利拉鲁肽专利技术构成及发展

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摘要 利拉鲁肽(Liraglutide)是一种通过基因重组技术并利用酵母生产的GLP-1类似物,主要用于治疗人II型糖尿病。围绕利拉鲁肽展开的专利申请自1999年以来连年增多,技术方案的类型也多种多样,主要分为核心专利、DDS专利、联用专利和第二药用专利。核心专利的特点在于先发制人,以原研药专利为中心开展早期布局;DDS专利常用于创造与"新药"的技术交集,利于企业立足自身优势,专注自身发展方向;联用专利以防御为主,在技术交叠区域布局,避免对原研企业的侵权;第二药用专利的特点是在对手已有布局的情况下开发新的技术方向,有利于企业重新占领市场。

关键词 利拉鲁肽;专利;技术构成

利拉鲁肽(Liraglutide),是一种通过基因重组技术、利用酵母生产的GLP-1类似物,化学名称为Arg34Lys26-(N-ε-(γ-Glu(N-α-十六酰基)))-GLP-1,分子式为$C_{172}H_{265}N_{43}O_{51}$,分子量为3751.20 Da。利拉鲁肽与人GLP-1具有97%的序列同源性。与天然GLP-1不同的是,利拉鲁肽在人体中的药代动力学和药效动力学特性更适用于每天1次的给药方案。皮下注射给药后,其主要通过如下机理延长作用时间:一是通过自联作用使吸收减慢,二是与白蛋白结合,三是对DPP-IV和NEP具有更高的酶稳定性,从而具有较长的血浆半衰期。在II型糖尿病患者中,单次给予利拉鲁肽可以观察到胰岛素分泌率以葡萄糖浓度依赖的模式增加[1]。

利拉鲁肽于2009年7月在欧盟上市,2010年1月在日本和美国上市。在中国,利拉鲁肽则是在2011年4月13日获国家食品药品监督管理局批准用于治疗成人II型糖尿病,于同年10月9日正式上市,商品名为诺和力®。本文对全球范围内技术主题涉及利拉鲁肽的专利申请进行分析,揭示利拉鲁肽专利技术发展路线,并分析主要申请者专利布局策略[2]。

1 专利现状

1.1 全球利拉鲁肽专利态势

截至2015年5月31日,WPI数据库中检索到涉及利拉鲁肽的全球专利申请共计271项。如图1所示,针对利拉鲁肽的专利申请始于1999年[3]。1999—2004为萌芽阶段,申请量徘徊在个位数,说明这一时期利拉鲁肽尚未引起业界重视,仅是小部分药企的探索方向。2005—2009为平稳增长阶段,申请量在震荡中攀升,在此阶段,中国药企开始将关注的目光投向利拉鲁肽。从2010年利拉鲁肽在世界各地陆续上市开始,专利申请量进入了快速增长期,并于2011年达到第一个峰值;同年,利拉鲁肽在中国被批准上市。

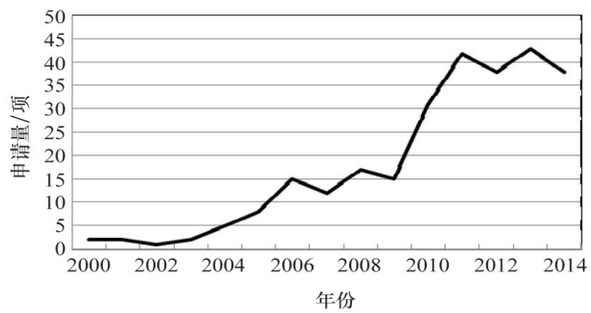

图1 利拉鲁肽全球专利申请年份分布

Fig.1 Yearly Global Layout of Patent Applications Regarding Liraglutide

各国中(图2),来自美国、中国、欧洲、丹麦和印度的利拉鲁肽专利申请量分别占据全球前5位,这5个国家和地区之和几乎覆盖了全部的申请量(94%)。首先,这说明利拉鲁肽专利申请集中度高。其次,来自美国的利拉鲁肽专利申请在数量上占据第一,这与其全球最大糖尿病药物消费市场的身份遥相呼应。最后,值得特别一提的是丹麦,其4%的申请量

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份额全部来自诺和诺德,仅诺和诺德一家公司的申请量就占全球总量的4%。诺和诺德在利拉鲁肽专利方面的实力不容小觑。

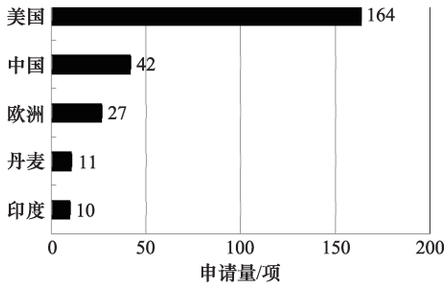

图2 利拉鲁肽全球专利申请量排名前5位国家、区域性组织分布

Fig.2 Top 5 Countries/Regions in Global Patent Applications Regarding Liraglutide

全球拥有利拉鲁肽相关专利申请的专利申请者与权利人共计374位,本文列出了申请量在前8位的申请者(表1)。不难发现,首先,各大申请者的申请量之间差距较小,呈"平均化"态势;其次,几乎所有的大型制药公司都手握利拉鲁肽相关专利,足见利拉鲁肽在抗糖尿病药物中受到了重点关注;最后,中国申请者,如深圳翰宇药业股份有限公司,也在积极跟进利拉鲁肽的专利申请,在短短4年间申请了数量可观的相关专利,在利拉鲁肽专利角逐中站稳了脚跟。

表1 全球利拉鲁肽申请量排名前8位的申请者及申请量

Table 1 Top 8 Applicants and Numbers Thereof in Global Patent Applications Regarding Liraglutide

排名	申请者	国家	申请量/项
1	辉瑞	美国	19
2	赛诺菲	法国	17
3	诺和诺德	丹麦	16
4	深圳翰宇药业	中国	11
5	勃林格殷格翰	德国	11
6	Cure DM	美国	10
7	艾米林	美国	6
8	礼来	美国	3

1.2 中国利拉鲁肽专利态势

利拉鲁肽在中国的专利申请量走势与全球基本上步调一致。这是因为:(1)中国作为全球前5的糖尿病药物消费市场,处在利拉鲁肽专利争夺战的风暴中心;(2)利拉鲁肽最早由丹麦的诺和诺德研发得到,后续的技术改进也由其一马当先。相较之下,中国申请者提交的利拉鲁肽专利申请对该药物全球专利格局的影响十分有限;(3)利拉鲁肽制备工艺相对简单,仿制难度较低,因此以诺和诺德为代表的国外知名药企基本在2012年前后就完成了其在中国的专利布局,故从2014年开始,在中国的申请量相应地减少。

在华利拉鲁肽相关专利申请的申请者与权利人共计74位。总体上来说,利拉鲁肽在华专利市场还是受国外大型医药公司主导(表2)。无论是全球范围还是在中国,赛诺菲与诺和诺德都是领跑者——前者开发了适用于GLP-1的给药器械,而后者则是诺合力®的原研单位。值得一提的是深圳翰宇药业股份有限公司,通过改良利拉鲁肽合成方法申请了大量专利,成为国内申请者中的翘楚,比肩海外巨头。

表2 中国利拉鲁肽专利申请量前9位的申请者及申请量

Table 2 Top 9 Applicants and Numbers Thereof in Chinese Patent Applications Regarding Liraglutide

排名	申请者	国家	申请量/项
1	赛诺菲	法国	12
2	深圳翰宇药业	中国	11
3	诺和诺德	丹麦	10
4	勃林格殷格翰	德国	9
5	辉瑞	美国	6
6	先灵药业	德国	4
7	礼来	美国	3
8	瑞立普萨	美国	3
9	深圳健元医药	中国	3

表2同时还展现了在中国提交利拉鲁肽专利申请较多的几类申请者。在申请量占前9位的申请者中,中国占两席。其中与赛诺菲不相伯仲的是深圳翰宇药业股份有限公司,在利拉鲁肽生产工艺相对简单、生产门槛不高的情况下,该公司通过与注射笔企业绑定的方式,已经预先划分了利拉鲁肽仿制药的大块蛋糕,2014年实现利拉鲁肽原料药出口2000万元(注册使用),值得关注。

此外,通过对在华利拉鲁肽专利申请法律状态进行梳理发现,1/2数量的利拉鲁肽专利申请依然在实审阶段,前途不甚明朗。而在已获授权的专利申请中,只有极少部分终止了权利,说明在华的利拉鲁肽专利权利状态较稳定。

2 主要技术构成及发展

针对表1所列企业申请的与利拉鲁肽有关的专利,通过对其最早优先权时间及主要技术分支进行交叉统计分析,能够清晰地看到围绕利拉鲁肽铺开的专利版图,如图3、图4和图5所示。

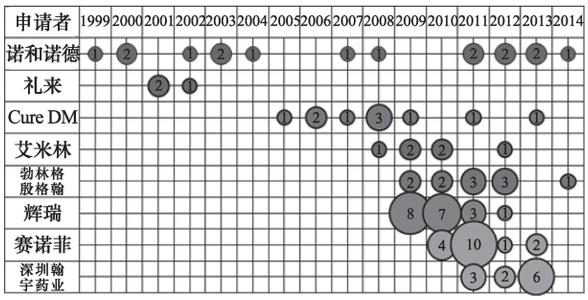

图3　全球主要申请者利拉鲁肽专利申请量趋势

Fig. 3　Applicant-Year Layout of Global Patent Application Regarding Liraglutide

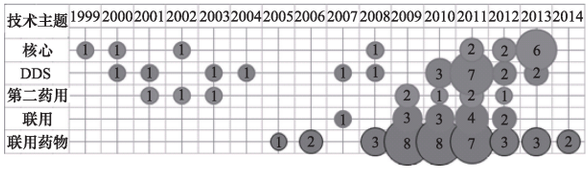

图4　利拉鲁肽各技术分支专利申请量趋势

Fig. 4　Yearly Layout of Technical Theme in Global Patent Application Regarding Liraglutide

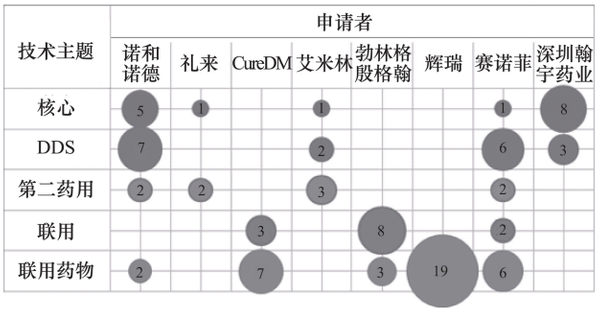

图5　全球主要申请者对利拉鲁肽各技术分支的专利申请量分布

Fig. 5　Technical Theme Layout towards Applicants in Global Patent Application Regarding Liraglutide

按照技术主题,可将关于利拉鲁肽的专利申请分成4类:核心专利、药物递送系统(DDS)专利、第二药用专利和联用专利。核心专利,指那些发明点与利拉鲁肽本身直接相关的专利,包括利拉鲁肽与衍生物、合成方法、治疗糖尿病及相关疾病的用途等主题。DDS专利,指那些发明点是如何将利拉鲁肽递送至体内的专利,包括制剂、给药器械等。联用专利,指利拉鲁肽与其他抗糖尿病药物联合使用的专利。第二药用专利,指发明点不同于其他抗糖尿病药理作用的专利。

2.1　核心专利

从图4不难发现,利拉鲁肽核心专利是唯一在时间上贯穿始终的技术分支。这意味着对核心技术的争夺始终没有结束。结合图5,还可以发现,尽管诺和诺德、礼来、赛诺菲和深圳翰宇等企业都拥有利拉鲁肽核心专利,但在核心专利上优势较大的是诺和诺德与深圳翰宇,且两者在时间上有一定的承接关系。

诺和诺德作为利拉鲁肽原研药的专利权者,围绕利拉鲁肽申请了5项核心专利[3~7],请求范围覆盖利拉鲁肽及其衍生物、合成方法、纯化方法以及治疗糖尿病的用途,基本上已经形成针对利拉鲁肽核心技术的全面布局,堪称架构范本。诺合力®在GLP-1领域至今依然领跑就是一个印证。

相较于诺和诺德,深圳翰宇起步较晚。深圳翰宇申请的首个关于利拉鲁肽的专利出现在2011年,此时诺和诺德已经基本完成利拉鲁肽核心专利布局,在市场上拥有话语权。对此,深圳翰宇另辟蹊径,同时申请了一种通过固相合成制备利拉鲁肽的新方法[8]和一种对利拉鲁肽结构修饰得到的衍生物,并分别于2014年1月1日和2013年11月13日在中国获得授权。尽管对于有明确结构的已知化合物,其新制备方法的保护范围无法延及化合物本身,但面对原研药专利2018年即将到期的情况,制备方法及衍生物专利对抢占仿制药市场意义重大。随后几年内,深圳翰宇先后申请了5件利拉鲁肽制备方法专利[9~13],1件利拉鲁肽纯化方法专利[14],准备与诺和诺德竞争仿制药市场。

对原研药来说,首先完成研发并获得专利的权利人无疑具备最大优势。但对于科研实力还在不断发展的后来者,也并非无路可走。主动出击,对原研药结构与制备方法进行改进,同样能够占领部分市场。申请此类专利,一方面为提前谋划自身的仿制药策略,另一方面也堵住了对手变相延长原研药专利保护时间的通道。

2.2　药物递送系统(DDS)专利

除核心专利外,DDS专利也是倍受申请者关注的一个分支。针对该分支的申请紧随核心专利之后,在2011年达到顶峰(图4)。在这个分支中有2家企业值得关注——诺和诺德和赛诺菲。他们有2个共同点——一是在本文归纳的所有技术分支都有专利申请(图5),是全面性选手;二是都很倚重DDS分支。但两者还有更显著的不同点——诺和诺德偏重传统DDS,即药物制剂[15~21];赛诺菲着力开发给药器械,即注射器[22~27]。赛诺菲拥有原研药物利司那肽®(Lixisenatide),其与利拉鲁肽同为短效GLP-1类似物降糖药,相互间存在竞争,上述注射器同样也能用于利司那肽[22]。

与核心专利较强的针对性相比,从DDS分支开始,随着相关专利越来越向外围发展,“一物多用”的情况逐渐增多。而由于DDS自身的特点,相关专利具备一定普适性,该分支下的专利申请容易获得较大保护范围,适合竞争对手间相互渗透。

2.3　联用专利

针对联用的专利申请主要有2类:发明点为联用本身及发明点为联用的某些药物的(非利拉鲁肽)。相较于前面提及的2个分支,联用专利是利拉鲁肽相关专利中数量最多的一个分支(图4)。

在进行分析的八家企业中,有3家——辉瑞、CureDM和勃林格殷格翰的申请主题全部是联用。其中,辉瑞共提交了19件关于利拉鲁肽的专利申请,位居8家公司之首[28~46]。技术主题全部是化学药与利拉鲁肽联用降糖,且发明点为所述化学药,即利拉鲁肽仅出现在补充型权利要求中;CureDM是一家生物制药公司,擅长多肽类药物合成,提交了10件关于利拉鲁肽的专利申请[47~56],其中7件的技术主题是多肽与利拉鲁肽联用降糖,发明点为所述多肽[47~50,52,54,56];勃林格殷格翰提交了11件关于利拉鲁肽的专利申请[57~67],其中8件技术主题为DPP-IV类药物和/或胰岛素类药物与利拉鲁肽联合降糖,发明点为联用本身[57~64]。

当企业想涉足自己不擅长的药物时,可从联用专利入手。通过分析上述3家企业专利申请的特点,我们可以发现,利拉鲁肽并不是他们的优势产品——这3家企业均没有申请任何利拉鲁肽核心专利。但这并不妨碍他们分享与利拉鲁肽有关的专利权益,诀窍就是申请与自己的优势产品的联用专利。然而,在这种情况下,因相关专利涉及利拉鲁肽的技术方案处于保护外围,其价值和受保护的力度均明显低于以利拉鲁肽为核心的专利,以量取胜就变得重要——这3家企业提交的利拉鲁肽联用专利申请在8家企业中分列前3位。

2.4 第二药用专利

第二药用虽然是处于最外围的技术分支,但由于其涉及的技术主题范围极广,又有不可预见性,往往容易成为企业突出重围甚至引导市场重组的关键。万艾可®的成功使第二药用的开发受到了越来越多的关注。

在8家企业所有关于利拉鲁肽的专利申请中,以第二药用为主题的申请占约10%,时间为2001—2012年。用途从治疗胃轻瘫到治疗酗酒或药物成瘾[68,69],涉及了8种完全不同的疾病,其中一些与糖尿病存在一定关联[70]。仅艾米林一家,就提出了延长非快速眼动睡眠时间、治疗胰腺炎和治疗阻塞性睡眠呼吸暂停3种截然不同的第二药用申请[71~73]。

目前,利拉鲁肽的第二药用未在市场上引起足够反响,多数停留在探索阶段。

3 结论

通过分析利拉鲁肽主要专利权人的专利布局与申请策略发现,对药物技术进行专利保护的途径是多种多样的:有的企业先发制人,以原研药专利为中心开展早期布局,并以此为契机迅速渗透各技术分支;有的企业立足自身优势,专注自身发展方向,不断创造“老药”与“新药”的技术交集;有的企业防御为主,在技术交叠区域积极布局联合用药等“副产品”发明,有效避免对原研企业的侵权;还有的企业瞄准各大制药巨头拳头专利相继到期的时间点,在制备方法和结构修饰上下功夫,占领仿制药市场先机。

参考文献(References)

[1] 杨文英. 人GLP-1类似物利拉鲁肽的最新研究进展[J]. 中华内分泌代谢杂志, 2010, 26(9): 840-843.
Yang Wenying. Review on the human GLP-1 analogues[J]. Chinese Journal of Endocrinology and Metabolism, 2010, 26(9): 840-843.

[2] 杨铁军. 产业专利分析报告-糖尿病药物. 北京: 知识产权出版社, 2016.
Yang Tiejun. Industrial analysis report on Diabetes medicine. Beijing: Intellectual Property Publishing House, 2016.

[3] Novo Nordisk. Acylating amino group of peptide or protein, for reducing in vivo clearance rate, by reacting with alkanoyl carboxylate ester acylating agent and saponifying acylated peptide ester: WO, 0055119A1[P]. 2000-09-21.

[4] Novo Nordisk. Ion exchange chromatographic separation process for separating glucagon like peptide-1, its analog or derivative from a mixture containing the peptide and other related impurities, comprises use of a organic modifier for elution: WO, 0055203A1[P]. 2000-09-21.

[5] Novo Nordisk.. Preparation of N-acylated peptides involves reacting a peptide having free amino groups with a reactive ester or N-hydroxy imide ester of an aminoacid derivative under basic conditions in an aqueous mixture: WO, 2004029077A2[P]. 2004-04-08.

[6] Novo Nordisk.. New glucagon-like peptide-1 (GLP-1) derivative comprising modified GLP-1(7-37) sequence having derivatized with an albumin binding residue, is albumin binder, useful e.g. for treating or preventing hyperglycemia and type 2 diabetes: WO, 2009030738A1[P]. 2009-03-12.

[7] Novo Nordisk. Use of a glucagon-like peptide-1 receptor agonist for treating type 1 diabetes and reducing e.g. the number of hypoglycemias or hypoglycemic episodes and the amount of exogenous glucose needed for recovering from the episodes: WO, 2014202780A1[P]. 2014-12-24.

[8] Hybio Pharm Co. Ltd.. Method for solid phase synthesizing liraglutide, involves coupling solid phase vector of resin with glycine, and performing solid-phase synthesis process by coupling amino acid with N-terminal- fluorenylmethyloxycarbonyl protection: WO, 2013037266A1[P]. 2013-03-21.

[9] Hybio Pharm Co. Ltd.. Synthesizing liraglutide, by synthesizing five polypeptide fragments of e.g. amino acid: CN, 102875665A[P]. 2013-01-16.

[10] Hybio Pharm Co. Ltd.. Synthesizing liraglutide, involves bonding first polypeptide fragment, second polypeptide fragment, third polypeptide fragment, and fourth polypeptide fragment with resin, and subjecting obtained peptide resin to e.g. purification: CN, 104045705A[P]. 2014-09-17.

[11] Hybio Pharm Co. Ltd.. Synthesizing liraglutide peptide involves combining dipeptide fragment and/or tripeptide fragment to obtain Gly-resin: CN, 104045706A[P]. 2014-09-17.

[12] Hybio Pharm Co. Ltd.. Preparing liraglutide peptide comprises e.g. preparing glycine-resin, carrying out primary successive coupling to obtain polypeptide segment-resin, carrying out side chain modification, secondary successive coupling, and cracking: CN, 103288951A[P]. 2013-09-11.

[13] Hybio Pharm Co. Ltd.. Solid phase preparation of liraglutide, by cleaving second peptide fragment-second resin, coupling second polypeptide fragment with first polypeptide fragment-first resin and purifying remaining coupled liraglutide amino acids: CN, 103304659A[P]. 2013-09-18.

[14] Hybio Pharm Co. Ltd.. Purifying solid-phase synthesized liraglutide coarse peptide, comprises e.g. dissolving solid-phase synthesized peptide in acetonitrile water solution, and performing first high-perfor-

mance liquid chromatography purification: WO, 2013117135A1[P]. 2013-08-15.

[15] Novo Nordisk. Pharmaceutical composition useful for treatment of e.g. hyperglycemia comprises insulinotropic peptide, meal-related insulin peptide and preservative: WO, 2005046716A1[P]. 2005-05-26.

[16] Novo Nordisk. Composition useful for treating hyperglycemia comprises insulinotropic peptide, insulin peptide, and ligand for the HisB10 anion site which improves stability by blocking an interaction between the two peptides: WO, 2006029634[P]. 2006-03-23.

[17] Novo Nordisk. Soluble pharmaceutical composition for treating type 2 diabetes, comprises insulinotropic glucagon-like peptide-1 compound, basal insulin peptide, additives and zinc: WO, 2009063072A2[P]. 2009-05-22.

[18] Novo Nordisk. Particle used as pharmaceutical composition or medicament for treating metabolic diseases chosen from diabetes mellitus and obesity, comprises glucagon-like peptide-1 compound, divalent metal and polycationic compound: WO, 2012098188A1. 2012-07-26.

[19] Novo Nordisk. New pulmonary liquid or dry formulation comprises a GLP-1 compound to which a lipophilic substituent is attached, optionally via a spacer, useful in a pulmonary delivery device: WO, 0151071A2. 2001-07-19.

[20] Novo Nordisk. Composition useful for treating diabetes such as type 2 diabetes, comprises glucagon- like peptide-1 compound, divalent metal and polycationic compound: WO, 2012098187A1. 2012-07-26.

[21] Novozymes Biopharma. Highly purified albumin composition, used to reduce formation of insulin fibrils in zinc ion free formulation and to reduce formation of peptide fibrils, comprises peptide, albumin, and optionally octanoate or polysorbate 80: WO, 2014096440A2[P]. 2014-06-26.

[22] Hoechst Marion Roussel, Sanofi-Aventis. Aqueous pharmaceutical formulation, useful for treating diabetes mellitus, comprises an insulin analog, zinc, a preservative and an isotonic agent: WO, 2011003823A1 [P]. 2011-01-13.

[23] Sanofi-Aventis. Medicated module for drug delivery device to deliver human insulin through single dose setter to patient, has output needle portion whose distal end partially pierces fluid seal that is positioned at base of needle cover: WO, 2012059449A1[P]. 2012-05-10.

[24] Sanofi-Aventis. Medicated module for use with drug delivery device by healthcare professional to deliver e.g. medicament, to patient, has engagement needle and output needle which are primed with medicament when module is attached to drug delivery device: WO, 2012059455A1. 2012-05-10.

[25] Sanofi-Aventis. Medicated module for use with pen injector that is utilized for delivering e.g. A21-Gly human insulin from separate reservoirs to patient to treat diabetes mellitus, has shroud compressing reservoir to dispense medicament: WO, 2012059457A1. 2012-05-10.

[26] Sanofi-Aventis. Medicated module for attaching drug delivery device of drug delivery system for use by healthcare professional to deliver e.g. drug agents to patient, has lockout feature preventing module from being reconnected to drug delivery device: WO, 2012059459A1[P]. 2012-05-10.

[27] Sanofi-Aventis. Medicated module for drug delivery system to deliver medicaments e.g. human insulin, to patient for treating diabetes, has needle in fluid communication with reservoir of drug delivery device after module is attached to delivery device: WO, 2012059453A1[P]. 2012-05-10.

[28] Agouron Pharma. New benzofuranyl derivatives useful for treating obesity and obesity-related disorders and Type 2 diabetes and diabetes-related disorders e.g. diabetic neuropathy, diabetic retinopathy, diabetic cardiomyopathy, anorexia nervosa: WO, 2010103437A1[P]. 2010-09-16.

[29] Agouron Pharma. New L-(piperidin-4-yl)-pyrazole derivatives are G-protein coupled receptor modulators useful to treat e.g. diabetes, coronary heart disease, ischemic stroke, peripheral vascular disease, intermittent claudication and myocardial infarction: WO, 2010140092A1 [P]. 2010-12-09.

[30] Agouron Pharma. New pyrazole compounds useful for treating e.g. diabetes, hyperlipidemia, coronary heart: WO, 2012069948A1[P]. 2012-05-31.

[31] Agouron Pharma. New substituted pyrazolospiroketone compounds used for treating e.g. obesity, diabetes -related disorders, nonalcoholic fatty liver disease, hyperglycemia and metabolic syndrome; and in drug and substrate tissue distribution assay: WO, 2012056372A1[P]. 2012-05-03.

[32] Agouron Pharma. New substituted 2,3-dihydro-1H-inden-1-yl-2,7-diazaspiro(3.5)nonane derivatives are ghrelin receptor modulators, useful to e.g. treat obesity, type II diabetes and their related disorders (e.g. impaired glucose tolerance) in animals: WO, 2011114271A1[P]. 2011-09-22.

[33] Pfizer Inc. New pyrazolospiroketone compounds useful for treating disease treated by inhibiting acetyl-coenzyme A carboxylase e.g. obesity, diabetes, hepatic insulin resistance and nonalcoholic fatty liver disease: WO, 2009144554A1[P]. 2009-12-03.

[34] Pfizer Inc. New substituted 3-oxa-7-azabicyclononane compounds are G-protein-coupled receptor-119 agonists, useful to treat e.g. diabetes, metabolic disorder e.g. hyperlipidemia, myocardial infarction, arthritis, obesity, osteoporosis and hypertension: WO, 2010106457A2[P]. 2010-09-23.

[35] Pfizer Inc. New pyrimidin- 4- yl- tetrahydro- pyrrolo(3,4- c)pyrazole compounds are G-protein-coupled: WO, 2011036576A1[P]. 2011-03-31.

[36] Pfizer Inc. New imidazo-pyrazole derivatives are G-protein-coupled receptor inhibitors, useful for treatment of e.g. hyperlipidemia, diabetes, coronary heart disease, or ischemic stroke: WO, 2011061679A1 [P]. 2011-05-26.

[37] Pfizer Inc. New 4-amino-5-oxo-7,8-dihydropyrimido(5,4-f)(1,4) oxazepin-6(5H) -yl-phenyl compounds are diacyl-glycerol O-acyltransferase 1 inhibitors, useful to treat e.g. diabetic nephropathy, hypertension, diabetic nephropathy and skin cancer: WO, 2010086820A1[P]. 2010-08-05.

[38] Pfizer Inc. New (4-(4-(4-amino-5-oxo-7,8-dihydro-5H-pyrido(4,3-d) pyrimidin-6-yl) -phenyl)- cyclohexyl)-acetic acid derivatives are diacylglycerol acyltransferase-1 inhibitors useful e.g. for treating obesity and type 2 diabetes: WO, 2010089685A1[P]. 2010-08-12.

[39] Pfizer Inc. New 4-amino-7,8-dihydropyrido(4,3-d) pyrimidin-5(6H)-one derivative useful for treating Type 2 diabetes, diabetes-related disorders, obesity and obesity- related disorders in animals: US, 2010197591A1[P]. 2010-08-05.

[40] Pfizer Inc. New fused pyrrolidine compounds are G-protein coupled receptor 119 modulators, useful for treating e.g. diabetes, coronary heart disease, ischemic stroke, peripheral vascular disease, hypertension and congestive heart failure: WO, 2010128414A1[P]. 2010-11-11.

[41] Pfizer Inc. New pyrimidine compound useful for treating e.g. coronary heart disease, intermittent claudication, myocardial infarction, osteoporosis, hypertension, congestive heart failure, chronic renal failure, diabetic neuropathy, metabolic syndrome: WO, 2010128425A1[P]. 2010-11-11.

[42] Pfizer Inc. New pyrrolidinyl-pyrimidine compounds are G-protein coupled receptor 119 modulators, useful for treating e.g. diabetes, coronary heart disease, ischemic stroke, peripheral vascular disease, hypertension and congestive heart failure: US, 2010285145A1[P]. 2010-11-11.

[43] Pfizer Inc. New dioxa-bicyclo(3.2.1) octane-2,3,4-triol derivatives are sodium-glucose co- transporter-2 inhibitors, useful for treating obesity and type 2 diabetes and diabetes-related disorders e.g. impaired glucose tolerance and hyperinsulinemia: WO, 2011051864A1[P]. 2011-05-05.

[44] Pfizer Inc. New 1-methylcyclopropyl-3-fluoro-4-((5-methyl-6-((2-methylpyridin-3-yl) oxy) pyrimidin-4-yl)oxy)piperidine-1-carboxylate is G-protein-coupled receptor modulator, useful for treating e.g. hyperlipidemia, diabetes and Alzheimers disease: WO, 2013011402A1[P]. 2013-01-24.

[45] Pfizer Inc. New substituted 3H-imidazo(4,5-b) pyridine compounds are diacylglycerol acyltransferase 2 modulator, useful for treating e.g. diabetes, obesity, ketosis, hyperlipidemia, chronic renal failure and endothelial dysfunction: WO, 2013150416A1[P]. 2013-10-10.

[46] Pfizer Inc. New 2-tert-butyl-1-(1H-indazol-5-ylcarbonyl) -2H-spiro (piperidine-4,5-pyrano(3,2- c)pyrazol)-7(6H) -one for treating disease treated by inhibiting acetyl-coenzyme A carboxylase e.g. obesity, diabetes and nonalcoholic fatty liver disease: WO, 2009144555A1[P]. 2009-12-03.

[47] Cure DM Group Holdings LLC. New optimized proislet peptide, useful for treating a pathology associated with impaired pancreatic function, e.g. type 1 diabetes, metabolic syndrome/dysmetabolic syndrome, overweightness, obesity, and hyperlipidemia: WO, 2009029847A1[P]. 2009-03-05.

[48] Cure DM Inc. Treatment of type 1 diabetes mellitus involves co-administration of agent that stimulates pancreatic islet cell regeneration and/or transformation and agent that specifically inhibits the activity autoimmune cells: US, 2006198839A1. 2006-09-07.

[49] Cure DM Group Holdings LLC. New isolated human proislet, useful e.g. to increase insulin production, induce pancreatic islet neogenesis, and to treat pathology associated with impaired pancreatic function e.g. pre- diabetes and latent autoimmune diabetes in humans: EP, 2295066A1[P]. 2011-03-16.

[50] Cure DM Group Holdings LLC. New proislet peptide, e.g. huntingtin interacting protein peptides, and human regenerating islet-derived peptides, with an optimization modification, useful for stimulating islet neogenesis or stimulating pancreatic islet cell regeneration: EP, 2559700A2[P]. 2013-02-20.

[51] Cure DM Group Holdings LLC. Treating a pathology associated with impaired pancreatic function comprises administering to the subject a human proislet peptide: US, 2011280833A1[P]. 2011-11-17.

[52] Cure DM Group Holdings LLC. Treating pathology associated with impaired pancreatic function including prediabetes, type 2 diabetes hyperglycemia and latent autoimmune diabetes, comprises administering human pro-islet peptide comprising specific amino acid sequences: US, 2013190233A1. 2013-07-25.

[53] Cure DM Group Holdings LLC, Curedm Inc. Treating pathology associated with impaired pancreatic function including type 2 diabetes, latent autoimmune diabetes or hyperglycemia in subject e.g. human, involves administering human proislet peptide: US, 2010093605A1. 2010-04-15.

[54] Cure DM Group Holdings LLC. Stimulating islet cell neogenesis in a subject comprises administering to the subject an amount of HIP2, useful for treating a disease or condition associated with impaired pancreatic function, e.g. type I diabetes, and bulimia: WO, 2008064306A2[P]. 2008-05-29.

[55] CureDM Inc. Use of islet neogenesis agent for treating newly diagnosed or pre-existing type 1 diabetes, treating newly diagnosed or pre-existing type 2 diabetes, and treating a pathology associated with impaired pancreatic function: US, 2009142338A1[P]. 2009-06-04.

[56] CureDM Inc. New human proIslet peptide which stimulates pancreatic islet cell regeneration, useful for treating diseases or disorders having impaired pancreatic function, e.g. type 1 diabetes, type 2 diabetes, and latent autoimmune diabetes: US, 2008300190A1[P]. 2008-12-04.

[57] Boehringer Ingelheim Int. Co. Ltd. Method for slowing progression of, delaying or treating of pre-diabetes in a patient diagnosed of being overweight or obese, comprises administering one or more antiobesity drugs: WO, 2013139777A1[P]. 2013-09-26.

[58] Boehringer Ingelheim Int. Co. Ltd. Pharmaceutical combination, composition or kit useful for e.g. treating obesity, comprises dipeptidyl peptidase-4 inhibitor, preferably linagliptin, and glucagon-like peptide-1 (GLP- 1) analog having short half life e.g. exendin- 4: WO, 2013098372A1[P]. 2013-07-04.

[59] Boehringer Ingelheim Int. Composition, useful e.g. to treat and prevent hyperuricemia, kidney stones and hyponatremia, comprises a sodium-dependent glucose cotransporter-2 inhibitor, a dipeptidyl peptidase-IV inhibitor, and an antidiabetic agent e.g. biguanides: WO, 2010092125A1. 2010-08-19.

[60] Boehringer Ingelheim Int. Pharmaceutical compound, composition or combination used for preventing and/or treating metabolic disorder e.g. type 1 diabetes mellitus, comprises dipeptidyl peptidase-4 inhibitor, and optionally antidiabetic agents: WO, 2011064352A1[P]. 2011-06-03.

[61] Boehringer Ingelheim Int. Composition, useful e.g. to treat e.g. impaired glucose tolerance and metabolic syndrome, comprises 6-(2-hydroxy-2-methylpropyl) -3-(1-(1-methyl-2-oxo-1, 2-dihydropyridin-4-yl) phenyl-ethyl) -6-phenyl-1, 3-oxazinan-2-one and therapeutic agent: WO, 2012059416. 2012-05-10.

[62] Boehringer Ingelheim Int. Composition, useful for e.g. treating diabetes mellitus, hypoglycemia, postprandial hyperglycemia, myocardial infarction, and heart failure, comprises sodium glucose cotransporter inhibitor, and glucagon- like peptide receptor agonist: WO, 2012107476A1[P]. 2012-08-16.

[63] Boehringer Ingelheim Int. Combination, useful for e.g. treating hyperglycemia, overweight, obesity, hyperlipidemia, hypertension and atherosclerosis, comprises a glucagon-like peptide-1 receptor agonist and a dipeptidyl peptidase-4 inhibitor i.e. linagliptin: WO, 2011138421A1[P]. 2011-11-10.

[64] Boehringer Ingelheim Int. Pharmaceutical composition used for, e.g. preventing type 1 diabetes mellitus, comprises dipeptidyl peptidase-4 inhibitor: WO, 2010092163A2[P]. 2010-08-19.

[65] Boehm M. F. New substituted phenyl keto compounds are glucagon-

like peptide 1 receptor agonists useful to treat type I diabetes, type II diabetes, gestational diabetes, obesity, excessive appetite, insufficient satiety or metabolic disorder: WO, 2013090454A2. 2013-06-20.

[66] Boehm M. F. New substituted heterocyclic compound useful for treating malcondition e.g. type I diabetes, type II diabetes, gestational diabetes, obesity, excessive appetite, insufficient satiety or metabolic disorder in a patient: WO, 2014201172A1[P]. 2014-12-18

[67] Boehm M. F. New substituted aryl compounds are glucagon-like peptide agonists useful to treat malconditon comprising type I diabetes, type II diabetes, gestational diabetes, obesity, excessive appetite, insufficient satiety and metabolic disorder: WO, 2012166951A1[P]. 2012-12-06.

[68] Lilly&Co Eli. Treating gastroparesis, e.g. a delay in gastric emptying time, in a patient with type 2 diabetes comprising administering to a patient a GLP-1 compound: WO, 03087139A2[P]. 2003-10-23.

[69] Novo Nordisk. Preventing or treating alcoholism or drug addiction, comprises administering an amount of a glucagon-like peptide-1 (GLP-1) (I) agonist to a subject: WO, 2013083826A2[P]. 2013-06-13.

[70] Novo Nordisk. Use of glucagon like peptide-1 agonist for e.g. reducing food intake; treating binge eating disorder, bulimia nervosa, craving for food, obesity; changing the snack preference; and lowering the snack intake: WO, 2005056036A2[P]. 2005-06-23.

[71] Amylin Pharm Inc. Use of glucagon like peptide 1 (GLP-1) receptor agonist compound or a pharmaceutical composition comprising a GLP-1 receptor agonist compound for treating, e.g. non-rapid eye movement sleep disorder, sleepwalking disorder, or sleep bruxism: WO, 2010138671A1[P]. 2010-12-02.

[72] Amylin Pharm Inc. Method for treating e.g. pancreatitis, diabetes and their associated symptoms or reducing plasma amylase and plasma lipase concentrations in human involves administering exenatide or glucagon-like peptide-1 receptor agonist to human: WO, 2011156407A2 [P]. 2011-12-15.

[73] Amylin Pharm Inc. Treating obstructive sleep apnea in a patient involves administering to the patient glucagon-like protein-1 receptor agonist compound or pharmaceutical composition comprising glucagon-like protein-1 receptor agonist compound: WO, 2011056713A2[P]. 2011-05-12.

Technical composition and developments of patents regarding Liraglutide

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Abstract Liraglutide is a GLP-1 analogue produced from yeasts via the gene recombination, mainly used in treatment of type II diabetes. The patents related with liraglutide have been increasing since 1999 with diverse technical solutions, which could be categorized into the core patents, the DDS patents, the combination patents and the second medicinal use patents. The core patents are to gain primary interests, the DDS patents create shortcuts to an already-patented medicine, the combination patents prevent possible infringements involving liraglutde, and the second medicinal use patents can lead to a re-capture of the market.

Keywords liraglutide; patent; technical composition

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