UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

SCHEDULE TO

Tender Offer Statement under Section 14(d)(1) or 13(e)(1)
of the Securities Exchange Act of 1934

Alpine Immune Sciences, Inc.
(Name of Subject Company (issuer))

Adams Merger Sub, Inc.
(Offeror)
a wholly-owned subsidiary of

Vertex Pharmaceuticals Incorporated
(Parent of Offeror)
(Names of Filing Persons (identifying status as offeror, issuer or other person))

Common stock, $0.01 par value per share
(Title of Class of Securities)

92532F100
(CUSIP Number of Class of Securities)

Jonathan Biller
Executive Vice President, Chief Legal Officer
Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, Massachusetts 02210
Telephone: (617) 341-6100
(Name, address, and telephone numbers of person authorized to receive notices and communications on behalf of filing persons)

Copy to:

Graham Robinson
Skadden, Arps, Slate, Meagher & Flom LLP
500 Boylston Street
Boston, MA 02116
(617) 573-4850

Faiz Ahmad
Skadden, Arps, Slate, Meagher & Flom LLP
1 Rodney Square, P.O. Box 636
Wilmington, DE 19899
(302) 651-3250

CALCULATION OF FILING FEE

Transaction Valuation*	Amount of Filing Fee*
N/A	N/A

* A filing fee is not required in connection with this filing as it relates solely to preliminary communications made before the commencement of the tender offer.

☒ Check the box if the filing relates solely to preliminary communications made before the commencement of a tender offer.

Check the appropriate boxes below to designate any transactions to which the statement relates:

☒ Third-party tender offer subject to Rule 14d-1.
☐ Going-private transaction subject to Rule 13e-3.
☐ Issuer tender offer subject to Rule 13e-4.
☐ Amendment to Schedule 13D under Rule 13d-2.

Check the following box if the filing is a final amendment reporting the results of the tender offer: ☐

If applicable, check the appropriate box(es) below to designate the appropriate rule provision(s) relied upon:

☐ Rule 13e-4(i) (Cross-Border Issuer Tender Offer).
☐ Rule 14d-1(d) (Cross-Border Third-Party Tender Offer).

This Tender Offer Statement on Schedule TO relates solely to preliminary communications made before the commencement of a planned tender offer by Adams Merger Sub, Inc., a Delaware corporation ("Merger Sub") and wholly-owned subsidiary of Vertex Pharmaceuticals Incorporated, a Massachusetts corporation ("Parent"), for all of the outstanding shares of common stock of Alpine Immune Sciences, Inc., a Delaware corporation (the "Company"), pursuant to the Agreement and Plan of Merger, dated as of April 10, 2024 (the "Merger Agreement"), among Parent, Merger Sub and the Company.

Additional Information and Where to Find It

The tender offer for the outstanding shares of common stock of the Company referenced in this communication has not yet commenced. This communication is for informational purposes only and is neither an offer to purchase nor a solicitation of an offer to sell shares of the Company, nor is it a substitute for any tender offer materials that Parent, or the Company will file with the Securities and Exchange Commission ("SEC"). At the time the tender offer is commenced, Parent will file with the SEC a Tender Offer Statement on Schedule TO which will include an Offer to Purchase, a related Letter of Transmittal and certain other tender offer documents (together, the "Tender Offer Materials"), and the Company will file with the SEC a Solicitation/Recommendation Statement on Schedule 14D-9 (the "Solicitation/Recommendation Statement") with respect to the tender offer. THE COMPANY'S SECURITY HOLDERS ARE URGED TO READ THE TENDER OFFER MATERIALS AND THE SOLICITATION/RECOMMENDATION STATEMENT WHEN THEY BECOME AVAILABLE BECAUSE THEY WILL CONTAIN IMPORTANT INFORMATION WHICH SHOULD BE READ CAREFULLY BEFORE ANY DECISION IS MADE WITH RESPECT TO THE TENDER OFFER. The Tender Offer Materials, as well as the Solicitation/Recommendation Statement, will be sent to all stockholders of the Company at no expense to them. The Tender Offer Materials and the Solicitation/Recommendation Statement will be made available for free at the SEC's website at www.sec.gov. Additional copies may be obtained free of charge under the "Investors" section of Parent's website at https://investors.vrtx.com/financial-information/sec-filings or by contacting Parent by email at Investorinfo@VRTX.com, or by directing requests for such materials to the information agent for the offer, which will be named in the Tender Offer Materials. In addition to the Tender Offer Materials and the Solicitation/Recommendation Statement, the Company and Parent file periodic reports and other information with the SEC. Parent's and the Company's filings with the SEC are also available for free to the public from commercial document-retrieval services and at the website maintained by the SEC at www.sec.gov and their respective investor relations websites at the addresses above.

Cautionary Statement Regarding Forward-Looking Statements

This communication contains forward-looking statements related to Parent, the Company and the proposed acquisition of the Company by Parent (the "Transaction") that are subject to risks, uncertainties and other factors. While Parent believes the forward-looking statements contained in this communication are accurate, these forward-looking statements represent Parent's belief only as of the date of this communication, and there are a number of risks and uncertainties that could cause actual events or results to differ materially from those expressed or implied by such forward-looking statements. All statements other than statements of historical fact are statements that could be deemed forward-looking statements, including all statements regarding the intent, belief or current expectation of the companies' and members of their senior management teams. Forward-looking statements are not purely historical and may be accompanied by words such as "anticipates," "may," "forecasts," "expects," "intends," "plans," "potentially," "believes," "seeks," "estimates," and other words and terms of similar meaning. Such statements may relate to: the ability of Parent to advance the Company's platform technology and potential therapies, such as povetacicept, on a timely basis; filings and approvals relating to the Transaction; the expected timing of the completion of the Transaction; the ability to complete the Transaction considering the various closing conditions; difficulties or unanticipated expenses in connection with integrating the companies; and any assumptions underlying any of the foregoing.

Forward-looking statements are subject to certain risks, uncertainties, or other factors that are difficult to predict and could cause actual events or results to differ materially from those indicated in any such statements due to a number of risks and uncertainties. Those risks and uncertainties that could cause the actual results to differ from expectations contemplated by forward-looking statements include, among other things: uncertainties as to the timing of the Transaction; uncertainties as to how many of the Company's stockholders will tender their stock in the offer; the

possibility that competing offers will be made; the possibility that various closing conditions for the Transaction may not be satisfied or waived, including that a governmental entity may prohibit, delay or refuse to grant approval for the consummation of the Transaction; the effects of the Transaction on relationships with employees, other business partners or governmental entities; the difficulty of predicting the timing or outcome of FDA approvals or actions, if any; the impact of competitive products and pricing; that Parent may not realize the potential benefits of the Transaction; other business effects, including the effects of industry, economic or political conditions outside of the companies' control; Transaction costs; and actual or contingent liabilities related to the Transaction. In addition, the product candidates being developed by the Company are subject to all the risks inherent in the drug development process, and there can be no assurance that the development of these product candidates will be commercially successful. Forward-looking statements in this communication should be evaluated tother with the many uncertainties that affect Parent's and the Company's businesses, particularly those risks listed under the heading "Risk Factors" and the other cautionary factors discussed in the parties' periodic reports filed with the SEC, including Parent's annual report on Form 10-K for the year ended December 31, 2023, and its quarterly reports on Form 10-Q and current reports on Form 8-K, and the Company's annual report on Form 10-K for the year ended December 31, 2023, and its quarterly reports on Form 10-Q and current reports on Form 8-K, as well as the Solicitation/Recommendation Statement to be filed by the Company and the Tender Offer Materials to be filed by Parent and Merger Sub, a direct wholly owned subsidiary of Parent, all of which are available, or will be available when filed, for free on the SEC's website at www.sec.gov. You should not place undue reliance on these statements. All forward-looking statements are based on information currently available to Parent, and Parent disclaims any obligation to update the information contained in this communication as new information becomes available, except as required by law.

Item 12. Exhibits

Exhibit No.	Description
Exhibit 99.1	Transcript of Investor Presentation Call on April 10, 2024.

APRIL 10, 2024 / 8:30PM, VRTX.OQ - Vertex Pharmaceuticals Inc Enters Into Agreement to Acquire Alpine Immune Sciences- Conference Call

CORPORATE PARTICIPANTS

Charles F. Wagner *Vertex Pharmaceuticals Incorporated - Executive VP & CFO*

Jeffrey Marc Leiden *Vertex Pharmaceuticals Incorporated - Executive Chairman*

Reshma Kewalramani *Vertex Pharmaceuticals Incorporated - CEO, President & Director*

Stuart A. Arbuckle *Vertex Pharmaceuticals Incorporated - Executive VP & COO*

Susie Lisa *Vertex Pharmaceuticals Incorporated - SVP of IR*

CONFERENCE CALL PARTICIPANTS

Alexandria Hammond *BofA Securities, Research Division - Associate*

Christopher Joseph Raymond *Piper Sandler & Co., Research Division - MD & Senior Research Analyst*

David Reed Risinger *Leerink Partners LLC, Research Division—Senior MD & Senior Research Analyst*

Elias Nicholas Lenard *JPMorgan Chase & Co, Research Division - Research Analyst*

Evan David Seigerman *BMO Capital Markets Equity Research - MD & Senior BioPharma Research Analyst*

Gao Yi Chen *Wolfe Research, LLC - Biotech Analyst*

Liisa Ann Bayko *Evercore ISI Institutional Equities, Research Division - MD & Fundamental Research Analyst*

Mohit Bansal *Wells Fargo Securities, LLC, Research Division - Senior Equity Analyst*

Salveen Jaswal Richter *Goldman Sachs Group, Inc., Research Division - VP*

PRESENTATION

Operator

Good day, and welcome to the Vertex Pharmaceuticals conference call. (Operator Instructions) I would now like to turn the conference over to Ms. Susie Lisa. Please go ahead, ma'am.

Susie Lisa - *Vertex Pharmaceuticals Incorporated - SVP of IR*

Thanks, Chuck. Good afternoon, all, and thanks for joining us on short notice for this exciting announcement. My name is Susie Lisa, and as the Senior Vice President of Investor Relations, it is my pleasure to welcome you to this conference call to discuss Vertex's acquisition of Alpine Immune Sciences.

Making prepared remarks on today's call, we have Dr. Jeffrey Leiden, Executive Chairman of Vertex; Dr. Reshma Kewalramani, Vertex's CEO and President; and Charlie Wagner, Chief Financial Officer. Stuart Arbuckle, our Chief Operating Officer, will be joining us for Q&A.

We recommend that you access the webcast slides as you listen to this call. The call is being recorded, and a replay will be available on our website.

We will be making forward-looking statements on this call that are subject to the risks and uncertainties discussed in detail in today's press release and in our filings with the Securities and Exchange Commission. These statements, including, without limitation, those regarding Vertex's marketed medicines for cystic fibrosis, sickle cell disease and beta thalassemia, our pipeline and Vertex's future financial performance are based on management's current assumptions. Actual outcomes and events could differ materially.

I would also note that select financial guidance that we will discuss on the call this evening is presented on a non-GAAP basis.

Please consult our forward-looking statements on Slide 2 and see our filings for more information.

I'll now turn things over to Reshma.

Reshma Kewalramani - *Vertex Pharmaceuticals Incorporated - CEO, President & Director*

Thanks, Susie, and good afternoon, all. We are very pleased to announce that we've entered into a definitive agreement to acquire Alpine Immune Sciences for $65 per share in cash in a transaction valued at approximately $4.9 billion.

Alpine brings to Vertex its lead asset, povetacicept or pove, a Phase III-ready molecule in IgA nephropathy or IgAN.

Pove is also a molecule that holds a pipeline-in-a-product potential in a number of other serious immune renal diseases and cytopenias, protein engineering and immunotherapy expertise along with a strong talent and culture aligned with Vertex's focus on innovation and serving patients.

We see this acquisition of Alpine as just the right fit with just the right assets at that just the right phase of development where Vertex can add value. Vertex's capabilities can accelerate pove's development in IgAN and other indications while Alpine adds protein engineering and immunotherapy expertise to Vertex. We are excited to work with the Alpine team, and together, advanced pove into Phase III in IgAN and bring it to more patients faster.

As many of you know, Jeff Leiden, my predecessor and Executive Chairman at Vertex, the Vertex executive team and I have continued to work together over the past 4 years on external innovation and business development. Jeff is uniquely experienced in immunology and working on medicines with pipeline-in-a-product opportunity, having brought HUMIRA to Abbott via the Knoll acquisition.

Let me now turn over the call to Jeff and ask him to provide additional color on this opportunity, and most importantly, the science behind povetacicept and the protein engineering and immunology expertise at Alpine.

Jeffrey Marc Leiden - *Vertex Pharmaceuticals Incorporated - Executive Chairman*

Thanks, Reshma. Good afternoon, all. I'm really happy to be here today and to share my thoughts about the Alpine acquisition and our excitement behind the science and the product. One of the keys to Vertex's success over the years is a mindset that embraces both internal and external innovation, and you can see that reflected in the pipeline today with about 40% of our clinical stage pipeline derived from partnerships, in-licensing of assets and acquisitions, including deals with CRISPR, Moderna and Semma.

When evaluating R&D opportunities, external or internal, we're looking to create first-in-class or best-in-class medicines for serious diseases in areas of high unmet need. And when considering acquisitions, we're equally focused on the R&D pipeline, the science and the people.

In Alpine, we see extraordinary strength across all of these dimensions. Specifically and as Reshma will discuss in greater detail, the key elements that lead to our enthusiasm and our conviction to acquire Alpine are: first, Phase III-ready pove with best-in-class potential in IgAN; second, pipeline-in-a-product potential in multiple serious immune renal diseases and cytopenias; third, Alpine's protein engineering and immunology expertise; and lastly, talented people and a great corporate cultural fit.

We're particularly excited about this transaction because we believe strongly that Vertex's capabilities will accelerate pove's development and bring this potential best-in-class medicine to patients faster while adding important protein engineering and immunotherapy expertise to Vertex's toolbox.

By way of its mechanism of action, dual inhibition of BAFF and APRIL, which interdict on different parts of the B cell maturation and proliferation pathway, pove holds the promise of a pipeline-in-a-product for a number of B cell-driven serious diseases. This reminds me very much of the potential we saw in HUMIRA in the early days of biologics for the treatment of autoimmune diseases.

Alpine's approach with pove is dual inhibition of the BAFF and APRIL pathways. Some perspective on the mechanism of action and why dual inhibition is so important. Pathogenic B cells are drivers of multiple autoimmune diseases, including IgAN, and multiple studies have shown that BAFF and APRIL play critical roles in the activation, differentiation and survival of B cells. There's both human genetic validation and pharmacologic validation that the BAFF and APRIL pathways are implicated in IgAN and inhibiting BAFF and APRIL leads to therapeutic benefit. Furthermore, targeting both BAFF and APRIL is likely to lead to greatest efficacy.

Alpine has brought forward an asset in pove that not only inhibits both BAFF and APRIL, but does this with high affinity and potency. In preclinical studies, this increased potency has manifested in superior efficacy in biochemical and B cell assays as well as animal models of disease.

Lastly, I want to highlight Alpine's protein engineering and immunology experience in the directed evolution of immune proteins and multi-targeted therapeutics, which can be used against a variety of relevant targets. This will be important as we utilize Alpine's protein engineering technology to advance Alpine-identified diseases as well as in Vertex sandbox diseases such as gentler conditioning of sickle cell disease and beta thalassemia for CASGEVY and immune evasion of allogeneic stem cell-derived islets in our type 1 diabetes programs.

With that, let me turn the call back over to Reshma.

Reshma Kewalramani - *Vertex Pharmaceuticals Incorporated - CEO, President & Director*

Thanks, Jeff. Slide 5 provides an overview of Alpine Immune Sciences. Alpine is headquartered in Seattle and was founded in 2015 to focus on the development of protein-based immunotherapies for autoimmune and inflammatory diseases and has made impressive progress. Their lead asset, povetacicept, discovered internally through Alpine's own protein engineering platform has already demonstrated proof of concept in IgAN and is on track to enter Phase III in IgAN in the second half of this year and is in 2 Phase Ib/II basket studies in multiple other diseases.

The renal basket study includes IgAN, primary membranous nephropathy, lupus nephritis and ANCA-associated disease.

The immune cytopenias basket study includes idiopathic thrombocytopenia, warm hemolytic anemia and cold agglutinin disease.

Not only has Alpine made tremendous progress clinically with its lead asset demonstrating best-in-class potential through Phase II development and is already Phase III-ready in IgAN, but with the innovative basket design of the Phase Ib/II studies, there are likely to be multiple additional clinical data readouts this year in immune renal diseases and cytopenias providing the opportunity for rapid advancement assuming the data are supportive.

We look forward to welcoming the talented team at Alpine to Vertex.

As you may have seen, this afternoon Alpine released updated data on povetacicept in IgAN from their ongoing RUBY-3 clinical trial, which will also be presented in a late-breaking poster at the World Congress of Nephrology next week. We have seen these data and they are impressive. Alpine leadership is hosting a conference call today at 5:15 Eastern Time to review the data in more detail.

As Jeff mentioned, we see Alpine as an excellent strategic fit for Vertex. Vertex's strategy is disease-focused as we aim to deliver transformative benefits to patients with serious diseases and to do this through efficient regulatory pathways and a specialty sales and marketing model.

IgAN fits the strategy perfectly. It is a serious disease with high unmet need and there are no approved therapies that target its underlying cause. BAFF and APRIL are validated targets in IgAN, both genetically and pharmacologically. And by targeting both, we believe we can potentially deliver a transformative therapy for patients with IgAN. There are biomarkers that can facilitate rapid development of a therapy, and we see an efficient regulatory pathway and we believe we can serve patients very well with the specialty infrastructure.

Beyond IgAN, povetacicept's mechanism of action is applicable to a number of other diseases and it is already in clinical trials in a number of these disease areas such as membranous nephropathy, lupus nephritis and autoimmune cytopenias. With our expertise and resources in development, regulatory and commercialization, we have the opportunity to further accelerate povetacicept's development so as to reach more patients faster. In addition, Alpine's expertise in protein engineering and immunotherapy will add important new capabilities to Vertex's toolbox.

Slide 7 provides more information on IgA nephropathy and why it fits so well with Vertex. There are approximately 130,000 patients in the U.S. with IgAN and many more globally who currently do not have a therapy that targets the underlying cause of their disease.

IgAN is a serious, progressive potentially life-threatening chronic kidney disease and the most common form of glomerulonephritis. Most patients are diagnosed before the age of 40 and more than 1/3 will progress to end-stage renal disease, that is to say, kidney failure within 20 years. Even with the best standard of care today, which includes ACE inhibitors, ARBs and steroids, most patients' kidney function continues to decline as these agents do not prevent the progression to end-stage renal disease.

We believe that a highly potent dual inhibitor of BAFF and APRIL, like pove, can provide transformative benefit to patients by addressing the underlying pathophysiology of IgAN. Given a large number of patients with this disease, the serious and relentlessly progressive nature of the condition and the high unmet need, IgAN presents a large market opportunity, and in medicine, with the profile of pove, has multibillion dollar potential.

With this background, let me now focus on povetacicept on Slide 8. Pove is a novel, highly potent and effective dual BAFF and APRIL inhibitor that has been shown to have best-in-class potential. In multiple preclinical models, povetacicept demonstrated high affinity for BAFF and APRIL as well as effective B cell inhibition and depletion, suggestive of a differentiated profile with strong clinical efficacy potential.

You can hear from Alpine on their call tonight for more details on the updated data from the ongoing RUBY-3 trial. Last November, they showed promising reductions in proteinuria of more than 50% at approximately 6 months of treatment. And the latest data from RUBY-3 with pove 80 milligrams shows continued decline in proteinuria of greater than 60% at 36 weeks. And it appears that the decrease has not yet plateaued with the potential for continued improvement out to 48 weeks.

Again, we leave further commentary on the data to Alpine, but today's updated data from RUBY-3 with more patients and longer follow-up further demonstrate pove's transformative potential with best-in-class efficacy as assessed by reductions in proteinuria, hematuria, stabilization of GFR and remission in patients treated over a longer period of time.

Povetacicept has also been well tolerated in all its studies to date with no severe infections.

Lastly, of note and not to be underestimated in the biologics market, dosing interval, route of administration and volume are all important considerations and differentiators for patients and health care providers. Povetacicept is administered every 4 weeks subcutaneously with a small volume injection.

Switching now to Slide 9 and focusing on the potential of pove as a pipeline-in-a-product. Povetacicept is already in 2 Phase Ib/II basket clinical trials. RUBY-3 is in serious immune-mediated kidney diseases and RUBY-4 in autoimmune cytopenias. We look forward to reading out the data from a number of these studies later this year.

I'll now turn over the call to Charlie to cover the financial terms of the transaction and provide some closing remarks.

Charles F. Wagner - *Vertex Pharmaceuticals Incorporated - Executive VP & CFO*

Thanks, Reshma. As previously mentioned, Vertex is acquiring Alpine for $65 a share in cash in a transaction valued at $4.9 billion. We will fund this acquisition through cash on hand and expect to complete it this quarter subject to certain customary conditions.

This transaction is consistent with Vertex's capital allocation priorities, which remain focused on internal and external innovation in disease areas where we can provide a transformative benefit to patients. As you've heard from Reshma and Jeff, given its transformative potential in a disease area with high unmet need, we see multibillion-dollar opportunity for povetacicept in IgAN alone and we look forward to exploring its full potential in other serious diseases.

Vertex 2024 non-GAAP OpEx guidance of $4.3 billion to $4.4 billion as of February 6 remains unchanged for Alpine OpEx, excluding the potential impacts of transaction accounting, which will be determined upon closing. Note that Alpine operating expenses were $30 million in the fourth quarter of 2023 and $103 million for full year 2023, including the cost of being a public company. Their ongoing costs for the remainder of 2024 can be absorbed in our OpEx guidance range for the year.

Post close, we aim to leverage Vertex clinical regulatory and commercial capabilities to accelerate development and commercialization of pove and are targeting approval in IgAN in 2027. With significant revenue potential, povetacicept can bring - can begin to contribute to Vertex's revenue growth and diversification in 2028, while a highly attractive margin and commercial profile adds to profitability thereafter.

So to wrap up, we find the acquisition of Alpine Immune Sciences a highly compelling fit with Vertex's strategy. Alpine's lead asset, povetacicept, has demonstrated best-in-class potential in IgAN and is ready to enter Phase III in the second half of this year. Beyond IgAN, pove holds the potential as a pipeline-in-a-product.

Vertex capabilities can accelerate pove development in IgAN and other indications, and Alpine's expertise in protein engineering and immunology add to the Vertex toolbox.

Finally, we see strong alignment of our innovation and patient-centric cultures.

We look forward to providing you with more details and news of our progress over the coming quarters. With that, we'll be happy to take your questions.

QUESTIONS AND ANSWERS

Operator

(Operator Instructions) Our first question will come from Geoff Meacham with Bank of America.

Alexandria Hammond - *BofA Securities, Research Division - Associate*

This is Alex Hammond on for Geoff Meacham. Congrats on the deal. Is today's acquisition marking a change in Vertex BD strategy? And should we expect similar deals in the future? And finally, can you talk about your capacity to do future deals?

Reshma Kewalramani - *Vertex Pharmaceuticals Incorporated - CEO, President & Director*

I heard the first part of your question around Vertex's strategy. First, thanks for the kind words. Vertex has been interested in deploying our capital towards innovation, both internal and external, for a long time. And I'm going to sound like a broken record on this, but nothing has changed.

Alpine presents this really special opportunity to bring into Vertex a Phase III-ready asset in a Vertexian disease, IgA nephropathy. It brings also this pipeline-in-a-product for multiple other serious diseases that are also Vertexian. And it brings to us protein engineering and immunology experience as well as talented people. This is just a win-win-win all around.

Alexandria Hammond - *BofA Securities, Research Division - Associate*

Could you just comment a little bit on any future deals that we might expect and the capacity there as well?

Charles F. Wagner - *Vertex Pharmaceuticals Incorporated - Executive VP & CFO*

Yes. I don't think you should read anything into this. We've been very disciplined as we've pursued our BD strategy, and it's very consistent with the corporate and research strategy. This was just the right deal at the right time and the right fit.

We did fund it from the balance sheet. We continue to have significant flexibility. This purchase price represents roughly 1x non-GAAP EBITDA. So we'll just continue with the strategy that's served us so well in recent years.

Operator

The next question will come from Jessica Fye with JPMorgan.

Elias Nicholas Lenard - *JPMorgan Chase & Co, Research Division - Research Analyst*

This is Nick on for Jess. Congrats again on the deal. Maybe two from us. First one on pove, how do you think about the correlation between proteinuria and eGFR and IgAN? And what gives you confidence in this eGFR differentiation based on what you've seen to date and kind of thinking about generally in the context of what docs ultimately think is the most important.

Reshma Kewalramani - *Vertex Pharmaceuticals Incorporated - CEO, President & Director*

Yes. Thanks for the kind words. Let me put my nephrology hat on and tell you one of the reasons that this — the data that Alpine is going to share later today is so important is because it's longer duration of treatment with more patients and you really start to see the profile of pove emerge.

Proteinuria in IgAN is one of the accepted accelerated endpoints, so that's really great. But as a nephrologist, the other elements that I look for is hematuria. One of the seminal findings in a patient with IgA nephropathy is hematuria, and the absence of hematuria is a really positive sign and it's being included more and more in the clinical remission definition. So what I'm looking for here is the improvements in proteinuria and now we're up to greater than 60%, and that hasn't even plateaued yet. We're looking at hematuria that's remitting, and we're looking at a stabilizing of GFR. This is really very impressive and best-in-class from what we can see today.

Elias Nicholas Lenard - *JPMorgan Chase & Co, Research Division - Research Analyst*

Great. And maybe just one follow-up. Can you just kind of talk about a little bit the potential Phase III design here? And is that 2027 approval you mentioned, what endpoint is that based on the Phase III design?

Reshma Kewalramani - *Vertex Pharmaceuticals Incorporated - CEO, President & Director*

I'll have a lot more to say about the Phase III design and time lines after the deal closes. But you should expect this to be a fairly standard study of povetacicept on top of standard of care versus placebo on top of standard of care. And in this disease area, as I said, the regulators are very open to proteinuria as an accelerated endpoint, and so of course, we'd be looking to make that pathway available for pove approval.

Operator

The next question will come from Salveen Richter with Goldman Sachs.

Salveen Jaswal Richter - *Goldman Sachs Group, Inc., Research Division - VP*

Reshma, as you looked at this asset and evaluated it, you talked about the profile and you suggested best-in-class here. Can you just put the drug in the context of how it looks versus competitors out there, your comfort with the dose work that's been done to date? And then how you think about the probability of success in terms of read-through to the other indications here?

Reshma Kewalramani - *Vertex Pharmaceuticals Incorporated - CEO, President & Director*

Yes, yes. Sure thing. So Salveen, the reason I think of this molecule as best-in-class comes from the preclinical data, the clinical data through Phase II and the attributes of the molecule itself so let me double click on each of those.

The really important thing to know about pove is that it's a dual APRIL/BAFF inhibitor and the characteristics preclinically are that it is potent and it has high affinity. And the data that we've seen preclinically in models of an animal models of disease and in B-cell human cell models, it looks to be best-in-class.

Then moving to the clinical realm. In through Phase II data and now we've seen a number of patients over the latest time point is 48 weeks, proteinuria that starts to decrease by week 12. And by 48 weeks, we're up to greater than 60% protein reduction and it doesn't look like it's plateaued yet. So we have one patient out further than that and that looks like a greater than 70% reduction, but that's just one patient's worth of data.

The other numbers that I look at are the hematuria, the GFR and this concept of clinical remission.

And then when I extend it out to the other disease areas, Salveen, one of the reasons I like this deal so much and we're so pleased with what we've seen is that these diseases are genetically validated diseases and sometimes both genetically and pharmacologically validated diseases. So I take a lot of enthusiasm and I have high conviction across these diseases, which are all B cell-mediated diseases.

And remember, pove, as Jeff talked about, hits the B cell maturation and proliferation pathway at 2 points, which is what I think leads to this very good-looking efficacy and safety profile.

Operator

The next question will come from Andy Chen with Wolf.

Gao Yi Chen - *Wolfe Research, LLC - Biotech Analyst*

Congratulations to both teams. So just looking at the indications, I'm wondering if you can talk about prioritization because in addition to IgAN, there are also multiple other indications. Can you maybe rank order some of these that you're more interested in? Or maybe are you pursuing all of these together simultaneously in Phase II and Phase IIIs?

And also a slightly related question. So povetacicept, there was a presentation a few days ago talking about how distribution is very high in the kidney. I'm just wondering if you can talk about whether that really derisks the lupus nephritis or SLE and how you're thinking about these 2 indications.

Reshma Kewalramani - *Vertex Pharmaceuticals Incorporated - CEO, President & Director*

Yes. Sure thing, Andy. Let me break this up into two questions: one around the preclinical immunologic basis of this therapy, Jeff is the best immunologist I know and he happens to be sitting next to me, so I'll ask Jeff to talk about that; and then I'll come back and tell you a little bit about the indications in clinical development. Jeff?

Jeffrey Marc Leiden - *Vertex Pharmaceuticals Incorporated - Executive Chairman*

Thanks, Reshma. You clearly don't know enough immunology. So let me start a little bit on the preclinical profile, if you will, of the molecule and then turn it back to Reshma for the clinical profile.

As you know, pove was engineered by Alpine to be higher affinity for both BAFF and APRIL and we think that's very important. It's a dual inhibitor, so it hits the pathway twice. We think that's very important. So those are sort of the scientific and theoretical bases.

But then when you look at the molecule in biochemical assays, B cell assays and animal models, all of that plays out very nicely.

And finally, as Reshma mentioned, the PK and PD of the molecule looks very, very good. Once a month dosing with very good PD with a very small volume, that really matters in these kinds of markets. And if you compare that to many of the other inhibitors out there that are once a week or twice a week, we think from a clinical, patient and commercial standpoint, those things will play out very, very nicely as we bring the drug to market.

So Reshma, maybe I'll turn it back to you for the clinical data.

Reshma Kewalramani - *Vertex Pharmaceuticals Incorporated - CEO, President & Director*

Yes. So Andy, one of the reasons you heard me say in my prepared remarks that we look forward to working with the Alpine team to accelerate the development is the very question you asked. Vertex brings to this resources and expertise in development, regulatory and commercialization. And I am looking forward to investment behind each of these indications as the data cards are turned over, and I expect the data cards to be positive based on the biology and what you heard Jeff talk about in terms of how pove works.

Operator

The next question will come from Liisa Bayko with Evercore ISI.

Liisa Ann Bayko - *Evercore ISI Institutional Equities, Research Division - MD & Fundamental Research Analyst*

Unlike some of your other products where you've been first to market, in this case, you're going to be coming behind. There's a couple of other products ahead, including one from Otsuka and other from Vera. Can you just tell us how you're thinking about the strategy of coming in as a third entrant there? That's my first question.

Reshma Kewalramani - *Vertex Pharmaceuticals Incorporated - CEO, President & Director*

Yes. So Liisa, two things to talk about here. One — maybe three things to talk about here. Let's first separate out IgA nephropathy, then let's talk about pove and then let's talk about the breadth of indications. Okay.

So first, let me tackle IgA nephropathy. This is a very significant disease. There's more than 100,000 people in the U.S. and more than 3x that number when you count up the global prevalence. And despite the fact that it's an aggressive disease — it's a disease of young people that within 20 years more than 1/3 of patients will go on to dialysis, there is no therapy that treats the underlying call, so high unmet need.

And when you think then about that kind of large market, that kind of unmet need, now let me talk about pove. Compared to the other molecules that appear to be in this class, I would think very carefully and separate out the BAFF-only molecules and the APRIL-only molecules. And then I think about the subgroup then that's BAFF plus APRIL. In the BAFF plus APRIL, this is best-in-class. And BAFF plus APRIL, from everything that we can see for the reason that it interdicts on the B cell maturation and proliferation pathway in 2 places, is best-in-class.

So when I think about the size of the market and the fact that this is a best-in-class dual, you've got to separate out the individuals, I see us being very successful in bringing a therapeutic that has huge value to patients.

I'm going to make one more comment and I'll ask Stuart to comment on these kinds of markets. But my last comment is, when you look at the breadth of indications that some of the molecules that you mentioned are pursuing and the breadth of indications already in Phase II development for pove, it is seismically different. The breadth of indications is very comprehensive for pove and it is because of the conviction based on dual BAFF inhibition. Some of these diseases — probably all of the ones that you see on the chart are going to benefit from BAFF plus APRIL inhibition.

Stuart, I'll turn it over to you for your comments.

Stuart A. Arbuckle - *Vertex Pharmaceuticals Incorporated - Executive VP & COO*

Yes. The only thing I'll add, Liisa, is the attributes that Reshma's described, that dual antagonism, the potency, the affinity and also the drug-like properties of povetacicept, we believe leads it to have the potential to be best-in-class both in terms of clinical profile, efficacy, tolerability but also other important attributes like dosing frequency and volume, which are particularly important in chronic markets like these.

And so as a result of that, we think we've got a drug which has the potential to have a best-in-class profile, and in my experience, best-in-class entrants tend to win even if they're not first-in-class. And Jeff referenced HUMIRA in his prepared remarks, that's probably the poster child for something that came to market, was not the first entrant in its class, but had a superior profile and went on to win the day.

Liisa Ann Bayko - *Evercore ISI Institutional Equities, Research Division - MD & Fundamental Research Analyst*

Fair enough. And can I just ask one more question? I think this is a great group to ask this out, but there's always been this debate in the IgA nephropathy space about really the contribution of BAFF and is APRIL alone enough and I would just be curious on how you think about that. And how — if that is contributing something special to IgAN, how you can show that clinically?

Reshma Kewalramani - *Vertex Pharmaceuticals Incorporated - CEO, President & Director*

Yes. Liisa, it's such a great question and you're right about the conversations in the renal field about contribution of BAFF and APRIL.

Let me just make the most important point first. In all of the data that we've seen, including in human cells preclinically, in disease models preclinically and the data through Phase II development BAFF plus APRIL and pove in particular, shows better efficacy than anything else we've seen: proteinuria, hematuria and on clinical remission.

My impression of this and my summary of this would be the following: BAFF is really important in the mesangium and I think you will see the impact of that when we look at GFR over time and I think it's going to be very important as you look at hematuria. But I do think that there is relevance of BAFF and much has been written about this. I think that the data seen to date is because of the BAFF plus APRIL inhibition versus APRIL alone, and you know that there is existing molecules that are BAFF alone. But the efficacy here is far superior to that.

Liisa Ann Bayko - *Evercore ISI Institutional Equities, Research Division - MD & Fundamental Research Analyst*

Great. Well, congratulations on the deal.

Reshma Kewalramani - *Vertex Pharmaceuticals Incorporated - CEO, President & Director*

Thanks so much, Liisa.

Operator

The next question will come from David Risinger with Leerink Partners.

David Reed Risinger - *Leerink Partners LLC, Research Division - Senior MD & Senior Research Analyst*

Yes. Let me add my congrats on the transaction. And I have two questions, please. First, given your pipeline-in-a-product vision, could you just talk about how you've thought about various other I&I mechanisms for those diseases because, obviously, the landscape in a number of those disease states is going to be quite crowded late decade. And I just wanted to, I guess, get a sense for how you see pove's efficacy versus other mechanisms that you're envisioning — or other indications that you're envisioning for pove. And then I have a separate question, please.

Reshma Kewalramani - *Vertex Pharmaceuticals Incorporated - CEO, President & Director*

Sure thing. Let me ask my favorite immunologist to comment on the landscape and how we see pove in that landscape. Jeff?

Jeffrey Marc Leiden - *Vertex Pharmaceuticals Incorporated - Executive Chairman*

Yes. It's a great question, and you're right, this will be a crowded landscape in some of these diseases. We have this conviction at Vertex, which has been borne out by our experience that the best way to go after a disease is to try to hit the underlying pathway of that disease. And what's very clear in all these diseases is that the B cell maturation, proliferation, activation, secretion pathways are the underlying pathways in most of these B cell autoimmune diseases. Doesn't mean that other ways can't work, but we do believe that by going directly after the pathway with this high-affinity dual inhibitor has the highest probability of success.

And it also has the possibility for true disease modification, and Reshma mentioned this. It remains to be seen, but I think one of the interesting things here is that by inhibiting BAFF and APRIL, we may not only just decrease autoantibody secretion, which clearly it does, we may actually have disease-modifying capabilities in some of these diseases, the underlying renal disease, for example, or the underlying cytopenia. And I think that's a very exciting potential here that we'll look very carefully at.

David Reed Risinger - *Leerink Partners LLC, Research Division - Senior MD & Senior Research Analyst*

Great. And then considering today's news, Reshma, if you could provide an update on inaxaplin, your enthusiasm for that program and the key developments to watch ahead?

Reshma Kewalramani - *Vertex Pharmaceuticals Incorporated - CEO, President & Director*

Yes, sure thing. So in the renal space, we have now inaxaplin, we have our ADPKD program, and with this announcement today, a program in IgAN. Inaxaplin is VX-147. The recent news on that program, which we probably announced a week ago or so, is that the dose selection has been made, it's 45 milligrams and we are well into Phase III. We are blinded, of course, to the data because this is a seamless Phase II/III study. But the milestones to look for now are continued enrollment. And the next big milestone is the potential for accelerated approval, and we've talked about the fact that we see a pathway to that through our conversations with the agency when we started the program. So really great news. And of course, ADPKD just went into the clinic in a Phase I trial.

Operator

The next question will come from Mohit Bansal with Wells Fargo.

Mohit Bansal - *Wells Fargo Securities, LLC, Research Division - Senior Equity Analyst*

Congrats on the deal as well from my side. Reshma, one question I want to understand is that I think the relationship between the UPCR reduction in IgAN with GFR reduction is well established, can you confirm that?

And if you look at the early data, it does look like there was an improvement in GFR, again, small patient count, do you think that should be the expectation going forward? How should we think about the GFR with this kind of proteinuria reduction in longer-term study?

Reshma Kewalramani - *Vertex Pharmaceuticals Incorporated - CEO, President & Director*

Thanks, Mohit. Really, really great question. So as we've talked about before in the context of AMKD, in homogeneous proteinuric kidney diseases like IgAN, the regulators have been open-minded to proteinuria as a regulatory enabling endpoint. So you're right about that. That relationship is known and it's strong.

So this question you asked about eGFR and there is tantalizing data, albeit a very small number of patients from Alpine on GFR, and GFR looks like it improves small numbers of patients. Honestly, Mohit, as a nephrologist, the most my mind could have imagined in the past is stabilization of GFR and that is a huge and positive benefit. But because of what you heard Jeff talk about, with this dual April/BAFF inhibition hitting multiple paths of the B cell pathway, there are theories that could explain what we are seeing as disease modification, particularly in the mesangium. I'll leave it at that and we'll look to see what the future data holds, but that is — that would be something that would be extraordinary.

Operator

The next question will come from Evan Seigerman with BMO Capital.

Evan David Seigerman - *BMO Capital Markets Equity Research - MD & Senior BioPharma Research Analyst*

Really, congrats on the deal. I wanted to dive in a little bit on the epidemiology you mentioned in the deck, specifically around the 130,000 patients. Can you walk me through the subset of patients that you're looking to target? And how do you kind of get to that multibillion dollar opportunity? Is addressing all 130,000 patients a specific subset? Or in another way, who do you plan to target first, and where would you grow from there?

Reshma Kewalramani - *Vertex Pharmaceuticals Incorporated - CEO, President & Director*

Why don't Stuart and I tag team this question? So the numbers you saw on the slide are straight prevalence data and what we shared were U.S. numbers, and it's about 3x that maybe a little bit more when you add up the patients around the globe. The patient numbers we showed you are not eligible patients. They're not patients that are necessarily being studied in the trial. These are not eligible patient numbers that we're showing.

And with regard to how we get to a multibillion dollar market, let me turn it over to Stuart who can maybe dimensionalize it a little bit with an existing therapy, the patient numbers and the price of some therapies so that you can sort of build that out in your own model. Stuart?

Stuart A. Arbuckle - *Vertex Pharmaceuticals Incorporated - Executive VP & COO*

Yes. So these - the numbers, the 130,000, is a recent estimate on the number of patients who are diagnosed with IgAN and confirmed diagnosed by biopsy. So these are not patients who are kind of unaware of their diagnosis and their physician is not unaware of their diagnosis.

As Reshma said, not all of those necessarily would be treated with a disease-modifying therapy, but if truly effective disease-modifying therapies were available, much as we've seen in many other diseases like, for instance, relapsing MS, in things like psoriasis, in things like RA, you would expect high percentages of patients to be treated with disease-modifying therapies.

As a result of that, depending on what price, pick a price, you can get to a multibillion dollar to market. Just to give you an example, one of the most recent drugs, which has received full approval in IgAN is TARPEYO. The WAC price for TARPEYO here in the United States is $150,000.

So I think it's relatively easy with relatively simple math to imagine this as a multibillion-dollar market opportunity.

Reshma Kewalramani - *Vertex Pharmaceuticals Incorporated - CEO, President & Director*

Just to close out on that discussion, Evan, TARPEYO is not a disease-modifying drug. It is not a drug that targets the underlying cause of disease.

Stuart A. Arbuckle - *Vertex Pharmaceuticals Incorporated - Executive VP & COO*

And has very modest efficacy, it's fair to say.

Operator

Our next question will come from Chris Raymond with Piper Sandler.

Christopher Joseph Raymond - *Piper Sandler & Co., Research Division - MD & Senior Research Analyst*

Congrats from us as well on the deal. Just maybe a strategic sort of question on how you view the renal market. So I've heard your prepared remarks and answer to some of the questions on 147, for example, on AMKD and also on your nephrology expertise.

But sort of renal as a therapeutic silo has had maybe, one could describe, a spotty record in terms of launch successes. And just as you sort of view this from a commercial — strategic commercial standpoint, can you maybe give us a sense of your view. Are these — some of these disappointments of other drugs, and I know we're talking different indications, are these drugs specific? Or maybe just talk about your strategic view of nephrology sort of writ large.

Reshma Kewalramani - *Vertex Pharmaceuticals Incorporated - CEO, President & Director*

Yes. Sure thing. So let me say 3 things. One, until the recent past, we have not had any drugs that treat the underlying cause of disease. In fact, when I was a practicing nephrologist, we would often write papers about the fact that we have very few clinical trials in nephrology and the fact that we have very few drugs that were actually developed for nephrology indications. Most of our medicines were recycled medicines from cardiovascular disease or endocrinology. So that's one thing.

The second thing to say is we have had a real new understanding of renal medicine. We have better understanding of the genetics of disease, and we have had far better medicines that target the actual underlying cause of disease. I'll just call out the medicines from the Vertex portfolio, but that does include VX-147, which specifically targets the underlying cause of AMKD; and our latest molecule for polycystic disease, which specifically targets PC1 correction; and now today, of course, with Alpine specifically targeting the B cell pathway, which is the cause of disease in IgA nephropathy.

So when I stand back and look at renal medicine, it's like a renaissance in nephrology over the recent past. And I think Vertex is leading the way with these 3 medicines, each of which are innovative, treat the underlying cause of disease and have already demonstrated that they are medicines that have very good preclinical data, and in 2 of the cases, already have Phase II data that show them to be best-in-class. That, of course, is VX-147 and Alpine. The polycystic kidney disease is just entering Phase I development.

Operator

The conference has now concluded. Thank you for attending today's presentation. A replay of today's event will be available shortly after the call concludes by dialing 1(877) 344-7529 or 1 (412) 317-0088 using replay access code 10188202. Thank you, and have a great day.

Additional Information and Where to Find It

The tender offer for the outstanding shares of common stock of Alpine Immune Sciences, Inc. ("Alpine") referenced in this communication has not yet commenced. This communication is for informational purposes only and is neither an offer to purchase nor a solicitation of an offer to sell shares of Alpine, nor is it a substitute for any tender offer materials that Vertex Pharmaceuticals Incorporated (together with its subsidiaries, "Vertex"), or Alpine will file with the Securities and Exchange Commission ("SEC"). At the time the tender offer is commenced, Vertex will file with the SEC a Tender Offer Statement on Schedule TO which will include an Offer to Purchase, a related Letter of Transmittal and certain other tender offer documents (together, the "Tender Offer Materials"), and Alpine will file with the SEC a Solicitation/Recommendation Statement on Schedule 14D-9 (the "Solicitation/Recommendation Statement") with respect to the tender offer. ALPINE'S SECURITY HOLDERS ARE URGED TO READ THE TENDER OFFER MATERIALS AND THE SOLICITATION/RECOMMENDATION STATEMENT WHEN THEY BECOME AVAILABLE BECAUSE THEY WILL CONTAIN IMPORTANT INFORMATION WHICH SHOULD BE READ CAREFULLY BEFORE ANY DECISION IS MADE WITH RESPECT TO THE TENDER OFFER. The Tender Offer Materials, as well as the Solicitation/Recommendation Statement, will be sent to all stockholders of Alpine at no expense to them. The Tender Offer Materials and the Solicitation/Recommendation Statement will be made available for free at the SEC's website at www.sec.gov. Additional copies may be obtained free of charge under the "Investors" section of Vertex's website at https://investors.vrtx.com/financial-information/sec-filings or by contacting Vertex by phone at (617) 341-6108 or by email at InvestorInfo@vrtx.com, or by directing requests for such materials to the information agent for the offer, which will be named in the Tender Offer Materials. In addition to the Tender Offer Materials and the Solicitation/Recommendation Statement, Alpine and Vertex file periodic reports and other information with the SEC. Vertex's and Alpine's filings with the SEC are also available for free to the public from commercial document-retrieval services and at the website maintained by the SEC at www.sec.gov and their respective investor relations websites at the addresses above.

Special Note Regarding Forward-Looking Statements

This transcript contains forward-looking statements related to Vertex, Alpine and the proposed acquisition of Alpine by Vertex (the "Transaction") that are subject to risks, uncertainties and other factors. While Vertex believes the forward-looking statements contained in this communication are accurate, these forward-looking statements represent the beliefs of Alpine and Vertex only as of the date of this communication, and there are a number of risks and uncertainties that could cause actual events or results to differ materially from those expressed or implied by such forward-looking statements. All statements other than statements of historical fact are statements that could be deemed forward-looking statements, including all statements regarding the intent, belief or current expectation of the companies' and members of their senior management teams. Forward-looking statements are not purely historical and may be accompanied by words such as "anticipates," "may," "forecasts," "expects," "intends," "plans," "potentially," "believes," "seeks," "estimates," and other words and terms of similar meaning. Such statements may relate to: the ability of Vertex to advance Alpine's platform technology and potential therapies, such as povetacicept, on a timely basis; filings and approvals relating to the Transaction; the expected timing of the completion of the Transaction; the ability to complete the Transaction considering the various closing conditions; difficulties or unanticipated expenses in connection with integrating the companies; and any assumptions underlying any of the foregoing.

Forward-looking statements are subject to certain risks, uncertainties, or other factors that are difficult to predict and could cause actual events or results to differ materially from those indicated in any such statements due to a number of risks and uncertainties. Those risks and uncertainties that could cause the actual results to differ from expectations contemplated by forward-looking statements include, among other things: uncertainties as to the timing of the Transaction; uncertainties as to how many of Alpine's stockholders will tender their stock in the offer; the possibility that competing offers will be made; the possibility that various closing conditions for the Transaction may not be satisfied or waived, including that a governmental entity may prohibit, delay or refuse to grant approval for the consummation of the Transaction; the effects of the Transaction on relationships with employees, other business partners or governmental entities; the difficulty of predicting the timing or outcome of FDA approvals or actions, if any; the impact of competitive products and pricing; that Vertex may not realize the potential benefits of the Transaction; other business effects, including the effects of industry, economic or political conditions outside of the companies' control; Transaction costs; and actual or contingent liabilities related to the Transaction. In addition, the product candidates being developed by Alpine are subject to all the risks inherent in the drug development process, and there can be no assurance that the development of these product candidates will be commercially successful. Forward-looking statements in this communication should be evaluated together with the many uncertainties that affect Vertex's and Alpine's businesses, particularly those risks listed under the heading "Risk Factors" and the other cautionary factors discussed in the parties' periodic reports filed with the SEC, including Vertex's annual report on Form 10-K for the year ended December 31, 2023, and its quarterly reports on Form 10-Q and current reports on Form 8-K, and Alpine's annual report on Form 10-K for the year ended December 31, 2023, and its quarterly reports on Form 10-Q and current reports on Form 8-K, as well as the Solicitation/Recommendation Statement to be filed by Alpine and the Tender Offer Materials to be filed by Vertex and Adams Merger Sub, Inc., a direct wholly owned subsidiary of Vertex, all of which are available, or will be available when filed, for free on the SEC's website at www.sec.gov. You should not place undue reliance on these statements. All forward-looking statements are based on information currently available to Vertex and Alpine, and Vertex and Alpine disclaim any obligation to update the information contained in this communication as new information becomes available, except as required by law.