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Applicant GILEAD SCIENCES, INC.	
Third party observation submitted by Anonymous	Observation submitted on behalf of
Date of submission(day/month/year) 30 Sep 2025 (30/09/2025)	Language of observation English

Basis and contents of observation

1. The observation is made on the basis of the claims in the international application as filed.
2. The observation comprises:
References to documents: 7
Uploaded copies of documents: 3
3. Further explanations:
Uploaded copies of documents: 1

Citation # 1 (Patent/utility model) (# uploaded documents: 0):

Country code: WO	Publication number: 2019/035904	Document kind code: A1	
Patent Applicant/Patent Owner: Gilead Sciences, Inc.	Title of invention: Solid forms of an HIV capsid inhibitor		
Link to document: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019035904			
Publication Date: 21 Feb 2019 (21/02/2019)	Filing Date: 16 Aug 2018 (16/08/2018)	Priority Date: 17 Aug 2017 (17/08/2017)	
Source of Abstract:	Accession number:	Publication Date of Abstract:	Retrieval Date of Abstract:
Most relevant passages or drawings: Abstract; pp.2, 5, 7, 11–15, 24–33, 58, 64, 83–98; Ex. 6–11; Claims 1–74, 77–97		Relevant to Claims: 1 to 70	

Brief explanation of relevance:

WO2019035904 (WO904) relates to pharmaceutically acceptable salts, cocrystals of compound 1 (lenacapavir), and its crystalline forms of the sodium salts and co-crystals and method of treating or preventing HIV infection therewith, either alone or along with additional therapeutic agents (Abstract; pp.2, 6–7). The solid forms are identified using solid-state characterization methods such as X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC) (p.9).

WO904 discloses and/or claims:

1. A cocrystal refers to a compound crystallized together with one or more coformer molecules; depending on the chemical nature and proportion of cofomers in the cocrystal, different physical properties related to for e.g., dissolution and solubility may be observed compared to the solid forms of compound itself or its salts. The coformer may be protic acid, and whether the protic acid forms a salt or cocrystal will often depend on the relative pKa values of the compound and coformer (p.7).
2. Sodium salt or co-crystals of protic acid (methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, hydrochloric acid, sulfuric acid) (It may be noted that these salts and co-crystals may be solvated) are disclosed and their crystalline forms have been characterized by using XRPD and DSC (p.5, 11–15, 83–98; Ex. 6–11; Claims 1–74).
3. A pharmaceutical composition comprising crystalline forms I–III or co-crystals of protic acid of the sodium salt of lenacapavir, with at least one pharmaceutically acceptable excipient (p.58; Claim 77).
4. A method of treating or preventing HIV infection comprises administering a therapeutically effective amount of the crystalline forms I–III of a sodium salt of lenacapavir, or its co-crystals with protic acid, to a human in need thereof, for use in therapy, optionally in combination with 1–4 additional therapeutic agents. Such as HIV protease inhibitors, reverse transcriptase inhibitors [nucleotide (tenofovir), nucleoside (4'-ethynyl-2'-fluoro-2'-deoxyadenosine, abacavir sulfate, emtricitabine, or lamivudine), integrase inhibitors (e.g., bictegravir), entry and maturation inhibitors, latency reversing agents, capsid-targeting compounds, immune-based therapies, antibodies, pharmacokinetic enhancers, gene therapies, vaccines (pp.24–33; Claims 78–86, 97).

The present Application, WO2024249573 (WO573), claims solid forms (crystalline form, solvate, co-crystals) of a compound of Formula I [lenacapavir prodrug; note: the prodrug, i.e., Compound I, claimed in WO573 is the phosphate protected - Trimethyl Lock (TML) prodrug of lenacapavir], compositions thereof for treating or preventing HIV infection, methods of treatment or prevention of HIV therewith (Claims 1–70).

However, WO904 already discloses pharmaceutically acceptable crystalline forms I–III, of sodium salt or cocrystals formed with protic acids of lenacapavir (It may be noted that these salts and co-crystals may be solvated), wherein the solid forms characterized using XRPD, DSC. It also provides for a method of treating or preventing HIV infection by administering the salts, co-crystals or crystalline forms thereof, or a pharmaceutical composition either alone or along with additional therapeutic agents.

Further, WO2006007448 (WO448) and WO2019027920 (WO920) [Citations 6 and 6A] disclose the co-crystals of the API along with organic acids (e.g., maleic acid, succinic acid, tartaric acid, vanillic acid, oxalic acid, gentisic acid) as cofomers. It may be noted that these said organic acids of WO448 and WO920 also fall under the category of protic acids, i.e., acids which donate proton in a chemical reaction. Simplicio, et al. [Citation 5] and WO2020128525 [WO525, Citation 5A] disclose the TML strategy as a known strategy for developing prodrugs. Simplicio et al also disclose phosphate group masking for the TML hydroxyl group.

Hence, in light of WO904 [Citation 1] read along with WO448 and WO920 [Citations 6 and 6A] and Simplicio, et al., WO525 [Citations 5 and Citation 5A respectively], all Claims of WO573 lacks inventive step.

Citation # 2(Other) (# uploaded documents:1):

Identification of Document: Regulatory Classification of Pharmaceutical Co-Crystals – Guidance for Industry; Issued by the U.S. Department of Health and Human Services, Food and Drug Administration, Centre for Drug Evaluation and Research (CDER)	Publication Date: Feb 2018 (02/2018)
Link to document: https://www.fda.gov/media/81824/download	
DOI:	
Most relevant passages or drawings: pp.1-3	Relevant to Claims: 1 to 70
<p>Brief explanation of relevance:</p> <p>In 2018, the US Department of Health and Human Services' FDA – CDER issued nonbinding recommendations or a Guidance for Industry on the regulatory classification of pharmaceutical co-crystals, based on FDA's thinking at that point of time (p.1). The document defines co-crystals as "crystalline materials composed of two or more different molecules, typically active pharmaceutical ingredient (API) and co-crystal formers ("coformers") in the same crystal lattice" (p.1).</p> <p>It further lists the advantages of co-crystals: (i) they can be tailored to enhance drug product bioavailability, stability, and processability during manufacturing, and (ii) they can generate a diverse array of solid-state forms for APIs that lack ionizable functional groups, which is a prerequisite for salt formation (p.2). It states that co-crystals are distinguished from salts in that the components that co-exist in the co-crystal lattice with a defined stoichiometry interact non-ionically; co-crystals are more like solvates, in that both contain more than one element in the lattice (p.2).</p> <p>The document further states that for new drug applications (NDAs) claiming to contain a co-crystal form, the applicants should submit data supporting "if both API and coformer have ionizable functional groups, a conclusion that the component API and coformer co-exist in the co-crystal which interact non-ionically"; it notes that this decision can be guided by consideration of the delta pKa (pKa of the conjugate acid of base minus pKa of the acid); wherein, if delta pKa is less than 1, there will be less than substantial proton transfer and the API-coformer entity should be classified as a co-crystal; whereas if delta pKa is greater than or equal to 1, salt is potentially formed due to substantial proton transfer and ionization(p.2). It states that a co-crystal with a pharmaceutically acceptable coformer is not regarded as a new API, and has regulatory classification similar to that of a polymorph of the API. (id.).</p> <p>The FDA Guidance document states that the type and extent of characterization and release testing performed on the co-crystals should be sufficient to ensure the identity, strength, quality, and purity of the API(s) (p.3).</p> <p>Further, WO2021034804 [WO'804; Citation 2A] discloses long-acting formulations comprising tenofovir alafenamide (TAF) (TAF is a prodrug of tenofovir), or a pharmaceutically acceptable salt and/or co-crystals of TAF, in combination with additional therapeutic agents for treating HIV. WO' 804 provides for salts of TAF and lists various organic acids (protic acids), e.g., oxalic, succinic, L-tartaric, maleic, gentisic, vanillic acid, etc. that are routinely used in the forming of salt forms [pp.13–15]. The crystalline forms are characterised by XRPD pattern. WO'804 discloses the dog pK studies of compositions comprising crystalline form of TAF free base, TAF vanillate form (Fig. 6). The pharmaceutical formulation is for administration by injection (subcutaneous) to humans for treating HIV, and frequency of administration is once a month, up to once in three months, or less, at a dose of about 50–150 mg, and methods thereof, comprising another therapeutic agent, such as protease inhibitors, etc. and additional therapeutic agents, for treating or preventing HIV. [Abstract, pp. 1, 10–11, 13–20, 67–78, 81; Claims 1–7, 17–20, 23–24, 94–95, 105–109, 114; Fig.6 of WO'804].</p> <p>The present Application, WO2024249573 (WO'573) claims solid forms, including crystalline forms,</p>	

solvate forms and co-crystals (with maleic, succinic, oxalic, gentisic, L-tartaric, vanillic acids) of a prodrug of lenacapavir, which are characterised by XRPD, etc. and methods of treating and preventing HIV, by administering the solid forms, in combination with other therapeutic drugs for HIV, and use thereof (Claims 1-70)

However, the FDA Guidance document discloses the regulatory classification of pharmaceutical co-crystals, states the advantages thereof, and notes the significance of the delta pKa value and its relevance for the formation of the co-crystal or salt form of the API based on proton transfer and ionization. WO'804 [Citation 2A] discloses the salt formers of TAF (a prodrug of an anti-HIV agent) which include several organic acids, such as maleic, succinic, oxalic, gentisic, L-tartaric, vanillic acids (the identical acids that are claimed as coformers for co-crystals in the present Application, WO'573). Thus, it is obvious to develop the solid forms of prodrug of a known HIV capsid inhibitor lenacapavir, and prepare co-crystals by using known techniques [as disclosed by Lu and Rohani; Citation 4] by exploring organic acids which have already been listed as salt-formers (and thus potential co-crystal formers, depending on delta pKa value) of another anti-HIV drug.

Thus, all the claims of WO'573 lack inventive step.

Citation # 3 (Patent/utility model) (# uploaded documents: 0):

Country code: WO	Publication number: 2015/196137	Document kind code: A1	
Patent Applicant/Patent Owner: Gilead Sciences, Inc.		Title of invention: Crystalline forms of (2R,5S,13aR) –8-hydroxy–7,9–dioxo–N– (2,4,6-trifluorobenzyl) –2,3,4,5,7,9,13,13a–octahydro–2,5–methanopyrido [1',2':4,5] pyrazino [2,1–b] [1,3] oxazepine–10–carboxamide	
Link to document: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2015196137			
Publication Date: 23 Dec 2015 (23/12/2015)		Filing Date: 19 Jun 2015 (19/06/2015)	Priority Date: 20 Jun 2014 (20/06/2014)
Source of Abstract:	Accession number:	Publication Date of Abstract:	Retrieval Date of Abstract:
Most relevant passages or drawings: Abstract, pp. 1–5, 8, 13–23, 35–36, 38–39, 44–71, 77–78, 81–85, 89–90, 91–94, Table 1A–1D, 1F. 2A, 2A–I, 2C, Claims 1–52		Relevant to Claims: 1 to 70	
Brief explanation of relevance: WO2015196137 (WO'137) relates to crystalline forms and co-crystals of compound of formula I [It may be noted that Compound of formula I is bictegrovir, an integrase inhibitor] for the treatment of HIV-1. WO'137 discloses crystalline Forms I– VIII and the fumaric, citric, and oxalic acid co-crystals of Formula I, Form I of Formula II (sodium salt form), and polymorphic Forms I–III of Formula III (potassium, dimer, and polymorphic potassium forms), (Abstract, pp. 1–5, 8, 14). WO'137 discloses and/or claims (Claims 1–52): 1. The crystalline forms, polymorphic forms or polymorphs, or co-crystals may provide advantage of bioavailability and stability suitable for pharmaceutical uses; the crystalline forms may provide suitable hygroscopicity, particle size controls, dissolution rate, solubility, purity, physical and chemical stability, manufacturability, yield, and/or process control, and stability or storability of drug product (pp.12, 13). 2. Use of certain solvents, including methanol, ethanol, water, isopropyl acetate, acetonitrile, tetrahydrofuran, methyl isobutyl ketone (MIBK), or mixtures thereof, to produce different polymorphic forms I to VIII (pp.13–23). The solvents used for the preparation of different polymorphs of Formula I, included isopropyl acetate for forms I and II, methyl isobutyl ketone for Form III, methanol for Forms IV, VII and VIII, water for Form V and water-methanol mixture for Form VI (pp.67–71). Solvent used for oxalic acid co-crystals of Formula I is tetrahydrofuran (p.77)			

3. The polymorphs are characterized using XRPD patterns (degree 2 theta reflections (plus or minus 0.2 degrees 2theta), thermal techniques such as DSC TGA and/or DVS, wherein the results obtained for these analyses fall within the limits of experimental error or deviations, when considered by one of ordinary skill in the art (pp.13–23).
4. Co-crystals of Formula I, including the oxalic acid co-crystals characterized by its XRPD patterns unit cell dimensions, etc. (pp. 35–36).
5. The XRPD data of Formula I, its ranges, peaks for the crystalline forms of Form I–IV, and XRPD data for the oxalic acid co-crystals of Formula I Form 1 (pp. 62–67, Tables 1A–1D, 1F).
6. Preparation methods of Formula I and its forms described as isolation as solid form and characterised, mixture is heated, stirred, evaporated, cooled etc. Oxalic acid co-crystal form 1 were prepared by adding tetrahydrofuran, stirring, evaporation, etc. (pp.81–84, 85).
7. Pharmaceutical composition comprising the compound I (5–500 mg), along with suitable carriers, excipients, diluents, etc., and administered orally, parenterally, and sequentially, simultaneously, etc.; methods of treating HIV by administering the compounds in combination with other one or more additional therapeutic agents (pp.37, 45–62)

Further, WO2020214647 (WO'647) [hereto as Citation 3A] relates to solid forms of protease inhibitors for HIV. WO'647 discloses pharmaceutically acceptable salts and cocrystals, crystalline forms of the salts or cocrystals, and methods of treating and preventing HIV therewith [Abstract; pp. 1, 39]. It discloses and claims the solvates of amorphous forms, and crystalline forms of the maleate, succinate salts, etc. of compound 1, that are characterised by XRPD, DSC, TGA, DVS, etc., and also MIBK, 2 butanone (MEK) solvates of Compound 2, that are characterised by XRPD, and administered in combination with other therapeutic anti-HIV agents [pp. 1, 2, 6–8, 18–22, 25, 32, 43–45, 69, 73–74, 86, 88–94, Figs. 24, 26–28, 31–33, 37–38, Table 11 of WO'647]

The present Application, by Gilead, WO2024249573 (WO'573), claims crystalline forms, solvate forms and co-crystals (maleate, succinate, oxalic, etc.) of a prodrug of lenacapavir, the forms are characterised by XRPD patterns, DSC, TGA, DVS, using solvents like MEK, DCM, etc. (Claims 1–70).

However, WO'137 and WO'647 already disclose the several solid forms - crystalline forms, co-crystals (oxalic acid), salts (maleic acid/succinic acid) of various anti-HIV drugs, thus showing that it is routine to explore different polymorphic forms of a compound, its co-crystals and salts, to achieve desired physico-chemical properties such as stability, bioavailability, hygroscopicity, etc. of drugs.

Further, the FDA guidance [hereto annexed as Citation 2] also alludes to the use and classification of co-crystals, formed with several co-formers, and discloses the importance of difference in pKa of the drug and the co-former for formation of co-crystals and/or salts.

Thus, all claims of WO'573 lack inventive step.

Citation # 4(Periodical article) (# uploaded documents:1):

Author: Lu, J and Rohani, S	Title of article: Polymorphism and Crystallization of Active Pharmaceutical Ingredients (APIs)	Title of Periodical: Current Medicinal Chemistry	Publication Date: Mar 2009 (03/2009)
Issue Number of Periodical: Volume 16, Issue 7	Publisher of Periodical: Bentham Science Publishers	Place of publication: United Arab Emirates	
Page range of article within periodical: 884–905	ISBN:	ISSN: 0929-8673	

DOI: 10.2174/092986709787549299	
Most relevant passages or drawings: pp.884–886, 891, 893–894, 898–900; Figure 1, Tables 1 and 3	Relevant to Claims: 1 to 70
<p>Brief explanation of relevance:</p> <p>Lu and Rohani discuss the various solid state forms (polymorphs, pseudopolymorphs, co-crystals, etc.) of active pharmaceutical ingredients (APIs) and note that the different physical and chemical properties of the various solid state forms of APIs are known to affect the drug's bioavailability, hygroscopicity, stability, etc. (Abstract, p.884, LHC; Fig.1, p.885).</p> <p>Lu and Rohani disclose:</p> <p>1) Crystallization is a “major technological process for particle formation in pharmaceutical industry” (p.884, LHC).</p> <p>Polymorphism and characterisation thereof:</p> <p>2) Polymorphism is a wide-spread phenomenon observed for more than half of all APIs (p.884, RHC); there are several reported examples of polymorphic APIs (Table 3, pp.898–899). While “polymorphs have the same chemical composition”, they have “different lattice structures and/or different molecular conformations” (p.884, RHC). Due to differences in physicochemical properties, polymorphs exhibit differences in stability and bioavailability (id.).</p> <p>3) Various known methods are employed to produce different polymorphs of an API, such as cooling of melts, deposition, crystallization from single or mixed solvents, etc. (p.893, RHC); discovery of various polymorphs typically starts with crystallization of APIs from a number of solvents (p.894, RHC).</p> <p>4) Crystallization process of polymorphs “is consisted of competitive nucleation, growth, and the transformation from a metastable to a stable form”; the nucleation process is considered most important to control polymorphic crystallization (p.893, RHC).</p> <p>5) Polymorphs can be characterized using various analytical techniques (Table 1, p. 890). These include: (a) X-ray diffraction (powder or single-crystal) which provide definite proof of existence of polymorphism and information about crystal structure (p.891, LHC); and (b) thermal methods such as differential scanning calorimetry (DSC) which provide thermodynamic data such as melting point, heat capacity, etc; however, for characterization of polymorphs, DSC is to be used with other analytical methods such as PXRD, TGA, etc. (p.893, LHC).</p> <p>6) Polymorphic transformation is a known phenomenon that can affect stability and bioavailability of the drug product; relative stability and transformation kinetics of polymorphs are studied during drug development (p.899, RHC–p.900,LHC)</p> <p>Solvates:</p> <p>7) Pseudopolymorphs are “crystalline forms of a compound in which solvent molecules are integrated as an integral part of the structure” (p.885, LHC). They may be either hydrates or solvates and “may be either final or intermediate products of crystallization” (p.885, LHC; p. 886, LHC).</p> <p>8) They too are known to “show different solubilities, dissolution rates, mechanical behavior, stability and bioavailability from their unsolvated counterparts” (p.885, RHC).</p> <p>Co-crystals (p.886, RHC):</p> <p>9) Co-crystals “consist of two or more components that are solid at room temperature”, i.e, both components are in solid state.</p> <p>10) They differ from a salt in that “in salts a proton is transferred from the acidic to the basic functionality of the crystallization partner, or vice versa, whereas in co-crystals no such transfer occurs”.</p> <p>11) They can lead to improved solubility, bioavailability, stability, hygroscopicity, compressability and flowability.</p> <p>12) For example, co-crystals of itraconazole, a poorly water-soluble drug, were formed by using “various pharmaceutically acceptable acids, such as fumaric acid, succinic acid and L-, D- or DL-tartaric acid”; different carboxylic acid co-crystals exhibited faster dissolution rate than free itraconazole.</p>	

- 13) They can be prepared by melt-crystallization, grinding and recrystallization from solvents.
- 14) They can form solvates and also exhibit polymorphism.
- 15) They are increasingly recognised as an attractive alternate for solid forms of drug products.

The present Application, WO2024249573 (WO573), claims crystalline forms, solvate forms and co-crystals of a trimethyl-lock (TML) containing prodrug of lenacapavir (now known as lenacapavir pacfosacil), characterised by various known analytical techniques (Claims 1–50); pharmaceutical compositions thereof, alone or in combination with other anti-HIV agents; methods of treating / preventing therewith, use thereof, etc. (Claims 51–70).

However, lenacapavir is admittedly a known anti-HIV capsid inhibitor (p.9 of WO573). Further, such TML prodrug strategy have been previously explored, including for anti-HIV drugs [see Simplicio, et al. and WO2020128525; Citation 5 and 5A hereto].

As disclosed by Lu and Rohani, crystalline polymorphic forms, solvates and co-crystals are known strategies employed for solid forms of an API and they are routinely characterised using known analytical techniques.

In light of the above, Claims 1 to 70 of the present Application, WO573, lack inventive step.

Citation # 5(Periodical article) (# uploaded documents:1):

Author: Simplicio, A. L., et al.	Title of article: Prodrugs for Amines	Title of Periodical: Molecules	Publication Date: 03 Mar 2008 (03/03 /2008)
Issue Number of Periodical: Volume 13, Issue 3	Publisher of Periodical: MDPI	Place of publication: Switzerland	
Page range of article within periodical: 519–547	ISBN:	ISSN: 1420-3049	
DOI: 10.3390/molecules13030519			
Most relevant passages or drawings: Abstract; pp.519–522, 526, 530, 536–537; Table 1; Figure 1; Schemes 15, 16; compound number 11, 18		Relevant to Claims: 1 to 70	
Brief explanation of relevance: <p>Simplicio, et al. review the published strategies for the production of prodrugs of amines, reviews the 2 main group of approaches, that rely on enzymatic activation, and physio-chemical conditions for release of the drug, and their advantages and disadvantages (Abstract). They state that prodrug strategies are temporary derivatization of a functional group of a drug to improve its pharmaceutical utility and that efforts have been made to mask the amino groups due to their poor membrane penetration and instability issues (pp.519-520).</p> <p>Their review elucidates prodrug approaches to amine drugs that illustrate:</p> <ol style="list-style-type: none">1. Amide and carbamate prodrugs may improve lipid solubility and achieve slow release; there are several N-acyl prodrugs in clinical use and development (pp.521-522, Table 1)2. Phosphoryloxy methyl carbamates would be cleaved in vivo by alkaline phosphatase, in vitro tests with phosphate esters showed enzymatic triggering, a spontaneous cascade leads to release of the amines (pp.521, 526, compound 11)3. Double prodrug systems, that consist of PEG linked through a linker to the amine drug have been explored for drug solubilization and extending plasma half-life of the drug; ester, carbonates, carbamates, or amide bonds are introduced as linkers for enzymatic activation and release of PEG group (p.530, number 18)4. Lactonization makes it possible to manipulate the physio-chemical characteristics, wherein phenolic amides derived from lactones can be used as amine prodrugs at physiological pH; this prodrug system is referred to as the trimethyl lock (TML) system (pp. 521, 536; Table 1, Scheme			

15).

5. In the TML system, the side chain is “folded back to bring the amide carbonyl group into proximity with the nucleophilic phenolic oxygen. This conformation may account for the facile cyclisation that occurs independent of the drug attached to the side chain” (p.536, Scheme 15).

6. The half-life of TML lock is less than 1 minute, and hence, it is modified further at the phenolic position where the nucleophilic hydroxyl (OH) group is protected in a bioreversible manner to delay the enzymatic exposure of the phenolic group. These systems are susceptible to specific enzymes (e.g., esterases) (p.536).

6a. A variation in TML system is the introduction of phosphate esters at the OH group i.e., as the phenolic masking group, wherein the molecule is sensitive to alkaline phosphatase (pp.536–537, Figure 1).

7. The preparation of tripartite (double prodrug) that uses the coumarin system (spacer similar to the TML system) as a linker between drug and carrier group; the phenolic OH group and the cis-geometry of the double bond allows lactonization at rates comparable to those of the TML system. (p.537, Scheme 16).

Further, WO2020128525 [WO525, hereto as Citation 5A] discloses polymer of prodrug (POP) that incorporate water soluble NRTIs, such as tenofovir prodrug, tenofovir alafenamide (TAF) and EFdA wherein self-immolative TML groups amenable to coupling with the amino group of the polymer TAF2 for generating POP (polymer of prodrugs) structures, wherein the TML-TAF prodrugs are susceptible to esterase activation in-vivo in order to release TAF [p.11; Fig.6a]. Similarly, for EFdA, wherein the amine group can be masked with TML as shown for TAF (p12). The variation in TML ester group alters the hydrolysis rate and amine release [p.12; Fig.8]. Synthesis of TAF conjugates containing POP, TML group has been disclosed [pp.51-56, 59; Fig 6]. It may be noted that WO525 uses TML linker to create a TML-TAF polymer which has been used as a prodrug strategy.

The present Application, WO2024249573 (WO573), claims the crystalline, solvated and co-crystal of a lenacapavir prodrug and the methods thereof (Claims 1–50) and a pharmaceutical composition thereof, in combination with additional therapeutic agents for HIV (Claims 51–70).

However, Simplicio, et al. discloses TML linkers used as prodrug strategy for amine containing drugs and WO'525 [Citation 5A] describe polymers of prodrugs that are modified at the amine position with TML systems, wherein the TML is further derivatized by phosphate esters at hydroxyl group, for anti-HIV drugs. Note that although WO525 have explored the TML linkers in prodrugs and polymer type linkages thereof, Simplicio et al already disclose TML-based prodrugs for amine containing monomeric compounds. Further, crystalline forms, co-crystals of anti-viral drugs are routinely prepared, characterised, and disclosed in Lu and Rohani [Citation 4] hereto.

The Applicants of the present Application, WO573, have merely used the strategy used for prodrugs of NRTIs for prodrugs of HIV capsid inhibitor to modify its nitrogen on the sulphonamide group with TML linkage derivatized by phosphate group at the hydroxyl group.

Thus, in light of the above, Claims 1–70 of WO573, lacks inventive step.

Citation # 6 (Patent/utility model) (# uploaded documents: 0):

Publication number: WO 2006/007448			Document kind code: A2		
Patent Applicant/Patent Owner: Transform Pharmaceuticals, Inc.			Title of invention: Pharmaceutical co-crystal compositions and related methods of use		
Link to document: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2006007448					
Publication Date: 19 Jan 2006 (19/01/2006)		Filing Date: 16 Jun 2005 (16/06/2005)		Priority Date: 17 Jun 2004 (17/06/2004)	

Source of Abstract:	Accession number:	Publication Date of Abstract:	Retrieval Date of Abstract:
Most relevant passages or drawings: Abstract; pp.2-4,6-9,11,12-14,16-22,36,49-50,52-55,62-63; Tables I and II		Relevant to Claims: 1 to 70	
Brief explanation of relevance:			
<p>WO2006007448 (WO448) discloses a co-crystal pharmaceutical composition comprising an active pharmaceutical ingredient (API) and a co-crystal former (coformer), and methods of making and using the same (Abstract; pp.2, 11).</p> <p>WO448 discloses/claims:</p> <ol style="list-style-type: none">1. Co-crystalline forms of APIs often improve the properties of APIs as compared to its non-co-crystalline state (p.2, 7-8);2. A process for modulating the solubility of an API or to make co-crystals of unsaltable or difficult to salt APIs which comprises grinding, heating, co-subliming, co-melting, or contacting in solution the API with a co former under crystallisation conditions so as to form a co-crystal; co-crystals improve properties of the API, as compared to the API in a free form, particularly with respect to solubility, dissolution, bioavailability, stability, Cmax, Tmax, processability, hygroscopicity, etc.; the dose response of the API can also be improved (pp.7-8, 16-22);3. A co-crystal pharmaceutical composition comprising an API and a co former, where the API has at least one functional group, e.g., secondary amine, etc, such that the API and co former can co-crystallize from a solution phase under crystallization conditions or from the solid-state through grinding, heating or through vapor transfer (pp.2-3, 8, 12-13);4. The co-crystals can include an acid or base addition salt of an API; acid addition salts include organic acids such as maleic acid (Class 1), gentisic acid (Class 2), succinic acid (Class 1), oxalic acid (Class 2), tartaric acid (Class 1) etc. (p.6; Tables I and II);5. Co-crystals comprising H-bonding as the dominant interaction between the co former and an API; ; other non-covalent interactions, including pi-stacking and van der Waals interactions, may also be present (pp.2, 8);6. The ratio of API to co-crystal former may be stoichiometric (p.7);7. The presence of co-crystals can be assessed using convenient and routine methods such as powder X-ray diffraction technique (XRPD); other techniques include differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and single crystal X-ray diffraction (p.14, 52-55);8. General methods for the preparation of co-crystals including crystallization from solution, crystallization from the melt (co-melting) and mixing and/or grinding (pp.49-50);9. A list of solvents including ethyl acetate, isopropyl acetate, dichloromethane, chloroform, toluene, dimethyl sulfoxide, diethyl ether (ether), acetonitrile, alcohols, etc used in a co-crystallization process (p.50);10. APIs exemplified for co-crystal formation include stavudine, an anti-HIV drug (pp.62-63);11. Pharmaceutical compositions comprising co-crystal and one or more pharmaceutically acceptable carriers or diluents as excipients (p.36);12. A method for treating a human subject with a condition able to be treated with an API where the API is an effective active pharmaceutical for said condition (p.4). <p>Further, WO2019027920 [WO920; Citation 6A] discloses crystalline and amorphous forms of ethyl ((S)-(2R,5R)-5-(6-amino-9H-purin-9-yl)-4-fluoro-2,5-dihydrofuran-2-yl)oxy)methyl)(phenoxy)phosphoryl)-L-alaninate (Formula I; GS-9131), its salts, co-crystals and solvates, including Formula I vanillate form, and their use in the treatment of HIV (Abstract; pp.3-5,22-25).</p> <p>The present Application, WO2024249573 (WO573), claims solid forms such as crystalline forms, solvates and co-crystals of lenacapavir prodrug (lenacapavir pacfosacil), compositions thereof, and methods therewith for treatment or prevention of HIV infection (Claims 1-50; p.9). WO573 further claims the pharmaceutical composition comprising the solid form of the said prodrug, method of treating or preventing HIV, and the compound or composition for use in therapy or for use in method of treating or preventing HIV (Claims 51-70).</p>			

However, WO448 already discloses methods of preparation of co-crystalline forms of APIs and a list of co-formers and solvents which can be used therein, and that such forms can be routinely characterized using known analytical techniques, including XRPD, DSC and TGA. Further, WO920 [Citation 6A], discloses the crystalline forms of an anti-HIV compound (GS-9131), its salts (including vanillate salt), its co-crystals and solvates. It is known that the formation of a salt or a co-crystal depends on the difference in pKa of the API and the acid (co- or salt-former) [FDA Guidance document, Citation 2]. Thus, the Applicant of the present Application, WO573, has merely prepared the solid forms of a prodrug of an already known API, lenacapavir, using known co-formers, methods and solvents, and characterized the same using known analytical techniques.

Thus, in light of the above, all Claims of WO573 lack inventive step.

Citation # 7 (Patent/utility model) (# uploaded documents: 0):

Country code: WO	Publication number: 2023/102239	Document kind code: A1	
Patent Applicant/Patent Owner: Gilead Sciences, Inc.	Title of invention: Therapeutic compounds for HIV virus infection		
Link to document: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2023102239			
Publication Date: 08 Jun 2023 (08/06/2023)	Filing Date: 02 Dec 2022 (02/12/2022)	Priority Date: 03 Dec 2021 (03/12/2021)	
Source of Abstract:	Accession number:	Publication Date of Abstract:	Retrieval Date of Abstract:
Most relevant passages or drawings: Abstract; pp. 1–5, 7–8, 14, 16–23, 29–31, 33, 35–40, 57, 59, 62, 64, 66–79, 82–117, 197–201; Claims 1–3, 15–20, 28–35, 54, 64–78; Ex.44		Relevant to Claims: 1 to 70	

Brief explanation of relevance:

WO2023102239 (WO239), an application filed by Gilead Sciences, the Applicant of the present Application, WO2024249573 (WO573), was published after the priority date (31.05.2023) but before the filing date (30.05.2024) of the present Application, WO573 and would therefore be relevant in countries where the law permits use of such documents as prior art.

WO239 relates to compound of Formula I and compositions thereof for treatment or prevention of HIV infection (Abstract; pp.1–2). WO239 highlights a need for HIV therapies with better pharmacokinetics less frequent medication, smaller effective doses (pp.1–2). WO239 discloses that the compounds of Formula I are more soluble than lenacapavir (LEN; HIV capsid inhibitor) and can be administered orally, and that dosing therewith results in conversion of compound I to lenacapavir in the GI tract (pp.65–66, 82, 99). It may be noted that formula I of WO239 is a Markush structure for prodrugs of LEN wherein the prodrug moiety -C=O-X is attached to the N of the sulphonamide group.

WO239 discloses and/or claims:

1. Compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein (Claims 1–3, pp. 1–3, 7–8, 17–23):

1.a) X [i.e., the prodrug moiety] is C1–10 alkyl which is substituted with 1–3 Y groups (Claims 15–20; pp.29–30), particularly X is -(CH₂-CH(CH₂)₂)-Y (Claim 20) [It may be noted that, when X is alkyl, the Compound of formula I represents an amide-type prodrug of LEN]

1.b) Y is phenyl, which is substituted with 1–5 R₃ groups, e.g., 3 R₃ groups (Claims 28–30; pp.30–31, 33, 35) wherein:

1.c) each R₃ independently is -C(O)OR₄ (R₄ is H), R_a, R_b, R_c, or C1–6 alkyl; the C1–6 alkyl is independently optionally substituted with 1–3 groups selected from -C(O)OR₄, R_a; specifically, each R₃ independently is -OP(O)(OH)₂, -CH₂C(O)OH, methyl (Claims 31–35; pp.35–40)

2. Specific compound wherein X is -(CH₂-CH(CH₂)₂)-phenyl; wherein phenyl is substituted with -OP(O)(OH)₂ and -CH₂C(O)OH at the ortho positions and methyl at the para position from the point

of attachment to X (Claim 54 (p.297, row 1, structure 2); pp.57, 59, 62, 64, 197–201; Ex.44). [Refer to the accompanying Additional Comments for a structural comparison]

3. Solvate is formed by interaction of a solvent and a compound (p.14)

4. Salts derived from organic acids including oxalic acid, succinic acid, maleic acid, tartaric acid, etc (p.16)

5. Pharmaceutical composition comprising the claimed compound or a salt thereof, and a pharmaceutically acceptable excipient; further comprising 1, 2, 3 or 4 additional therapeutic agents (Claims 64–68; pp.4, 66–75)

6. Method of treating/preventing HIV infection in patient in need/heavily treatment-experienced patient by administering the claimed compound, its salt or pharmaceutical composition; the method further comprising administering 1, 2, 3 or 4 additional therapeutic agents (Claims 69–75; pp.4, 75–79, 82–117)

7. The claimed compound, its salt or its composition for use in therapy or for use in method of treating or preventing HIV (Claims 76–78; pp.4–5).

The present Application, WO573 claims the solid forms including the crystalline forms, the solvate forms and the co-crystal forms of the lenacapavir prodrug, wherein the promoiety is (oxobutanyl-(5-methyl-3-(phosphonooxy)phenyl)acetic acid, i.e. the nitrogen of the sulphonamido moiety is attached to -C(O)-(CH₂-CH(CH₂)₂)-phenyl and wherein phenyl is substituted with -OP(O)(OH)₂ and -CH₂C(O)OH at meta positions and methyl at para position; the solid forms characterized using XRPD, DSC, TGA (Claims 1–50). WO573 further claims the pharmaceutical composition comprising the solid form of the said prodrug, method of treating or preventing HIV in heavily treatment experienced patients, and the compound or composition for use in therapy or for use in method of treating or preventing HIV (Claims 51–70). [It may be noted that WO573 discloses that the claimed compound is a prodrug of lenacapavir (p.9 of WO573)].

However, WO239 already discloses the identical prodrug compound of LEN and its pharmaceutically acceptable salt, and its composition, method of treating or preventing HIV and use thereof. Also, Lu and Rohani [Citation 4], disclose that crystalline polymorphic forms, solvates and co-crystals are known strategies employed for solid forms of an API and they are routinely characterized using known analytical techniques, including XRPD, DSC, TGA. Further WO2019035904 [Citation 1], disclose the solid forms, including crystalline forms, salt and co-crystals with protic acids. Thus, the Applicant of the present Application, has merely prepared the solid forms of an already claimed prodrug of lenacapavir using known methods, solvents and co-formers, and characterized the same using known analytical techniques.

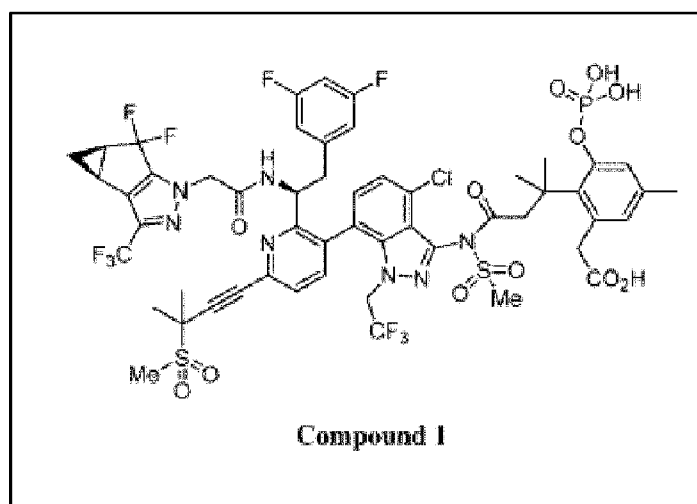
Thus, in light of the above, all claims of WO573 lack inventive step.

ADDITIONAL COMMENTS FOR WO 2024/249573

INTRODUCTION

The present Application, WO 2024/249573 (WO'573), by Gilead Sciences, Inc., claims the solid forms, including the crystalline forms, solvate forms and co-crystals of a prodrug of lenacapavir, useful for the treatment and prevention of HIV.

WO'573 relates to the solid forms of Compound 1, i.e., the prodrug of lenacapavir (p.9 of WO'573), of the following structure:



WO'573 claims:

- i) Crystalline form of Compound 1 selected from forms I, II and III, each form characterized by the XRPD pattern and a DSC thermogram (Claims 1–17)
- ii) Solvate form of Compound 1 selected from multiple solvate forms, such as acetonitrile, methyl ethyl ketone, methyl isobutyl ketone, etc. (Claims 18–19)

- iii) Co-crystal of Compound 1, the co-crystal prepared using one of the co-formers selected from maleic acid, succinic acid, oxalic acid, gentisic acid, L-tartaric acid and vanillic acid (Claims 20–50)
- iv) Pharmaceutical composition comprising the claimed solid forms of Compound 1, excipient and further comprising 1–4 additional therapeutic agents, combination of drugs for HIV, etc. (Claims 51–55)
- v) Method of treating/preventing HIV infection in patient in need or heavily treatment-experienced patient by administering the claimed solid form of Compound 1, or composition thereof; further comprising administering 1–4 additional therapeutic agents (Claims 56–62)
- vi) The claimed compound, or claimed composition for use in therapy or for use in a method of treating or preventing HIV infection (Claims 63–70).

It may be noted that Compound 1 is now known as lenacapavir pacfosacil (p.559 of International Nonproprietary Names for Pharmaceutical Substances (INN), WHO Drug Information, Vol. 39, No. 2, 2025¹).

The Additional Comments are being filed along with the accompanying

Third-Party Observation (TPO) to point out (i) Structural comparison of Compound 1 of the present Application WO'573, with the compound of the prior art document WO2023102239 (WO'239; "P" document); (ii) Lack of inventive step or obviousness of the solid forms claimed in the present Application, WO'573; (iii) Lack of sufficiency of disclosure

¹ [https://cdn.who.int/media/docs/default-source/international-nonproprietary-names-\(inn\)/pl133.pdf](https://cdn.who.int/media/docs/default-source/international-nonproprietary-names-(inn)/pl133.pdf)

II. STRUCTURAL COMPARISON OF COMPOUND DISCLOSED IN PRIOR ART DOCUMENT WO2023102239 WITH COMPOUND I OF PRESENT APPLICATION WO2024249573 (WO'573)

WO2023102239 (WO'239), is an earlier application filed by Gilead Sciences Inc., who is also the Applicant of the present Application, WO'573. WO'239 was published on 08.06.2023, that is after the priority date (31.05.2023), but before the filing date (30.05.2024) of the present Application, WO573. Thus, WO'239 would be relevant prior art in countries where the law permits use of such documents as prior art.

WO'239 claims and/or discloses prodrugs of lenacapavir for the treatment or prevention of HIV infection. One of the compounds claimed in WO'239 is the same prodrug compound for which solid forms are now being claimed by the Applicant in WO'573. The comparison of the compounds in the Table hereinbelow shows that Compound 44, the prodrug compound of lenacapavir that is disclosed and claimed in prior art document WO'239 is identical to Compound 1 of the present Application, WO'573.

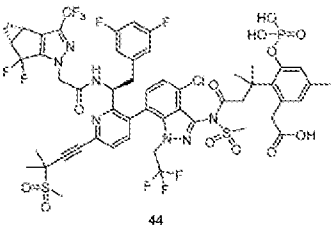
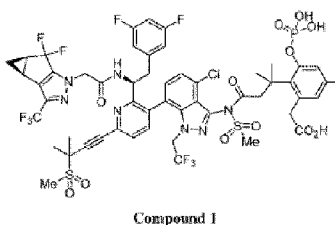
Table		
WO2023102239 (WO'239; Prior Art Document)	WO2024249573 (WO'573; Present Application)	Comments
Compound 44 	Compound 1 	WO'239 already discloses the identical prodrug compound of lenacapavir, which is Compound 1 of the

Table		
WO2023102239 (WO'239; Prior Art Document)	WO2024249573 (WO'573; Present Application)	Comments
(Claim 54; pp.57, 59, 62, 64, 197–201; Ex.44 of WO'239)		<p>present Application, WO'573.</p> <p>The present Application, WO'573, also claims crystalline forms, co-crystals, etc. of Compound 1. However, the accompanying TPO cites prior art documents to show that crystalline forms, co-crystals of known drugs or prodrugs of known drugs are known and routinely explored and characterised.</p> <p>Hence Claims 1–70 of WO'573 lack inventive step.</p>

III. LACK OF INVENTIVE STEP OR OBVIOUSNESS OF THE FORMS OF COMPOUNDS CLAIMED IN THE PRESENT APPLICATION WO'573

1. The accompanying TPO cites several prior art documents to show that crystalline forms, solvate forms, and co-crystals of antiviral drugs, or their prodrugs is known, and routinely explored for achieving desired properties, such as better bioavailability, stability, etc. [Refer to WO2019035904, WO2021034804, WO2015196137 and WO2020214647 attached as Citations 1, 2A, 3 and 3A, respectively, in the accompanying TPO].
2. The different crystalline forms are identified by known solid state characterization methods such as X-ray powder diffraction (XRPD) patterns, or differential scanning calorimetry (DSC) thermogram, thermogravimetric analysis (TGA) thermogram, dynamic vapor sorption (DVS), etc., which are well known in the art, and routinely used [Refer to Lu and Rohani as Citation 4 in the accompanying TPO].
3. Further, classifying salts or co-crystals based on the pKa values is also known in the art, and used routinely too [Refer to WO2019035904 and the FDA guidance document attached as Citations 1 and 2, respectively, in the accompanying TPO].
4. The method of preparing the solid forms including the reaction conditions such as solvents, anti-solvents, temperature, etc are already known [Refer to Lu and Rohani as Citation 4 in the accompanying TPO].
5. Further, lenacapavir, was approved in the United States in 2022, and is marketed under the brand name Sunlenca. The Label containing the prescribing information document (available at <https://www.gilead.com/>-

/media/files/pdfs/medicines/hiv/sunlenca/sunlenca_pi.pdf) for the tablets for oral use and injection for subcutaneous use, also gives indication of usage. The Label discloses that Sunlenca, is an HIV-1 capsid inhibitor, and is given in combination with other antiretrovirals, and “is indicated for the treatment of HIV-1 infection in heavily treatment-experienced adults with multi-drug-resistant HIV-1 infection failing the current antiretroviral regimen due to resistance, intolerance, or safety considerations” and indicates such use in clinical trials (pp.1–2, 6–7, 14–16, 20–21). It may be noted that the present Application, WO’573, claims a method of treating HIV in heavily treatment-experienced patients, by administering the solid forms of the prodrug of lenacapavir (Claim 57 of WO’573). However, the Label for Sunlenca, containing the prescribing information already discloses that lenacapavir is approved for use in heavily treatment-experienced patients, or multi-drug-resistant adults. Therefore, it is obvious that any other form of lenacapavir, such as its salt, prodrug, crystalline, co-crystals, solvates, etc. would also be indicated for use for the same purpose too. Thus, Claim 57 of WO573, too, lacks inventive step.

IV. LACK OF SUFFICIENCY OF DISCLOSURE

The present Application, WO’573 claims several solid forms of Compound 1, a prodrug of the known HIV capsid inhibitor, lenacapavir. However, the Description accompanying WO’573 does not disclose any biological or technical data or information about the claimed crystalline forms I, II or III, solvate forms or co-crystal forms of Compound 1.

Thus, in the absence of any biological data of the solid forms to show the improved technical effect or any technical advantage over the known drug lenacapavir, all claims of WO'573 fail due to insufficiency of disclosure.

V. CONCLUSION

Thus, in light of the above, and the documents cited as prior art in the accompanying TPO, all the claims (Claims 1–70) of the present Application, WO'573, that claims solid forms of the prodrug of lenacapavir, lack inventive step and / or fail for lack of sufficiency of disclosure.