UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAREPTA THERAPEUTICS, INC.,

Petitioner

v.

Genzyme Corporation,

Patent Owner

U.S. Patent No. 9,051,542

"Compositions and Methods to Prevent AAV Vector Aggregation"

IPR2025-01194

PETITION FOR *INTER PARTES* REVIEW

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LIST OF CHALLENGED CLAIMS[1]

Claim	Element
1 [pre]	A composition for the storage of purified, recombinant adeno-associated virus (AAV) vector particles, comprising:
1[a]	purified, recombinant AAV vector particles at a concentration exceeding $1x10^{13}$ vg/ml up to $6.4x10^{13}$ vg/ml;
1[b]	a pH buffer, wherein the pH of the composition is between 7.5 and 8.0; and
1[c]	excipients comprising one or more multivalent ions selected from the group consisting of citrate, sulfate, magnesium, and phosphate;
1[d]	wherein the ionic strength of the composition is greater than 200 mM,
1[e]	and wherein the purified AAV vector particles are stored in the composition without significant aggregation.
2	The composition of claim 1, further comprising ethylene oxide/propylene oxide block copolymer Pluronic® F68.
3	The composition of claim 2, wherein the Pluronic® F68 is present at a concentration of 0.001% (w/v).
4	The composition of claim 1, wherein the pH buffer is 10 mM Tris, pH 8.0 and the excipients comprise 100 mM sodium citrate.

[1] Claims 1 and 2 have been statutorily disclaimed by Patent Owner but are reproduced here because challenged claim 3 depends from claim 2, which depends from claim 1, and challenged claims 4, 5 and 6 depend from claim 1.

Claim	Element
5	The composition of claim 1, wherein the purified, recombinant AAV vector particles have an average particle radius (Rh) of less than about 20 nm as measured by dynamic light scattering.
6	The composition of claim 1, wherein recovery of the purified, recombinant virus particles is at least about 90% following filtration of the composition of said AAV vector particles through a 0.22 μm filter.

Sarepta Therapeutics, Inc. ("Sarepta" or "Petitioner") respectfully requests *inter partes* review of claims 3-6 (the "challenged claims") of U.S. Patent No. 9,051,542 ("the '542 patent") (EX1001). The '542 patent is assigned to Genzyme Corporation.

Petitioner is concurrently filing a petition requesting *inter partes* review of various claims of a related patent, U.S. Patent No. 7,704,721 ("the '721 patent"). The '542 patent is a continuation of U.S. Patent Application No. 11/141,996, which issued as the '721 patent.

I. INTRODUCTION

Adeno-associated virus (AAV) has been studied for decades as a useful tool to deliver therapeutic genes to patients to treat diseases such as Duchenne Muscular Dystrophy, cystic fibrosis, and various diseases of the eye. For both preclinical and clinical applications, researchers have sought to develop efficient methods to concentrate and purify recombinant AAV (rAAV) at a large scale. Such large scale preparations generally involve high physical titer stocks that need to be stable during storage.

Decades before the earliest priority date for the '542 patent, aggregation of viral particles was known to decrease viral infectivity. Aggregation was also known to be dependent on the concentration of viral particles in a preparation. A number of factors were also known to inhibit viral particle aggregation, including high ionic

strength, multivalent ions, non-ionic surfactants, and, for AAV in particular, pH values around 7.5.

The challenged claims are directed to a composition for the storage of purified rAAV particles without "significant" aggregation. The challenged claims recite a straightforward set of properties of the claimed composition, such as pH, ionic strength, the presence of multivalent ions, and particle concentration, all of which were well known to affect aggregation in the prior art for years before the earliest possible priority date for the '542 patent.

Specifically, the claimed composition comprises purified rAAV particles at a concentration between 1 x 10^{13} vg/ml and 6.4 x 10^{13} vg/ml, in a buffer within the pH range of 7.5 and 8.0, containing one or more specified multivalent ions, and having an ionic strength greater than 200 mM. The challenged claims also contain various additional limitations, such as the presence of the non-ionic surfactant Pluronic F68 at a concentration of 0.001% w/v (claim 3), an average particle radius for the rAAV particles of less than about 20 nm as measured by dynamic light scattering (claim 5), or a recovery of at least 90% following filtration of the composition through a 0.22 μm filter (claim 6).

Challenged claims 3-6 are obvious over two different combinations of prior art references: (1) Wu and Konz, and (2) Potter and Konz. Challenged claim 3 is

also obvious over two additional combinations of prior art references: (1) Wu, Konz, and Croyle, and (2) Potter, Konz, and Croyle.

Wu and Konz. Wu discloses an efficient method for large scale purification of rAAV, involving chloroform treatment of cell lysate, followed by PEG/NaCl precipitation, and chloroform extraction. Wu discloses that using this method, they produced a stock formulation of purified rAAV particles at a concentration of about 5×10^{13} vg/ml, in a buffer that a POSA would have understood to have a pH of about 7.4 or 7.5 to 8.0, which contained multivalent ions, and had an ionic strength greater than 200 mM. Wu discloses electron microscopy studies showing that the rAAV stock formulation did not exhibit any observable aggregation. Wu further discloses that the rAAV stock formulation could be stored at 4°C for more than a month without significant decrease of infectious titer, indicating that there was no significant aggregation during storage.

Wu states that, as a result of the use of chloroform as part of the purification, residual chloroform might be present in the rAAV stocks, which should be removed before the stocks are used in clinical trials. As a result, a person of ordinary skill in the art (POSA) at the relevant time would have been motivated to combine Wu with another reference similarly directed to large scale purification of stable rAAV stocks, disclosing formulation buffers useful for buffer exchange to remove residual chloroform from rAAV stocks produced by Wu's method. A POSA would further

have understood that electron microscopy is not an advantageous analytical technique for large scale purification, given that it is time and labor intensive, and would have been motivated to combine Wu with a reference that disclosed more efficient and cost-effective analytical techniques to assay for the presence of aggregates.

Konz is such a reference. Konz is directed to large scale purification of stable rAAV stocks and discloses formulation buffers that could be exchanged with the buffer in Wu's rAAV stocks to remove residual chloroform. These buffers include buffers similar to the buffer in Wu's stocks, with an ionic strength greater than 200 mM, containing multivalent ions, with a pH within the claimed pH range of 7.5 to 8.0. Konz further discloses the addition of non-ionic surfactants, including the Pluronic series of non-ionic surfactants, to reduce the possibility of aggregation even further. Konz also discloses filtration through a 0.22 μm filter after storage of the purified viral stocks at 4°C, followed by dynamic light scattering (DLS), as analytical techniques used to confirm that no aggregates formed during storage.

The challenged claims are therefore obvious over the combination of Wu and Konz.

Wu, Konz, and Croyle. Challenged claim 3 is also obvious over the combination of Wu, Konz, and Croyle. Croyle discloses that addition of 0.001% Pluronic F68 to a preparation of viral vectors for gene therapy enhanced transduction

of target cells by the virus and enhanced the physical stability of the virus during storage. In particular, 0.001% Pluronic F68 inhibited aggregation of the viral formulation, as determined by DLS. A POSA would have been motivated to combine Croyle with Wu and Konz given that Konz discloses the entire series of Pluronic non-ionic surfactants to inhibit aggregation, and Croyle demonstrated that addition of Pluronic F68 at 0.001% in particular improved transduction of target cells, enhanced stability, and inhibited aggregation of a viral formulation for gene therapy, as determined by DLS. Claim 3 is therefore obvious over the combination of Wu, Konz, and Croyle.

Potter and Konz. Potter is directed towards production of a high physical titer rAAV stock for use as a reference standard stock for preclinical studies. Potter discloses that the rAAV stock produced by their method was intended to be distributed to various laboratories for use in preclinical research, indicating that it was stable during storage and distribution. Potter discloses an efficient method for large scale rAAV purification, involving three column chromatography steps – Streamline Heparin affinity chromatography, phenyl-sepharose hydrophobic interaction chromatography, and heparin affinity chromatography. Potter discloses that using this method, they produced a stock formulation of purified rAAV particles at a concentration of about 1.12×10^{13} vg/ml to 1.46×10^{13} vg/ml, in a buffer that a POSA would have understood to have a pH of about 7.4 or 7.5 to 8.0, which

contained multivalent ions, and had an ionic strength greater than 200 mM. Potter discloses electron microscopy studies showing that the rAAV stock formulation did not exhibit any observable aggregation.

As with Wu, a POSA would have sought to replace electron microscopy as an analytical technique with more efficient and cost-effective approaches to assay for the presence of aggregates. A POSA would therefore have been motivated to combine Potter with Konz. The challenged claims are therefore obvious over the combination of Potter and Konz.

Potter, Konz, and Croyle. For the same reasons discussed above regarding the combination of Wu, Konz, and Croyle, a POSA would have been motivated to combine Croyle with Potter and Konz. The combination of Potter, Konz, and Croyle therefore renders challenged claim 3 obvious.

II. MANDATORY NOTICES

A. Real Parties-in-Interest (37 C.F.R. §42.8(b)(1))

Petitioner identifies Sarepta Therapeutics, Inc. and Sarepta Therapeutics Three, LLC as real parties-in-interest.

B. Related Matters (37 C.F.R. §42.8(b)(2))

Petitioner identifies the following related matters. The '542 patent is being asserted in currently-pending litigation: *Genzyme Corp. v. Sarepta Therapeutics, Inc.*, C.A. No. 24-cv-00882-RGA (D. Del.), D.I. 81. EX1011.

The ’542 patent was also asserted in a prior litigation to which Petitioner was not a party, *Genzyme Corp. v. Novartis Gene Therapies, Inc.*, C.A. No. 21-1736 (RGA) (D. Del.) (D.I. 17). EX1012. The question of the validity of the ’542 patent, however, was never presented to a jury, because the parties entered into a Joint Stipulation and Order of Dismissal With Prejudice on February 14, 2024, terminating the litigation. EX1013.

C. Related Patent Office Proceedings

Claims 1, 2, 5, and 6 of the ’542 patent were the subject of two petitions for *inter partes* review, IPR2023-00608 and IPR2023-00609, brought by Novartis Gene Therapies, Inc. and Novartis Pharmaceuticals Corporation. EX1014; EX1015. The Patent Trial and Appeal Board (PTAB) denied institution of both IPRs. EX1017; EX1018.

Patent Owner statutorily disclaimed claims 1 and 2 during these prior proceedings. EX1019. In addition, claims 3 and 4, two of the claims at issue here, were not at issue in these prior proceedings. EX1014, 11; EX1015, 13.

Wu, Konz, and Croyle were not cited or discussed during the prior proceedings. Potter was discussed as a background reference by Novartis, but not addressed by the Board in either decision denying institution. EX1014, 20, 22, 63; EX1015, 22, 24; EX1017; EX1018. Notably, as discussed in detail below (Section IV.B.3), Patent Owner and its expert, Dr. Martyn Davies, materially

mischaracterized Potter and the state of the art as of 2004 in responding to the 608 Petition. They did not address Potter in responding to the 609 Petition.

D. Lead and Back-up Counsel and Service Information

Petitioner provides the following counsel and service information. Pursuant to 37 C.F.R. §42.10(b), a Power of Attorney accompanies this Petition.

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III. REQUIREMENTS FOR IPR

A. Payment of Fees

The undersigned authorizes the Office to charge the fee required for this Petition for *inter partes* review to Deposit Account No. 50-5708.

B. Grounds for Standing

Petitioner certifies that the '542 patent is available for IPR and Petitioner is not barred or estopped from requesting IPR on the grounds identified herein. Petitioner further certifies that the prohibitions of 35 U.S.C. §§315 (a)-(b) are inapplicable.

C. Statement of Relief Requested

Petitioner respectfully requests review and cancellation of claims 3-6 of the '542 patent. The challenged claims should be found unpatentable on the following grounds:

Prior Art References
Wu (EX1007); published in 2001; prior art under pre-AIA §102(b).
Konz (EX1008), published on November 27, 2003; prior art under at least pre-AIA §102(e).
Croyle (EX1009); published in 2001; prior art under pre-AIA §102(b).
Potter (EX1010); published in 2002; prior art under pre-AIA §102(b).

Ground	Claims	Description
1	3, 4, 5, 6	Obvious in view of Wu and Konz
2	3	Obvious in view of Wu, Konz, and Croyle
3	3, 4, 5, 6	Obvious in view of Potter and Konz
4	3	Obvious in view of Potter, Konz, and Croyle

Wu, Konz, Croyle, and Potter were not considered by the Patent Office during prosecution. EX1001 ("References Cited"); EX1002.

IV. BACKGROUND

A. Overview of the Technology

Since the 1990s, researchers have been working to develop methods to produce high titer, pure, large scale preparations of rAAV to use in gene therapy. EX1029; EX1005, ¶¶27-34. It was known in the art that certain AAV purification methods, such as particular types of gradient purification, would remove empty capsids from the preparation, while others, such as column chromatography, would not. EX1010, 14-17; EX1005, ¶35.

A POSA at the relevant time would have been aware of the phenomenon of aggregation of AAV particles, for example during storage at 4°C, or during dialysis, resulting in a loss of infectivity. EX1023, 5; EX1005, ¶36; EX1005, ¶¶68-75. It was known that empty AAV capsids have a tendency to aggregate during dialysis. EX1023, 6; EX1005, ¶¶36, 76-82. In addition, the size of AAV aggregates was known to be concentration dependent – the higher the concentration, the larger the aggregates and the less efficient the gene transfer. EX1043 (disclosing that when the rAAV vector titer reached 5-10 x 10^{13} genome copies ("GCs") per ml, gene transfer efficiency was 10-100 fold lower at the same dose as it was with the same rAAV vector at a titer of 1-5 x 10^{12} GCs/ml); EX1005, ¶36.

Researchers were actively working on developing formulations to inhibit rAAV aggregation at high vector concentrations. EX1043; EX1005, ¶¶33-36, 89-92. Factors that influence aggregation of viral particles, including the effects of ionic strength, pH, and the presence of ions such as Na^+ and multivalent ions such as Mg^{2+}, have been studied since at least the 1970s. EX1030; EX1031; EX1032; EX1041, 6 (finding that purified AAV particles aggregated at pH 7.2 and below, but that no aggregates were observed at pH 7.5); EX1005, ¶¶36-88. The Floyd studies showed that dilution of viral particle preparations, which reduces ionic strength, can result in aggregation. EX1030, Abstract, 2; EX1005, ¶¶38-39.

B. THE '542 PATENT

The '542 patent is titled "Compositions and Methods to Prevent AAV Vector Aggregation." EX1001. The patent names John Fraser Wright and Guang Qu as inventors. *Id*. The '542 patent issued on June 9, 2015. *Id*.

The '542 patent is assigned to Genzyme Corporation. *Id*.

1. The Claims

Claims 1 and 2 of the '542 patent were statutorily disclaimed by Patent Owner. EX1001, 14:15-26; EX1019. The challenged claims are reproduced in the list above. Challenged claim 3 depends from claim 2, which, in turn, depends from claim 1, and challenged claims 4, 5 and 6 depend from claim 1. EX1001, 14:29-41.

The challenged claims are directed to a composition of purified rAAV particles that can be stored without "significant" aggregation. The challenged claims recite certain properties of the claimed composition, namely, that the rAAV particles are present at a concentration between 1 x 10^{13} vg/ml and 6.4 x 10^{13} vg/ml, the ionic strength is greater than 200 mM, one or more multivalent ions is present, and the pH is between 7.5 and 8.0. Claim 3 further requires the presence of the non-ionic surfactant Pluronic F68 at a concentration of 0.001% (w/v). Claim 4 further requires that the pH buffer is 10 mM Tris, pH 8.0, with 100 mM sodium citrate. Claim 5 requires the rAAV particles in the composition to have an average particle radius less than about 20 nm as measured by DLS. Claim 6 recites that recovery of the purified rAAV particles is at least about 90% following filtration through a 0.22 μm filter.

2. The Specification

The specification of the '542 patent discusses the effect of different buffers and methods of purification on aggregation of AAV2-FIX particles. EX1001, Figs. 1B, 2, 4:14-32, 6:63-9:4; 10:19-11:50; EX1005, ¶¶98-126. "AAV2-FIX" vectors are AAV2 serotype viral vectors containing a human coagulation factor IX ("FIX") transgene. EX1001, 10:56-57; EX1005, ¶98. AAV2 is the only serotype tested in the '542 patent. EX1005, ¶98. The specification discusses "dilution stress" experiments in which rAAV2 aggregation was measured after dilution in various

buffers containing various different ions and excipients. EX1001, Figs. 1B, 2, 4:14-32, 6:63-9:4; 10:19-11:50; EX1005, ¶100. The specification discusses various methods to detect viral particle aggregation, including ultrafiltration and diafiltration, and dynamic light scattering. EX1001, 11:52-12:67; EX1005, ¶98..

The specification also discusses the effect of storage at 4°C, and of freeze-thaw cycles on the stability and infectivity of viral particles stored in three different buffers: Control Formulation (CF) (140 mM sodium chloride, 10 mM sodium phosphate, 5% sorbitol, pH 7.3); Test Formulation 1 (TF1) (150 mM sodium phosphate, pH 7.5); Test Formulation 2 (TF2) (100 mM sodium citrate, 10 mM Tris, pH 8.0). EX1001, 9:5-10:15, Table 3, 11:66-12:3; EX1005, ¶99.

3. The Prosecution History

(a) Prosecution of the ’542 Patent

During prosecution, the claims were rejected over multiple pieces of prior art and were amended multiple times. EX1002, 82-94, 125-35, 143-57, 164-74, 181-92, 199-205, 212-25, 236-45.

Ultimately, the Examiner proposed an Examiner’s Amendment, which was agreed to by the applicant. *Id*., 310-22, 325-28, 336-43. The Examiner’s Amendment specified that the multivalent ions must be “selected from the group consisting of citrate, sulfate, magnesium, and phosphate,” and also that the purified

AAV particles must be "stored in the composition without significant aggregation." *Id*., 339-41.

Notably, the primary prior art references at issue here – Wu, Konz, Croyle,[2] and Potter – were not before the USPTO during prosecution of the '542 patent. EX1001; EX1002.

(b) Prior IPR Petitions Challenging the '542 Patent

As discussed above (Section II.C), a different petitioner (Novartis), previously brought IPR petitions challenging claims 1, 2, 5, and 6 of the '542 patent. EX1014; EX1015. Patent Owner statutorily disclaimed claims 1 and 2 during these prior proceedings. EX1019. In addition, two of the claims at issue here, claims 3 and 4, were not at issue in IPR2023-00608 or IPR2023-00609. EX1014, 11; EX1015, 13. The PTAB denied institution of both IPRs. EX1017; EX1018.

[2] For the avoidance of confusion, a *different* reference by Croyle was cited during prosecution. EX1001, *passim* (citing Croyle *et al*., "Development of Formulations That Enhance Physical Stability of Viral Vectors for Gene Therapy," *Gene Therapy* 8(17): 1281-1290 (2001)).

Notably, Wu, Konz,[3] and Croyle[4] were not before the Board in these proceedings.

(i) Potter

The Potter reference was cited only as a background reference by Novartis, and was materially mischaracterized by Patent Owner in its POPR and Patent Owner's expert, Dr. Davies, in his declaration. EX1014, 20, 22, 63; EX1015, 22, 24; EX1016, 47-48, 68-69; EX1060, ¶¶121, 123-24, 151-52; EX1005, ¶¶26, 134, 252-60. Potter was never addressed by the Board in the decisions denying institution of the Novartis petitions. EX1017; EX1018.

Patent Owner addressed Potter in the 608 POPR (but did not discuss Potter in the 609 POPR). EX1016, 47-48, 68-69. Patent Owner and Dr. Davies materially mischaracterized Potter in several different respects.

First, Patent Owner and Dr. Davies mischaracterized the concentration of the disclosed formulations in Potter. EX1005, ¶¶252-56. Patent Owner and Dr. Davies argued that the formulations disclosed in Potter "contain virus particle concentrations ***several orders of magnitude below the claimed concentration***

[3] For the avoidance of confusion, a *different* publication by Konz is cited in Patent Owner's preliminary response in IPR2023-00608. EX1016, 10.

[4] *See* n.2, *supra*.

exceeding 10^{13} vg/ml." EX1016, 47 (emphasis added); EX1060, ¶121 (same); EX1005, ¶¶ 167-68, 252-56.

However, as discussed further below (Section VI.D), Potter actually disclosed formulations with concentrations of AAV particles (1.12×10^{13} viral genomes/ml and 1.46×10^{13} viral genomes/ml) that fall squarely within the range recited in the claims of the '542 patent. EX1010, 9-10, 12, Table II; EX1005, ¶¶167-68, 252-56. The Patent Owner and Dr. Davies therefore materially mischaracterized Potter in describing Potter's formulations as "several orders of magnitude below the claimed concentration exceeding 10^{13} vg/ml." EX1016, 47-48, 68-69; EX1060, ¶121; EX1005, ¶¶ 167-68, 252-56.

Patent Owner also incorrectly characterized the analytical method, electron microscopy, that Potter used to assess aggregation of the purified AAV preparations. Patent Owner stated that Potter was "unavailing" to show that a POSA would have had a reasonable expectation of success in making the claimed combination because "visual methods cannot accurately detect the presence of aggregates." EX1016, 68-69; EX1005, ¶¶257-60.

It is incorrect to describe electron microscopy, the analytical technique used in Potter, as a "visual method" that "cannot accurately detect the presence of aggregates." EX1005, ¶258. Electron microscopy was commonly used in the art to assess aggregation of viral particles, including AAV, and was described as a "gold

standard analytical method" for characterizing viral particles. EX1036, Abstract; EX1005, ¶¶72, 258. It is simply wrong to say, as Patent Owner did in the prior IPR proceeding, that electron microscopy "cannot accurately detect" AAV aggregates. EX1005, ¶258.

A POSA would generally have understood "visual methods" to mean methods such as visual inspection, or even light microscopy, rather than electron microscopy. EX1005, ¶259. Notably, while Potter does not use any technique that could be fairly described as "visual inspection" to assess the state of AAV aggregation, the '542 patent does disclose such a "visual inspection" method, light microscopy. EX1005, ¶258. The '542 patent repeatedly discloses assessing aggregation of rAAV preparations by visual inspection using light microscopy. EX1001, 1:65-2:8, 8:50-56, 9:50-52; EX1005, ¶260. Given these disclosures in the '542 patent, it is therefore particularly surprising that the Patent Owner disparaged "visual inspection" techniques in the 608 POPR.

(ii) Evans

In addition, the Evans reference, which was a principal reference in IPR2023-00608, is discussed in this Petition solely as incorporated by reference into Konz. EX1014, 11; EX1015, 13. Here, Petitioner relies on Konz's disclosure, as incorporated via Evans, of formulation buffers that meet the ionic strength,

multivalent ion, non-ionic surfactant, citrate, and pH limitation recited by the challenged claims.

The express teachings of Evans that Konz points to, and that Petitioner relies on here, are materially different from the disclosures of Evans that were contested and that the Board addressed in IPR2023-00608. EX1017, 17-21 (addressing issues of whether particle radius and product recovery were inherently taught by the prior art combination that included Evans, discussing Evans's disclosure of physical titer, and also addressing whether Evans taught ionic strength as a "results-effective variable for rAAV aggregation").

Here, Petitioner relies on the express disclosures of Wu and Potter regarding high physical titer, along with their disclosures of high ionic strength buffers containing multivalent ions in the claimed pH range, in combination with corresponding disclosures in Konz. Petitioner further relies on Konz's express disclosures of particle radius measurement by DLS and product recovery measurement by sterile filtration through a 0.22 μm filter.

And given that Wu, Konz, and Croyle were not cited in the prior IPRs, Petitioner's arguments here (and limited reliance on Evans) are therefore materially different from the issues in the prior IPRs, including those involving Novartis's reliance on Evans as a principal reference.

Moreover, Petitioner here relies on background, state of the art references (that were also not before the Patent Office during prosecution or the PTAB during the prior IPR proceedings) to demonstrate that a POSA at the relevant date would have been well aware that ionic strength was a "results-effective variable" for viral particle aggregation. EX1030; EX1031; EX1032.

4. Priority Date

The '542 patent claims priority to two provisional applications, 60/575,997, filed June 1, 2004, and 60/639,222, filed December 22, 2004. EX1001; EX1003; EX1004. The '542 patent issued from U.S. Patent Application No. 12/661,553, filed on March 19, 2010, and is a continuation of U.S. Patent Application No. 11/141,996, which issued as the '721 patent. EX1001.

The challenged claims of the '542 patent are not entitled to the June 1, 2004 priority date of the earlier of the two provisionals, the '997 provisional, because the '997 provisional does not sufficiently describe or enable the full scope of the challenged claims. EX1005, ¶¶138-161. The challenged claims do not recite any particular purification method for the rAAV particles in the composition, and therefore encompass purification methods that produce empty capsids in addition to full capsids. The '997 provisional, however, does not sufficiently describe or enable compositions of viral particles that include empty capsids. EX1005, ¶¶141, 144-56. In addition, the '997 provisional does not sufficiently describe or enable

compositions of viral particles at the claimed pH range of 7.5-8.0. *Id*., ¶142, 157-61.

The only data relating to a composition containing empty capsids in the '997 provisional are the dilution stress data shown in Appendix D (the "HS" and "HS + DNAse" formulations). EX1003, 13; EX1005, ¶¶147-56. The '997 provisional does not disclose ***any*** composition containing empty capsids that does not have "significant aggregation," other than possibly preparations containing DNAse. *Id*., ¶147-56. These data do not provide written description support for, or enable, the full scope of the challenged claims.

Second, the '997 provisional must describe and enable compositions at the claimed pH range of 7.5 to 8.0. But all of the dilution stress experiments testing for aggregation in the '997 provisional (Appendix B, Appendix C, and Appendix D) were carried out at pH 7.0. These data therefore do not provide any support for the challenged claims. EX1003, 11-13, Appendices B, C, and D; EX1005, ¶¶157-61.

Therefore, the challenged claims are not entitled to the June 1, 2004 priority date, and the earliest possible priority date is December 22, 2004.

V. LEVEL OF ORDINARY SKILL IN THE ART

A POSA in the technical field of the '542 patent would have had at least a Ph.D. in pharmaceutical sciences, biochemistry, molecular biology, genetics, or a related field and between one and four years of post-doctoral experience in the field

of gene therapy, including development of viral vector formulations. EX1005, ¶¶162-66. Alternatively, a POSA would have had at least a Master's or Bachelor's Degree in pharmaceutical sciences, biochemistry, molecular biology, genetics, or a related field, with a corresponding number of additional years of experience in the field of gene therapy, including development of viral vector formulations. EX1005, ¶¶162-66.

VI. OVERVIEW OF THE PRIOR ART

A. Wu

Wu *et al*., "A novel method for purification of recombinant adeno-associated virus vectors on a large scale," was published in 2001, more than a year before the earliest possible priority date for the '542 patent (June 1, 2004), and is therefore 35 U.S.C. 102(b) prior art, irrespective of whether the '542 patent is entitled to the June 1, 2004 priority date. EX1007.

Wu discloses a method for large scale purification of rAAV. EX1007, Abstract; EX1005, ¶¶170-72. Wu's purification method involves three steps: (1) chloroform treatment of cells containing rAAV; (2) PEG/NaCl precipitation by adding solid NaCl to a final concentration of 1 mol/L and then solid PEG8000 to a final concentration of 10% (w/v), resuspension of the precipitated rAAV particles in PBS^{2+}, and addition of DNase I and RNase to a final concentration of 1 μg/ml; and

(3) chloroform extraction and collection of the aqueous phase. EX1007, 6-7, Fig. 1; EX1005, ¶¶173-78.[5]

Wu discloses that using this method, they could reproducibly obtain purified rAAV stocks with titers of around 5 x 10^{13} particles/ml. EX1007, Abstract; EX1005, ¶179. Wu further discloses that the physical titers of rAAV were obtained by dot blot hybridization. EX1007, 2-3; EX1005, ¶180. A POSA would have understood the concentrations measured using this assay are "vg/ml" concentrations. EX1010, 17; EX1005, ¶180. Therefore, Wu discloses purified rAAV stocks with titers of around 5 x 10^{13} vg/ml. EX1005, ¶180.

Wu carried out electron microscopy analysis of the purified rAAV preparations. EX1007, 3, Fig. 3; EX1005, ¶181. There is no evidence of aggregation of the purified rAAV particles in Fig. 3. EX1007, 3, Fig. 3; EX1005, ¶182.

Wu states that the "purified rAAV stock could be stored at 4°C for more than 1 month without significant decrease of infectious titer." EX1007, 4; EX1005, ¶183.

[5] "PBS^{2+}" is a notation that would have been understood by a POSA to mean PBS with added $MgCl_2$ and $CaCl_2$. EX1065, 250-51; EX1005, ¶173.

Wu also states that "[f]urther steps should be taken to remove residual chloroform before the stocks are used in clinical trials." EX1007, 4; EX1005, ¶¶184, 288.

B. Konz

Konz, titled, "Methods of Adenovirus Purification," is an international publication of a PCT application, filed in English and designating the United States. EX1008. Konz was published on November 27, 2003, more than one year before the filing date of the '222 provisional, December 22, 2004, which would be the earliest possible priority date on the face of the '542 patent if it cannot claim priority to the '997 provisional. EX1008; EX1001. Therefore, to the extent that the challenged claims are not entitled to the '997 provisional date, at least for the reasons set out above (Section IV.B.4), Konz is 102(b) prior art against the challenged claims.

Should the Patent Office determine that the challenged claims are entitled to the priority date of the '997 provisional, then Konz is 102(e) prior art against the challenged claims. Konz has an international filing date of May 13, 2003, which is more than a year earlier than the earliest possible priority date on the face of the '542 patent, June 1, 2004. EX1008; EX1001.

Konz is directed towards efficient methods of purification of recombinant viral particles, including rAAV, in light of a "need for large scale manufacture and

purification of clinical-grade virus," for applications including gene therapy. EX1008, 1:25-27, 2:23-26, 5:1-3, 5:28-30, 14:24-29, 15:33-16:2; EX1005, ¶¶187-202.

Konz discloses high concentration viral particle preparations. EX1008, 6:23-25, 7:30-32, 12:21-23, 30:11-12, 34:18-21; EX1005, ¶196. Konz discloses that their invention is an improvement over the prior art "industry norm," which involved low column loadings ("<1 x 10^{12} vp/ml resin"). EX1008, 24:12-13; EX1005, ¶196.

Konz further discloses that "an appropriate formulation buffer (e.g., see PCT publication WO 01/66137) can be used to maximize product stability." EX1008, 22:15-16, 25:20-22; EX1005, ¶¶197, 199, 278. In turn, WO 01/66137 (Evans), discloses high ionic strength buffers in a pH range similar to the pH of Wu's buffer, including a buffer at pH 8.0, containing a multivalent ion and a non-ionic surfactant, with an ionic strength above 200 mM. EX1020, 11:31-12:4, 14:15-28; EX1005, ¶¶193, 197, 199.

Konz also discloses the addition of "the Pluronic series of non-ionic surfactants" to "inhibit aggregation in anion exchange and throughout the process." EX1008, 24:1-9; EX1005, ¶195.

Konz discloses sterile filtration through a 0.22 μm filter as a means of assaying the extent of particle aggregation after storage. EX1008, 23:1-5, Table 1, 25:29-30, 30:13-30, 36:24-28; EX1005, ¶200. Konz discloses high yields from

sterile filtration after storage at 4°C, including yields above 90%. EX1008, 36:24-27, 37:1-6, Table 2, 48:1-21, Table 12; EX1005, ¶ 200.

Konz discloses the use of dynamic light scattering (DLS) to determine yields and mean particle sizes, to assess aggregation after storage. EX1008, 30:13-30, 48:4-14; EX1005, ¶201. Using DLS, Konz found the mean particle size of an adenoviral preparation, which had been stored at 4°C and sterile filtered through a 0.22 μm filter, to be "123 nm, consistent with theoretical expectations," indicating that the particles were monomers and not aggregates. EX1008, 25:29-30, 30:19-20, 48:12-14; EX1005, ¶201. Notably, for this preparation, the recovery after storage followed by 0.22 μm filtration was very high (98%), indicating that sterile filtration had little if any effect on the preparation as far as removal of any aggregates. EX1008, 36:24-27, 48:11-21, Table 12; EX1005, ¶202. A POSA would therefore have understood that the DLS result was representative of the preparation after storage and before sterile filtration. EX1005, ¶202.

C. Croyle

Croyle, "Development of novel formulations that enhance adenoviral-mediated gene expression in the lung *in vitro* and *in vivo*," was published in 2001, more than a year before the earliest possible priority date for the '542 patent (June 1, 2004), and is therefore 35 U.S.C. 102(b) prior art, irrespective of whether the '542 patent is entitled to the June 1, 2004 priority date. EX1009; EX1001.

Croyle is directed towards development of a stable adenoviral formulation[6] with enhanced cellular absorption of adenoviral vectors in the lung. EX1009, Abstract; EX1005, ¶¶204-11. Croyle tested various different formulations *in vitro* and *in vivo*. EX1009, Abstract, 2-3; EX1005, ¶204. Croyle explained that Pluronic F68 was selected as an excipient to test in the formulation based on its known properties, including its ability to inhibit aggregation of proteins (which would include viral capsids), in solution. EX1009, 6; EX1005, ¶210.

Croyle determined that the formulation that was most successful at enhancing transduction of lung cells *in vitro* and *in vivo* was a blended formulation, consisting of a 1:4 ratio of sucrose to mannitol with 0.001% Pluronic F68 in PBS. EX1009, 2-3; EX1005, ¶¶206, 208-09.

[6] Given the teaching of Konz that its methods are applicable to rAAV formulations in addition to adenoviral formulations, and given that Konz discloses use of non-ionic surfactants, including the Pluronic series, to inhibit aggregation, a POSA would have understood that the teachings of Croyle regarding addition of the non-ionic surfactant Pluronic F68 were equally applicable to rAAV preparations. EX1008, 14:24-27, 24:1-9; EX1005 ¶367.

This formulation also enhanced the physical stability of the virus. EX1009, 3; EX1005, ¶208. After storage in this formulation for 30 days at 4°C, titer dropped by only 10%. EX1009, 3; EX1005, ¶208. After storage in PBS alone under the same conditions, titer dropped below detectable levels in five days. EX1009, 3; EX1005, ¶208.

Importantly, Croyle found that addition of 0.001% Pluronic F68 to the formulation successfully inhibited aggregation of the adenoviral particles, as determined by DLS. EX1009, 6; EX1005, ¶¶205, 207, 211.

D. Potter

Potter, "Streamlined Large-Scale Production of Recombinant Adeno-Associated Virus (rAAV) Vectors," was published in 2002, more than a year before the earliest possible priority date for the '542 patent (June 1, 2004), and is therefore 35 U.S.C. 102(b) prior art, irrespective of whether the '542 patent is entitled to the June 1, 2004 priority date. EX1010; EX1001.

Potter is directed towards large scale production of rAAV vectors to develop a National Reference Standard (NRS). EX1010, 1-2; EX1005, ¶¶213-15. Potter explains that there was a need for an NRS for rAAV to permit researchers to share preclinical data relating to the long-term potential risks for insertional mutagenesis and/or transmission of rAAV. EX1010, 2; EX1005, ¶216.

Potter explains that their goal was to generate the NRS stock, aliquot it into a large number of individual user vials, validate its utility as a reference standard among a handful of rAAV laboratories, and then transfer it to an appropriate distribution service for wider distribution. EX1010, 2; EX1005 ¶216.

Potter describes the generation of the NRS with the newly developed protocol. EX1010, 2; EX1005, ¶¶217-27. Potter used the AAV2 serotype for the capsids. EX1010, 1 (citing EX1026, which, in turn, cites EX1066 (describing protocol for purification of rAAV2)); EX1005, ¶217.

Potter used three different column chromatography steps to purify and concentrate the crude lysate: Streamline Heparin affinity chromatography, phenyl-Sepharose hydrophobic interaction chromatography, and heparin affinity chromatography. EX1010, 5-7; EX1005, ¶221-24. After the third and final column chromatography purification step, the sample was eluted with PBS (phosphate-buffered saline) containing 0.5 M NaCl. EX1010, 5-7; EX1005, ¶225.

Physical particle titers were determined by both a dot-blot assay (DBA) and a real-time polymerase chain reaction (PCR) assay (RTPA). EX1010, 7-17, Table II; EX1005, ¶¶228-42. Notably, Potter states that the DBA and RTPA are based on "quantification of packaged genomes, rather than on the assay of assembled particles." EX1010, 17; EX1005, ¶229. Therefore, removal of empty capsids would

have no effect on titers determined via these analytical methods. EX1010, 17; EX1005, ¶229.

Potter's physical titers therefore provide "vector genomes/ml" ("vg/ml") concentrations, despite the fact that they are referred to in Table II as "particles/ml." EX1005, ¶229. As Potter explains, and as a POSA would have understood, the meaning of "particles/ml" in Potter's Table II is "packaged genomes/ml," which is the same as "vg/ml." EX1067, 3, Table 2 (listing the "Unit Determination" for both the dot-blot assay and quantitative PCR as "Viral genome-containing particles/ml (vg/ml)"); EX1005, ¶¶230-31.

The purified rAAV was also analyzed using electron microscopy. EX1010, 16-17, Fig. 5A; EX1005, ¶¶243-51. Potter examined multiple grids in carrying out the electron microscopy. EX1010, 17; EX1005, ¶¶243-46. A POSA would have understood that because a sample was placed on multiple grids, particles from each sample were visualized across multiple grids. EX1005, ¶¶243-46. Therefore, a POSA would have understood that the electron micrographs in Figure 5 of Potter were representative of particles on multiple grids. EX1010, 16-17, Fig. 5; EX1005, ¶¶243-46. There is no evidence of aggregation in these micrographs. EX1005, ¶247.

VII. CLAIM CONSTRUCTION

Challenged claims 3-6 of the '542 patent recite a composition of purified, recombinant AAV vector particles, where the AAV vector particles are stored

"without significant aggregation." EX1001, 14:15-41. The '542 patent does not define the degree to which aggregation is or is not "significant." Nor does the prosecution history of the '542 patent define the term "significant aggregation." For purposes of the determination of the validity of the challenged claims here, however, the term "significant aggregation" need not be construed. As discussed below, the prior art discloses formulations that do not show evidence of aggregation upon storage. EX1005, ¶261. Thus, the prior art formulations meet this element of the challenged claims, regardless of how it is construed. EX1005, ¶261.

The remaining terms recited in claims 3-6 should be analyzed according to their plain and ordinary meaning. EX1005, ¶262.

Several terms in the challenged claims were construed by the District Court in *Genzyme Corp. v. Novartis Gene Therapies, Inc.*, C.A. No. 21-1736 (RGA) (D. Del.), D.I. 268. EX1061. The following terms of the '542 patent were construed (shaded terms were agreed upon, the others were disputed between the parties and construed by the Court):

Claim Term	Claim(s)	District Court's Construction
"filtration . . . through a 0.22 μm filter"	6	passing a liquid through a 0.22 μm filter to remove materials
"ionic strength"	3, 4, 5, 6	one half of the sum of the molar concentration of each solute species times the square of the charge on each species for all excipients present in the solution

Claim Term	Claim(s)	District Court's Construction
		(calculated according to the equation: $\mu=\frac{1}{2}\Sigma c_i z_i^2$)
"multivalent ion"	3, 4, 5, 6	an ionic species having a charge valency greater than one (whether positive or negative)
"recombinant adeno-associated virus (AAV) vector particles" / "AAV vector particles" / "recombinant virus particles"	3, 4, 5, 6	recombinant AAV virion or virus particles
"dynamic light scattering"	5	a technique in physics that can be used to determine a size distribution profile of small particles in suspension or polymers in solution
"purified"	3, 4, 5, 6	having been subjected to a purification procedure
"significant aggregation"[7]	3, 4, 5, 6	plain and ordinary meaning
"storage" / "stored"	3, 4, 5, 6	maintenance in a frozen or non-frozen state

EX1063, 12; EX1062, 18-26; EX1061, 7.

[7] For this term, the Court rejected Novartis's indefiniteness arguments, ruling instead that the term was defined by the additional limitations in claims 5 and 6, in relation to particle radius as measured by DLS, and product recovery after filtration through a 0.22 μm filter. EX1062, 22-24. As a result, claims 5 and 6, according to the Court's ruling, would be interpreted to require that the formulation meet the limitations of particle radius and product recovery after storage.

The arguments presented here do not change if the District Court's constructions above are applied to the challenged claims, rather than the plain and ordinary meaning. EX1005, ¶264.

VIII. DETAILED EXPLANATION OF GROUNDS

A. Ground 1: Claims 3-6 Are Obvious Over Wu and Konz

Claims 3-6 of the '542 patent are obvious over Wu and Konz. EX1005, ¶¶265-361.

Claims 1 and 2, which have been statutorily disclaimed, are addressed below because challenged claim 3 depends from claim 2 (which, in turn, depends from claim 1), and challenged claims 5 and 6 depend from claim 1.

A POSA would have been motivated to combine Wu and Konz for the following reasons. First, a POSA would have been motivated to remove residual chloroform from Wu's rAAV stocks by exchanging Wu's buffer with a buffer in Konz (as incorporated via Evans), which similarly has high ionic strength and multivalent ions, with a pH around 8.0. EX1005, ¶¶266-75.

Second, a POSA would have been motivated to combine Wu with Konz because both are directed to high titer, large scale preparation of rAAV, and Konz's methods of assessing aggregation – DLS and 0.22 μm filtration – would have been more efficient and cost effective than the electron microscopy used in Wu. EX1005, ¶¶ 266-75.

Third, a POSA would have been motivated to combine Wu with Konz to increase the stability even further of Wu's high physical titer rAAV formulation by addition of a non-ionic surfactant, for example, one from the Pluronic series. EX1005, ¶¶87, 266-75.

1. Claim 1

(a) "A composition for the storage of purified, recombinant adeno-associated virus (AAV) vector particles"

Wu discloses a composition for the storage of purified rAAV vector particles comprising purified, high titer rAAV particles, that is stable during storage for a month at 4°C. EX1007, Abstract, 3-4; EX1005, ¶277.

Konz, and Evans as incorporated into Konz, disclose formulation buffers to maximize stability during storage of high physical titer purified viral preparations. EX1008, 22:15-16, 25:20-22; EX1020, 1:16-19, 3:12-14, 11:31-12:4, 14:15-28, 20:19-24; EX1005, ¶¶278-79.

Wu and Konz thus both meet this limitation of claim 1. EX1005, ¶280.

(b) "purified, recombinant AAV particles at a concentration exceeding 1 x 10^{13} vg/ml up to 6.4 x 10^{13} vg/ml"

Wu discloses purified, rAAV particles at concentrations exceeding 1 x 10^{13} vg/ml and less than 6.4 x 10^{13} vg/ml. Wu discloses concentrations of purified rAAV

stock, determined by dot blot, of about 5 x 10^{13} particles/ml. EX1007, 4; EX1005, ¶¶281-85.

Wu thus meets this limitation of claim 1. EX1005, ¶286.

(c) "a pH buffer, wherein the pH of the composition is between 7.5 and 8.0"

The buffer used in Wu is PBS^{2+} with additional NaCl. EX1007, 2; EX1005, ¶¶287, 310-12. A POSA would understand that the pH of PBS^{2+} varies depending on the exact preparation and conditions such as temperature, but is generally in the range of about 7.4 or 7.5 to 8.0. EX1057; EX1023, 2-3; EX1070, 9; EX1065, 251; EX1005, ¶287.

Konz discloses that higher pH buffers improve viral particle stability. EX1008, 26:12-17; EX1005, ¶289. Konz discloses, through incorporation of Evans, a formulation buffer with high ionic strength (greater than 200 mM), containing multivalent ions and a non-ionic surfactant, at pH 8.0. EX1020, 11:31-12:4, 14:15-28; *see also* 8:23-28, 11:13-30, 36:16-18 (claim 3), 41:9-11 (claim 36); EX1005, ¶290.

Wu, in combination with Konz, thus meets this limitation of claim 1. EX1005, ¶¶291-92.

(d) "excipients comprising one or more multivalent ions selected from the group consisting of citrate, sulfate, magnesium, and phosphate"

Wu discloses a phosphate buffer (PBS^{2+}) containing Mg^{2+} ions, which thus contains two different multivalent ions (phosphate and magnesium). EX1007, 2; EX1005, ¶293. A POSA would have understood "PBS^{2+}" to mean "phosphate buffered saline" with added $MgCl_2$ and $CaCl_2$. EX1065, 250-51; EX1005, ¶293.

Konz incorporates Evans by reference, and Evans, in turn, discloses formulation buffers that meet this limitation of the claims, including a buffer with high ionic strength at pH 8.0, containing $MgCl_2$. EX1020, 11:31-12:4, 14:15-28; *see also*, 9:6-9, 11:13-30, 36:25-27 (claim 5); EX1005, ¶¶294. The presence of $MgCl_2$ in this buffer meets this limitation of the claims.

Wu and Konz thus both meet this limitation of claim 1. EX1005, ¶¶295-96.

(e) "wherein the ionic strength of the composition is greater than 200 mM"

The buffer disclosed in Wu contains 1X PBS^{2+}, along with residual NaCl from the PEG/NaCl precipitation, given the lack of a washing step. EX1007, 2; EX1065, 250-51; EX1005, ¶297. A POSA would have understood the ionic strength of the final resuspension to be about 209 mM at pH 7.5, and 212 at pH 8.0, both of which meet the ionic strength limitation of the challenged claims. EX1005, ¶¶297-312.

Konz incorporates Evans by reference, and Evans, in turn, discloses formulation buffers that meet this limitation of the claims, including a buffer at pH 8.0, which includes a multivalent ion, a non-ionic surfactant, and NaCl at a

concentration up to 250 mM. EX1020, 11:31-12:4, 14:15-28; *see also* 11:13-30, 36:21-22 (claim 4), 41:14-15 (claim 37); EX1005, ¶313. A POSA would have understood that the ionic strength of this buffer would be at least 250 mM. EX1005, ¶314.

Wu, in combination with Konz, thus meets this limitation of claim 1. EX1005, ¶¶315-16.

(f) "and wherein the purified AAV vector particles are stored in the composition without significant aggregation."

Wu discloses an electron microscopy analysis of rAAV particles purified according to its method, which does not show any evidence of aggregation. EX1007, 2-3, Fig. 3; EX1005, ¶317. Moreover, Wu discloses that the rAAV purified stock was stored at 4°C for a month with no significant loss of infectious titer, indicating that the absence of aggregates was maintained during storage. EX1007, 4; EX1005, ¶317. Wu therefore meets this limitation of the claims.

Konz also discloses methods to inhibit particle aggregation and promote stability during storage, including by reference to Evans. EX1020, 8:30-33; EX1008, 23:17-19, 48:11-21, Table 12 (showing DLS results indicating no aggregation, along with high yield (98%) for the sterile filtration process step), 50:1-5, Table 14 (showing 100% yield for the sterile filtration process step), 51:5-10, Table 16 (showing 99% yield for the sterile filtration process step); EX1005, ¶318.

And Konz teaches that sterile filtration and DLS were both carried out after storage at 4ºC. EX1008, 30:13-30, 42:4-19, 48:4-5; EX1005, ¶319. A POSA would have understood that the high yield (98%) following sterile filtration after storage, but before DLS, indicates that sterile filtration had little if any effect on the preparation as far as removal of any aggregates, and therefore that the DLS result was representative of the preparation before sterile filtration. EX1008, 48:11-21, Table 12; EX1005, ¶320.

A POSA would have understood that Konz teaches stable formulations that do not aggregate, even after storage. EX1005, ¶320.

Wu, in combination with Konz, thus meets this limitation of claim 1. EX1005, ¶321.

2. Claim 2: "The composition of claim 1, further comprising ethylene oxide/propylene oxide block copolymer Pluronic® F68."

The combination of Wu and Konz discloses the additional limitation of dependent claim 2. EX1005, ¶322.

Konz discloses formulations containing Pluronic non-ionic surfactants to inhibit aggregation, including by reference to Evans. EX1008, 23:17-24:9; EX1020, 8:30-9:5; EX1005, ¶323.

As Konz states, it was well within the skill of a POSA at the time to have selected the most appropriate non-ionic surfactant from the limited classes of non-

ionic surfactants disclosed, one of which is the Pluronic series, which included Pluronic F68. EX1005, ¶324.

Therefore Wu, in combination with Konz, meets the additional limitation of dependent claim 2. EX1005, ¶325.

3. Claim 3: "The composition of claim 2, wherein the Pluronic® F68 is present at a concentration of 0.001% (w/v)."

The combination of Wu and Konz discloses the additional limitation of dependent claim 3. EX1005, ¶326.

Konz, by reference to Evans, discloses formulation buffers where the non-ionic surfactant is present at a concentration of 0.001% w/v. EX1020, 11:13-21, 11:31-12:4, 14:15-28; EX1005, ¶327.

As Konz explains, a POSA would have known to select the appropriate detergent and how to choose the appropriate concentration of non-ionic sufactant for a given formulation. EX1008, 23:19-24:1; EX1005, ¶328.

Therefore, Wu, in combination with Konz, meets the additional limitation of dependent claim 3. EX1005, ¶329.

4. Claim 4: "The composition of claim 1, wherein the pH buffer is 10 mM Tris, pH 8.0 and the excipients comprise 100 mM sodium citrate."

Konz incorporates Evans by reference, and Evans, in turn, discloses adding a non-reducing free radical scavenger/chelator such as sodium citrate to formulation

buffers to maximize short and long term stability of viral preparations. EX1020, 13:8-34; EX1005, ¶330. Evans discloses adding 100 mM citrate to enhance stability. EX1020, 15:29-31; EX1005, ¶330.

A POSA would have understood that high ionic strength inhibits aggregation of viral particles, particularly at a high physical titer, and therefore would have been motivated to add citrate to the formulation buffer at a 100 mM concentration. EX1005, ¶331.

A POSA, furthermore, as discussed above, would have been motivated to select a formulation buffer similar to the buffer in Wu that successfully inhibited aggregation and maintained stability. EX1005, ¶332. A POSA, therefore, would have chosen the buffer disclosed in Evans with a pH of 8.0, containing NaCl at a concentration of about 250 mM, in addition to $MgCl_2$ and sodium citrate. EX1020, 14:15-28; EX1005, ¶332. This buffer contains Tris in a range up to 7.5 mM, which a POSA would have understood to provide similar buffering capacity as 10 mM Tris to achieve and maintain the desired pH. EX1005, ¶332.

Konz, by reference to Evans, therefore meets the additional limitations of claim 4. EX1005, ¶333.

5. Claim 5: "The composition of claim 1, wherein the purified, recombinant AAV vector particles have an average particle radius (Rh) of less than about 20 nm as measured by dynamic light scattering."

The combination of Wu and Konz discloses the additional limitation of dependent claim 5. EX1005, ¶334.

A POSA would have been motivated to combine Wu with Konz to use analytical methods for assessing particle aggregation that were less labor intensive and more efficient and cost effective than electron microscopy – such as DLS. EX1005, ¶¶271, 273.

Konz discloses using DLS to evaluate particle aggregation after storage. EX1008, 30:13-30, 48:4-15; EX1005, ¶¶335-42. Konz discloses that the mean particle size by DLS analysis was as expected for individual adenovirus particles that were not aggregated, after storage at 4°C followed by sterile filtration. EX1008, 30:13-30, 48:4-21, Table 12; EX1005, ¶335. As discussed above, a POSA would have understood that the high yield following sterile filtration after storage (98%), indicates that sterile filtration had little if any effect on the preparation as far as removal of any aggregates, and therefore that the DLS result was representative of the preparation before sterile filtration. EX1008, 48:11-21, Table 12; EX1005, ¶341.

Given that Konz states expressly that its teachings are applicable to rAAV, a POSA would have understood that this DLS result showing no aggregation of formulations prepared per Konz's methods would be applicable to rAAV. EX1008, 14:24-29; EX1005, ¶192.

Wu, in combination with Konz, therefore meets the additional limitation of dependent claim 5. EX1005, ¶343.

6. Claim 6: "The composition of claim 1, wherein recovery of the purified, recombinant virus particles is at least about 90% following filtration of the composition of said AAV vector particles through a 0.22 μm filter."

The combination of Wu and Konz discloses the additional limitation of dependent claim 6. EX1005, ¶344.

A POSA would have been motivated to combine Wu with Konz to use analytical methods for assessing particle aggregation that were less labor intensive and more efficient and cost effective than electron microscopy – such as sterile filtration through a 0.22 μm filter. EX1005, ¶¶271, 273.

Konz discloses using sterile filtration of purified recombinant viral particles through a 0.22 μm filter, with a recovery greater than 90%, after storage. EX1008, 25:29-30, 30:13-30, 48:15-21, Table 12 (98% yield), 50:1-5, Table 14 (100% yield), 51:6-10, Table 16 (99% yield); EX1005, ¶¶345-52.

Therefore, Wu, in combination with Konz, meets the additional limitation of dependent claim 6. EX1005, ¶353.

7. A POSA Would Have Had a Reasonable Expectation of Success in Making the Claimed Combination

A POSA would have had a reasonable expectation of success in combining Wu with Konz to arrive at the claimed combination. EX1005, ¶354. The techniques required to make the claimed combination, namely, diafiltration,[8] sterile filtration, and the use of DLS, were well known to people of skill in the art at the time and would have required nothing more than routine experimentation. EX1005, ¶¶354, 356.

In addition, a POSA would have had a reasonable expectation of success that the combination of Wu and Konz would produce an rAAV formulation meeting all the limitations of the challenged claims. EX1005, ¶354.

Wu's methods produced a high titer rAAV stock formulation in a high ionic strength buffer at around pH 7.4 or 7.5 to 8.0, containing multivalent ions that did

[8] A POSA at the time would have understood that diafiltration is a technique to exchange one buffer with another, and would have understood how to carry out diafiltration. EX1068, 2; EX1005, ¶274.

not aggregate, as demonstrated by electron microscopy analysis, and that was stable after storage for a month at 4°C. EX1005, ¶¶355, 357.

Konz's methods, in turn, showed no aggregation after storage of a high physical titer formulation, containing multivalent ions and a non-ionic surfactant, as measured by DLS and recovery after 0.22 μm filtration. EX1005, ¶¶356, 358.

A POSA would have chosen one of the Konz high ionic strength (250 mM NaCl) buffers, with a multivalent ion ($MgCl_2$), at a pH similar to that of Wu (about 7.4 or 7.5 to 8.0), and added a non-ionic surfactant, in accordance with Konz's teachings. EX1005, ¶358. Given all of these steps to inhibit aggregation, given the starting point of Wu's formulation where no aggregation was detected, and given Konz's data showing greater than 90% yields and no aggregation per assessment by 0.22 μm sterile filtration after storage at 4ºC, followed by DLS, a POSA would have had a reasonable expectation of success in achieving the claimed combination – a high titer, high ionic strength formulation containing a multivalent ion and 0.001% Pluronic F68 without significant aggregation after storage, as measured by DLS and sterile filtration with a 0.22 μm filter. EX1005, ¶358.

8. Secondary Considerations Do Not Change the Conclusion of Obviousness

Petitioner is not aware of any secondary considerations of non-obviousness with the required nexus to the claims of the '542 patent. EX1005, ¶359. For

example, Petitioner is not aware of any commercial success attributable to a formulation meeting the limitations of the challenged claims.[9] EX1005, ¶359. Similarly, Petitioner is not aware of any licenses directed specifically to the '542 patent or the subject matter recited in challenged claims 3, 5, or 6.[10] EX1005, ¶359.

Finally, Petitioner is not aware of any unexpected results having a nexus to the claimed subject matter. EX1005, ¶360. The '542 patent does not disclose unexpected properties of the claimed formulation. EX1005, ¶360. Effects of pH, multivalent ions, and ionic strength on viral particle aggregation had all been studied

[9] If Patent Owner attempts to rely on the commercial success of Sarepta's gene therapy treatment for Duchenne muscular dystrophy – Elevidys® – there is no nexus to the challenged claims of the '542 patent. There is no nexus between the commercial success of Elevidys® and the formulation recited in the challenged claims. EX1005, ¶359.

[10] If Patent Owner attempts to rely on any license to Novartis in the earlier case brought by Genzyme, any such license was executed in connection with the settlement of litigation and involved at least one other patent in addition to the '542 patent. Thus, there is no nexus between any Novartis license and the formulation recited in the challenged claims. EX1005, ¶359.

for decades before the '542 patent and disclosed in prior art references such as Floyd I, II, and III. EX1030; EX1031; EX1032; EX1005, ¶360. And high titer rAAV formulations had been developed where aggregation was not present before the '542 patent and disclosed in prior art references such as Wu. EX1005, ¶360. The use of techniques such as DLS and sterile filtration using 0.22 μm filters for preparation of viral formulations had been disclosed in prior art references such as Konz. EX1005, ¶360.

To the extent Patent Owner attempts to raise secondary considerations that have only a marginal nexus, if any, to claims 3-6 of the '542 patent, such evidence of secondary considerations should not outweigh the compelling evidence of obviousness, discussed above. Thus, secondary considerations do not alter the conclusion that claims 3-6 of the '542 patent are obvious over the combination of Wu and Konz. EX1005, ¶361.

B. Ground 2: Claim 3 Is Obvious Over Wu, Konz, and Croyle

Dependent claim 3 is also obvious over the combination of Wu, Konz, and Croyle. EX1005, ¶¶362-84.

A POSA would have been motivated to combine Wu and Konz for the reasons set out above for Ground 1. EX1005, ¶363. The combination of Wu and Konz meets all the limitations of claim 1, for the reasons set out above for Ground 1. EX1005, ¶363.

A POSA would have been motivated to combine Wu and Konz with Croyle because Croyle discloses the use of a non-ionic surfactant, 0.001% Pluronic F68, not only to inhibit aggregation of a viral formulation but also to improve gene transfer and expression of a viral vector in a difficult to reach tissue. EX1009, Abstract, 2-4, 6; EX1005, ¶364.

Croyle disclosed that addition of 0.001% Pluronic F68 alone to an adenoviral preparation substantially improved transduction of lung cells *in vivo* and *in vitro*. EX1009, 2-3; EX1005, ¶365. In addition, Croyle disclosed that addition of 0.001% Pluronic F68 to the formulation completely inhibited aggregation of adenoviral particles, as determined by dynamic light scattering. EX1009, 6; EX1005, ¶366.

Given that Wu and Konz are directed to high physical titer preparations of viral particles without aggregation, and that Konz discloses the use of non-ionic surfactants such as the Pluronic series of surfactants to inhibit aggregation, a POSA would have been motivated to select 0.001% Pluronic F68 based on the disclosures of Croyle, to add to a high titer rAAV formulation to inhibit aggregation and also to improve transduction and expression of the viral vector. EX1005, ¶367.

1. Claim 2: "The composition of claim 1, further comprising ethylene oxide/propylene oxide block copolymer Pluronic® F68"

The combination of Wu, Konz, and Croyle discloses the additional limitation of dependent claim 2. EX1005, ¶368.

For the reasons set out above for Ground 1, Wu and Konz disclose all the limitations of claim 1. EX1005, ¶369. Croyle discloses specifically the use of Pluronic F68 non-ionic surfactant to inhibit viral particle aggregation and improve transduction of target cells. EX1005, ¶370.

Therefore, the combination of Wu, Konz, and Croyle discloses the additional limitation of dependent claim 2. EX1005, ¶371.

2. Claim 3: "The composition of claim 2, wherein the Pluronic® F68 is present at a concentration of 0.001% (w/v)"

The combination of Wu, Konz, and Croyle discloses the additional limitation of dependent claim 3. EX1005, ¶372.

For the reasons set out above for Ground 1, Wu and Konz disclose all the limitations of claim 1. EX1005, ¶369. Croyle discloses the use of 0.001% Pluronic F68 non-ionic surfactant to inhibit viral particle aggregation. EX1005, ¶373.

A POSA would have understood that the disclosure in Croyle of "0.001% Pluronic F68" refers to 0.001% "w/v" Pluronic F68. EX1005, ¶374.

3. A POSA Would Have Had a Reasonable Expectation of Success in Making the Claimed Combination

A POSA would have had a reasonable expectation of success in combining Wu and Konz with Croyle to arrive at the claimed combination. EX1005, ¶375. For the reasons set out regarding Ground 1, a POSA would have had a reasonable

expectation of success in combining Wu and Konz to arrive at the claimed combination. EX1005, ¶¶375, 377-80. And to combine Croyle with Wu and Konz required only the addition of 0.001% Pluronic F68, which was clearly within the skill of a POSA at the relevant time. EX1005, ¶375.

Wu's methods produced high physical titer rAAV that did not aggregate in a high ionic strength buffer containing multivalent ions. EX1005, ¶376. Konz teaches the addition of a non-ionic surfactant, including the Pluronic series, to high ionic strength buffers containing multivalent ions to decrease the probability of aggregation further, along with the use of sterile filtration and DLS to evaluate aggregation after storage. EX1005, ¶¶376, 380.

In accordance with Croyle's teachings that addition of 0.001% Pluronic F68 completely inhibited aggregation of a formulation of viral particles, a POSA would have selected 0.001% Pluronic F68 from the non-ionic surfactants disclosed in Konz. EX1005, ¶379.

Given all these steps to inhibit aggregation, given the starting point of Wu's formulation where no aggregation was detected, and given Konz's results, a POSA would have had a reasonable expectation of success in achieving the claimed combination – a high titer, high ionic strength formulation containing a multivalent ion and 0.001% Pluronic F68 without significant aggregation after storage. EX1005, ¶¶380-81.

4. Secondary Considerations Do Not Change the Conclusion of Obviousness

For the reasons discussed above regarding Ground 1, secondary considerations do not alter the conclusion that claim 3 of the '542 patent would have been obvious over the combination of Wu, Konz, and Croyle. EX1005, ¶¶382-84.

C. Ground 3: Claims 3-6 Are Obvious Over Potter and Konz

Claims 3-6 of the '542 patent are obvious over Potter and Konz. EX1005, ¶¶385-463.

A POSA would have been motivated to combine Potter with Konz because both Potter and Konz are directed towards large scale production of concentrated, high physical titer formulations of rAAV that are stable during storage. EX1010, 2; EX1008, 1:25-27, 22:15-16, 25:20-22, 30:19-20; EX1005, ¶386. Nonetheless, Potter includes the analytical technique of electron microscopy, which is labor and time intensive and difficult to adapt to scale. EX1010, 16-17, Fig. 5; EX1005, ¶387.

Konz is also directed to methods of preventing aggregation, such as the use of non-ionic surfactants, and analytical techniques to evaluate the extent of aggregation, such as dynamic light scattering and 0.22 μm filtration, that are more adaptable to scale than the electron microscopy used in Potter. EX1008, 24:1-9, 48:11-21, Table 12; EX1005, ¶388.

A POSA would therefore have been motivated to combine Potter's methods for large scale purification of rAAV with the additional improvements in Konz to streamline the production and make it even more adaptable to scale up. EX1005, ¶389.

Moreover, a POSA would have understood that the methods of Potter produced a high physical titer rAAV preparation with no evidence of aggregation in a high ionic strength buffer (0.5 M NaCl), with a multivalent ion (phosphate), around pH 7.4 or 7.5 to pH 8.0. EX1005, ¶391. Therefore a POSA would have been motivated to preserve these general characteristics in choosing one of the Konz buffers with the addition of a non-ionic surfactant to inhibit aggregation even further. EX1005, ¶¶390-91.

As discussed above, claims 1 and 2 were statutorily disclaimed. EX1019. Nonetheless, these claims are addressed below because challenged claim 3 depends from claim 2 (which, in turn, depends from claim 1), and challenged claims 4, 5 and 6 depend from claim 1.

1. Claim 1

(a) "A composition for the storage of purified, recombinant adeno-associated virus (AAV) vector particles"

Potter discloses a composition for the storage of purified rAAV vector particles comprising a "reference standard stock of rAAV with a precisely defined

titer." EX1010, 2; EX1005, ¶393. This reference standard would be aliquoted into a large number of individual user vials, validated as a reference standard among a handful of rAAV laboratories, and then transferred to an appropriate distribution service. EX1010, 2; EX1005, ¶393. The distribution of the reference stock among a large number of rAAV laboratories requires storing the rAAV particles and maintaining their titer during storage. EX1005, ¶393. Otherwise, these aliquoted preparations of the standard would vary from the original stock, an outcome contrary to the entire purpose of creating a reference standard. EX1005, ¶393.

Konz, including by reference to Evans, discloses formulation buffers to maximize stability during storage of high physical titer purified viral preparations. EX1008, 22:15-16, 25:20-22; EX1020, 1:16-19, 3:12-14, 11:31-12:4, 14:15-28, 20:19-24; EX1005, ¶¶394-95.

Potter, in combination with Konz, therefore meets this limitation of claim 1. EX1005, ¶396.

(b) "purified, recombinant AAV particles at a concentration exceeding 1 x 10^{13} vg/ml up to 6.4 x 10^{13} vg/ml"

Potter discloses purified, rAAV particles at concentrations exceeding 1 x 10^{13} vg/ml and less than 6.4 x 10^{13} vg/ml. EX1010, 19, Table II (disclosing preparations with physical titers measured by dot blot and real-time PCR of 1.12 x 10^{13} vg/ml and

1.46 x 10^{13} vg/ml, respectively); EX1005, ¶¶397-401. Both of these concentrations fall within the claimed range. EX1010, 19, Table II; EX1005, ¶402.

Therefore, Potter meets this limitation of claim 1. EX1005, ¶403.

(c) "a pH buffer, wherein the pH of the composition is between 7.5 and 8.0"

The buffer used in Potter is PBS containing 0.5 M NaCl. EX1010, 7; EX1005, ¶404. A POSA would have understood that the pH of PBS varies depending on the exact preparation and conditions such as temperature, but is generally in the range of approximately 7.4 or 7.5 to 8.0. EX1057; EX1023, 2-3; EX1070, 9; EX1065, 257, 294; EX1005, ¶404.

Konz discloses that higher pH buffers improve viral particle stability. EX1008, 26:12, 26:16-17. EX1005, ¶405. Konz incorporates Evans by reference, and Evans, in turn, discloses formulation buffers, including a buffer with high ionic strength (greater than 200 mM) and containing multivalent ions and a non-ionic surfactant at pH 8.0. EX1020, 11:31-12:4, 14:15-28; *see also* 8:23-28, 11:13-30, 36:16-18 (claim 3), 41:9-11 (claim 36); EX1005, ¶406.

Potter, in combination with Konz, therefore meets this limitation of claim 1. EX1005, ¶¶ 407-08.

(d) "excipients comprising one or more multivalent ions selected from the group consisting of citrate, sulfate, magnesium, and phosphate"

Potter discloses a phosphate buffer (PBS), which meets this limitation. EX1010, 7. EX1005, ¶409. A POSA would have understood "PBS" to mean "phosphate buffered saline." EX1005, ¶409.

Konz incorporates Evans by reference, and Evans, in turn, discloses formulation buffers that meet this limitation of the claims, including a buffer with high ionic strength at pH 8.0, containing $MgCl_2$. EX1020, 11:31-12:4, 14:15-28; *see also*, 9:6-9, 11:13-30, 36:25-27 (claim 5); EX1005, ¶410. The presence of $MgCl_2$ in this buffer meets this limitation of the claims. EX1005, ¶410.

Potter, in combination with Konz, therefore meets this limitation of claim 1. EX1005, ¶¶411-12.

(e) "wherein the ionic strength of the composition is greater than 200 mM"

The buffer disclosed in Potter contains 0.5 M NaCl. EX1010, 7; EX1005, ¶413. A POSA would have understood that the ionic strength of that solution, not even taking into account additions to the ionic strength from the phosphate ions in the buffer, is 500 mM, which is greater than 200 mM. EX1005, ¶¶413-14.

Konz incorporates Evans by reference, and Evans, in turn, discloses formulation buffers that meet this limitation of the claims, including a buffer at pH

8.0, which includes a multivalent ion, a non-ionic surfactant, and NaCl at a concentration up to 250 mM. EX1020, 11:31-12:4, 14:15-28; *see also* 11:13-30, 36:21-22 (claim 4), 41:14-15 (claim 37); EX1005, ¶415. A POSA would have understood that the ionic strength of this buffer would be at least 250 mM. EX1005, ¶416.

Potter, in combination with Konz, therefore meets this limitation of claim 1. EX1005, ¶¶417-18.

(f) "and wherein the purified AAV vector particles are stored in the composition without significant aggregation."

Potter discloses an electron microscopy analysis of the purified rAAV particles. EX1010, 16-17, Fig. 5; EX1005, ¶419. There is no evidence of aggregation in this study. EX1005, ¶419. Potter therefore meets this limitation of the claims. EX1005, ¶419.

Konz discloses methods that inhibited particle aggregation, including by reference to Evans. EX1008, 23:17-19, 48:11-21, Table 12, 50:1-5, Table 14, 51:5-10, Table 16; EX1020, 8:30-33; EX1005, ¶420.

Konz teaches that sterile filtration and DLS were both carried out after storage at 4ºC. EX1008, 30:13-30, 42:4-19, 48:4-5; EX1005 ¶421. Konz teaches that recovery after sterile filtration was greater than 90%, and that DLS carried out after sterile filtration showed no aggregation of the purified vector particles. EX1008,

48:4-21, Table 12 (Example 9); EX1005, ¶422. A POSA would have understood that the high yield after sterile filtration, following storage at 4°C (98%) but before DLS, would have indicated that sterile filtration had little if any effect on the preparation as far as removal of any aggregates, and therefore that the DLS result was representative of the preparation before sterile filtration. EX1005, ¶422.

Therefore, a POSA would have understood that in the examples in which the preparation of viral particles is found not to contain aggregation as assessed by sterile filtration or DLS, the sterile filtration and DLS were carried out after storage in formulation buffer. EX1005, ¶422.

Potter, in combination with Konz, therefore meets this limitation of claim 1. EX1005, ¶423.

2. Claim 2: "The composition of claim 1, further comprising ethylene oxide/propylene oxide block copolymer Pluronic® F68."

The combination of Potter and Konz discloses the additional limitation of dependent claim 2. EX1005, ¶424.

Konz discloses formulations containing Pluronic non-ionic surfactants to inhibit aggregation, including by reference to Evans. EX1008, 23:17-24:9; EX1020, 8:30-9:5; EX1005, ¶425.

As Konz states, it was well within the skill of a POSA at the time to have selected the most appropriate non-ionic surfactant from the limited classes of non-

ionic surfactants disclosed, one of which is the Pluronic series, which included Pluronic F68. EX1005, ¶426.

Therefore Potter, in combination with Konz, meets the additional limitation of dependent claim 2. EX1005, ¶427.

3. Claim 3: "The composition of claim 2, wherein the Pluronic® F68 is present at a concentration of 0.001% (w/v)."

The combination of Potter and Konz discloses the additional limitation of dependent claim 3. EX1005, ¶428.

Konz, by reference to Evans, discloses formulation buffers where the non-ionic surfactant is present at a concentration of 0.001% w/v. EX1020, 11:31-12:4, 14:15-28; EX1005, ¶429.

As Konz explains, a POSA would have known to select the appropriate detergent and how to choose the appropriate concentration of non-ionic sufactant for a given formulation. EX1008, 23:19-24:1; EX1005, ¶430.

Therefore, Potter, in combination with Konz, meets the additional limitation of dependent claim 3. EX1005, ¶431.

4. Claim 4: "The composition of claim 1, wherein the pH buffer is 10 mM Tris, pH 8.0 and the excipients comprise 100 mM sodium citrate."

Konz incorporates Evans by reference, and Evans, in turn, discloses adding a non-reducing free radical scavenger/chelator such as sodium citrate to formulation

buffers to maximize short and long term stability of viral preparations. EX1020, 13:8-34l; EX1005, ¶432. Evans discloses adding 100 mM citrate to enhance stability. EX1020, 15:29-31; EX1005, ¶432.

A POSA would have understood that high ionic strength inhibits aggregation of viral particles, particularly at a high physical titer, and therefore would have been motivated to add citrate to the formulation buffer at a 100 mM concentration. EX1005, ¶433.

A POSA, furthermore, as discussed above, would have been motivated to select a formulation buffer similar to the buffer in Potter that successfully inhibited aggregation and maintained stability. EX1005, ¶434. A POSA, therefore, would have chosen the buffer disclosed in Evans with a pH of 8.0, containing NaCl at a concentration of about 250 mM, in addition to $MgCl_2$ and sodium citrate. EX1020, 14:15-28; EX1005, ¶434. This buffer contains Tris in a range up to 7.5 mM, which a POSA would have understood provides similar buffering capacity as 10 mM Tris to achieve and maintain the desired pH. EX1005, ¶434.

Konz, by reference to Evans, therefore meets the additional limitations of claim 4. EX1005, ¶435.

5. Claim 5: "The composition of claim 1, wherein the purified, recombinant AAV vector particles have an average particle radius (Rh) of less than about 20 nm as measured by dynamic light scattering."

The combination of Potter and Konz discloses the additional limitation of dependent claim 5. EX1005, ¶436.

Konz discloses using DLS to evaluate particle aggregation after storage followed by 0.22 μm sterile filtration. EX1008, 30:13-30, 48:4-21, Table 12; EX1005, ¶¶437-42, 444. Konz discloses that the mean particle size by DLS analysis was as expected for individual particles that were not aggregated. EX1008, 48:4-15; EX1005, ¶437. As discussed above, a POSA would have understood that the high yield following sterile filtration after storage (98%), indicates that sterile filtration had little if any effect on the preparation as far as removal of any aggregates, and therefore that the DLS result was representative of the preparation before sterile filtration. EX1008, 48:11-21, Table 12; EX1005, ¶443.

Given that Konz states expressly that its teachings are applicable to rAAV, a POSA would have understood that these DLS results showing no aggregation of formulations prepared per Konz's methods would be applicable to rAAV. EX1005, ¶335.

Potter, in combination with Konz, therefore meets the additional limitation of dependent claim 5. EX1005, ¶445.

6. Claim 6: "The composition of claim 1, wherein recovery of the purified, recombinant virus particles is at least about 90% following filtration of the composition of said AAV vector particles through a 0.22 μm filter."

The combination of Potter and Konz discloses the additional limitation of dependent claim 6. EX1005, ¶446.

Konz discloses using sterile filtration of purified recombinant viral particles through a 0.22 μm filter, with a recovery greater than 90%, after storage. EX1008, 25:29-30, 30:13-30, 48:15-21, Table 12 (98% yield), 50:1-5, Table 14 (100% yield), 51:6-10, Table 16 (99% yield); EX1005, ¶¶447-54.

Therefore, Potter, in combination with Konz, meets the additional limitation of dependent claim 6. EX1005, ¶455.

7. A POSA Would Have Had a Reasonable Expectation of Success in Making the Claimed Combination

A POSA would have had a reasonable expectation of success in combining Potter with Konz to arrive at the claimed combination. EX1005, ¶456. The techniques required to make the claimed combination, namely, diafiltration, sterile filtration, and the use of DLS, were well known to people of skill in the art at the time and would have required nothing more than routine experimentation. EX1005, ¶¶456, 458.

Potter's methods produced high physical titer rAAV that did not aggregate in a high ionic strength buffer containing a multivalent ion. EX1005, ¶457. Konz

teaches the addition of a non-ionic surfactant to high ionic strength buffers containing multivalent ions at a pH around 8.0 to decrease the probability of aggregation further, along with the use of sterile filtration and DLS to evaluate aggregation after storage, producing yields greater than 90%, and DLS results indicating individual viral particles without aggregation. EX1005, ¶457, 459-60.

As discussed above, a POSA would have understood that the high yield following sterile filtration after storage (98%), indicates that sterile filtration had little if any effect on the preparation as far as removal of any aggregates, and therefore that the DLS result was representative of the preparation before sterile filtration. EX1008, 48:11-21, Table 12; EX1005, ¶443.

Therefore, a POSA would have had a reasonable expectation of success in achieving the claimed combination. EX1005, ¶456.

8. Secondary Considerations Do Not Change the Conclusion of Obviousness

For the reasons set out regarding Ground 1, secondary considerations do not alter the conclusion that claims 3-6 of the ’542 patent are obvious over the combination of Potter and Konz. EX1005, ¶¶461-63.

D. Ground 4: Claim 3 Is Obvious Over Potter, Konz, and Croyle

Dependent claim 3 is also obvious over the combination of Potter, Konz, and Croyle. EX1005, ¶¶464-86.

A POSA would have been motivated to combine Potter and Konz for the reasons set out above regarding Ground 3. EX1005, ¶465.

A POSA would have been motivated to combine Potter and Konz with Croyle because Croyle discloses the use of a non-ionic surfactant, 0.001% Pluronic F68, not only to inhibit aggregation of a viral formulation but also to improve gene transfer and expression of a viral vector in a difficult to reach tissue. EX1009, Abstract, 2-4, 6; EX1005, ¶466.

Croyle disclosed that addition of 0.001% Pluronic alone to an adenoviral preparation substantially improved transduction of lung cells *in vivo* and *in vitro*. EX1009, 2-4; EX1005, ¶467.

In addition, Croyle discloses that addition of 0.001% Pluronic F68 to the formulation completely inhibited aggregation of adenoviral particles, as determined by dynamic light scattering. EX1009, 6; EX1005, ¶468.

Given that Potter and Konz are directed to high titer preparations of viral particles without aggregation, and that Konz discloses the use of non-ionic surfactants such as the Pluronic series of surfactants to inhibit aggregation, a POSA would have been motivated to select 0.001% Pluronic F68 based on the disclosures of Croyle, to add to a high titer rAAV formulation to inhibit aggregation and perhaps also to improve transduction and expression of the viral vector. EX1005, ¶469.

1. Claim 2: "The composition of claim 1, further comprising ethylene oxide/propylene oxide block copolymer Pluronic® F68"

The combination of Potter, Konz, and Croyle discloses the additional limitation of dependent claim 2. EX1005, ¶470.

For the reasons set out above for Ground 1, Potter and Konz disclose all the limitations of Claim 1. EX1005, ¶471. Croyle discloses specifically the use of Pluronic F68 non-ionic surfactant to inhibit viral particle aggregation. EX1005, ¶¶471-72.

Therefore, the combination of Potter, Konz, and Croyle discloses the additional limitation of dependent claim 2. EX1005, ¶473.

2. Claim 3: "The composition of claim 2, wherein the Pluronic® F68 is present at a concentration of 0.001% (w/v)"

The combination of Potter, Konz, and Croyle discloses the additional limitation of dependent claim 3. EX1005, ¶474.

Croyle discloses the use of 0.001% Pluronic F68 non-ionic surfactant to inhibit viral particle aggregation. EX1005, ¶475.

A POSA would have understood that the disclosure in Croyle of "0.001% Pluronic F68" refers to 0.001% "w/v" Pluronic F68. EX1005, ¶476.

3. A POSA Would Have Had a Reasonable Expectation of Success in Making the Claimed Combination

A POSA would have had a reasonable expectation of success in combining Potter and Konz with Coyle to arrive at the claimed combination. EX1005, ¶477. The techniques required to combine Potter and Konz to make the claimed combination, namely, diafiltration, sterile filtration, and the use of DLS, were well known to a POSA at the time and would have required nothing more than routine experimentation. EX1005, ¶¶477-79. To combine Croyle with Potter and Konz requires only the addition of 0.001% Pluronic F68, which is clearly within the skill of a POSA at the relevant time. EX1005, ¶477.

A POSA would have a reasonable chance of success that the rAAV preparation would be without significant aggregation after storage. EX1005, ¶480, 480. A POSA would have started with Potter's high titer rAAV preparation that did not aggregate, per Potter's EM analysis, and then take further measures to ensure no aggregation. EX1005, ¶480.

A POSA would have chosen one of the Konz high ionic strength (250 mM NaCl) buffers, with a multivalent ion ($MgCl_2$), at a pH similar to that of Potter (7.4 or 7.5 to 8.0), and added a non-ionic surfactant, in accordance with Konz's teachings. EX1005, ¶481. In accordance with Croyle's teachings that addition of 0.001% Pluronic F68 completely inhibited aggregation of a formulation of viral particles, a

POSA would have selected 0.001% Pluronic F68 from the limited classes of non-ionic surfactants disclosed in Konz, one of which is the Pluronic series. EX1005, ¶481.

Konz discloses purified preparations in formulation buffer containing a non-ionic surfactant that, after storage, produced yields greater than 90% after sterile filtration using a 0.22 μm filter, with no evidence of aggregation as evaluated by DLS. EX1005, ¶482. As discussed above, a POSA would have understood that the high yield following sterile filtration after storage (98%), indicates that sterile filtration had little if any effect on the preparation as far as removal of any aggregates, and therefore that the DLS result was representative of the preparation before sterile filtration. EX1008, 48:11-21, Table 12; EX1005, ¶341.

A POSA would have understood from Croyle that selection of Pluronic F68 as the non-ionic surfactant to add to the formulation buffer in Konz would have further decreased the chance of aggregation. EX1005, ¶482.

Given all these steps to inhibit aggregation, given the starting point of Potter's formulation where no aggregation was detected, and given Konz's results, a POSA would have had a reasonable expectation of success in achieving the claimed combination – a high titer, high ionic strength formulation containing a multivalent ion and 0.001% Pluronic F68 without significant aggregation after storage. EX1005, ¶483.

4. Secondary Considerations Do Not Change the Conclusion of Obviousness

For the reasons discussed above regarding Ground 1, secondary considerations do not alter the conclusion that claim 3 of the '542 patent would have been obvious over the combination of Potter, Konz, and Croyle. EX1005, ¶¶484-86.

IX. CONCLUSION

Sarepta respectfully requests institution of IPR for claims 3-6 of the '542 patent based on the grounds specified in this Petition.

Respectfully submitted,

June 26, 2025

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WORD COUNT CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. §42.24(d), Petitioner hereby certifies, in accordance with and reliance on the word count provided by the word-processing system used to prepare this Petition, that the number of words in this paper is 12,830. Pursuant to 37 C.F.R. §42.24(d), this word count excludes the table of contents, table of authorities, mandatory notices under §42.8, certificate of service, certificate of word count, appendix of exhibits, and any claim listing.

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §42.6 (e) and 37 C.F.R. §42.105, I hereby certify that on June 26, 2025, I caused the foregoing Petition for *Inter Partes* Review, Power of Attorney, and Exhibits 1001–[ ] to be served on Patent Owner by depositing them for shipment with Federal Express to the correspondence address of record listed on the Patent Center:

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