IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

VIIV HEALTHCARE UK LTD. AND VIIV HEALTHCARE CO.,	:	
Plaintiffs,	:	
v.	:	C.A. 11-576-RGA
LUPIN LTD. AND LUPIN PHARMACEUTICALS, INC.,	:	
Defendants.	:	
VIIV HEALTHCARE UK LTD. AND VIIV HEALTHCARE CO.,	:	
Plaintiffs,	:	
v.	:	C.A. 11-688-RGA
TEVA PHARMACEUTICALS USA, INC.,	:	
Defendant.	:	

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November 16, 2012
Wilmington, Delaware

ANDREWS, UNITED STATES DISTRICT JUDGE:

This is a claim construction opinion. Plaintiffs Viiv Healthcare UK Ltd. and Viiv Healthcare Co. assert U.S. Patent No. 6,417,191 ("'191 Patent") against Defendants Lupin Ltd., Lupin Pharmaceuticals, Inc., and Teva Pharmaceuticals, USA, Inc.[1] The '191 Patent relates to therapeutic combinations of anti-HIV drug compounds.

I. Agreed Upon Term

The parties have agreed to the construction of the term "simultaneously" as follows:

Undisputed Claim Term	Agreed Upon Construction
"simultaneously" (claims 8, 21, 27, 36)	at the same time, either in the same or separate pharmaceutical formulations

II. Disputed Terms

This brings the Court to the disputed terms. The disputed terms "animal," "physiologically functional derivative," and "symptoms or effects of an HIV infection" are construed as follows:

Disputed Claim Term	Court's Construction
"animal" (claims 1, 11, 20, 24, 30, 32, 39)	Plain and ordinary meaning.

[1] Viiv filed suit against the Lupin entities and Teva separately. The claim construction briefing and hearing were conducted jointly for purposes of efficiency.

"physiologically functional derivative" (claims 1, 2, 13, 15, 48, 51)	Any physiologically acceptable salt, ether, ester, salt of such ester of 1592U89, zidovudine or 3TC; or solvates of any thereof and their physiologically functional derivatives; or any other compound which upon administration to the recipient, is capable of providing (directly or indirectly) such a compound or an antivirally active metabolite or residue thereof.
"symptoms or effects of an HIV infection" (claims 1, 20, 32)	Plain and ordinary meaning.

The remaining terms present more complicated issues of claim construction and merit written explanation.

A. "Synergism"

Disputed Claim Term/Phrase from Patent-in-Suit	**ViiV's Proposed Construction**	**Lupin's Proposed Construction**	**Teva's Proposed Construction**
"(1S, 4R)-cis-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-y1]-2-cyclopentene-1-methanol or a physiologically functional derivative thereof and (2R, cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one or a physiologically functional derivative thereof" (claim 48)	Plain and ordinary meaning. If the Court wishes to further construe the term, its plain and ordinary meaning is a combination of (1S, 4R)-cis-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-y1]-2-cyclopentene-1-methanol or a physiologically functional derivative and (2R, cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one or physiologically functional derivative.	[Lupin takes no position on this term.]	Synergistic combination of (1S, 4R)- cis-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]- 2-cyclopentene-1-methanol or a physiologically functional derivative thereof and (2R, cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one or a physiologically functional derivative thereof

Disputed Claim Term/Phrase from Patent-in-Suit	ViiV's Proposed Construction	Lupin's Proposed Construction	Teva's Proposed Construction
"combination" (claims 1, 8, 10, 20, 21, 23, 27, 29, 32, 36, 38)	Plain and ordinary meaning. If the Court wishes to further construe the term, its plain and ordinary meaning is combination.	Synergistic combination.	Synergistic combination
Disputed Claim Term/Phrase from Patent-in-Suit	**ViiV's Proposed Construction**	**Lupin's Proposed Construction**	**Teva's Proposed Construction**
"pharmaceutical formulation" /"formulation" (claims 10, 16, 23, 29, 38, 48, 51)	Plain and ordinary meaning. If the Court wishes to further construe the term, its plain and ordinary meaning is a combination of one or more active ingredients with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents.	Synergistic pharmaceutical formulation / Synergistic formulation.	Teva does not seek construction of this claim term and therefore does not proffer a construction.
Disputed Claim Term/Phrase from Patent-in-Suit	**ViiV's Proposed Construction**	**Lupin's Proposed Construction**	**Teva's Proposed Construction**
"combination" (claims 1, 8, 10, 20, 21, 23, 27, 29, 32, 36, 38)	Plain and ordinary meaning. If the Court wishes to further construe the term, its plain and ordinary meaning is combination.	Synergistic combination.	Synergistic combination
Disputed Claim Term/Phrase from Patent-in-Suit	**ViiV's Proposed Construction**	**Lupin's Proposed Construction**	**Teva's Proposed Construction**
"pharmaceutical formulation" /"formulation" (claims 10, 16, 23, 29,	Plain and ordinary meaning. If the Court wishes to further construe the term, its	Synergistic pharmaceutical formulation / Synergistic	Teva does not seek construction of this claim term and therefore does not

38, 48, 51)	plain and ordinary meaning is a combination of one or more active ingredients with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents.	formulation.	proffer a construction.
Disputed Claim Term/Phrase from Patent-in-Suit	**ViiV's Proposed Construction**	**Lupin's Proposed Construction**	**Teva's Proposed Construction**
"therapeutically effective amount" (claims 1, 20, 32)	Plain and ordinary meaning. If the Court wishes to further construe the term, its plain and ordinary meaning is an amount that will treat or prevent symptoms or effects of an HIV infection in an infected animal.	Amount sufficient to cause a synergistic response.	Teva does not seek construction of this claim term and therefore does not proffer a construction.

The construction of all of these terms hinges upon the same dispute: whether the "synergism" achieved by the drug combination functions to limit the '191 Patent's claims. Synergism is not mentioned within any of the claims. Defendants, however, argue that the specification and prosecution history demonstrate that synergism is an essential element of the claimed drug combination. They argue that the patentee disavowed non-synergistic combinations and the claims should be construed accordingly. Viiv argues that the synergistic activity is not an element of the drug combination itself, but is an unexpected effect or result of

the drug combination's administration, which was emphasized in order to overcome repeated rejections for obviousness.

Claim terms should generally be given their ordinary and customary meaning. *ICU Med., Inc. v. Alaris Med. Sys., Inc.*, 558 F.3d 1368, 1374 (Fed. Cir. 2009). That meaning is determined by how a person of ordinary skill in the art in question would understand the terms at the time of the invention. *Id.* In determining this meaning, the claims must be read in view of the specification, of which they are a part. *SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc.*, 242 F.3d 1337, 1340 (Fed. Cir. 2001). "Where the specification makes clear that the invention does not include a particular feature, that feature is deemed to be outside the reach of the claims of the patent, even though the language of the claims, read without reference to the specification, might be considered broad enough to encompass the feature in question." *Id.* at 1341. "The patentee may demonstrate intent to deviate from the ordinary and accustomed meaning of a claim term by including in the specification expressions of manifest exclusion or restriction, representing a clear disavowal of claim scope." *Id.* "Mere criticism of a particular embodiment encompassed in the plain meaning of a claim term is not sufficient to rise to the level of clear disavowal. . . . It is likewise not enough that [all of the embodiments] contain a particular limitation." *Thorner v. Sony Computer Entm't Am. LLC*, 669 F.3d 1362, 1366 (Fed. Cir. 2012). Any disclaimer must be clear and unmistakable. *Id.* at 1366-67.

Defendants begin their disavowal argument with reliance on the specification. Defendants point to the title of the '191 Patent itself, which emphasizes the synergistic aspect of the invention: "Synergistic Combinations of Zidovudine, 1592U89, and 3TC." Defendants then refer to description that explains the synergistic anti-viral activity achieved by the invention:

> Unexpectedly, it has now been found that by combining 1592U89, zidovudine and 3TC a synergistic anti-HIV effect is achieved. The result is surprising since all three drugs act upon the same molecule, HIV Reverse Transcript use. It is a feature of this invention that the use of this drug combinations [sic] will provide synergistic antiviral effects, more complete viral suppression over a longer period, limit the emergence of drug resistant HIV mutants and allow better management of drug-related [toxicity].

Patent '191, ll. 2:08-15. Defendants particularly emphasize the language describing "synergistic antiviral effects" as a "feature of the invention." Defendants argue that this statement speaks to the scope of the invention itself as requiring synergism and the claims should be limited accordingly.

Defendants next cite another passage from the specification: "If there is sequential administration, the delay in administering the second and third active ingredients should not be such as to lose the benefit of a synergistic therapeutic effect of the combination of the active ingredients." *Id.* at 3:62-65. Defendants argue that these directions explicitly mandate a particular method of administration to ensure that the synergistic drug activity is not lost. Defendants also point to the description of specific drug ratios aimed at ensuring synergism.[2] According to Defendants, these are additional pieces of evidence that synergism is an essential part of the invention and that non-synergistic drug combinations have been disclaimed by the patentee.

The Court does not find that the specification evinces "manifest statements of exclusion or restriction" giving rise to clear and unmistakable disclaimer. Disclaimer of claim scope most

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[2] The ratios are explained as follows:

> The synergistic effects of the combination of 1592U89, zidovudine and 3TC (or, alternatively to 3TC, FTC), or a physiologically functional derivative of any thereof are seen over a ratio, for example, of 1 to 20:1 to 20:1 to 10 (by weight), preferably 1 to 10:1 to 10:1 to 5 (by weight), particularly 1 to 3:1 to 3:1 to 2 (by weight)[.] Conveniently each compound will be employed in the combination in an amount at which it exhibits antiviral activity when used alone.

Id. at 4:17-25.

typically occurs through a patentee's differentiation of prior art. Here, at no point does the patentee criticize a prior art for lacking synergism and then distinguish the drug combination for its synergistic aspect. To the contrary, the patentee differentiates her invention by emphasizing the novelty of combining the drugs in the first place.[3] Further, when the specification explains what the "present invention" consists of, it describes the drug combination.[4] Synergism or synergistic effects are only discussed insofar as they constitute unexpected results. The description of "synergistic anti-viral effects" as a "feature of the invention" does not give rise to disavowal of non-synergism. The discussion just preceding this description makes clear that this synergism feature came along "unexpectedly" and that the "result [was] surprising."[5] This confirms the nature of synergism as an incident of the claimed drug combination, but not as a component or property of the combination itself.[6]

Despite Defendants' arguments, the specification's detailing of preferred drug combination ratios for the delivery of synergy is not persuasive evidence of disclaimer.

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[3] The specification describes the prior art in relation to the present invention as follows:

> To date the treatment of HIV infection has relied to a large extent upon monotherapy with nucleoside reverse transcriptase inhibitors such as zidovudine, didanosine (ddI), zalcitabine (ddC) and stavudine (D4T). However, these drugs eventually become less effective due either to the emergence of HIV resistant mutants [or] because of toxicity. Thus, new therapies are needed.
>
> The combination of zidovudine with either ddC or ddI has shown promising results in HIV infected patients[.]

Id. at 1:59-67.

[4] For example, the specification states, "[T]he present invention provides a combination comprising 1592U89 or a physiologically functional derivative thereof, zidovudine or a physiologically functional derivative thereof and 3TC (or, alternatively to 3TC, FTC) or a physiologically functional derivative thereof." *Id.* at 2:18-23.

[5] "Unexpectedly, it has now been found that by combining 1592U89, zidovudine and 3TC a synergistic anti-HIV effect is achieved. This result is surprising since all three drugs act upon the same molecule, HIV Reverse Transcript use." *Id.* at 2:7-9.

[6] It makes sense for the patentee to have emphasized these unexpected results, as the '191 Patent's application was repeatedly rejected for obviousness. (D.I. 67, Exhs. 37-41).

Dependent claims 2-4 claim these same ratios. These claims are dependent to claim 1, which does not mention any ratio. The rule of claim differentiation suggests that claim 1 should be read more broadly than its dependent claims 2-4 and is thus not limited to the described ratios. It therefore follows that the effects of these ratios are not limiting on the independent claim. Finally, the specification's advice that the combination "should" be taken within a certain time period is not strong enough language to justify finding a "clear and unmistakable" disclaimer. Moreover, even in this context, synergism is described as an effect of the combination rather than a property of the combination itself. In addition, the claims describe numerous distinct methods of administration, and they are not limited to sequential administration, thus undermining the argument that the statements should limit every claim. For all these reasons, the Court holds that specification disclaimer does not render "synergism" as a limit on claim scope.

Defendants also argue for prosecution disclaimer. "[A] patentee may limit the meaning of a claim term by making a clear and unmistakable disavowal of scope during prosecution." *Computer Docking Station Corp. v. Dell, Inc.*, 519 F.3d 1366, 1374 (Fed. Cir. 2008). This may occur where an applicant clearly characterizes an invention in order to overcome rejections based on prior art. *Id.* Prosecution disclaimer is not found where the file history is ambiguous. *Id.* at 1375.

Defendants argue that the patentee's responses to the PTO Examiner's rejections disclaimed non-synergistic drug combinations. The '191 Patent application was rejected numerous times for obviousness. (D.I. 67, Exhs. 37-41). The rejections were predicated on the rationale that "[i]t is generally considered prima facie obvious to combine two compounds each of which is taught by the prior art to be useful for the same purpose, in order to form a composition which is to be used for the very same purpose." (*See, e.g.*, D.I. 67, Exh. 41 at 2-3).

In response to these rejections, the patentee emphasized the originality of combining the drug compounds and the unexpected results of the combination. The patentee stated the following within a November 19, 1998 response:

> Nothing in the references suggests that HIV infections can be successfully treated with [the triple drug combination]. Figure 1 of the instant specification demonstrated that no measurable HIV-1 mediated cytopathic effect remained upon treatment of HIV-1 infected MT4 cells with all three compounds. Furthermore, these compounds were found to be synergistic[.]

(D.I. 67, Exh. 26 at 2). Despite this response, the application was again rejected for obviousness. Within the next response, dated September 14, 1999, the patentee again attempted to change the examiner's mind, referencing proof of the drug combination's synergistic effects:

> The Examiner contends that Applicants fail to illustrate the presence of unexpected benefits. On the contrary, the specification at page 2 states the combinations of the present invention are synergistic and data provided in Figure 1 indicates the excellent anti-HIV effect of the combinations of the present invention.

(D.I. 67, Exh. 2 at 2). The patentee further explained why the synergism of the combination was to be unexpected and that it rendered the drug combination non-obvious and patentable:

> [D]rugs having the same mode of action would be expected to be antagonistic. The drugs of the instant application are all inhibitors of HIV reverse transcriptase and therefore, would be expected to be antagonistic or at best additive. This is not the case, as illustrated in the specification and in the Daluge article. In summary, the demonstration of synergy between [the combined drugs] is an unexpected effect.

(*Id.* at 3). Despite the patentee's insistence, the Examiner again rejected the application as obvious. Only after the patentee filed a March 14, 2001 response with the affidavit of Inventor Martha Heider St. Clair attached was the Examiner persuaded. This response again insisted that "the combination is synergistic." (D.I. 67, Exh. 42 at 2). It also explained that this result was surprising and unexpected, as "[i]t would not be obvious to one skilled in the art to combine

three drugs that have the same viral mechanism of action to achieve a synergistic effect." (*Id.*). The attached St. Clair affidavit stated the following:

> 8. The results of this experiment indicate that the triple combination of zidovudine, 3TC and 1592U89 was synergistic in suppression of viral replication in lymphocytes *in vitro*.
>
> 9. The synergistic effects of zidovudine, 3TC and 1592U89 was unexpected because zidovudine, 3TC and 1592U89 are all nucleoside reverse transcriptase inhibitors, and therefore, act upon the same viral target in cells. Because of the same mechanism of action of zidovudine, 3TC and 1592U89 it would not be obvious to one skilled in the art that combining these three agents would result in the synergistic effect described above.

(D.I. 67, Exh. 3 at ¶¶ 8-9). In response to this filing, the Examiner finally allowed the application, agreeing that "it would not be obvious for the skilled artisan to employ the claimed compounds concomitantly and expect the therapeutic effect herein claimed." (D.I. 67, Exh. 30 at 2). The Examiner specifically cited paragraphs eight and nine of the St. Clair affidavit as support for overcoming the rejections for obviousness. (*Id.*).

Defendants argue that this file history makes clear that the applicants only intended to claim synergistic combinations of the drug compounds and disavowed all non-synergistic combinations. Classic prosecution disclaimer occurs when an applicant escapes rejection for anticipation through narrowing statements to the examiner differentiating the application from the prior art. The claimant then attempts to "recapture" the disclaimed scope by submitting a final patent application with claims covering the scope of the prior art that was previously distinguished. This is not what occurred here. The '191 application was never rejected as anticipated by prior art, as the Examiner agreed that nothing in the prior art disclosed the combined use of the drug compounds.[7] It was thus not necessary for the patentee to narrow

[7] "That the prior art failed to employ one, or another prior art antiviral compound concomitantly in the prior art medicament composition fails to reduce the prior art's obviation power." (D.I. 67, Exh. 38 at 2).

claim scope in order to defeat the Examiner's rejections. Instead, the patentee was required to prove that it would not be obvious to administer a combination of drugs known to be individually effective against the HIV virus for that same effective purpose. The patentee eventually proved the nonobvious nature of the invention by successfully arguing that the combined use of the drug compounds would not be expected to be as effective as proven. This was because the drug compounds have the same "mode of action" in fighting the HIV virus, and typically drugs with the same mode of action have antagonistic rather than synergistic therapeutic effects. These arguments were accepted by the Examiner. They should not be considered clear and unmistakable disclaimer, because they did not require the claims to be narrowed, distinguished, or amended. Had the patentee proved the existence of synergistic effects (and thus non-obviousness) via responses that altered the chemical or physical characteristics of the drug combination itself, those responses would arguably limit the scope of the claims, as the invention itself would have been re-characterized. Instead, the properties of the drug combination never needed to be altered or narrowed in order to prove the existence of synergism, as synergism was maintained as an intended result from the beginning of the application process. Statements during prosecution that purely concern the intended results of the administration of drug compounds do not limit the patent's claims. *See Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc.*, 246 F.3d 1368, 1375 (Fed. Cir. 2001). For these reasons, Defendants have failed to show clear and unmistakable disclaimer of non-synergistic combinations.

The Court thus adopts the plain and ordinary meaning for each term in this group.

2. "A single combined formulation"

The Court next construes "a single combined formulation." The parties' proposed constructions are as follow:

Disputed Claim Term/Phrase	**Viiv's Proposed Construction**	**Lupin's Proposed Construction**	**Teva's Proposed Construction**
"a single combined formulation" (claims 10, 23, 29, 38)	Plain and ordinary meaning. If the Court wishes to further construe the term, its plain and ordinary meaning is one formulation.	A dosage form wherein the 1592U89, zidovudine and 3TC are mixed together in the same admixture. (Claims 10 and 23). A dosage form wherein the 1592U89 and 3TC are mixed together in the same admixture. (Claims 29 and 38).	No position, as none of the claims asserted against Teva contain this term.

"A single combined formulation" is used within claims 10, 23, 29, and 38 of the '191 Patent. The claim construction dispute hinges on whether the word "combined" within this phrase requires the drug compounds to be mixed together within the same admixture. Viiv argues that "combined" only requires that the individual drug compounds be contained within one formulation and places no restrictions on how the drugs are physically composed within that formulation. "A single combined formulation" is thus arguably due its plain and ordinary meaning. In the alternative, Viiv offers "one formulation." Lupin argues that Viiv's construction fails to give "combined" any meaning. Lupin points to claim 6, which claims a "unit dosage form." According to Lupin, a "unit dosage form" already claims Viiv's

construction, i.e., a single formulation of the drug compounds with no restriction on how the drugs are physically composed within the formulation. Lupin argues that the presence of the word "combined" within the phrase "single combined formulation" necessarily makes the scope of that phrase narrower than "unit dosage form." Lupin concludes that "combined" can only be construed faithfully with the specification if it requires the drug compounds to be uniformly mixed in the same admixture.

I do not agree with Lupin. It is not the case that the word "combined" within "a single combined formulation" makes that phrase narrower than "unit dosage form." The specification states, "The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials[.]" '191 Patent, ll. 7:27-29. This indicates that a single formulation is not equivalent to a "unit-dosage form," as a single formulation may encompass both "unit-dose" and "multi-dose" containers. The fact that a "single formulation" is not equivalent to a "unit dosage form" defeats the inference that a "single combined formulation" must be more narrowly construed than "unit dosage form." This undermines Lupin's argument that "combined" necessarily gives rise to the admixture limitation. Further consideration of the claims reveals that "combined" simply requires that the drug compounds are contained within a single pharmaceutical formulation, regardless of admixture. Claim 1 broadly covers the administration of the claimed combination and places no limits on the methods of administration. This means that drugs that can be administered at the same or separate times, whether in separate formulations (one compound per formulation) or combined formulations (at least two compounds combined in the same formulation). Various dependent claims then narrow the scope of the "methods" of "administ[ration]" of the claimed "combination." Dependent claim 21 refers to methods "wherein the combination is administered simultaneously," dependent claim 22

refers to methods "wherein the combination is administered sequentially," and dependent claim 23 refers to methods with a "single combined formulation." Claim 21's use of "simultaneously" would cover the scenario where the drug combination is taken all at once, but not necessarily in the same pill. Claim 22's use of "sequentially" would cover the scenario where pills are given over a period of time as opposed to all at once. Finally, claim 23's use of "single combined formulation" would cover the scenario where all the drugs are administered within a single pill. Thus, it is not accurate to say that "combined" restricts the claim to require admixing, when its most naturally reading in comparison with the other claims merely requires that the drugs are administered in one formulation. For these reasons, the Court adopts Viiv's proposal and construes "a single combined formulation" according to its plain and ordinary meaning.