Vereenigde Octrooibureaux N.V.
Johan de Wittlaan 7
P.O. Box 87930
2508 DH The Hague
The Netherlands

Telephone +31 70 416 67 11
Telefax +31 70 416 67 99

B.Hermann@vo.eu
www.vo.eu

European Patent Office
Directorate General 2
Erhardstr. 27
D-80298 Munich
Germany

Your ref. 05724887.4//1725234
Our ref. BCH/O23380EP00 21 August 2013

Re: Opposition against European Patent No. 1725234
in the name of The Trustees of The University of Pennsylvania
Opponent: Evan Stein MD, PhD

Herewith an

OPPOSITION

is filed against **European Patent No. 1 725 234 B9**

in the name and on behalf of

Evan Stein MD PhD
25 E Superior St #4602
Chicago, Illinois USA 60611
USA

The subject matter of the opposed patent is based on former studies with microsomal triglyceride transfer protein (MTP) inhibitor implitapide, which is (2S)-2-cyclopentyl-2-[4-[(2,4-dimethyl-9H-pyrido[2,3-b]indol-9-yl)methyl]phenyl]-N-[(1S)-2-hydroxy-1-

phenylethyl]ethanamide, a phenylglycinolamide derivative such as the claimed subject matter, particularly specified in claim 6, which is lomitapide (i.e., N-(2,2,2-Trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]2-yl]carbonyl]amino]-1-piperidinyl]butyl]9H-fluoren-9-carboxamde). One of the co-inventors, Dr. Daniel Rader, was a consultant and clinical investigator in clinical research projects with implitapide.

Prior art

D1 – Hussain et al., "Multiple functions of microsomal triglyceride transfer protein ", Nutrition & Metabolism, 2012 (http://www.nutritionandmetabolism.com/content/pdf/1743-7075-9-14.pdf)

D2 - http://en.wikipedia.org/wiki/Microsomal_triglyceride_transfer_protein

D3 – Implitapide presentation to financial analysts in New York on 5 February 2004

D3a – News Releases of 15 January 2004 regarding announcement of PPD presenting their business in New York on 5 February 2004

D4 – Chandler et al., „CP-346086: an MTP inhibitor that lowers plasma cholesterol and triglycerides in experimental humans and animals", Journal of Lipid Research, 2003, Vol. 44, 1887-1901

D5 – Gruetzmann et al., „Implitapide (BAY 13-9952) inhibits secretion of apoB associated lipoproteins by inhibition of the microsomal triglyceride transfer protein (MTP)", Eur Heart J 2000, 21(Suppl), Abst 3271

D6 - Bischoff et al., „BAY 13-9952 (implitapide): Pharmacodynamic effects of a new microsomal triglyceride transfer protein (MTP) inhibitor on plasma lipids and adipose tissue in animals", Eur Heart J 2000, 21(Suppl), Abst P3501

D7 – Zaiss et al., "BAY 13-9952 (implitapide), an inhibitor of the microsomal triglyceride transfer protein (MTP), inhibits atherosclerosis and prolongs lifetime in apo-E knockout mice", Eur Heart J 2000, 21(Suppl), Abst 194

D8 – Excerpt of ClinicalTrials.gov., "Implitapide in patients with homozygous familial

hypercholesterolemia (HoFH) on maximal concurrent lipid-lowering therapy" (ClinicalTrials.gov Identifier: NCT00079846); "Implitapide in patients with homozygous familial hypercholesterolemia (HoFH) on maximal concurrent lipid-lowering therapy" (ClinicalTrials.gov Identifier: NCT00079859), and "Implitapide in patients with homozygous familial hypertriglyceridemia (HTG) on maximal, concurrent tiglyceride-lowering therapy" (ClinicalTrials.gov Identifier: NCT00080132)

D9 – Dam et al., "Efficacy and safety of implitapide (BAY 13-9952), a microsomal triglyceride transfer protein inhibitor, in patients with primary hypercholesterolemia", Dissertation, 2001, 204.

Lack of patentability

The opposed patent comprises 30 claims, wherein claims 1, 2, 21, 22, 27 and 29 are independent claims. The granted claims comprise added matter, lack enablement as well as novelty and inventive step as will be shown in the following.

The subject matter of granted claim 1 refers to

1) Use of an MTP inhibitor
2) in the manufacture of a medicament
3) for the treatment of a subject suffering from a disorder
3a) associated with hyperlipidemia and/or
3b) hypercholesteremia
4) wherein said treatment comprises the administration of at least three step-wise, increasing dosages of said MTP inhibitor to said subject.

Hence, claim 1 represents a second medical use claim.

The subject matter of granted claim 2 is directed to

1) An MTP inhibitor
2) for use in treating a subject suffering from a disorder
2a) associated with hyperlipidemia and/or
2b) hypercholesterolemia
3) wherein said treatment comprises the administration of at least three step-wise, increasing dosages of said MTP inhibitor to said subject.

Thus, the subject matter of claim 2 is a purpose-limited-product-claim allowable under EPC 2007.

1. Added matter, Art. 123(2) EPC

The granted set of claims comprises added matter in claims 5, 6, 26, and 28.

The subject matter of claims 5 and 6 was originally filed as subject matter of claims 3 and 4, wherein the percentage of reduction of Total Cholesterol, LDL, fasting triglycerides (TG) etc. was specified "*compared to control levels*". This is supported by the specification as filed on p. 14, paragraph 0043, disclosing a comparison with control blood levels.

In granted claims 4 and 5 the percentage is specified "*as a result of said treatment, compared to control levels*" (emphasis added). However, neither the specification nor the clams as originally filed describe the percentage of the reduction as a result of the treatment and do not provide proof that the reduction solely is based on the treatment.

The subject matter of granted claim 26 corresponds to the subject matter of claims 17, 20 and 23 as originally filed, but refers now back to claims 21 and 23 to 25. Thus, the subject matter of granted claim 26 is not limited to an administration of the dose level for 1 to 4 weeks.

Further, the subject matter of granted claim 28 has been amended to refer to a fifth set of dosage units for a fifth interval in the amount of 75 mg/day. Taking the amounts of the first to third dose levels of claim 27 into account, where claim 28 refers back, only the fourth dose level is described in the amount of 75 mg/day according to the specification as filed (see p. 17, paragraphs 0060 and 0061).

Therefore, the subject matter of the granted set of claims does not fulfil the requirements under Art. 123(2) EPC.

2. Lack of enablement, Art. 83 EPC

The microsomal triglyceride transfer protein (MTP) plays for example a role in the lipoprotein assembly, and deficiency or malfunction of the MTP can cause very low production of lipoproteins resulting in severe diseases such as hypolipidemia and/or abetalipoproteinemia. However to treat diseases where there is impaired clearance of cholesterol or triglyceride carrying lipoproteins which then accumulate in the blood stream to cause blockage of arteries or inflammation of the pancreas, inhibitors of MTP are developed to reduce or control lipoprotein production and numerous MTP inhibitors, for example JTT-130, SLx40-90 (see **D1**, p. 12, right col., 2nd paragraph), lomitapide, dirlotapide, mitratapide (see **D2**) or implitapide (Bay13-9952; see **D9**, p. 149, 2nd paragraph), are known. These inhibitors show different chemical structures and are used for treating humans and animals.

The subject matter of granted claim 1 and 2, respectively, of the opposed patent refers to the use of an MTP inhibitor for treating a subject suffering from a disorder associated with hyperlipidemia and/or hypercholesterolemia, wherein the MTP inhibitor is administered in at least three stepwise, increasing dosages of said MTP inhibitor to said subject. All the examples of the opposed patent refer to one specific MTP inhibitor which is BMS-201038, which is specified in dependent claim 6.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.