

PATENT COOPERATION TREATY
PCT
THIRD PARTY OBSERVATION
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Applicant's or agent's file reference 70062	
International application number PCT/IB2022/059780	International filing date (day/month/year) 12 Oct 2022 (12/10/2022)
Applicant VIIV HEALTHCARE UK (NO.5) LIMITED	
Third party observation submitted by Anonymous	Observation submitted on behalf of
Date of submission(day/month/year) 13 Feb 2024 (13/02/2024)	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: 4
Uploaded copies of documents: 0
3. Further explanations:
Uploaded copies of documents: 1

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

Country code: WO	Publication number: 2018/035359	Document kind code: A1
Patent Applicant/Patent Owner: Gilead Sciences Inc.	Title of invention: Therapeutic compounds useful for the prophylactic or therapeutic treatment of and HIV virus infection	
Link to document: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018035359		
Publication Date: 22 Feb 2018 (22/02/2018)	Filing Date: 17 Aug 2017 (17/08/2017)	Priority Date: 19 Aug 2016 (19/08/2016)
Source of Abstract:	Accession number:	Publication Date of Abstract: Retrieval Date of Abstract:
Most relevant passages or drawings: pp.11–12, 29–30, 34–35, 38–40, 47–48, 51–56, 68, Figs.4–6, 10, Claims 17–22, 35–38, 42–45, 51–57, 60–65, 69–72, 77–81, 84–86		Relevant to Claims: 1–68

Brief explanation of relevance:

WO2018035359 (WO'359) relates to HIV capsid inhibitors and its pharmaceutical compositions. The pharmaceutical compositions contain pharmaceutically acceptable excipients, in parenteral (injectable) form (pp.11–12). WO'359 discloses pharmaceutical compositions of capsid inhibitors, their method and use:

1. Excipients such as those set forth in Rowe, et al. Handbook of Pharmaceutical Excipients, 5th edition (p.47), and may be prepared using techniques and formulations found in Remington: The Science and Practice of Pharmacy, 21st edition, (p.48); for parenteral administration, suitable excipients are well known to a person skilled in the art and may be found in the Handbook of Pharmaceutical Excipients (Ed. Rowe, Sheskey and Quinn), 6th edition 2009 (p.51).
2. Examples of solubilizing excipients in parenteral formulation include, but not limited to: poloxamers (such as poloxamer 338, 188 or 207), in particular poloxamer 338 (p.51), and wherein poloxamer 188 ranges in molecular weight from about 7860 to 9510 Daltons (Da), and poloxamer 338 has a range in molecular weight from 12700 to about 17400 Da (p.52);
3. In some embodiments, excipients include polyethylene glycol (PEG) (p.51); the PEG has an average molecular weight approx. 100 to 1000, whereas average is about 200 to approx. 600, including PEG 200, 300, 400 (p.52)
4. In some embodiments, the suspension comprises saline and poloxamer (P188 or P338), where concentration of poloxamer 188 in saline is 1–10% (2%) (Figs. 4 to 6); or poloxamer and mannitol with concentration of poloxamer in mannitol from 0.1% to 20% (pp.53–54, Claims 63–65, 69–72);
5. In some embodiments that parenteral formulation comprises the compound or a pharmaceutical salt thereof and water (p.54, Claim 77); and in some embodiments it further comprises an alcohol, where the alcohol is ethanol (id. Claims 78–79); and it further comprises PEG200 (id., Claims 80–81) (p.55);
6. In some embodiments the formulation comprises of 5–20% ethanol, 5–20% water, about 60–90% PEG200 (p.55, Fig.10, Claims 84–86).
7. In some embodiments, the oral form, includes excipients including acceptable oils such as sesame oil (p.56)
8. Routes of administration include intravenous, subcutaneous or intramuscular (pp.29–30, 68; Claims 60–62)
9. Combination therapy with one to four additional therapeutic agents (pp.24–29), including HIV integrase inhibitors like dolutegravir, bictegravir, etc. and entry inhibitors like CCR5 inhibitors, etc. and others like lamivudine, and various combinations, etc. (pp.34–35, 38–40; Claims 17–22, 35–38, 42–45, 51–57).

Another application, by Gilead, WO2019035904 (WO'904), similar to WO'359, claims solid forms of capsid inhibitors, that also discloses injectables, such as sterile injectable aqueous and non-aqueous, that use wetting agents, sterile fixed oils, water, fatty acids, buffers, and suitable excipients such as polysorbates, poloxamers (338, 188, 207) – poloxamer 338 [pp.60–62]. WO'904 exemplifies intravenous administration of a capsid inhibitor formulated in 5% ethanol, 20%PG, 45% PEG300, 30% pH2 water at 0.5 mg/ml, and of other capsid inhibitors with 5% ethanol, 45% PEG400, and 50% water at 0.5 mg/ml [p.101]. WO'904 also provides formulation examples – example A that contains 2% poloxamer 188 in saline, and Example C that contains ethanol, water and PEG200 [pp.105–106]; the pharmacokinetic data for Example C at day 28 demonstrates extended release pharmacokinetics.

The present Application, WO2023062559 (WO'559) claims formulations of capsid inhibitors that contain either PEG-based formulations (water, ethanol and PEG) or poloxamer-based formulations (poloxamer 338, 188, mannitol, buffer) to be administered via intramuscular or subcutaneous injection, that can be given in combination with other agents (Claims 1 to 68).

However, the excipients used in the formulations of WO'559 are known to be used for preparing parenteral long-acting formulations, are commonly and routinely used—as shown in WO'359 (Citation 1) and WO'904 (Citation 1A) (with extended release pharmacokinetic data for capsid inhibitor, PEG, ethanol and water formulation), and also include those that are known in the art and/or set forth in text books.

Thus, all the claims of WO'559 lack inventive step.

Citation # 2 (Patent/utility model) (# uploaded documents: 0):

Country code: WO	Publication number: 2020/018459	Document kind code: A1
Patent Applicant/Patent Owner: Gilead Sciences, Inc.	Title of invention: Capsid Inhibitors for the treatment of HIV	
Link to document: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2020018459		
Publication Date: 23 Jan 2020 (23/01/2020)	Filing Date: 15 Jul 2019 (15/07/2019)	Priority Date: 16 Jul 2018 (16/07/2018)
Source of Abstract:	Accession number:	Publication Date of Abstract:
Retrieval Date of Abstract:		
Most relevant passages or drawings: pp. 4, 27–28, 30, 32–34, 36–37, 40–41, 56, 58–59, 61, 113, 129–150; Figs. 4–10; Claims 88 to 94		Relevant to Claims: 1-68
Brief explanation of relevance: WO2020018459 (WO'459) relates to HIV capsid inhibitor compounds and its salts, useful in the treatment of an HIV (Abstract).

WO'459 discloses the formulations of these compounds that can be administered parenterally – subcutaneously, intravenously, etc. (p. 4) and also specifically claims compositions in the form of a solution (Claims 88 to 94).

With respect to liquid, parenteral formulations, WO'459 discloses the following relating to compounds of formula Ia and Ib and its pharmaceutically acceptable salts:
1. Pharmaceutical compositions contain the active ingredient together with or more pharmaceutically acceptable excipients and optionally other therapeutic agent, in ordinary practice — any form suitable for the intended method of administration (p.27);

2. Composition can be in the form of formulations suitable for parenteral administration including aqueous or non-aqueous sterile injectable solution or suspension (p.33)

3. Solution formulation comprising N-methyl-2-pyrrolidone (NMP), polyethylene glycol (PEG- PEG 200, 300), water, glycofurol, ethanol, dimethyl sulfoxide (DMSO) (pp.33, 59).

4. In one embodiment, the formulation has 10% ethanol, 13% water, and 77% PEG200 – for subcutaneous administration (pp.33–34, 36, Fig. 3). There are similar compositions with PEG300 too — The solution comprising PEG 300 and water comprises PEG 300 (about 50–85% w/w) and water (about 5–25% w/w or about 10–12% w/w); this solution may further comprise an inorganic base (e.g., sodium hydroxide; 0.5–3% w/w) (pp.34, 40–41, 56, 61, Figs. 4–10).

5. Solubilizing excipients in a parenteral formulation (e.g., subcutaneous) include, but are not limited to polysorbates (e.g., Polysorbate 20 and 80) and poloxamers (e.g., Poloxamer 338, 188, 207; pp.34, 35, Figs. 12). In some embodiments, a suspension comprising of the compound or salt thereof, in poloxamer and mannitol where the concentration of poloxamer 188 in mannitol is 0.1 to 20% (pp.58–59)

6. In certain embodiments the alcohol is ethanol, and PEG 200 is used, the formulation comprises of ethanol, water, and PEG200 (pp.60–61)

7. Administration of the disclosed compounds or its pharmaceutically acceptable salt with one or more therapeutic agents, either intravenously, subcutaneously, intramuscularly (p. 113) either simultaneously or sequentially (pp.132–150).

8. All compositions can further contain excipients such as antioxidants, chelating agents (e.g., EDTA), etc – that are disclosed in textbooks on pharmaceutical excipients – and that suitable excipients for parenteral formulation are known in the art (pp. 28, 32). It also discloses that compositions can be formulated using techniques and formulations known in the art. (p. 30).

9. Combination therapy with one to four additional therapeutic agents, including HIV combination therapy, such as lamivudine, bictegravir, etc. (pp.129–150)

The present Application, WO2023062559 (WO'559) claims formulations of capsid inhibitors that contain either PEG-based formulations (water, ethanol and PEG) or poloxamer-based formulations (poloxamer 338, 188, mannitol, buffer) to be administered via intramuscular or subcutaneous injection, that can be given in combination with other agents (Claims 1 to 68).

However, WO'459 already discloses the excipients commonly used for preparing parenteral formulations of HIV capsid inhibitors, and the use of the formulated compounds in combination with other agents.

Thus, all claims of WO'559 lack inventive step.		

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

Country code: WO	Publication number: 2021/116872	Document kind code: A1
Patent Applicant/Patent Owner: ViiV Healthcare Company	Title of invention: Pharmaceutical compositions comprising cabotegravir	
Link to document: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2021116872		
Publication Date: 17 Jun 2021 (17/06/2021)	Filing Date: 07 Dec 2020 (07/12/2020)	Priority Date: 09 Dec 2019 (09/12/2019)
Source of Abstract:	Accession number:	Publication Date of Abstract: Retrieval Date of Abstract:
Most relevant passages or drawings: Abstract, pp.1–11, 14–18.23, 28, 32; Examples 3, 7 and 9; Table 2a, 7, 8, 15, 19; Fig. 2		Relevant to Claims: 33–68

Brief explanation of relevance:

WO2021116872 (WO872) discloses pharmaceutical compositions (compositions) comprising cabotegravir, an HIV integrase inhibitor, poloxamer and optionally polyethylene glycol (PEG) (as it may be 0), useful as a long-acting HIV treatment (Abstract, p.1; Table 2a).
WO872 discloses – (a) the need for long-acting injectable for HIV that can be dosed at fewer intervals and overcoming known difficulties with high concentration suspensions; (b) compositions that overcomes these difficulties and exhibit particle size stability (pp.1–2).
WO872 discloses and/or claims:
1. Compositions comprising cabotegravir or its salt (350–600 mg/mL), poloxamer (4–50 mg/mL), mannitol (20 mg/mL) and optionally PEG (0 to 75 mg/mL) (pp.3, 5–6; Table 2a)
2. Poloxamers are nonionic triblock copolymers composed of a central hydrophobic chain of polyoxypropylene (polypropylene oxide) flanked by two hydrophilic chains of polyoxyethylene (PEG), and may be P237, P338 or P407 (p.4).
3. The use of poloxamer allows a high concentration of cabotegravir to be present in the composition; it is thought that (a) the hydrophobic polyoxypropylene chains adsorb onto the surface of the cabotegravir particles and thus provide steric hindrance between particles and provides stabilization against particle aggregation or flocculation; (b) PEG chains provide stabilisation through steric hindrance, thus allowing a higher concentration of cabotegravir in the composition and minimising particle to particle interactions usually associated with high particle concentrations (pp.4–5).
4. Use of poloxamer P237, P407 or P338 gives enhanced physical stability to the compositions, possibly as they contain more PEG chains p.5).
5. The composition may not comprise PEG3350 (0 mg/mL), which otherwise acts as a stabilizer, as the PEG chains in poloxamer itself provide stabilisation by steric hindrance (pp.5–6).
6. The median particle diameter (MPD) of cabotegravir in the composition is 0.1 to 10.0 microm; compositions with MPD of 0.15 to 0.25 microm (about 0.2 microm) have improved resuspension over those with larger particle sizes (p.7).
7. Mannitol (present at a concentration of 15–40 mg/mL) is used as a tonicity adjuster (pp.7–8).
8. Composition may be administered parenterally (subcutaneous, intravenous, etc.) (p.3)
9. Composition for treatment or prevention of HIV; suitable for use as an injectable composition; use and method thereof (pp.8, 14–15).
10. Composition may be administered in combination with other anti-HIV agents, including capsid inhibitors (p.9).
11. Capsid inhibitors used in combination may include Compounds 1 and 2 or lenacapavir (pp.9–11, 15–18). It may be noted that Compounds 1 and 2 are Formula Ia and Ib of the present Application WO2023062559.
12. Exemplified compositions include those of 400 mg/mL and 500 mg/mL cabotegravir with P338 or P407 and mannitol; the lack of change in particle size after 1 month indicated stability of the suspensions (p.23, Ex. 3, Tables 7 and 8; p.32, Ex. 9, Table 19).
13. Pharmacokinetic profile for suspension of cabotegravir (400 mg/mL) with P338 and mannitol showed it to be similar to those with PEG3350; long-acting profile is maintained (p.28, Ex. 7; Table 15, Fig. 2).
The present Application, WO2023062559 (WO559), claims pharmaceutical compositions of compound of Formula Ia or Ib or its salt (previously disclosed HIV capsid inhibitors) particularly either PEG based formulations (Set A) or poloxamer based formulations (Set B).
In Set B, the claimed compositions (heterogeneous; Claim 45) comprise:
1. Water and less than 1% PEG (Claims 33–34);
2. further comprises one or more of sodium acetate, acetic acid, mannitol, sodium chloride, P338, or P188 (Claims 35–38);
3. with described MPD for compounds of Formula Ia and Ib of less than or equal to 0.2 microm (Claims 39–42). It specifically claims formulations with P338, mannitol and water or acetate buffer (Claims 43–44).
WO559 further claims method of treating HIV by administering the claimed composition via intramuscular, subcutaneous administration, either alone or in combination with another agent (Claim 59–65), composition for use (Claims 66–68). It may be noted that that Claims 46 to 58 appear to be identical to Claims 33 to 45.
However, WO872 already discloses the use of P338 and mannitol to make stable, long-acting formulations of cabotegravir, an anti-HIV drug, in a suspension form, with desired particle size of the compound, for treating HIV. WO872 also discloses the use of cabotegravir in combination with capsid inhibitors of compounds 1 and 2 (identical to compounds of formula Ia and Ib of WO559).
The applicant of WO559 has merely applied the strategy disclosed in WO872 to make long-acting formulations for the admittedly known HIV capsid inhibitors of formula Ia and Ib.
Thus, Claims 33 to 68 of the present Application, WO559, lack inventive step

Citation # 4 (Patent/utility model) (# uploaded documents: 0):

Country code: WO	Publication number: 2021/209900	Document kind code: A1	
Patent Applicant/Patent Owner: ViiV Healthcare UK (No.5) Limited		Title of invention: Inhibitors of human immunodeficiency virus replication	
Link to document: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2021209900			
Publication Date: 21 Oct 2021 (21/10/2021)	Filing Date: 13 Apr 2021 (13/04/2021)	Priority Date: 15 Apr 2020 (15/04/2020)	
Source of Abstract:	Accession number:	Publication Date of Abstract:	Retrieval Date of Abstract:
Most relevant passages or drawings: Abstract, pp. 3–6, 8–12, 57–58; Claims 1–18		Relevant to Claims: 1–68	

Brief explanation of relevance:

Though WO2021209900 (WO900) was published on (21/10/2021), after the priority date of the present Application, WO2023062559 (WO559) (13/10/2021), it claims an earlier priority date (15/04/2020). It is therefore relevant in those countries whose patent law consider such documents as relevant.

Both WO900 and WO559 are applications by ViiV Healthcare and relate to specific HIV capsid inhibitors (p. 12 of WO900; p. 1 of WO559).

WO900 claims pharmaceutical compositions comprising compounds of Formula Ia and Id, which are identical to compounds Ia and Ib respectively of the present Application, WO559 (Abstract).

WO900 discloses and/or claims

1. Pharmaceutical compositions of Formula Ia or Id or a salt thereof, and a solvent or diluent "selected" from the group consisting of water, an alcohol (ethanol), polyethylene glycol (PEG) – PEG 200, PEG300, PEG400; N-methyl-2-pyrrolidone (NMP), ethyl lactate, propylene glycol, glycofurol, and dimethylsulfoxide (DMSO) (pp.3–5, 9–10; Claims 1, 5–8)
2. The composition further comprises a solubilizing excipient selected from polysorbate 20, polysorbate 80, poloxamer 188 (P188) (at least 90% by weight), poloxamer 207 (P207), poloxamer 338 (P338), a fatty acid (with poloxamer), sodium chloride, and sodium hydroxide, (pp.3–4, 6; Claims 2, 9 (poloxamer188), 10)
3. The composition which specifically comprises (a) specifically water and PEG200 (p.6); (b) at least 90% by weight of solvents/diluents are water and PEG300 (Claims 11, 13–14); (c) at least 90% by weight of excipient is P188 (Claim 12).
4. The composition also comprises a buffer, such as acetate buffer (pH 4.8–5.2) (pp.8–9)
5. The compound or salt is present in the composition at a concentration of 50 to 500 mg/ml or 225 to 275, 275 to 350, 350 to 425 mg/ml based on weight of the free compound (p.4, 8–9; Claims 15–18)
6. The composition is a solution or suspension (p.3; Claims 3–4)
7. Method of treating HIV infection by administering the claimed composition (p.3)
8. Pharmaceutical composition for use in therapy and for use in treating HIV infection (p.3)
9. The use of the pharmaceutical composition in the manufacture of a medicament for the treatment of HIV infection (p.3)
10. Composition may be employed alone or in combination with other anti-HIV agents (p.11).
11. The exemplified formulation that was tested for pharmacokinetic parameters via subcutaneous injection comprised compound of Formula Ia, PEG300 and water (pp.57–58).

The present Application, WO559, claims pharmaceutical compositions of compound of Formula Ia or Ib or its salt, particularly either PEG based formulations (Set A) or poloxamer based formulations (Set B). The claimed compositions comprise:

Set A: 1. PEG (particularly PEG200, PEG300, PEG400; 40–50% by weight) and ethanol (5–25% by weight) (Claims 1–2, 8–13); 2. further comprises one or more of water, lecithin (soy), propylene glycol, benzyl alcohol, or sesame oil (Claim 3–7); 3. Composition is homogenous solution (Claim 14). It specifically claims formulations comprising PEG200, ethanol and lecithin (Claims 15–16).

Set B: 1. Water and less than 1% PEG (Claims 33–34); 2. further comprises one or more of sodium acetate, acetic acid, mannitol, sodium chloride, P338, or P188 (Claims 35–38), 3. with described mean particle diameters for compounds of Formula Ia and Ib (Claims 39–42). 3. It specifically claims formulations with P338, mannitol and water or acetate buffer (Claims 43–44). 4. The composition is a heterogenous suspension (Claim 45).

WO559 further claims method of treating HIV by administering the claimed composition via intramuscular, subcutaneous administration, either alone or in combination with another agent (Claim 59–65), composition for use in therapy and use in treating HIV infection and in the manufacture of a medicament for the treatment of HIV infection in a human (Claims 66–68).

It may be noted that that Claims 17 to 31 and Claims 46 to 58 appear to be identical to Claims 1 to 16 and Claims 33 to 45, respectively.

Thus, WO900 already discloses the claimed compounds and pharmaceutical compositions thereof, specifically with PEG200, PEG300 or PEG400, ethanol and water as well as with P338 or P188 and other excipients (water, sodium chloride, acetate buffer), for treating HIV.

The applicant of WO559 has merely used routine experimentation to prepare and determine the characteristics of the formulations prepared using excipients already known in the art for HIV capsid inhibitors (WO900 as well as WO2018035359, WO2019035904 and WO2020018459 (Citations 1, 1A and 2)).

In light of the above, Claims 1 to 68 of the present Application, WO559, lack inventive step.

ADDITIONAL COMMENTS FOR WO2023062559

The Third-Party Observation (TPO) accompanying this Additional Comment for WO2023062559 (WO'559) brings out the following through various prior art. The details of the TPO are as follows:-

Prior art: Citation 1: WO2018035359 and Citation 1A: WO2019035904

Country Code: WO	Publication Number: 2018/035359	Document Kind Code: A1
Patent Applicant/ Owner: Gilead Sciences Inc.	Title of Invention: Therapeutic compounds useful for the prophylactic or therapeutic treatment of and HIV virus infection	
Link to Document: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018035359		
Publication Date: 22.02.2018	Filing Date: 17.08.2017	Priority Date: 19.08.2016
Source of Abstract:	Accession Number:	Publication date of Abstract:
Most relevant passages or drawings: pp.11–12, 29–30, 34–35, 38–40, 47–48, 51–56, 68, Figs.4–6, 10, Claims 17–22, 35–38, 42–45, 51–57, 60–65, 69–72, 77–81, 84–86		Retrieval date of Abstract:
Relevant to Claims: 1–68		
Brief Explanation of Relevance:		
WO2018035359 (WO'359) relates to HIV capsid inhibitors and its pharmaceutical compositions. The pharmaceutical compositions contain pharmaceutically acceptable excipients, in parenteral (injectable) form (pp.11–12). WO'359 discloses pharmaceutical compositions of capsid inhibitors, their method and use: 1. Excipients such as those set forth in Rowe, et al. Handbook of Pharmaceutical Excipients, 5th edition (p.47), and may be prepared using techniques and formulations found in Remington: The Science and Practice of Pharmacy, 21st edition, (p.48); for parenteral administration, suitable excipients are well known to a person skilled in the art and may be found in the Handbook of Pharmaceutical Excipients (Ed. Rowe, Sheskey and Quinn), 6th edition 2009 (p.51). 2. Examples of solubilizing excipients in parenteral formulation include, but not limited to: poloxamers (such as poloxamer 338, 188 or 207), in particular poloxamer 338 (p.51), and wherein poloxamer 188 ranges in molecular weight from about 7860 to 9510 Daltons (Da), and poloxamer 338 has a range in molecular weight from 12700 to about 17400 Da (p.52); 3. In some embodiments, excipients include polyethylene glycol (PEG) (p.51); the PEG has an average molecular weight approx. 100 to 1000, whereas average is about 200 to approx. 600, including PEG 200, 300, 400 (p.52)		

4. In some embodiments, the suspension comprises saline and poloxamer (P188 or P338), where concentration of poloxamer 188 in saline is 1–10% (2%) (Figs. 4 to 6); or poloxamer and mannitol with concentration of poloxamer in mannitol from 0.1% to 20% (pp.53–54, Claims 63–65, 69–72);

5. In some embodiments that parenteral formulation comprises the compound or a pharmaceutical salt thereof and water (p.54, Claim 77); and in some embodiments it further comprises an alcohol, where the alcohol is ethanol (id. Claims 78–79); and it further comprises PEG200 (id., Claims 80–81) (p.55);

6. In some embodiments the formulation comprises of 5–20% ethanol, 5–20% water, about 60–90% PEG200 (p.55, Fig.10, Claims 84–86).

7. In some embodiments, the oral form, includes excipients including acceptable oils such as sesame oil (p.56)

8. Routes of administration include intravenous, subcutaneous or intramuscular (pp.29–30, 68; Claims 60–62)

9. Combination therapy with one to four additional therapeutic agents (pp.24–29), including HIV integrase inhibitors like dolutegravir, bictegravir, etc. and entry inhibitors like CCR5 inhibitors, etc. and others like lamivudine, and various combinations, etc. (pp.34–35, 38–40; Claims 17–22, 35–38, 42–45, 51–57).

Another application, by Gilead, WO2019035904 (WO'904), similar to WO'359, claims solid forms of capsid inhibitors, that also discloses injectables, such as sterile injectable aqueous and non-aqueous, that use wetting agents, sterile fixed oils, water, fatty acids, buffers, and suitable excipients such as polysorbates, poloxamers (338, 188, 207) – poloxamer 338 [pp.60-62]. WO'904 exemplifies intravenous administration of a capsid inhibitor formulated in 5% ethanol, 20%PG, 45% PEG300, 30% pH2 water at 0.5 mg/ml, and of other capsid inhibitors with 5% ethanol, 45% PEG400, and 50% water at 0.5 mg/ml [p.101]. WO'904 also provides formulation examples – example A that contains 2% poloxamer 188 in saline, and Example C that contains ethanol, water and PEG200 [pp.105–106]; the pharmacokinetic data for Example C at day 28 demonstrates extended release pharmacokinetics.

The present Application, WO2023062559 (WO'559) claims formulations of capsid inhibitors that contain either PEG-based formulations (water, ethanol and PEG) or poloxamer-based formulations (poloxamer 338, 188, mannitol, buffer) to be administered via intramuscular or subcutaneous injection, that can be given in combination with other agents (Claims 1 to 68).

However, the excipients used in the formulations of WO'559 are known to be used for preparing parenteral long-acting formulations, are commonly and routinely used—as shown in WO'359 (Citation 1) and WO'904 (Citation 1A) (with extended release pharmacokinetic data for capsid inhibitor, PEG, ethanol and water formulation), and also include those that are known in the art and/or set forth in text books.

Thus, all the claims of WO'559 lack inventive step.

Prior art: Citation 2: WO2020018459

Country Code: WO	Publication Number: 2020/018459	Document Kind Code: A1	
Patent Applicant/ Owner: Gilead Sciences, Inc.		Title of Invention: Capsid Inhibitors for the treatment of HIV	
Link to Document: https://patentscope.wipo.int/search/en/detail.jsf?docid=WO2020018459			
Publication Date: 23/01/2020		Filing Date: 15/07/2019	Priority Date: 16/07/2018
Source of Abstract:	Accession Number:	Publication date of Abstract:	Retrieval date of Abstract:
Most relevant passages or drawings: pp. 4, 27–28, 30, 32–34, 36–37, 40–41, 56, 58–59, 61, 113, 129–150; Figs. 4–10; Claims 88 to 94		Relevant to Claims: 1 to 68	
Brief Explanation of Relevance:			
WO2020018459 (WO'459) relates to HIV capsid inhibitor compounds and its salts, useful in the treatment of an HIV (Abstract).			
WO'459 discloses the formulations of these compounds that can be administered parenterally – subcutaneously, intravenously, etc. (p. 4) and also specifically claims compositions in the form of a solution (Claims 88 to 94).			
With respect to liquid, parenteral formulations, WO'459 discloses the following relating to compounds of formula Ia and Ib and its pharmaceutically acceptable salts:			
1. Pharmaceutical compositions contain the active ingredient together with or more pharmaceutically acceptable excipients and optionally other therapeutic agent, in ordinary practice — any form suitable for the intended method of administration (p.27);			
2. Composition can be in the form of formulations suitable for parenteral administration including aqueous or non-aqueous sterile injectable solution or suspension (p.33)			
3. Solution formulation comprising N-methyl-2-pyrrolidone (NMP), polyethylene glycol (PEG-PEG 200, 300), water, glycofurol, ethanol, dimethyl sulfoxide (DMSO) (pp.33, 59).			
4. In one embodiment, the formulation has 10% ethanol, 13% water, and 77% PEG200 – for subcutaneous administration (pp.33–34, 36, Fig. 3). There are similar compositions with PEG300 too — The solution comprising PEG 300 and water comprises PEG 300 (about 50–85% w/w) and water (about 5–25% w/w or about 10–12% w/w); this solution may further			

comprise an inorganic base (e.g., sodium hydroxide; 0.5–3% w/w) (pp.34, 40–41, 56, 61, Figs. 4–10).

5. Solubilizing excipients in a parenteral formulation (e.g., subcutaneous) include, but are not limited to polysorbates (e.g., Polysorbate 20 and 80) and poloxamers (e.g., Poloxamer 338, 188, 207; pp.34, 35, Figs. 12). In some embodiments, a suspension comprising of the compound or salt thereof, in poloxamer and mannitol where the concentration of poloxamer 188 in mannitol is 0.1 to 20% (pp.58–59)

6. In certain embodiments the alcohol is ethanol, and PEG 200 is used, the formulation comprises of ethanol, water, and PEG200 (pp.60–61)

7. Administration of the disclosed compounds or its pharmaceutically acceptable salt with one or more therapeutic agents, either intravenously, subcutaneously, intramuscularly (p. 113) either simultaneously or sequentially (pp.132–150).

8. All compositions can further contain excipients such as antioxidants, chelating agents (e.g., EDTA), etc – that are disclosed in textbooks on pharmaceutical excipients – and that suitable excipients for parenteral formulation are known in the art (pp. 28, 32). It also discloses that compositions can be formulated using techniques and formulations known in the art. (p. 30).

9. Combination therapy with one to four additional therapeutic agents, including HIV combination therapy, such as lamivudine, bicitgravir, etc. (pp.129–150)

The present Application, WO2023062559 (WO'559) claims formulations of capsid inhibitors that contain either PEG-based formulations (water, ethanol and PEG) or poloxamer-based formulations (poloxamer 338, 188, mannitol, buffer) to be administered via intramuscular or subcutaneous injection, that can be given in combination with other agents (Claims 1 to 68).

However, WO'459 already discloses the excipients commonly used for preparing parenteral formulations of HIV capsid inhibitors, and the use of the formulated compounds in combination with other agents.

Thus, all claims of WO'559 lack inventive step.

Prior art: Citation 3: WO2021116872

Country Code: WO	Publication Number: 2021/116872	Document Kind Code: A1	
Patent Applicant/ Owner: ViiV Healthcare Company		Title of Invention: Pharmaceutical compositions comprising cabotegravir	
Link to Document: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2021116872			
Publication Date: 17.06.2021		Filing Date: 07.12.2020	Priority Date: 09.12.2019
Source of Abstract:	Accession Number:	Publication date of Abstract:	Retrieval date of Abstract:
Most relevant passages or drawings: Abstract, pp.1–11, 14–18.23, 28, 32; Examples 3, 7 and 9; Table 2a, 7, 8, 15, 19; Fig. 2		Relevant to Claims: 1–68	
Brief Explanation of Relevance:			
WO2021116872 (WO872) discloses pharmaceutical compositions (compositions) comprising cabotegravir, an HIV integrase inhibitor, poloxamer and optionally polyethylene glycol (PEG) (as it may be 0), useful as a long-acting HIV treatment (Abstract, p.1; Table 2a).			
WO872 discloses – (a) the need for long-acting injectable for HIV that can be dosed at fewer intervals and overcoming known difficulties with high concentration suspensions; (b) compositions that overcomes these difficulties and exhibit particle size stability (pp.1–2).			
WO872 discloses and/or claims:			
1. Compositions comprising cabotegravir or its salt (350–600 mg/mL), poloxamer (4–50 mg/mL), mannitol (20 mg/mL) and optionally PEG (0 to 75 mg/mL) (pp.3, 5–6; Table 2a)			
2. Poloxamers are nonionic triblock copolymers composed of a central hydrophobic chain of polyoxypropylene (polypropylene oxide) flanked by two hydrophilic chains of polyoxyethylene (PEG), and may be P237, P338 or P407 (p.4).			
3. The use of poloxamer allows a high concentration of cabotegravir to be present in the composition; it is thought that (a) the hydrophobic polyoxypropylene chains adsorb onto the surface of the cabotegravir particles and thus provide steric hindrance between particles and provides stabilization against particle aggregation or flocculation; (b) PEG chains provide stabilisation through steric hindrance, thus allowing a higher concentration of cabotegravir in the composition and minimising particle to particle interactions usually associated with high particle concentrations (pp.4–5).			
4. Use of poloxamer P237, P407 or P338 gives enhanced physical stability to the compositions, possibly as they contain more PEG chains p.5).			

5. The composition may not comprise PEG3350 (0 mg/mL), which otherwise acts as a stabilizer, as the PEG chains in poloxamer itself provide stabilisation by steric hindrance (pp.5–6).
6. The median particle diameter (MPD) of cabotegravir in the composition is 0.1 to 10.0 microm; compositions with MPD of 0.15 to 0.25 microm (about 0.2 microm) have improved resuspension over those with larger particle sizes (p.7).
7. Mannitol (present at a concentration of 15–40 mg/mL) is used as a tonicity adjuster (pp.7–8).
8. Composition may be administered parenterally (subcutaneous, intravenous, etc.) (p.3)
9. Composition for treatment or prevention of HIV; suitable for use as an injectable composition; use and method thereof (pp.8, 14–15).
10. Composition may be administered in combination with other anti-HIV agents, including capsid inhibitors (p.9).
11. Capsid inhibitors used in combination may include Compounds 1 and 2 or lenacapavir (pp.9–11, 15–18). It may be noted that Compounds 1 and 2 are Formula Ia and Ib of the present Application WO2023062559.
12. Exemplified compositions include those of 400 mg/mL and 500 mg/mL cabotegravir with P338 or P407 and mannitol; the lack of change in particle size after 1 month indicated stability of the suspensions (p.23, Ex. 3, Tables 7 and 8; p.32, Ex. 9, Table 19).
13. Pharmacokinetic profile for suspension of cabotegravir (400 mg/mL) with P338 and mannitol showed it to be similar to those with PEG3350; long-acting profile is maintained (p.28, Ex. 7; Table 15, Fig. 2).

The present Application, WO2023062559 (WO559), claims pharmaceutical compositions of compound of Formula Ia or Ib or its salt (previously disclosed HIV capsid inhibitors) particularly either PEG based formulations (Set A) or poloxamer based formulations (Set B).

In Set B, the claimed compositions (heterogeneous; Claim 45) comprise: 1. Water and less than 1% PEG (Claims 33–34); 2. further comprises one or more of sodium acetate, acetic acid, mannitol, sodium chloride, P338, or P188 (Claims 35–38); 3. with described MPD for compounds of Formula Ia and Ib of less than or equal to 0.2 microm (Claims 39–42). It specifically claims formulations with P338, mannitol and water or acetate buffer (Claims 43–44).

WO559 further claims method of treating HIV by administering the claimed composition via intramuscular, subcutaneous administration, either alone or in combination with another agent (Claim 59–65), composition for use (Claims 66–68). It may be noted that that Claims 46 to 58 appear to be identical to Claims 33 to 45.

However, WO872 already discloses the use of P338 and mannitol to make stable, long-acting formulations of cabotegravir, an anti-HIV drug, in a suspension form, with desired particle size of the compound, for treating HIV. WO872 also discloses the use of cabotegravir in combination with capsid inhibitors of compounds 1 and 2 (identical to compounds of formula Ia and Ib of WO559).

The applicant of WO559 has merely applied the strategy disclosed in WO872 to make long-acting formulations for the admittedly known HIV capsid inhibitors of formula Ia and Ib.

Thus, Claims 33 to 68 of the present Application, WO559, lack inventive step.

Prior art: Citation 4: WO2021209900

Country Code: WO	Publication Number: 2021/209900		Document Kind Code: A1
Patent Applicant/ Owner: ViiV Healthcare UK (No.5) Limited		Title of Invention: Inhibitors of human immunodeficiency virus replication	
Link to Document: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2021209900			
Publication Date: 21.10.2021		Filing Date: 13.04.2021	Priority Date: 15.04.2020
Source of Abstract:	Accession Number:	Publication date of Abstract:	Retrieval date of Abstract:
Most relevant passages or drawings: Abstract, pp. 3–6, 8–12, 57–58; Claims 1–18		Relevant to Claims: 1–68	
Brief Explanation of Relevance: Though WO2021209900 (WO900) was published on (21/10/2021), after the priority date of the present Application, WO2023062559 (WO559) (13/10/2021), it claims an earlier priority date (15/04/2020). It is therefore relevant in those countries whose patent law consider such documents as relevant. Both WO900 and WO559 are applications by ViiV Healthcare and relate to specific HIV capsid inhibitors (p. 12 of WO900; p. 1 of WO559). WO900 claims pharmaceutical compositions comprising compounds of Formula Ia and Id, which are identical to compounds Ia and Ib respectively of the present Application, WO559 (Abstract). WO900 discloses and/or claims 1. Pharmaceutical compositions of Formula Ia or Id or a salt thereof, and a solvent or diluent “selected” from the group consisting of water, an alcohol (ethanol), polyethylene glycol (PEG) – PEG 200, PEG300, PEG400; N-methyl-2-pyrrolidone (NMP), ethyl lactate, propylene glycol, glycofurol, and dimethylsulfoxide (DMSO) (pp.3–5, 9–10; Claims 1, 5–8) 2. The composition further comprises a solubilizing excipient selected from polysorbate 20, polysorbate 80, poloxamer 188 (P188) (at least 90% by weight), poloxamer 207 (P207), poloxamer 338 (P338), a fatty acid (with poloxamer), sodium chloride, and sodium hydroxide, (pp.3–4, 6; Claims 2, 9 (poloxamer188), 10)			

3. The composition which specifically comprises (a) specifically water and PEG200 (p.6); (b) at least 90% by weight of solvents/diluents are water and PEG300 (Claims 11, 13–14); (c) at least 90% by weight of excipient is P188 (Claim 12).
4. The composition also comprises a buffer, such as acetate buffer (pH 4.8–5.2) (pp.8–9)
5. The compound or salt is present in the composition at a concentration of 50 to 500 mg/ml or 225 to 275, 275 to 350, 350 to 425 mg/ml based on weight of the free compound (p.4, 8–9; Claims 15–18)
6. The composition is a solution or suspension (p.3; Claims 3–4)
7. Method of treating HIV infection by administering the claimed composition (p.3)
8. Pharmaceutical composition for use in therapy and for use in treating HIV infection (p.3)
9. The use of the pharmaceutical composition in the manufacture of a medicament for the treatment of HIV infection (p.3)
10. Composition may be employed alone or in combination with other anti-HIV agents (p.11).
11. The exemplified formulation that was tested for pharmacokinetic parameters via subcutaneous injection comprised compound of Formula Ia, PEG300 and water (pp.57–58).

The present Application, WO559, claims pharmaceutical compositions of compound of Formula Ia or Ib or its salt, particularly either PEG based formulations (Set A) or poloxamer based formulations (Set B). The claimed compositions comprise:

- Set A: 1. PEG (particularly PEG200, PEG300, PEG400; 40–50% by weight) and ethanol (5–25% by weight) (Claims 1–2, 8–13); 2. further comprises one or more of water, lecithin (soy), propylene glycol, benzyl alcohol, or sesame oil (Claim 3–7); 3. Composition is homogenous solution (Claim 14). It specifically claims formulations comprising PEG200, ethanol and lecithin (Claims 15–16).
- Set B: 1. Water and less than 1% PEG (Claims 33–34); 2. further comprises one or more of sodium acetate, acetic acid, mannitol, sodium chloride, P338, or P188 (Claims 35–38), 3. with described mean particle diameters for compounds of Formula Ia and Ib (Claims 39–42). 3. It specifically claims formulations with P338, mannitol and water or acetate buffer (Claims 43–44). 4. The composition is a heterogenous suspension (Claim 45).

WO559 further claims method of treating HIV by administering the claimed composition via intramuscular, subcutaneous administration, either alone or in combination with another agent (Claim 59–65), composition for use in therapy and use in treating HIV infection and in the manufacture of a medicament for the treatment of HIV infection in a human (Claims 66–68).

It may be noted that that Claims 17 to 31 and Claims 46 to 58 appear to be identical to Claims 1 to 16 and Claims 33 to 45, respectively.

Thus, WO900 already discloses the claimed compounds and pharmaceutical compositions thereof, specifically with PEG200, PEG300 or PEG400, ethanol and water as well as with

P338 or P188 and other excipients (water, sodium chloride, acetate buffer), for treating HIV.

The applicant of WO559 has merely used routine experimentation to prepare and determine the characteristics of the formulations prepared using excipients already known in the art for HIV capsid inhibitors (WO900 as well as WO2018035359, WO2019035904 and WO2020018459 (Citations 1, 1A and 2.)).

In light of the above, Claims 1 to 68 of the present Application, WO559, lack inventive step.