Mark White – Chief Business Officer and Board Member, Annovis Bio



Alzheimer's will not be solved by a single breakthrough, but by layered strategies that combine scientific precision with real-world applicability.

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As the search for effective Alzheimer's treatments continues to evolve, Annovis Bio is taking a distinct approach with buntanetap, a novel oral candidate designed to intervene more broadly in disease progression. In this interview, Chief Business Officer Mark White discusses the company's clinical learnings, operational discipline, and the realities of navigating a high-stakes, high-scrutiny therapeutic area.

How has buntanetap progressed from early research to receiving Phase III authorisation in Alzheimer's disease?

The journey of buntanetap, Annovis Bio's investigational therapy for neurodegenerative disorders, has been marked by both scientific rigour and strategic perseverance. Dr Maria Maccecchini, Founder and CEO of Annovis Bio, licensed the molecule over a decade ago and spearheaded its development from preclinical research through to clinical trials. Her early work focused on Alzheimer's disease and Parkinson's disease, supported by a robust programme of animal studies that provided encouraging initial signals. These findings laid the groundwork for Phase I trials in both indications, which in turn progressed to a successful Phase II study and a subsequent Phase II/III trial in Alzheimer's disease, an ambitious study large enough in scale to approach Phase III standards, though not formally structured as such.

In parallel, a Phase III trial in Parkinson's disease was also undertaken. While the Alzheimer's trial did not meet its two primary endpoints – ADAScog11 and ADCS-CGIC – a significant symptomatic benefit as measured by ADAScog11 emerged within the specific subgroups of early-stage, biomarker-confirmed Alzheimer's patients. These results became the focus of Annovis' engagement with the US Food and Drug Administration (FDA). Following a comprehensive end-of-Phase II meeting, the agency granted clearance to initiate pivotal Phase III trials in Alzheimer's disease, marking a critical inflection point in buntanetap's clinical development.

How did insights from the Phase II/III trial shape Annovis Bio's strategic focus in Alzheimer's disease?

One of the most consequential findings to emerge from the Phase II/III trial was the realisation that a significant proportion of participants, nearly 40 percent, did not have biomarker-confirmed Alzheimer's disease. At the time the study was designed, diagnostic confirmation relied primarily on clinical evaluation, given that PET scans – commonly used in antibody-based trials – were prohibitively costly and burdensome for patients. However, midway through the study, a new blood-based diagnostic assay received approval from FDA, allowing Annovis to retrospectively test all trial participants. This analysis revealed that many had been misclassified, lacking biochemical markers consistent with Alzheimer's pathology.

Further examination of the dataset showed that buntanetap had limited impact on patients in advanced stages of the disease. However, among those who were both biomarker-positive and at an early disease stage, the treatment demonstrated a clear and statistically significant benefit compared to placebo. In this subgroup of early Alzheimer patients, the therapeutic was compelling. These findings not only clarified buntanetap's mechanism of action but also provided a rationale for refining the company's development strategy. The ongoing Phase III trial is now focused exclusively on biomarker-confirmed patients in the early stages of Alzheimer's disease. Significantly, the FDA has indicated that, should this trial deliver strong results, it may – together with prior data – support a regulatory filing for approval.

What is the approach behind the Phase III trial design for buntanetap, and how does Annovis Bio assess its potential market in Alzheimer's disease?

The design of Annovis Bio's Phase III trial for buntanetap strategically combines an initial six-month evaluation with an 18-month continuation to assess both symptomatic relief and potential disease-modifying effects in early Alzheimer's patients. At the six-month point, if the drug shows significant efficacy, Annovis plans to seek approval based on symptomatic improvements. The extended 18-month trial will allow the company to explore the treatment's longer-term impact, positioning it as a potential disease-modifying. While FDA does not distinguish between symptomatic and disease-modifying indications, a prolonged, positive effect over 18 months would suggest that the therapy has a role in altering the course of the disease.

From a commercial perspective, Annovis Bio is primarily targeting the early-stage Alzheimer's population, which represents around half of the total patient pool. While the drug is not intended for advanced stages, there may be an opportunity to use it in moderate cases as well. Given the complexity of Alzheimer's and the absence of a definitive cure, a well-tolerated oral treatment with both symptomatic and potentially disease-modifying properties could capture a significant share of the market, making it a promising therapeutic option in a highly competitive landscape.

How has Annovis Bio refined its clinical operations to optimise the outcome of its Phase III trial?

Annovis Bio has significantly evolved its clinical strategy, drawing on the hard-earned lessons of earlier development phases to ensure the highest standards of execution as it progresses buntanetap through Phase III. A central realisation has been the importance of maintaining adequate internal oversight when working with Contract Research Organisations (CROs). The company had previously advanced its lead candidate through early-stage trials with a highly streamlined team – fewer than 5 employees – relying extensively on external contractors. While this lean model allowed Annovis to operate with agility and efficiency, it also exposed gaps in the direct management of critical trial processes. In response, the organisation has expanded its internal capabilities and now maintains closer, more structured collaboration with CROs to uphold quality, consistency, and regulatory compliance throughout the trial lifecycle.

In parallel, one of the most consequential adjustments has come from the integration of diagnostic advances that were unavailable during prior studies. At the time of earlier trials, there was no accessible, validated biomarker-based diagnostic to confirm Alzheimer's pathology, leading to the inclusion of a significant proportion of misdiagnosed patients. With the recent acceptance of the plasma p-tau217 assay by FDA, Annovis now has the ability to rigorously screen and stratify

participants prior to enrolment. This methodological refinement ensures that only biomarker-confirmed patients are included in the current trial, enhancing its scientific robustness, interpretive clarity, and ultimately, its regulatory credibility.

How is Annovis Bio exploring combination strategies with buntanetap, and what potential do these preclinical findings hold?

Annovis Bio, aligning with the broader scientific consensus that complex neurodegenerative diseases will likely require multi-pronged therapeutic approaches, has undertaken preclinical studies exploring the combination of buntanetap with other pharmacological agents. Under the guidance of Dr Maria Maccecchini, these investigations have focused on two classes of compounds: glucagon-like peptide-1 (GLP-1) receptor agonists – currently used in the treatment of diabetes and obesity – and phosphodiesterase type 5 (PDE-5) inhibitors such as sildenafil (Viagra). In animal models, both combinations have demonstrated superior outcomes compared to either agent used in isolation, suggesting a potential synergistic interaction that enhances therapeutic efficacy. Although these results remain at the preclinical stage, they offer a compelling rationale for further exploration. At present, Annovis does not intend to pursue clinical development of these combinations independently; however, the company remains open to partnering with an organisation capable of advancing these findings into human trials. This openness to collaboration underscores Annovis Bio's broader strategy of leveraging scientific innovation through focused partnerships in order to extend the impact of its lead candidate across multiple treatment paradigms.

How would you assess current investor sentiment in the neurodegeneration field, and how is Annovis Bio approaching strategic partnerships in this context?

Investor sentiment in the Alzheimer's field has seen significant shifts in recent years, driven largely by the approval and subsequent controversy surrounding the first generation of amyloid-targeting monoclonal antibodies. While their regulatory success initially reignited enthusiasm, questions around their clinical utility, limited real-world uptake, and the eventual withdrawal of one early agent have introduced a level of caution across the industry. As a result, large pharmaceutical companies are now more selective, often adopting a conservative stance when evaluating neurodegenerative assets, particularly those where efficacy has been demonstrated primarily in post hoc subgroup analyses.

Against this backdrop, Annovis Bio has positioned buntanetap as a differentiated and potentially complementary therapeutic, with an oral formulation and a broad mechanism targeting multiple neurotoxic proteins. Although interest in the molecule is strong, particularly among mid-sized and large pharmaceutical companies, there remains a clear preference to wait for additional data before engaging in formal partnership discussions. The company has held extensive dialogues with potential partners and is open to multiple models, ideally a global licensing agreement with a single commercial leader, but also regional arrangements if they offer strategic alignment and operational reach.

Patient enrolment in the ongoing Phase III trial is expected to conclude by the end of 2025, with top-line six-month results anticipated by the end of next year. A robust outcome at that point would likely serve as a key inflection, unlocking wider investor confidence and triggering more concrete partnership activity. The final 18-month data, which will be central to determining disease-modifying potential, is expected approximately one year later and may further shape the strategic trajectory for buntanetap’s commercialisation.

How has Annovis scaled its internal capabilities to support late-stage development, and where is the trial being conducted?

To meet the demands of its ongoing Phase III trial, Annovis Bio has carefully expanded its internal capabilities while preserving the agility of a streamlined organisation. From a team that once numbered just four, the company has grown to approximately 15 staff, reflecting deliberate and strategic hiring over the past 18 months. This evolution has allowed Annovis to build the necessary expertise to manage the complexities of late-stage clinical development while maintaining a focused and execution-driven structure. According to Mark White, the team now in place is sufficient to carry out the trial, with no immediate need for further expansion. The emphasis is firmly on execution, ensuring efficient site activation, patient recruitment, and operational oversight. Encouragingly, patient interest in the study has been robust, although the process of getting trial sites up and running remains inherently time-consuming.

In designing the Phase III study, Annovis has opted to concentrate all trial activity within the United States. While the company’s earlier trial included European sites, the logistical and regulatory burdens of managing international operations proved disproportionately demanding for a company of its size. By focusing exclusively on US-based sites, Annovis aims to simplify trial management, ensure tighter control, and avoid the administrative complexities that can often delay progress in

smaller biotechs navigating multinational frameworks. This decision reflects a broader effort to enhance operational efficiency and increase the likelihood of delivering clean, well-controlled data within the projected timelines.

What is your outlook on the Alzheimer's field, and what gives you both concern and optimism moving forward?

A key concern in the Alzheimer's space today is the growing hesitancy among large pharmaceutical companies to fully commit to high-risk innovation in this area. This caution has been fuelled in part by the tempered reception of recently approved monoclonal antibodies, which – despite representing a significant scientific milestone – have faced regulatory scrutiny, commercial challenges, higher than expected side effect profiles, and a slower-than-expected rate of clinical adoption. These setbacks have led some industry leaders to step back, re-evaluate pipeline priorities, and become more conservative in their investment strategies. This reduction in momentum from major players presents a risk of stagnation in a field where progress is both urgently needed and inherently complex.

Yet, there remains strong cause for optimism. Scientific understanding of Alzheimer's disease continues to advance at a steady pace, revealing new pathways, mechanisms, and targets that could lead to more effective treatments. There is increasing consensus that the future of Alzheimer's therapy may lie not in a single intervention, but in combination regimens addressing multiple aspects of disease pathology. This evolution opens the door for smaller, highly focused biotechs to make a meaningful impact, particularly those developing novel compounds that complement existing treatment strategies or serve well-defined patient subgroups. As the field moves toward more personalised, multi-mechanistic solutions, the therapeutic landscape may become more inclusive, dynamic, and innovation-driven, offering renewed hope for patients and new opportunities for scientific and commercial success across the ecosystem.

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