopharma watchers must make do with a collaboration between Beam and Pfizer for $300m up front – the largest cheque written today – and several other licensing deals in cancer and gene editing.

One notable exception to this theme was the exercise of an option by Novartis over Molecular Partners' Covid-19 antiviral ensovibep. This appears to have been triggered by encouraging phase 2 data from the Empathy trial, also announced today, showing a 78% reduction in the risk of events.

Ensovibep is delivered via a single intravenous dose so would not be as convenient as the oral antivirals from Pfizer and Merck & Co. Novartis has apparently seen enough to sign on the dotted line, however, with the press release talking up the project's "pan-variant activity". It is also notable that Empathy allowed vaccinated subjects and made no mention of focusing on high-risk patients, features that have undone other Covid-19 antiviral trials.

Elsewhere, it is clear that in vivo gene editing is a big focus for developers, with Beam Therapeutics and Mammoth benefitting from the attentions of Pfizer and Bayer. While Beam claims

greater precision than the conventional Crispr/Cas9 approach, Mammoth boasts an "ultra-small" Crispr system (JP Morgan 2022 – Beam and Mammoth hook big pharma partners, January 10, 2022).

**JP Morgan 2022: selected day one deals**

| Company | Partner/Aquirer | Detail |
|---|---|---|
| Beam Therapeutics | Pfizer | Four-year research collaboration focused on in vivo base editing for rare genetic diseases of the liver, muscle and central nervous system; $300m up front |
| Molecular Partners | Novartis | Novartis exercises its option to license ensovibep, a DARPin-based Covid-19 antiviral, for SFr150 million ($162m); follows previous SFr60m payment |
| Stoke Therapeutics | Acadia Pharmaceuticals | Research collaboration to develop RNA-based medicines for rare genetic CNS disorders including SYNGAP1 and Rett syndrome; $60m up front |
| Century Therapeutics | Bristol Myers Squibb | Research collaboration and licensing agreement for up to four iPSC-derived allogenic cell therapies for haematological and solid tumours; $100m up-front cash, $50m equity investment |
| Carisma Therapeutics | Moderna | Research collaboration to develop up to 12 in vivo engineered chimaeric antigen receptor monocyte (Car-M) therapeutics for cancer; $45m up-front cash, $35m convertible debt |
| Crescendo Biologics | Biontech | Research collaboration based on Crescendo's Humabody VH tech to develop mRNA-based antibodies and engineered cell therapies; $40 million up front, comprising cash and equity |
| Mammoth Biosciences | Bayer | Research collaboration and option agreement for the use of Mammoth's Crispr systems to develop in vivo gene editing therapies; $40m up front |
| Shanghai Junshi Biosciences | Coherus Biosciences | Coherus exercises option to license JS006, Junshi's anti-Tigit MAb, in the US and Canada; deal expands initial 2021 agreement; $35 million up front |
| Adaptate Biotherapeutics | Takeda | Takeda exercises option to buy Adaptate to obtain Adaptate's antibody-based γδ T-cell engager tech, including a preclinical candidate and discovery pipeline programmes; no terms disclosed |
| Novavita Thera | Castle Creek | Acquisition of Novavita, a privately-held preclinical gene therapy company focused on rare liver and metabolic diseases, via in vivo approaches; terms undisclosed |

Source: company releases.

Several of the transactions also involved cell therapies, a field that continues to attract a lot of research dollars. While the Biontech/Cresendo and Bristol/Century deals concern work with T cells, the Takeda and Moderna transactions are focused on more novel approaches.

After the success of Car-T, work on adaptive cell therapies moved into Car-NK, Car-Treg and Car-γδ T cells. The last of those delivered a takeover last year, with Takeda buying out the UK's Gammadelta, and today the Japanese group followed this by acquiring Adaptate Biotherapeutics, a business Gammadelta had earlier spun out.

Adaptate works not on Car-based therapeutics but on antibodies, specifically those that engage γδ T cells. The γδ T-cell field was given a boost last month by the first reports of efficacy from an Adicet project.

A Car-engineered approach involving yet another cell type recorded a separate deal today, with Moderna teaming up with Carisma for development of Car-M therapies. The M in this case stands for monocytes (Carisma separately works on Car-macrophages), and interestingly the deal focuses on in vivo editing, thanks to Moderna's mRNA and LNP knowhow.

Monocytes are a type of white blood cell, but unlike B and T cells they are part of the myeloid not the lymphoid lineage; they can further differentiate into macrophages, and are associated with innate immunity. Directing them at a specific target using a Car could add a further approach to the anticancer armoury.

It is also apparent from today's business development moves that cancer remains high on biopharma's shopping list. In this area Coherus's collaboration with Junshi in particular is notable; the partners already have an anti-PD-1 MAb filed with the FDA, although whether this will win approval on the back of trials conducted in China is a matter of much debate, as with other projects like it (Days of reckoning for immune checkpoint blockers, January 4, 2022).

The transactions highlighted above involved more than half a billion dollars in up-front fees, though of course this is little more than spare change for biopharma. Meanwhile biotech

investors have seen the US bear market deepen further in the opening days of 2022.

To make the sector more appealing they will need M&A activity to pick up substantially. With Fed interest rate hike fears causing a global selloff perhaps it was too much to ask for the JP Morgan conference to reverse sentiment.

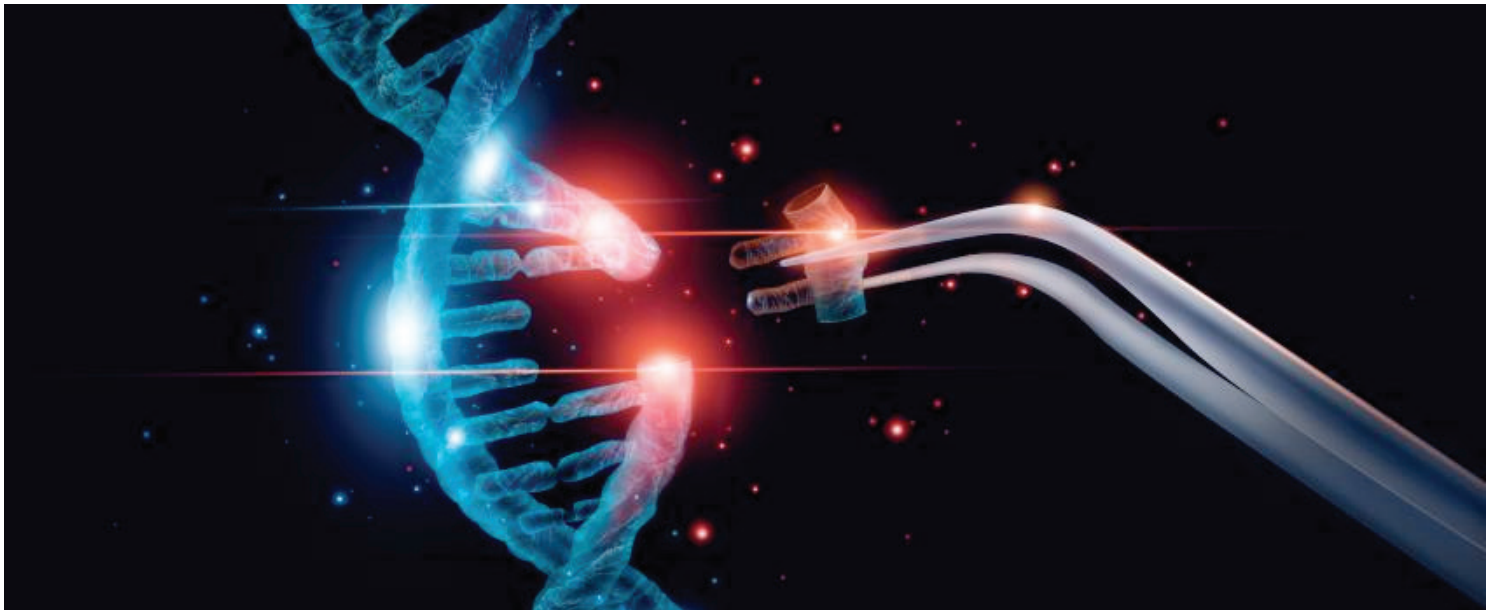
*This story has been updated to include Castle Creek's acquisition of Novavita.*

*Published on January 10, 2022*

# Beam and Mammoth hook big pharma partners

BY MADELEINE ARMSTRONG

Beam signs Pfizer up for $300m up front, while Mammoth's deal with Bayer is worth a more modest $40m.



Some investors believe that 2022 will be the year in which in vivo gene editing eclipses in vitro technology. And some big pharma groups obviously see potential here, with Pfizer and Bayer both announcing deals in the space today.

Pfizer has bet $300m up front on Beam Therapeutics' base-editing technology, which promises greater precision than the conventional Crispr/Cas9 approach. Meanwhile, Bayer is paying $40m to collaborate with Mammoth on its "ultra-small" Crispr systems – joining Vertex, which already has an agreement with the private biotech for a similar sum.

## BEAM ME UP

Details on both partnerships are sparse. Pfizer and Beam will only say that they are targeting three undisclosed rare genetic diseases of the liver, muscle and central nervous system, which are separate from Beam's existing programmes. And the groups will be using mRNA and lipid nanoparticles to deliver base editors to the target organs.

Beam's own in vivo projects primarily target liver diseases, the most advanced being for glycogen storage disorder type 1a. The company also has in vitro projects for sickle cell disease, like various other groups, as well as base-edited Car-T therapies for blood cancers.

Beam is already working with Apellis on in vivo editing for complement-driven diseases, but this agreement is dwarfed by today's deal with Pfizer.

Pfizer has long been interested in gene therapies, but progress has been far from smooth: assets in development for haemophilia A and Duchenne muscular dystrophy are on clinical hold, the latter after the death of a patient in a phase 1b trial. The DMD project, fordadistrogene movaparvovec – which Pfizer gained through the $625m purchase of Bamboo

Therapeutics – had already been linked with severe muscle weakness and myocarditis.

And pivotal results with the Roche-partnered haemophilia B asset, which had once been expected last year, are not due until 2023.

Getting into gene editing – and in vivo gene editing at that – is an obvious next step for Pfizer. The group will have to hope that it has chosen wisely in Beam, which has likened its base-editing approach to a pencil versus the scissors of other gene editing technologies (Interview – Beam heralds new Crispr edit, but patent issues remain, May 17, 2018).

## FAR FROM MAMMOTH

Meanwhile, Mammoth is facing criticism from some quarters for its deals being "underwhelming" in terms of the up-front sums involved – but the group's chief business officer, Peter Nell, defended its agreements.

"You have to put it into perspective," he told Evaluate Vantage. "We're in the discovery phase, and for that stage I think the deal terms are pretty good."

He is adamant that Mammoth is not giving away too much, too cheaply. "That was part of our consideration, that we avoid that. But we cannot do 20 indications [alone]."

Otherwise Mammoth and Bayer are not saying much, apart from that the collaboration will involve five indications with an initial focus on liver disease, and that these do not overlap with the two undisclosed rare diseases covered by the Vertex deal (Vertex goes small with Mammoth deal, October 26, 2021). As with the Vertex tie-up, Mammoth is not disclosing whether the gene editing will be delivered via lipid nanoparticles or more conventional AAV vectors.

The unique selling point with Mammoth's systems is that they use enzymes such as Cas14 and CasΦ, which are much smaller than Cas9. This is particularly relevant for AAV vectors, which have a limit on the size of the cargo they can carry.

Bayer's pharma division first got involved in Crispr/Cas9 gene editing through Casebia, a joint venture with Crispr Therapeutics formed in 2016. However, the German group took a step back in late 2019, and things have been quiet since.

Bayer does have various gene therapy projects in development, via the arm's length acquisitions of Askbio and Bluerock, plus other collaborations (Bayer's gene therapy juggling act, February 5, 2021).

Stefan Oelrich, head of Bayer's pharmaceuticals division, told Vantage over email that Mammoth's technology could be combined with its stem cell-based efforts, as well as being a "standalone IND-generating engine".

Last year Intellia provided the first evidence that in vivo gene editing could work, and the approach is clearly flavour of the month. Next, the partnerships announced today must bear some fruit to help justify the hype.

*Published on January 10, 2022*

# A late Christmas present for Allogene

BY JACOB PLIETH

US clinical hold over Allogene's entire pipeline has just been lifted.

Three months is all it has taken for the FDA to lift its hold on Allogene's clinical pipeline. The news, revealed today just as the JP Morgan conference is getting under way, will be welcomed by investors who had seen 45% of the company's market cap erased since October 8.

This will also come as a relief to other biotechs developing allogeneic Car-T therapies, a field that has moved slowly, and over which Allogene's clinical hold had hung. It was especially worrying that chromosomal abnormalities were involved, but Allogene today revealed that these were unrelated to its gene editing process or manufacturing, and "had no clinical significance".

The company was able to make this assessment, and to convince the FDA of it, thanks to "complex analytical assays that allowed us to interrogate samples, map and sequence inversion site, and facilitate a deep analysis related to various aspects of gene editing and product quality", it told Evaluate Vantage.

Allogene reckons such a process could have taken a year to develop, but it managed to do so in less than three months. Interestingly, the company now sees the fact that it has such assays in place as a competitive advantage, and this has made it increasingly confident of its position.

That said, it will clearly take some time for the company's studies to restart. The hold concerned five trials of five different Car-T projects, and all Allogene will say for now is that these will resume as quickly as possible.

Additionally, a sixth study, a pivotal phase 2 test of ALLO-501A in relapsed/refractory large B-cell lymphoma, is to begin in mid-2022, pending final FDA discussions.

| Allogene's clinical pipeline | | | |
|---|---|---|---|
| **Project** | **Trial** | **Indication** | **Status** |
| ALLO-501A (anti-CD19 without Rituxan switch) | Pivotal ph2 | R/r non-Hodgkin lymphoma | Starting mid-2022 |
| | Alpha-2 | R/r non-Hodgkin lymphoma | Resuming as soon as possible |
| ALLO-501 (anti-CD19 with Rituxan switch) | Alpha | R/r non-Hodgkin lymphoma | Resuming as soon as possible |
| ALLO-715 (anti-BCMA) | Universal | R/r multiple myeloma | Resuming as soon as possible |
| ALLO-316 (anti-CD70) | Traverse | Renal cell carcinoma | Resuming as soon as possible |
| ALLO-605 (anti-BCMA with chimaeric cytokine receptor) | Ignite | R/r multiple myeloma | Resuming as soon as possible |

Source: company website & clinicaltrials.gov.

The hold resulted when "chromosomal abnormality of unclear clinical significance" was detected in ALLO-501A cells in a lymphoma patient in the Alpha-2 trial after this subject underwent bone marrow biopsy to investigate progressive pancytopenia.

It was curious that only some ALLO-501A cells in the patient were affected, and Allogene has now revealed that the abnormality had occurred after the cell product was administered. It was not detected in any of its manufactured allogeneic Car-T products or in any other patient treated with the same lot of ALLO-501A.

Of particular concern was that the abnormality occurred on chromosome 14, which contains the Trac locus that Allogene's Talen nucleases knock out to prevent expression of endogenous T-cell receptors. Thus there was a major worry that Talen gene editing had brought about the chromosomal change.

However, Allogene says the exact site of the inversion, identified by sequencing analysis, was not the Trac locus, or indeed "any other potential Talen gene-editing site", thus apparently clearing the group's manufacturing process of possible involvement. The abnormality can now be said to have involved regions of the T-cell receptor and immunoglobulin genes that naturally undergo rearrangement as part of T cell or B cell maturation.

There will undoubtedly be lessons here for all developers of car-T therapies. Allogene says the data from its investigation into this issue will be published at a future scientific forum.

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