

BEFORE THE CONTROLLER OF PATENTS

THE PATENT OFFICE, DELHI

IN THE MATTER OF

Section 25(1) and **Section 15** of The Patents Act, 1970 as
amended by The Patents (Amendment) Act, 2005,

AND

IN THE MATTER OF: Rule 55 of The Patents Rules, 2003,

AND

IN THE MATTER OF: The application no. 6148/DELNP/2011 filed on 12th August, 2011

AND

IN THE MATTER OF: Two Pre-grant REPRESENTATIONS U/S 25(1) OF THE PATENT
ACT filed by

Opponent : 1 . Mr. D. Sankar Rajkumar, 114/5, 2nd Main, 9 th Cross. Chamarajpet Bangalore-
18. India, through

Ms. Bina Dandekar (Regn.No.IN/PA 2917) of Gopakumar Nair Associates ...**Attorney of the
Opponent**

Opponent : 2 . VEE EXCEL DRUGSAND PHARMACEUTICAL(P) LTD, 703, 7th Floor,
Devika Tower, Chander Nagar Ghaziabad-201011, India through

Ms. Isha Sharma IN/PA 2386...**Attorney of the Opponent**

APPLICANT: BOEHRINGER INGELHEIM INTERNATIONAL GMBH through

Ms. Archana Shanker IN/PA 149 Of Anand and Anand, Advocates. ... **Attorney of the Applicant**

Hearing Date: 7th February, 2024

Present on behalf of Applicant: Ms. Archana Shanker, Mr. Devinder Rawat, Dr. Sachin Mailk

Present on behalf of the Opponent-1 (Dr. D. Sankar Rajkumar): Ms. Bina Dandekar

Present on behalf of the Opponent-2 (Vee Excel Drugs and Pharmaceutical (P) LTD): Not attended

DECISION

1. The bibliographic details of the application no. 6148/DELNP/2011 filed on 12th August, 2011 and titled as “PHARMACEUTICAL COMPOSITION COMPRISING LINAGLIPTIN AND OPTIONALLY A SGLT2 INHIBITOR, AND USES THEREOF” can be seen on the official website of Intellectual Property India www.ipindia.nic.in.
2. Two pre-grant representations u/s 25(1) of the patent act was filed respectively on 1st February, 2017 and 11th April 2019 by the Opponent-1, Mr. D. Sankar Rajkumar, 114/5, 2nd Main, 9 th Cross. Chamarajpet Bangalore-18. India, through Ms. Bina Dandekar (Regn.No.IN/PA 2917) of Gopakumar Nair Associates, Attorney of the Opponent and Opponent-2, VEE EXCEL DRUGS AND PHARMACEUTICAL(P) LTD, 703, 7th Floor, Devika Tower, Chander Nagar Ghaziabad-201011, India through Ms. Isha Sharma IN/PA 2386, **Attorney of the Opponent** to grant of the patent application no. 6148/DELNP/2011.
3. As per the provisions under Section 13 (3) of Patents Act, the said amended case after reply to FER, was again examined and investigated in like manner as the original specification. The applicant was offered a hearing u/s 25(1) and u/s 14 on 4th October,

2023 vide official communication dated 18th August, 2023. After repeated adjournments hearing finally conducted on 7th February, 2024. The statement of objections which were to be discussed during hearing and be complied consequently is as follows:

3.1. Objections

Definitiveness

1. Claim 1 does not sufficiently define the invention in respect of the composition percentages and technical features. Further, claim 1 is vague and unclear in respect to the invention. Therefore it is required to characterize the essential compositional percentages and technical features for which protection is sought. Bring novel and inventive features of the invention in claim 1. Further, all the essential features of the invention with their weight percentage ratios should be defined in the principal product/composition claim.

Formal Requirement(s)

1. Form-3 filed on 13-02-2014 is filed after the prescribed time given in rule 12 of Patents Act, 1970 and therefore cannot be taken on record. A petition is required for condonation of irregularity.

Invention u/s 2(1)(j)

1. The subject matter of the Claims 1-3 and 15 does not constitute an invention under section 2[1(j)] of the Patents Act, 1970 as it is anticipated by prior claiming in view of document D1(1006/DELNP/2010). D1 in claim 1 discloses a composition comprising a glucopyranosyl-substituted benzene derivative of the formula (I)(i.e Empagliflozin, embodiment B of the present application) in combination with a DPPIV inhibitor of formula (I)(i.e Linagliptin embodiment A of the present application). Linagliptin is present in the range of 0.5-10 mg and Empagliflozin is present in the range of 5-50 mg. Glucopyranosyl-substituted benzene derivative and the DPP IV inhibitor are present in a single dosage form. D1 further in claim 4 and 5 specifically discloses

that amount Empagliflozin is present in 10 mg and 25 mg. D1 in claim 7 discloses that Linagliptin is present in the amount of 5mg in composition. therefore claims 1-3 and 15 is considered not novel. Further, as D1 does not disclose that first active ingredient has a particle size distribution of $X_{90} < 200 \mu\text{m}$ and the second active ingredient has a particle size distribution of $1 \mu\text{m} < X_{90} < 200 \mu\text{m}$ claims 4 and 5 are considered novel. The subject matter of the claims 1-15 does not constitute an invention as it lacks inventive step under section 2[1(j)(a)] of the Patents Act, 1970 in view of prior art citation nos. D1-D21 (Cited in FER).

D6: WO 2005/085246

D7: 2006/0079541

D8: 2006/029769

D9: WO 2006/078593

D10: WO 2007/033350

D11: WO 2002/068420

D12: WO 2004/018468

D13: US2004/097510

D14: US 2007/0281940

D15: Katsuno, et al., "Sergliflozin, a Novel Selective Inhibitor of Low-Affinity Sodium Glucose Cotransporter (SGLT2), Validates the Critical Role of SGLT2 in Renal Glucose Reabsorption and Modulates Plasma Glucose Level" (2007) The Journal of Pharmacology and Experimental Therapeutics 320:323–30

D16: US Publication No. 2007/0281940

D17: Tim Heise, et al., "Treatment with BI 1356, a Novel and Potent DPP-IV Inhibitor, Significantly Reduces Glucose Excursions after an oGTT in Patients with Type 2 Diabetes" (2007) Diabetes Jun 2007 Supplement 1, 56: A156 (abstract) (Exhibit O-1) :: American Diabetes Association 67th Scientific Sessions (2007) Abstract No. 0588-P (Exhibit O-2)

D18: Thomas, et al., “(R)-8-(3-Amino-piperidin-1-yl)-7-but-2-ynyl-3-methyl-1-(4-methylquinazolin-2-ylmethyl)-3,7-dihydro-purine-2,6-dione (BI 1356), a Novel Xanthine-Based Dipeptidyl Peptidase 4 Inhibitor, Has a Superior Potency and Longer Duration of Action Compared with Other Dipeptidyl Peptidase-4 Inhibitors” (2008) *The Journal of Pharmacology and Experimental Therapeutics* 325:175–82

D19: Thomas et al., “Chronic Treatment with the Dipeptidyl Peptidase-4 Inhibitor BI 1356 [(R)-8-(3-Amino-piperidin-1-yl)-7-but-2-ynyl-3-methyl-1-(4-methyl-quinazolin-2-ylmethyl)-3,7-dihydro-purine-2,6-dione] Increases Basal Glucagon-Like Peptide-1 and Improves Glycemic Control in Diabetic Rodent Models” (2009) *The Journal of Pharmacology and Experimental Therapeutics* 328:556–63 (published on 1 February 2009)

D20: Fiese and Hagen, “Preformulation”, in Lachman and Lieberman (eds), *The Theory and Practice of Industrial Pharmacy* (1987)

D21: WO 2006/117359

It is an admitted position that linagliptin, methods of manufacture thereof [see Complete Specification, internal page 18], its preferred crystalline forms [see Complete Specification, internal pages 18 and 34] and its pharmaceutical compositions [see Complete Specification, internal page 2] were known.

In WO 2007/128724 (hereinafter referred to as WO '724”), titled “DPP IV inhibitor formulations” and published on 15 November 2007, the Patent Applicant sets out the alleged problem of incompatibilities and degradation faced by DPPIV inhibitors with primary or secondary amino groups, including linagliptin [see WO '724, internal page 1].

WO '724 discloses the choice of excipients—a first and second diluent, a binder, a disintegrant, and further second disintegrant, a lubricant and an optional glidant— and sets out preferred excipients to solve this alleged problem [see WO '724, internal pages 1 to 3 and 10 to 17 (examples 1 to 6)]. The examples also set out the dosage of active ingredient 0.5 mg, 1 mg, 2.5 mg, 5 mg, 10 mg [see WO '724, internal pages 10 to 17 (examples 1 to 6)] and provide an example of a high dose formulation too [see WO '724, internal page 17 (example 6.3)]. Thus, as

of the priority date, linagliptin and its pharmaceutical composition comprising preferred excipients to overcome the alleged problems of degradation and incompatibilities were known. Empagliflozin was known. It is an admitted position that empagliflozin and its preferred crystalline forms were known [see Complete Specification, internal pages 2 and 18 to 20].

As stated earlier, WO '877 and its Indian equivalent IN '4844 disclose empagliflozin [see IN '4844 (Exhibit E above), internal pages 1 to 8, 29 (compound 3) and granted claim 5]. IN '4844 discloses (i) the SGLT2 inhibiting effect of the compounds claimed, including empagliflozin [see IN '4844, internal page 7] and (ii) the use of the claimed compounds for treatment and / or prevention of diseases or conditions which could be influenced by inhibiting the sodium-dependent cotransporter SGLT, particularly SGLT2, and for treatment of metabolic disorders [see IN '4844, internal pages 7 and 46]. Combination of DPPIV inhibitors with other anti-diabetic drugs, including SGLT2 inhibitors, was known. As shown below, combinations of DPPIV inhibitors with other antidiabetic drugs, including SGLT2 inhibitors, were known in the art as of the priority date. Patent documents such as WO 2005/085246 titled "8-[3-aminopiperidin-1-yl]-xanthine, the production thereof and the use in the form of a DPP inhibitor" (published on 15 September 2005) and US Publication No. 2006/0079541 titled "3-methyl-7-butinylxanthines, the preparation thereof and their use as pharmaceutical compositions" (published on 13 April 2006) (equivalent of WO 2006/029769 published on 23 March 2006) disclose DPPIV inhibitors and their combination with SGLT2 inhibitors.

WO 2006/078593 (hereinafter referred to as "WO '593"), titled "Direct compression formulation and process" published on 27 July 2006, discloses an oral tablet formulation of vildagliptin in the form of a tablet. It also discloses a combination of DPPIV inhibitors with other therapeutic agents [see WO '593, internal pages 49 to 50] as well as excipients such as diluents, disintegrants, lubricants, diluents, fillers, binders [see WO '593, internal pages 16 to 18]. The rationale for combining different drugs was well-known.

For example, WO 2007/033350 (hereinafter referred to as "WO '350"), titled "Dipeptidyl peptidase inhibitors for treating diabetes" and published on 22 March 2007, discloses some such reasons. WO '350 disclosed pharmaceutical compositions comprising a DPPIV inhibitor (referred to as "Compound I") and other anti-diabetic compounds [see WO '350, internal pages 4 to 8]. It stated that the combinations provide excellent effects such as (i) enhancement in

therapeutic effects of either of Compound I and / or the antidiabetic compounds, (ii) reduction in side-effects of Compound I and / or the anti-diabetic compounds and (iii) reduction in dose of Compound I and / or the anti-diabetic compounds [see WO '350, internal page 4]. These reflect the benefits that were expected to arise out of a combination of different active ingredients. Thus, the combination of DPPIV inhibitors with other anti-diabetic drugs, including SGLT2 inhibitors, and the rationale for such combination was known in the art. Combination of linagliptin with other anti-diabetic drugs, including SGLT2 inhibitors, was known.

For example, WO 2002/068420, titled "Xanthine derivative, production and use thereof as a medicament" and published on 6 September 2002, discloses xanthine compounds as DPP-IV inhibitors and their combinations. Because this patent document is in German, reference is being made to its Indian national phase equivalent, i.e. 01092/DELNP/2003 (hereinafter referred to as "IN '1092") titled "Xanthine derivatives, the preparation thereof and their use as pharmaceutical compositions" which was published on 12 January 2007. The bibliographic page and relevant extracts of the complete specification and claims of IN '1092, as retrieved from the website of the Indian Patent Office, are hereto annexed and marked as "Exhibit J". IN '1092 discloses xanthine compounds as DPP-IV inhibitors [see IN '1092, internal page 1] and also discloses a combination of DPP-IV inhibitors with other antidiabetic drugs [see IN '1092, internal pages 101 to 102]. It discloses a dosage of DPP-IV inhibitors of 1 to 100 mg [see IN '1092, internal page 102] and also examples of compositions of DPP-IV inhibitors in different dosage forms [see IN '1092, internal pages 282 to 287].

WO 2004/018468, titled "8-[3-amino-piperidin-1-yl]-xanthines, the production thereof and the use of the same as medicaments" and published on 4 March 2004, discloses xanthine compounds as DPPIV inhibitors, including linagliptin, and also its combination with other anti-diabetic drugs. Because this patent document is in German, reference is being made to its Indian national phase equivalent, i.e. 567/DELNP/2005 (hereinafter referred to as "IN '567"), titled 8-[3-amino-piperidin-1-yl]-xanthine compounds" which was published on 23 January 2009. Its divisional application, i.e. IN 6108/DELNP/2007, makes similar disclosures and is not included herein for the sake of brevity.

IN '567 discloses (i) xanthine compounds having valuable pharmacological properties—particularly an inhibiting effect on the activity of the enzyme dipeptidylpeptidase—including linagliptin and their compositions, (ii) the combination of DPPIV inhibitors with other anti-diabetic drugs and (iii) their use in various disorders [see IN '567, internal pages 1, 26 (compound 13), 37 to 38, page 161 (example 2(142) and claims]. It also discloses the dosage range of 1 to 100 mg for oral administration [see IN '567, internal page 38] and examples of compositions of DPPIV inhibitors in different dosage forms [see IN '567, internal pages 189 to 193]. Thus, IN '567 discloses a combination of linagliptin with other antidiabetic drugs. US Publication No. 2004/097510 titled “8-[3-amino-piperidin-1-yl]-xanthines, the preparation thereof and their use as pharmaceutical compositions” (hereinafter referred to as “US '510”) and published on 20 May 2004, make disclosures similar to that of IN '567.

US Publication No. 2007/0281940 (hereinafter referred to as “US '940”), titled “Use of DPP-IV inhibitors” and published on 6 December 2007 describes the use of selected DPP IV inhibitors, including linagliptin which is identified as a preferred compound, for the treatment of physiological functional disorders including diabetes and obesity and for reducing the risk of the occurrence of such functional disorders in at-risk patient groups [see US '940, title page and internal pages 2 to 3]. It describes the use of the DPP-IV inhibitors in combination with other active substances, including SGLT1 and SGLT2 inhibitors, for treating various disease conditions by means of which improved treatment outcomes can be achieved [see US '940, internal page 5, para 0060 and 0061 and internal page 12, example 15]. More particularly, example 15 discloses the dosage ranges of both the DPP-IV inhibitor and SGLT-2 inhibitor and exemplifies how the appropriateness and effectiveness of a combination of DPP-IV inhibitor with an SGLT-2 inhibitor can be determined [see US '940, internal page 12].

US '940 also discloses excipients for the manufacture of compositions of DPP-IV inhibitors as well as methods for manufacture of dosage forms [see US '940, internal pages 4 to 5]. Thus, a person skilled in the art would only have to engage in routine tests and experimentation to determine a preferred combination of DPP-IV inhibitor and SGLT-2 inhibitor. Katsuno, et al.

discusses the benefits of SGLT-2 inhibitors [see Katsuno, et al., “Sergliflozin, a Novel Selective Inhibitor of Low-Affinity Sodium-Glucose Cotransporter (SGLT2), Validates the Critical Role of SGLT2 in Renal Glucose Reabsorption and Modulates Plasma Glucose Level” (2007) The Journal of Pharmacology and Experimental Therapeutics 320:323–30, a copy of which is hereto annexed and marked as “Exhibit M”]. They noted that sergliflozin, an SGLT2 inhibitor, had glucose-lowering effects by increasing urinary glucose excretion, without inducing hypoglycaemia or excessive insulin secretion. They also noted that these properties enabled SGLT-2 inhibitors to meet the suitable (sic) for blood glucose control with body weight control and preservation of insulin secretion.

Katsuno, et al., concluded that SGLT2 inhibitors offered advantages over existing anti-diabetic drugs and were a useful new category for treatment of diabetes: “In this sense, SGLT2 inhibitors offers some advantages as antidiabetic drugs over existing antidiabetic drugs such as sulfonylureas, α -glucosidase inhibitors, thiazolidinediones, and biguanides. Our results with sergliflozin, a novel selective SGLT2 inhibitor developed by us, demonstrate that SGLT2 plays a major role in renal glucose reabsorption. We propose this SGLT2 inhibitor as a representative of a useful new category of drug for the treatment of diabetes mellitus.” (emphasis supplied) Thus, US '940 (Exhibit L) discloses a combination of DPPIV inhibitors, including linagliptin as a preferred compound, and SGLT2 inhibitors. As shown below, linagliptin had already emerged as a preferred DPP-IV inhibitor. Katsuno, et al. (Exhibit M) too provides support for the choice of an SGLT2 inhibitor for a combination drug. A person skilled in the art would only have to engage in routine tests and experimentation to determine an appropriate combination. The determination of an appropriate combination of preferred ingredients is thus obvious to a person skilled in the art. It also does not involve a technical advance. Therefore, in light of the disclosures contained in IN '1092 (Exhibit J), IN '567 (Exhibit K) and/or US '940 (Exhibit L), supported by Katsuno, et al. (Exhibit M), the combination of linagliptin with other SGLT2 inhibitors is obvious to a person skilled in the art and does not involve a technical advance.

WO 2008/055940 (hereinafter referred to as “WO '940”), titled “Combination therapy with SGLT-2 inhibitors and their pharmaceutical compositions” discloses pharmaceutical compositions comprising one or more SGLT2 inhibitors, including empagliflozin, in combination with one or more therapeutic agents and the conditions that could be treated [see WO '940,

internal pages 1, 5 to 7, 17 and 19]. It sets out that anti-diabetic drugs that have different mechanisms of action are suitable for combination treatment [see WO '940, internal page 2]. It discloses that the combination can be administered individually or as a single pharmaceutical composition, such as a single dosage form [see WO '940, internal page 5].

WO '940 notes that the administration of the combination can have an additive or over additive effect [see WO '940, internal page 8]. It also discloses a dosage range of 1 to 100 mg for the SGLT-2 inhibitor [see WO '940, internal page 26]. As adverted to earlier, IN '4844 (Exhibit E) discloses that the SGLT-2 inhibitor compounds, including empagliflozin, can be used in conjunction with other active substances, including DPPIV inhibitors, particularly for treatment and / or prevention of diseases or conditions including metabolic disorders or conditions such as type-1 and type-2 diabetes mellitus and complications of diabetes and obesity [see IN '4844, internal pages 47 to 49 and granted claim 9]. It provides the rationale for such combination, i.e. a combination with active substances which can potentiate the therapeutic effect of the claimed SGLT inhibitor and/or which will allow its dosage to be reduced [see IN '4844, internal page 47]. Amongst the DPPIV inhibitors specifically listed are LAF 237, i.e. vildagliptin, and MK-431, i.e. sitagliptin [see IN '4844, internal pages 47 to 48]. IN '4844 discloses a pharmaceutical composition comprising the claimed SGLT-2 inhibitors and a second active substance, including DPPIV inhibitors, to treat or prevent diseases or conditions which could be affected by inhibiting SGLT, particularly metabolic diseases such as diabetes or diabetes complications [see IN '4844, internal page 49]. It also claims empagliflozin as and when used in the preparation of a pharmaceutical composition [see IN '4844, granted claim 6] together with at least one anti-diabetic agent including DPPIV inhibitors [see IN '4844, granted claims 7 and 8]. It discloses a composition optionally together with one or more inert "conventional" carriers and/or diluents [see IN '4844, internal pages 7, 8 and 47] as well as pharmaceutical composition of such a combination optionally with one or more inert carriers or diluents [see IN '4844, internal page 49]. IN '4844 also discloses that the use of the claimed SGLT-2 inhibitor in combination with the other active substance, including DPPIV inhibitors, could take place simultaneously or at staggered times [see IN '4844, internal page 49]. When used simultaneously, the two substances would be present together in one formulation, for example a tablet [see IN '4844, internal page 49].

Thus, IN '4844 discloses a pharmaceutical composition comprising empagliflozin, DPP-IV inhibitors and other inert carriers known to persons skilled in the art. As of the priority date, linagliptin was already known as a DPP-IV inhibitor. As adverted to in the "Background" above, DPP-IV inhibitors were a known class of promising drugs that allowed glycaemic control without the risk of hypoglycaemia or weight gain and were known to possess advantages over other anti-diabetic agents. In 2007, Heise, et al., reported the safety, pharmacokinetic and pharmacodynamic properties of BI-1356, i.e. linagliptin and conclude that it had the potential to be a best in class DPP-IV inhibitor [see Tim Heise, et al., "Treatment with BI 1356, a Novel and Potent DPP-IV Inhibitor, Significantly Reduces Glucose Excursions after an oGTT in Patients with Type 2 Diabetes", (2007) *Diabetes Jun 2007 Supplement 1*, 56: A156 (abstract) :: American Diabetes Association 67th Scientific Sessions (2007) Abstract No. 0588-P. In 2008, Thomas, et al. (hereinafter referred to as "Thomas, et al. (2008)") provided data to show that BI 1356, i.e. linagliptin, inhibited DPP-IV more effectively than vildagliptin, sitagliptin, saxagliptin and alogliptin and concluded that it had the potential to become a once-a-day DPP-IV inhibitor for treatment of type 2 diabetes [see Thomas, et al., "(R)-8-(3- Amino-piperidin-1-yl)-7- but-2-ynyl-3-methyl-1-(4-methyl-quinazolin-2-ylmethyl)-3,7- dihydro-purine-2,6-dione (BI 1356), a Novel Xanthine-Based Dipeptidyl Peptidase 4 Inhibitor, Has a Superior Potency and Longer Duration of Action Compared with Other Dipeptidyl Peptidase-4 Inhibitors" (2008) *The Journal of Pharmacology and Experimental Therapeutics* 325:175–82. Again, in early February 2009, Thomas, et al. (hereinafter referred to as "Thomas, et al. (2009)") concluded that the effects on HbA1c and GLP-1 were superior to the short-acting DPP-4 inhibitor vildagliptin, demonstrating the potential of BI 1356 as a once daily treatment for type 2 diabetes at low therapeutic doses [see Thomas et al., "Chronic Treatment with the Dipeptidyl Peptidase-4 Inhibitor BI 1356 [(R)-8-(3-Amino-piperidin-1-yl)-7- but-2-ynyl-3- methyl-1-(4-methyl-quinazolin-2-ylmethyl)-3,7- dihydro-purine- 2,6- dione] Increases Basal Glucagon-Like Peptide-1 and Improves Glycemic Control in Diabetic Rodent Models" (2009) *The Journal of Pharmacology and Experimental Therapeutics* 328:556–63. Since both DPP-IV inhibitors and SGL T-2 inhibitors are known to be used in the treatment of disorders related to diabetes, it must be prima facie obvious to use combinations thereof for the same indications.

The present applications refers to a synergistic effect, but the effect shown does only appear to be additive. An additive effect cannot be considered unexpected. In addition the alleged effect

has only been shown for one of the claimed combinations. if applicant is able to prove synergism following argument holds. It is not considered inventive to combine two or more active ingredients for treating a particular disease in the case where said two or more active agents are each known to be therapeutically effective in treating said particular disease. In this regard, it would normally be expected that such a composition of active agents would be more effective than either active agent alone. Under these circumstances any synergistic effect is to be considered a mere bonus effect that the skilled person can reasonably expect and identify with routine experimentation, and consequently an inventive step cannot be at present recognized. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have selected the various combinations of features claimed from within the prior art disclosure D1-D21 to arrive at the instantly claimed subject matter.

Non-Patentability u/s 3

1. 1. Claims 1-15 fall u/s 3(d) of the Patents (Amended) Act, 2005 as the said claims define the new combination of the known compounds. it is not clear if the claimed composition act to provide an enhancement of the known efficacy i.e., demonstrate a greater technical effect and/or differ significantly in properties w.r.t the constituents. the Complete Specification provides data for only one pharmacological example to show an alleged glucose excursion effect for the combination against a control, linagliptin alone and empagliflozin alone [see Complete Specification, internal pages 54 to 55]. The Patent Applicant has not shown significantly enhanced efficacy for linagliptin or empagliflozin or the claimed combination. Further, the Patent Applicant has not shown significantly enhanced efficacy for the combination over simultaneous or sequential administration of the known active ingredients. Therefore, the Patent Applicant has failed to discharge the burden of showing enhanced therapeutic efficacy for the claimed composition.

2. Claims 1-15 fall u/s 3(e) of the Patents (Amended) Act, 2005 as the said claims define a mere admixture resulting only in the aggregation of the properties of the components thereof. It is not clear if the combined agents act together to provide a technical effect that is greater than just the

sum of the two or more agents alone, or whether the combination is, in fact, a mere juxtaposition with no interaction of the agents.

Other Requirement(s)

1. The hearing u/s 25(1) will be conducted for grounds of opposition, reply statements filed by both parties for each pre-grant representation

4. Present Subject Matter:

4.1 The present invention is directed to A solid pharmaceutical dosage form as a one-layer tablet comprising: (a) 5 mg of linagliptin (DPP IV Inhibitor) and its pharmaceutically acceptable salts thereof, including hydrates and solvates thereof, and crystalline forms thereof, as a first active pharmaceutical ingredient, (b) 10-25 mg of 1-chloro-4-(β -D-glucopyranos-1-yl)-2-[4-((S)-tetrahydrofuran-3- yloxy)-benzyl]-benzene and its hydrates, solvates and polymorphic forms thereof, (SGLT-2 inhibitor) as a second pharmaceutical ingredient, and one or more excipients.

4.2.Total number of claims: There are total 10 amended claims along with 1 independent claim in present application.

4.3.Independent Claims:

1. A solid pharmaceutical dosage form as a one-layer tablet comprising:

- a) 5mg of linagliptin (DPP IV Inhibitor) and pharmaceutically acceptable salts thereof, including hydrates and solvates thereof, and crystalline forms thereof, and crystalline forms thereof as a first active pharmaceutical ingredient,
- b) 10-25mg of 1-chloro-4-(β -D-glucopyranos-1-yl)-2-[4-((S)-tetrahydrofuran-3- yloxy)-benzyl]-benzene and its hydrates, solvates and polymorphic forms thereof, (SGLT-2 inhibitor) as a second pharmaceutical ingredient, and one or more excipients, the first

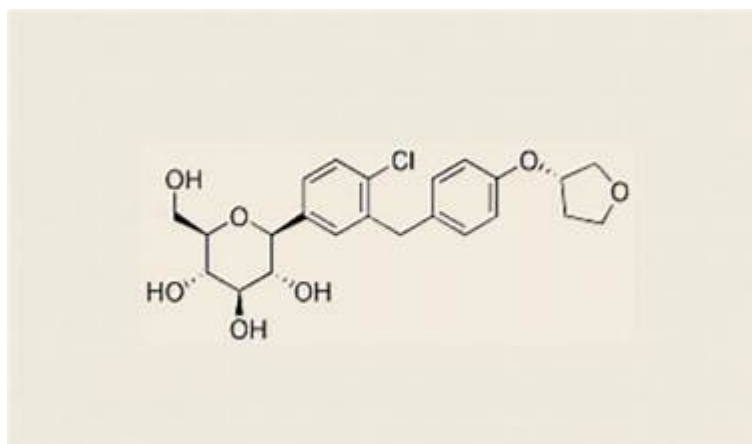
active ingredient and second active ingredient are present in amount of 0.5-25% by wt of the total composition,

c) 40-88% by wt of the total composition of one or more diluents selected from the group consisting of cellulose, dibasic calcium phosphate, erythritol, mannitol, starch, pregelatinized starch, and xylitol, including derivatives and hydrates of the before mentioned substances,

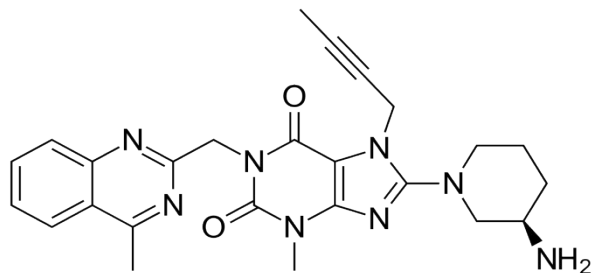
d) 0.5-20% by wt of the total composition of the one or more binders by wt of the total composition, and

e) 0.5-20% by wt of the total composition of the one or more disintegrants by wt of the total composition.

Empagliflozin (INN assigned by WHO) which is SGLT2 inhibitor has a chemical name 1-chloro-4-(β -D-glucopyranos-1-yl)-2-[4-((S)-tetrahydro-furan-3-yloxy)- benzyl]-benzene and is an SGLT2 inhibitor, and



Linagliptin (INN assigned by WHO), which is DPP IV inhibitor has a chemical name, 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyln-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine.



4.4. Combined Cited documents in FER & Opposition:

D1: IN 1006/DELNP/2010 Exhibit A

D2: WO 2004/018468 A2

D3: WO 2008/055870 A1

D4: WO 2007/093610 (Exhibit F of Pre-grant opposition)

D5: 4844/DELNP/2006 (WO 2005/092877)

D6: WO 2005/085246

D7: 2006/0079541

D8: 2006/029769

D9: WO 2006/078593

D10: WO 2007/033350 (Exhibit E of Pre-grant opposition)

D11: WO 2002/068420

D12: WO 2004/018468

D13: US2004/097510

D14: US 2007/0281940

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D18: Thomas, et al., “(R)-8-(3-Amino-piperidin-1-yl)-7-but-2-ynyl-3-methyl-1-(4-methylquinazolin-2-ylmethyl)-3,7-dihydro-purine-2,6-dione (BI 1356), a Novel Xanthine-Based Dipeptidyl Peptidase 4 Inhibitor, Has a Superior Potency and Longer Duration of Action Compared with Other Dipeptidyl Peptidase-4 Inhibitors” (2008) The Journal of Pharmacology and Experimental Therapeutics 325:175–82

D19: Thomas et al., “Chronic Treatment with the Dipeptidyl Peptidase-4 Inhibitor BI 1356 [(R)-8-(3-Amino-piperidin-1-yl)-7-but-2-ynyl-3-methyl-1-(4-methyl-quinazolin-2-ylmethyl)-3,7-dihydro-purine-2,6-dione] Increases Basal Glucagon-Like Peptide-1 and Improves Glycemic Control in Diabetic Rodent Models” (2009) The Journal of Pharmacology and Experimental Therapeutics 328:556–63 (published on 1 February 2009)

D20: Fiese and Hagen, “Preformulation”, in Lachman and Lieberman (eds), The Theory and Practice of Industrial Pharmacy (1987)

D21: WO 2006/117359

Exhibit D: 9506/DELNP/2008

4.5. The documents Relied upon by Opponent -1 are following

1. IN 1006/DELNP/2010 Exhibit A
2. IN 4811/DELNP/2011 Exhibit C
3. WO2005/092877; (IN 4844/DELNP/2006) published on 6 October 2005 Exhibit E
4. WO2007/093610 Exhibit F
5. WO 2007/128724 published on 15 November 2007 Exhibit G
6. WO 2006/078593 published on 27 July 2006 Exhibit H
7. WO 2007/033350 published on 22 March 2007 Exhibit I
8. IN 01092/DELNP/2003 pub. 12 January 2007 (WO ‘420) Exhibit J
9. IN 567/DELNP/2005 published on 23 January 2009 Exhibit K

10. US 2007/0281940 published on 6 December 2007 Exhibit L
11. Katsuno, et al., “Sergliflozin, a Novel Selective Inhibitor of Low-Affinity Sodium Glucose Cotransporter (SGLT2), Validates the Critical Role of SGLT2 in Renal Glucose Reabsorption and Modulates Plasma Glucose Level” (2007) The Journal of Pharmacology and Experimental Therapeutics 320:323–30 Exhibit M
12. WO 2008/055940 published on 15 May 2008 Exhibit N
13. Tim Heise, et al., “Treatment with BI 1356, a Novel and Potent DPP-IV Inhibitor, Significantly Reduces Glucose Excursions after an oGTT in Patients with Type 2 Diabetes” (2007) Diabetes Jun 2007 Supplement 1, 56: A156 Exhibit O-1 Exhibit O-2 (abstract); American Diabetes Association 67th Scientific Sessions (2007) Abstract No. 0588-P
14. Thomas, et al., “(R)-8-(3-Amino-piperidin-1-yl)-7-but-2-ynyl-3-methyl-1-(4-methyl-quinazolin-2-yl-methyl)-3,7-dihydro-purine-2,6-dione (BI 1356), a Novel XanthineBased Dipeptidyl Peptidase 4 Inhibitor, Has a Superior Potency and Longer Duration of Action Compared with Other Dipeptidyl Peptidase-4 Inhibitors” (2008) The Journal of Pharmacology and Experimental Therapeutics 325:175– 82 Exhibit P
15. Thomas et al., “Chronic Treatment with the Dipeptidyl Peptidase-4 Inhibitor BI 1356 [(R)-8-(3-Amino-piperidin-1-yl)-7-but-2-ynyl-3-methyl-1-(4-methyl-quinazolin-2-ylmethyl)-3,7-dihydro-purine-2,6-dione] Increases Basal Glucagon-Like Peptide-1 and Improves Glycemic Control in Diabetic Rodent Models” (2009) The Journal of Pharmacology and Experimental Therapeutics 328:556–63 (published on 1 February 2009) Exhibit Q
16. Fiese and Hagen, “Preformulation”, in Lachman and Lieberman (eds), The Theory and Practice of Industrial Pharmacy (1987) Exhibit R
17. WO 2006/117359 published on 9 November 2006 Exhibit S
18. Exhibit T (Wang et al)

5. GROUNDS OF OPPOSITION:

- 1) Section 25(1)(b) - that the invention so far as claimed in the claims of the complete specification has been published before the priority date of the claims in India and elsewhere read with section 2(1)(j)
- 2) Section 25(1)(c) - **Anticipation by Prior Claiming**, that the invention so far as claimed in any claim of the complete specification is claimed in a claim of a complete specification

published on or after priority date of the applicant's claim and filed in pursuance of an application for a patent in India, being a claim of which the priority date is earlier than that of the applicant's claim;

3) Section 25(1)(e) - that the invention so far as claimed in the claims of the complete specification is obvious and clearly does not involve any inventive step, having regard to the matter published as mentioned in Section 25(1)(b) above and/or having regard to what was used in India before the priority date of the Applicant's claims; read with section 2(1)(ja),

4) Section 25(1)(f) - that the subject of the claims of the complete specification is not an invention within the meaning of the Patents Act, or is not patentable under the Patents Act; read with section 2(1)(ja), section 3(d) and section 3(e)

5) Section 25(1)(g) - that the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed;

5.1. OBSERVATIONS ON VARIOUS GROUNDS OF OPPOSITION

The detailed discussions on various grounds of oppositions filed specifically by Opponent-1 are as follows

6. Anticipation by Prior Claiming- Section 25(1)(c)

6.1 The Opponent submits that the pharmaceutical dosage of linagliptin in an amount of 5 mg and 1-chloro-4-(β -D-glucopyranos-1-yl)-2-[4-(S)-tetrahydrofuran-3-yloxy]-benzyl]- benzene (herein after will be referred as empagliflozin) in an amount of 10mg or 25mg together with one or more excipients are prior claimed in Indian Patent Application no. 1006/DELNP/2010 (D1)(Exhibit A).

6.1.1 Claim 1 of 1006/DELNP/2010 claims a pharmaceutical composition comprising empagliflozin in combination with the DPP IV inhibitor or a pharmaceutically acceptable salt thereof wherein the amount of empagliflozin is from 5 mg to 50 mg and wherein the amount of the DPP IV inhibitor is from 0.5 mg to 10 mg.

6.1.2 The Opponent states that each and every feature of the present claim is anticipated by claims of the application no. 1006/DELNP/2010.

6.1.3 The Applicant argued saying that the present claim does not overlap the claims of 1006/DELNP/2010 since the claims do not claim the pharmaceutical composition as a one-layer tablet. The Opponent states that the term “pharmaceutical composition...” in the claim 1 of 1006/DELNP/2010 itself is very broad and encompasses the variant forms of the composition including the one layer (mono-layer) tablets as claimed in the impugned invention. Further, the subsequent claims of 1006/DELNP/2010 “characterizes” the pharmaceutical composition as formulated for oral administration in solid form.

6.1.4 The Applicant during rebuttal submitted that the claims of said document 1006/DELNP/2010 are amended to 4 claims, reproduced below:

*1. A pharmaceutical composition comprising the glucopyranosylsubstituted benzene derivative 1-chloro-4-(β -D-glucopyranos-1-yl)-2- [4-((S)- tetrahydro-furan-3-yloxy)-benzyl]-benzene in combination with the **DPP IV** inhibitor 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7- (2-butyn-1-yl)- 8-(3-(R)-amino-piperidin-1-yl)-xanthine or a pharmaceutically acceptable salt thereof wherein the amount of the glucopyranosyl-substituted benzene derivative is from **5 mg to 50 mg**, and wherein the amount of the DPP IV inhibitor is from **0.5 mg to 10 mg**.*

2. The pharmaceutical composition as claimed in claim. 1, comprising an amount of 10 mg to 25 mg of the glucopyranosyl-substituted benzene derivative.

3. The pharmaceutical composition as claimed in any one of the claims 1 and 2, comprising an amount of 1 mg to 5 mg of the DPP IV inhibitor.

*4. The pharmaceutical composition as claimed in any one of the previous claims characterized in that the pharmaceutical composition is formulated **for oral administration in solid form**.*

6.1.5 The Opponent reiterated that the claim 1 of the impugned application squarely falls within the ambit of the further amended claims and that it is a case of ever greening of the patent which should be dismissed out rightly. It is reiterated that the Applicant was unable to overcome this aspect and was unable to show anything over and above the prior art 1006/DELNP/2010 as

shown herein. In fact the Applicant admitted that claim 1 of 1006/DELNP/2010 relates to a **combination of linagliptin and empagliflozin** and not the composition.

6.1.6 Further, internal page 44 (pdf page 134), para 3 of 1006/DELNP/2010 disclose that “the pharmaceutical composition may be in the **form of tablets**, para 4 on page 44 discloses that the pharmaceutical composition and the dosage forms preferably comprises of one or more pharmaceutical acceptable carriers which must be “acceptable” in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Para 5 on page 44 states that **the tablets may contain conventional excipients such as binding agents, lubricants, disintegrants**. Examples 3 and 4 of 1006/delnP/2010 discloses tablet formulation comprising similar excipients such as (1) Active substance 50.0 mg, (2) Lactose 98.0 mg, (3) Maize starch 50.0 mg, (4) Polyvinylpyrrolidone 15.0 mg and (5) Magnesium stearate 2.0 mg.

6.1.7. It further states that “[t]he tablets may be coated according to methods well known in the art.” [see internal page 44]. Page 47, para 5, states that the combinations of a glucopyranosyl-substituted benzene derivative and DPPIV inhibitor significantly improves glucose excursion compared to each monotherapy as measured by reduction of peak glucose concentrations or reduction of glucose AUC. The combinations significantly reduce HbA1c compared to monotherapy. Para 1 on page 48 states that the combinations at lower doses significantly improve glycemic control compared to placebo treatment whereas the monotherapy at lower doses do not.

6.1.8 The Opponent therefore respectfully submits that each and every feature of the claim 1 and subsequently the dependent claims are anticipated wholly by prior claim of 1006/DELNP/2010 and ought to be rejected in totality.

6.2. The Opponent states that the claims 1-10 of the impugned application are anticipated by the claims of Indian Application No. 4811/DELNP/2011 (D2)-(Exhibit C).

6.2.1. The document 4811/DELNP/2011 (Exhibit C) claims in claim 1 a salt of 1-[(4- methyl-quinazolin-2-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine and a pharmaceutically acceptable acid in a 1:1 stoichiometry. Further subsequent claims 4, 6, 7, 8 claims a salt in the form of solvate, hydrate, crystalline forms. Further claim 9 claims a pharmaceutical composition with one or more pharmaceutically acceptable carriers and/or diluents. Claim 10 claims that the pharmaceutical composition comprises of one or more other active substances.

6.2.2. Para 2 to 5 on internal page 14 of said document (Exhibit C) disclose the form of tablets as **coated tablets which may comprise of several layers (mono-, bi-or trilayer)** with excipients such as diluents, lubricants and binders. Para 5 on page 16 discloses the dosage of linagliptin preferably in an amount of **1mg to 5mg**.

6.2.3. The Opponent states that 4811/DELNP/2011 claims linagliptin and the pharmaceutical composition which may further comprise other active substance. Page 18, para 1 of said document discloses SGLT2 inhibitors as example of antidiabetic **combination**. The Opponent states that empagliflozin is a known compound/ drug and was also known to the Applicant at the priority date and hence the composition of linagliptin with empagliflozin are anticipated by the claims of 4811/DELNP/2011.

6.2.4. From the foregoing, it is concluded that this ground of opposition is found to be valid and the claims 1-10 (as amended) of the impugned application are rejected under section 25(1)(c) of the Patents Act, 1970.

7. NOT NOVEL AND ANTICIPATION BY PRIOR PUBLICATION-Section 25(1)(b)

7.1. The Opponent states that the amended claims 1-10 are not novel and anticipated by publication by the disclosures of D5-WO 2005/092877, relied upon on its Indian national phase equivalent, i.e. Indian Application No. 4844/DELNP/2006 (Exhibit E).

7.1.1 The Opponent states that 4844/DELNP/2006 claims, in claim 5, glucopyranosylsubstituted benzene compound, 1-Chloro-4-(β -D-glucopyranos-1-yl)-2-[4-((S)- tetrahydrofuran-3-yloxy)-benzyl]-benzene, i.e. **empagliflozin** and on page 29 (compound 2). Page 47, para 1 disclose the dosage preferably in an amount of **1 to 100mg** by oral route. Claims 7, 8 and 9 of 4844/DELNP/2006 claim the compound when used in preparation of pharmaceutical composition that may comprise at least one antidiabetic agent, DPPIV inhibitors for treatment of type 1 and type 2 diabetes. The therapeutic agents listed include **DPPIV inhibitors**; of these, LAF237, i.e. vildagliptin, and MK-431, i.e. sitagliptin, [see internal pages 47 to 48]. It further discloses pharmaceutical composition of such a combination optionally with one or more inert **carriers or diluents** [internal page 49]. Page 47, para 1 disclose that pharmaceutical

compositions of compound of formula 1 may be formulated with other active substances with one or more carriers and or diluents to produce coated tablets.

7.1.2 The Opponent states that linagliptin is a known compound/ drug and was also known to the Applicant at the priority date. Therefore, pharmaceutical dosage form of linagliptin and empagliflozin together with acceptable excipients in the form of tablets as claimed (amended) in the impugned application is anticipated by prior publication in 4844/DELNP/2006.

7.2. The Opponent states that the claims of the impugned application are anticipated by the disclosure of D4-WO 2007/093610 (WO'610) (Exhibit F).

7.2.1. The Opponent states that WO'610 disclose discloses a pharmaceutical composition comprising the claimed **SGLT2-inhibitors** (Glucopyranosyl-substituted benzonitrile derivatives) and the second active substance, including **DPPIV inhibitors**, to treat or prevent diseases or conditions, particularly metabolic diseases such as diabetes or diabetes complications [see WO '610, internal pages 25 to 26]. WO'610 further discloses that the two substances would be present together in one formulation, for example a **tablet** [see WO '610, internal page 27]. It further discloses pharmaceutical composition of such a combination optionally with one or more inert carriers or diluents [see WO '610, internal page 27]. Though WO'610 discloses Glucopyranosyl-substituted benzonitrile derivatives, WO'610 particularly disclose glucopyranosyl-substituted benzene compounds, including empagliflozin in example XIV(2)] in internal page no. 37. The therapeutic agents listed include DPPIV inhibitors; of these, LAF237, i.e. vildagliptin, and MK-431, i.e. sitagliptin are specifically mentioned [see WO '610, internal page 26]. Linagliptin is also a known DPPIV inhibitor, and empagliflozin is a known SGLT-2 inhibitor.

7.2.2. The Opponent states that linagliptin and empagliflozin are known drugs used for the treatment of diabetes, and the same was also known to the Applicant at the priority date and hence the pharmaceutical composition comprising linagliptin and empagliflozin in tablet form as claimed in the impugned application are not novel over the disclosure of WO'610 which relates to a pharmaceutical composition of SGLT2 and DPPIV inhibitor for diabetes.

7.2.3. The amended claims 1-10 of the impugned application are anticipated by prior publication by the disclosures of either 4844/DELNP/2006 or WO 2007/093610 and this ground of

opposition is found to be valid and claims 1-10 are rejected under section 25(1)(b) read with section 2(1)(j) of the Patents Act, 1970.

8. Lack of Inventive step –Section 25(1)(e) The Opponent submits that the claims 1-10 (as amended) of the impugned application do not involve technical advance as compared to existing knowledge, lack inventive step and obvious to a person skilled in the art over the documents discussed below.

8.1 The document WO2007/128724 (WO'724) (Exhibit G) discloses pharmaceutical compositions of **DPPIV inhibitors** with an amino group to treat diabetes mellitus. Attention of Ld. Controller is drawn to internal page 1, lines 14 to 25 wherein it discloses that “In attempts to prepare pharmaceutical compositions of selected DPP-IV inhibitors it has been observed, that the DPP-IV inhibitors with a primary or secondary amino group show incompatibilities, degradation problems, or extraction problems with a number of customary excipients such as microcrystalline cellulose, sodium starch glycolate, croscarmellose sodium, tartaric acid, citric acid, glucose, fructose, saccharose, lactose, maltodextrines. Though the compounds themselves are very stable, they react with many **excipients** used in solid dosage forms and with impurities of excipients, especially in tight contact provided in tablets and at high excipient/drug ratios. The amino group appears to react with reducing sugars and with other reactive carbonyl groups and with carboxylic acid functional groups formed for example at the surface of microcrystalline cellulose by oxidation. These unforeseen difficulties are primarily observed in low dosage ranges which are required due to the surprising potency of the selected inhibitors. Thus, pharmaceutical compositions are required so solve these technical problems associated with the unexpected potency of selected DPP-IV inhibitor compounds”. The document WO'724 in lines 30 to 34 on page 1 discloses that “A pharmaceutical composition according to the present invention is intended for the treatment of to achieve glycemic control in a type 1 or type 2 diabetes mellitus patient and comprises a DPP-IV inhibitor with an amino group, especially a free or primary amino group, as an active ingredient, a first and second diluent, a binder, a disintegrant and a lubricant.

8.1.1 The DPPIV inhibitor, linagliptin is disclosed on page 4, line 15 of WO'724.

8.1.2 The document WO'724 on page 2, lines 14 to 16 discloses the lubricants selected from talc, polyethylene glycol, calcium behenate, calcium stearate, hydrogenated castor oil, magnesium stearate; Lines 18-22 on page 2 of WO'724 disclose binders which include copovidone, HPMC, hydroxypropylcellulose (HPC), low substituted hydroxypropylcellulose (L-HPC), polyvinyl pyrrolidone, pregelatinized starch; Lines 28- 30 on page 2 of WO'724 disclose disintegrants which include corn starch, crospovidone, low substituted hydroxypropylcellulose (L-HPC), pre-gelatinised starch.

8.1.3 The document WO'724 on page 3, lines 25-26 states that the pharmaceutical composition can be used in the dosage form as a film coated tablet. Lines 30-32 state that the exemplary coat composition may comprise hydroxypropylmethyl cellulose (HPMC), polyethylene glycol, talc, titanium dioxide and optionally iron oxide. Lines 28-29 on page 3 disclose that the film coat represents 2-4%, preferably 3% of the composition.

8.1.4 Lines 6-8 on internal page 3 of WO'724 that dosage ranges from 0.1-100mg, preferably the dosage are **0.5mg, 1mg, 2.5mg, 5mg and 10 mg**.

8.1.5 The Opponent in view of the preceding paragraph states that the unforeseen compatibility problems of linagliptin with conventional excipients is addressed in WO'724 and provides a solution to the problem by providing the excipients i.e. binder, lubricant and disintegrant. The Applicant while overcoming the alleged compatibility problems of linagliptin has employed the excipients diluent, binder and disintegrant (claimed in the subsequent claims 6 to 10) which is substantially similar to the excipients disclosed in WO'724. The Opponent further states that the film coat disclosed in the examples 1 to 3 of the impugned application on pages 59-61 are identical to the film coat composition of WO'724.

8.1.6 It is therefore submitted that WO'724 discloses, provides sufficient teachings and motivation to a person skilled in art to employ the excipients for a pharmaceutical composition of linagliptin without any incompatibility issues. Hence, the use of said excipients to overcome the alleged unforeseen compatibility issues of linagliptin in the present impugned Application is obvious and devoid of any inventive feature from the disclosure of WO'724. Further, empagliflozin is a known drug/ compound, and was also known to the Applicant at the priority

date and hence a pharmaceutical dosage as claimed in the amended claims is obvious and lacks inventive step.

9.1. The document WO2006/078593 (WO'593) (Exhibit H) (hereinafter referred as WO'593), disclose compressed DPP-IV inhibitor tablet with a particle size distribution of less than 250 μ m, preferably between 10 to 250 μ m. Though WO'593 particularly discloses Vildagliptin, the teachings of WO'593 provide enough motivation to a person skilled in the art to have a particle size distribution of less than 200 μ m. The Opponent therefore states that there is no inventive feature in the **particle size distribution** claimed in claims 4 and 5 (amended claims) of the impugned application. Further, the Applicant has failed to disclose enhanced feature in the pharmaceutical dosage of the present invention with the particle size distribution of less than 200 μ m.

9.1.1 The Opponent reiterates that a person skilled in the art can arrive at the impugned alleged invention without any undue experimentation and with reasonable expectation of success from the disclosures, teachings of WO2007/128724 (Exhibit G) and WO2006/078593 (Exhibit H), empagliflozin being known at the priority date.

9.2. The document WO2007/033350 (WO'350) (Exhibit I) discloses pharmaceutical compositions comprising a DPPIV inhibitor (referred to as Compound I) and other antidiabetic compounds [see WO 350, internal pages 4 to 8]. It stated that the combinations provide excellent effects such as (i) enhancement in therapeutic effects of either of Compound I and / or the antidiabetic compounds, (ii) reduction in side-effects of Compound I and / or the anti-diabetic compounds and (iii) reduction in dose of Compound I and / or the anti-diabetic compounds [see WO 350, internal page 4].

9.2.1 The Opponent states that the teachings of WO'350 reflect the benefits that were expected to arise out of a combination of different active ingredients. Thus, the combination of DPPIV inhibitors with other anti-diabetic drugs, including SGLT2 inhibitors, and the rationale for such combination as claimed in the impugned application is obvious and do not merit inventive step.

9.3. The document 01092/DELNP/2003 (Exhibit J; WO 2002/068420) on pages 695, 696 and 697(pdf pages) disclose xanthine derivatives as DPP-IV inhibitors for type I and type II diabetes, for preventing B-cell degeneration such as for example apoptosis or necrosis of pancreatic B-

cells. The document further discloses that the DPP-IV inhibitors may be used in conjunction with other active substances. On page 697, it discloses the excipients for formulating the dosage forms such as coated tablets which include corn starch, polyvinylpyrrolidone, magnesium stearate, propylene glycol. It further discloses the **dosage range 1 to 100mg for oral route**.

9.4. The document 567/DELNP/2005 (Exhibit K; WO 2004/018468) discloses (i) xanthine compounds as DPPIV inhibitors, including **linagliptin**, (ii) the **combination** of DPP-IV inhibitors with other anti-diabetic drugs and (iii) their use in various disorders [internal pages 1, 26 (compound 13), 37 to 38, page 161 (example 2(142) and claims]. It also discloses the dosage range of 1 to 100 mg for oral administration [internal page 38] and examples of compositions of DPPIV inhibitors in different dosage forms internal pages 189 to 193].

9.5. The document US2007/0281940 (Exhibit L) discloses the use of **DPP-IV inhibitors in conjunction with other active substances (SGLT2 inhibitors) for reducing diabetes**. Para [0032] on internal page 3 of WO 2004/018468 disclose Linagliptin. Internal page 4 and page 5, para [0046] to para [0051] disclose the dosage and excipients used for formulating linagliptin dosages which particularly include binders, lubricants and disintegrants which are similarly employed in the present invention. Example 11 of US'940 disclose DPP-IV inhibitor of film coated tablets. Example 15, para [0093] illustrates combined treatment with DPP-IV inhibitor-SGLT2 inhibitor. It is disclosed in said example 15 that "Evidence that the combination is appropriate and effective can be found in the fact that the 17 combination of a DPP-IV inhibitor with the SGLT-2 inhibitor leads to a significantly greater reduction in the fasting glucose and/or non-fasting glucose and/or the HbA1c value than either the DPP IV inhibitor alone or the SGLT-2 inhibitor alone".

9.5.1 The Opponent, in view of the preceding paragraph, states that a person skilled in the art would be motivated to formulate pharmaceutical dosage comprising of linagliptin (a DPP-IV) inhibitor and empagliflozin (SGLT2 inhibitor), in a single mono-layer tablet for greater reduction in glucose levels, using the excipients and the amount of the actives as disclosed and taught in US'940. In light of the same, the Opponent states that there is no inventive step in the claims 1-10 (as amended) being obvious and that the actives being known to the Applicant at priority date.

9.6. With reference to the article by Kastuno (Exhibit M), the Opponent states that the article discloses the benefits of SGLT2 as antidiabetic drugs over existing antidiabetic drugs; the document WO2008/055940 (WO'940) (Exhibit N) discloses pharmaceutical composition of SGLT2 inhibitor for treatment of diabetes with one or more second therapeutic agent(s).

9.7. The Opponent states in light of the disclosures contained in 01092/DELNP/2003 (Exhibit J), 567/DELNP/2005 (Exhibit K) and/or US2004/097510 (Exhibit L), supported by Katsuno, et al. (Exhibit M), and WO'940 Exhibit N, the combination of linagliptin with SGLT-2 inhibitor is obvious to a person skilled in the art and does not involve any inventive feature or technical advance. Furthermore, linagliptin and empagliflozin are known to be used as treatment for diabetes, and known DPP-IV inhibitor and SGLT-2 inhibitors, and this also would be known to the Applicant as of the priority date.

9.8. It is further submitted that the safety, pharmacokinetic and pharmacodynamic properties of BI-1356, i.e. linagliptin and its potential to be a best in class DPP-IV inhibitor is set out in "Exhibit O-1" and "Exhibit O-2" respectively; that BI 1356, i.e. linagliptin, inhibited DPP-IV more effectively than vildagliptin, sitagliptin, saxagliptin and alogliptin is taught in Exhibit P; that the effects on HbA1c and GLP-1 were superior to the short-acting DPP-4 inhibitor vildagliptin, demonstrating the potential of BI 1356 is disclosed, taught in Exhibit Q. A combination of empagliflozin and linagliptin would therefore have been obvious to a person skilled in the art reading the Exhibits O to Exhibit Q in combination with Exhibit L and Exhibit N.

9.9. The Opponent states that Exhibit R discloses, teaches the drug-excipient compatibility testing, WO 2006/117359 (WO'359) (Exhibit S), that discloses and claims allegedly advantageous crystalline forms of empagliflozin and discloses that the dosage may be from 1 to 100 mg [see WO '359, internal page 12]; Exhibit T (Wang et al) discloses BI-1356 as potent DPP-IV inhibitor for treatment of type 2 diabetes.

9.10. Thus, from the ample teachings and disclosures made in the prior art documents, the Opponent states that the amended claims 1-10 of the present Application lack inventive step because they are obvious to a person skilled in the art and do not involve a technical advance. Thus, it is evident that the claims of the impugned application have been conclusively proved to

be completely devoid of inventive step and this ground of opposition is found to be valid and claims 1-10 are rejected under Section 25(1)(e) of the Patents Act 1970.

10. SECTION 25(1)(f): FAILURE TO MEET SECTION 3(d)

10.1. Section 3(d)

10.1.1 The Opponent states that both linagliptin and empagliflozin and the excipients were known as of the priority date and that the Applicant has failed to show the therapeutic efficacy of the pharmaceutical dosage of linagliptin and empagliflozin as claimed in the impugned application. The Complete Specification accompanying the present Application does not allege an enhanced efficacy for the composition comprising linagliptin and empagliflozin over the known efficacy of DPP-IV-inhibiting activity of linagliptin or SGLT2 inhibiting activity of empagliflozin. Hence this ground of opposition is found to be valid and the present claimed pharmaceutical dosage as claimed in the amended claims 1-10 is rejected u/s 3(d) of the Patents Act, 1970.

10.2 Section 3(e)

10.2.1. The Opponent states that the claimed composition as claimed in amended claim 1 is a mere admixture of known substances resulting only in the aggregation of the properties of the components thereof without any synergistic effect.

10.2.2. The Opponent states that both linagliptin and empagliflozin are slightly soluble in water. The Applicant in example 1 has provided the glucose tolerance test on Zucker Diabetic Fatty (ZDF) rats by single oral administration of vehicle containing SGLT2 inhibitor, DPP-IV inhibitor or the combination of SGLT2 and DPP-IV inhibitor wherein the vehicle is 0.5% hydroxyethyl cellulose (HEC) containing 3mM HCl and 0.015% polysorbate 80 as a solubilizer. The Opponent states that the test performed in example 1 (Pharmacological examples) of the complete specification of the impugned application has used HEC and the solubilizer polysorbate 80. The Applicant has failed to demonstrate the synergy of the claimed pharmaceutical dosage in tablet forms along with the claimed excipients for demonstrating reduced glucose excursion.

10.2.3. The Opponent submits that the Applicant has failed to provide the compatibility study of empagliflozin along with Linagliptin as well as along with the claimed excipients proving the fact that the claimed solid pharmaceutical composition/dosage form is a mere admixture.

10.2.4. In light of the same, this ground of opposition is found to be valid and claimed pharmaceutical dosage in claims 1-10 is rejected u/s 3(e) of the patents Act, 1970.

11. SECTION 25(1)(g): INSUFFICIENCY OF DESCRIPTION

11.1. The Opponent states at the instant that there is no comparative stability data of Linagliptin, the pharmaceutical dosage of Linagliptin and empagliflozin with the claimed excipients over the conventional/customary excipients.

11.2. The Opponent states that the Applicant on internal page 69 has merely mentioned the physical tests of the pharmaceutical dosage claimed such as disintegration test, the tablet hardness and friability test but has failed to show comparative study of the said dosage in terms of bioavailability and glucose reduction/reduced glucose excursion. The Opponent reiterates that the pharmacological studies provided in example 1 are for the APIs along with the HEC and the solubilizer polysorbate 80 and not for the pharmaceutical dosage as claimed in the amended claims 1-10.

11.3. Further, the examples of pharmaceutical composition show that there is no such solubilizer used in the formulation of mono-layer tablet and hence the dissolution test cannot be correlated to the bioavailability of the said APIs considering the solubility of the API's which are slightly soluble.

11.4. Under Section 10(4)(a) of the Patents Act, every complete specification shall fully and particularly describe the invention and its operation or use and the method by which it is to be

performed. It is evident that the description and the claims are not clear and are insufficient. Therefore, because the complete specification does not sufficiently and clearly describe the invention, this ground of opposition is found to be valid and claims 1-10 are rejected under section 25(1)(g) of the Patents Act.

12. Based on the above facts and on the circumstances of the case, the invention did not meet the technical objections for lack of novelty u/s 2(1)(j)- 25(1)(b), 25(1)(c), for lack of inventive step u/s 2(1)(ja)- -25(1)(e), for Non-Patentability u/s 3(d), 3(e) -25(1)(f), and for insufficiency of disclosure- u/s 25(1)(g) of The Patents Act. Therefore, it is hereby ordered that the invention disclosed and claimed in the instant application No. 6148/DELNP/2011 filed on 12th August, 2011 and titled as “PHARMACEUTICAL COMPOSITION COMPRISING LINAGLIPTIN AND OPTIONALLY A SGLT2 INHIBITOR, AND USES THEREOF” **has been refused** to proceed further u/s 15 of the Patents Act, 1970 and the two pre-grant representations u/s 25(1) of the patent act filed respectively on 1st February, 2017 and 11th April 2019 by the Opponent-1, Mr. D. Sankar Rajkumar, 114/5, 2nd Main, 9 th Cross. Chamarajpet Bangalore-18. India, through Ms. Bina Dandekar (Regn.No.IN/PA 2917) of Gopakumar Nair Associates, Attorney of the Opponent and Opponent-2, VEE EXCEL DRUGS AND PHARMACEUTICAL(P) LTD, 703, 7th Floor, Devika Tower, Chander Nagar Ghaziabad-201011, India through Ms. Isha Sharma IN/PA 2386, **Attorney of the Opponent** to grant of the patent application no. 6148/DELNP/2011 are also disposed off.

Dated, the 14th March, 2024.

(Dr. Sunita Rani)

Deputy Controller of Patents & Designs.