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Report criteria development of compounds for the treatment of metabolic diseases

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1. Introduction.

In recent years, there has been an unprecedent increase in the number of diabetic, namely type 2, diabetic patients, and in parallel an increased development of obesity has been reported. Based on the enormous abundance of these two metabolic disorders, we will refer in this report to diabetes or obesity when talking to metabolic diseases.

Type 2 diabetes (T2D) has become one of the more challenging health problems of our time. Its proportions are now epidemic in most of the world: it is estimated that there are currently 246 million people affected worldwide, and they could reach 380 million by 2025 according to the predictions. Chronic hyperglycemia, even in the absence of symptoms, causes injuries in multiple tissues, and small vessels of the retina, kidneys and peripheral nerves are particularly sensitive. Thus, diabetes is one of leading causes of blindness, amputations and end stage renal disease in developed societies. Additionally, diabetes poses a significant risk to develop cardiovascular disease (CVD), both by itself and by its association other risk factors such as hypertension and dyslipidemia. The costs of treatment and prevention of diabetes is a major aspect in public heath care. Therefore, the prevalence of T2D is of paramount importance both to determine the health of the population and for planning resources for their care and prevention.

Recently, the Di@bet.es study has addressed the need to update the data on the prevalence of T2D in Spain and other risk factors for cardio-metabolic. Thus, a major national study of epidemiology of the diabetes mellitus and associated cardiovascular risk factors such as obesity or hypertension, among others, as well as health habits has been performed. The study was conducted by the CIBERDEM, a virtual research center funded by the Institute of Health Carlos III (Soriguer et al., Diabetologia 2011). A population-based, cross-sectional, cluster sampling study was carried out, with target population being the entire Spanish population. Five thousand and seventy-two participants in 100 clusters (health

centres or the equivalent in each region) were randomly selected with a probability proportional to population size. Participation rate was 55.8%. Study variables were a clinical and demographic structured survey, lifestyle survey, physical examination (weight, height, BMI, waist and hip circumference, blood pressure) and OGTT (75 g). Almost 30% of the study population had some carbohydrate disturbance. The overall prevalence of diabetes mellitus adjusted for age and sex was 13.8%, of which about half had unknown diabetes: 6.0%. The age- and sex-adjusted prevalence rates of isolated impaired fasting glucose (IFG), isolated impaired glucose tolerance (IGT) and combined IFG–IGT were 3.4%, 9.2% and 2.2%, respectively. The prevalence of diabetes and impaired glucose regulation increased significantly with age, and was higher in men than in women.

Diabetes is a serious and continuously growing health problem. At present, no any available treatment is able to prevent diabetes onset and novel pharmacological treatments are needed. In this respect, FDA recommends to develop new pharmacological treatments acting on the pathogenesis of the disease more than on its symptoms. Indeed, glycemic control does not always improve major CVD outcomes in diabetic individuals.

Obesity is a major cause of morbidity and mortality through cardio- and cerebrovascular diseases and cancer. The metabolic consequences of obesity include dyslipidaemia, hypertension, proinflammatory atherogenesis, pre-diabetes and Type 2 diabetes. The prevalence of obesity in Spain is 30% of th adult population (CIBERDEM press release, 2011). For a significant proportion of patients, pharmacotherapy to tackle obesity is required as adjunctive support to diet, exercise and lifestyle modification. There is currently only one prescription drug (orlistat) for the long-term management of obesity, and its efficacy is limited.

2. Objectives and Methodology.

The objective is to establish criteria for the development of compounds, to guarantee the transferability of technological innovations that arise from the project to the industrial sector.

The criteria will be established for the two priority areas of study, i.e., for the development of drugs for the management of weight control, and for the treatment of diabetes:

- Situation regarding the development of drugs for the treatment of diabetes.
- Situation regarding the development of drugs for the management of weight control.

The methodology has been based on the discussion with regulatory agencies (FDA), with professionals of the biotechnology or pharmaceutical sectors, and in professional involved in clinical practice and in clinical research. News regarding the approval of new compounds has been followed too.

3. Results achieved.

3.1.- Development of compounds for the treatment of diabetes.

a. Drugs that have been suspended by regulatory agencies or that they have been withdrawn.

- In September of 2010, the anti-diabetic drug Avandia (active ingredient, rosiglitazone) was withdrawn from the European Market, due to the existence of cardiovascular events associated with its administration. Also, the FDA is urging the recall of Avandia because of the risk to health associated with the drug, and in September 2010 restricted the use of Avandia in patients with type 2 diabetes that can not be controlled with other medicines.

This has dealt a serious blow to the development of antidiabetic drugs. The reason is that from this point on, companies developing antidiabetic compounds will have to demonstrate the absence of cardiovascular events, and these studies should be performed on thousands of patients, and represent a considerable additional investment. As a consequence of this, companies in "venture capital" international view diabetes as a business activity that is associated with high risk of failure.

- In April 2012, Takeda Pharmaceuticals failed to gain the backing of the U.S. Food and Drug Administration for its new diabetes treatment, alogliptin. The company has been hoping that alogliptin sales could replace revenue the company will lose when Actos, its blockbuster type 2 diabetes drug, loses patent protection later this year. The FDA has asked for more information on the use of the medicine in other countries. Takeda initially applied to the FDA in 2007 for approval to sell alogliptin and in June 2009 was told that its clinical data was insufficient based on new guidelines on cardiovascular risks. The company conducted the additional

studies and resubmitted the drug for review, but the FDA again rejected it. Alogliptin is already approved in Japan and is sold under the brand name of Nesina.

b. New drugs approved by regulatory agencies.

The main anti-diabetic drugs approved during the last 2 years have been:

-In July 2009, the FDA approved the use of "saxagliptin" (Onglyza) (an inhibitor of DPP-4), and in October 2009 was approved by EMEA. This drug has been developed by Bristol-Myers Squibb and AstraZeneca. Other inhibitors of DPP-4 had been previously approved.

- In January 2010, the FDA approved the use of "Liraglutide" (an analog of GLP-1). This drug has been developed by Novo. Other GLP-1 analogs had been previously approved.

- In November 2010, the FDA approved the use of "Kombiglyze XR" (combination of saxagliptin and metformin) as a combination daily fixed dose of saxagliptin and metformin slow-release for the treatment of type 2 diabetes.

- In July 2011, the FDA approved the type 2 diabetes medication linagliptin (Tradjenta). Linagliptin, which will be jointly marketed by Boehringer Ingelheim Pharmaceuticals and Eli Lilly Co., is in a class of prescription medications known as DPP-4 inhibitors, which lower blood glucose by increasing the body's production of insulin after meals. The medication, taken as a once-daily tablet, can be used alone or in combination with other type 2 medicines.

- In January 2012, the FDA approved the use of Bydureon, a once-weekly version of Amylin's diabetes shot, developed by Amylin Pharmaceuticals Inc. (AMLN) and Alkermes Plc (ALKS). They succeeded in their third attempt to gain U.S. clearance. Bydureon is a long-acting form of Byetta, a twice-daily injection that San Diego-based Amylin developed with Eli Lilly & Co. in a partnership that ended last year. Amylin lost almost half its market value on Oct. 20, 2010, after the FDA rejected Bydureon for a second time and sought a study on cardiac effects. The companies refiled for approval last year after the trial did not tie the drug to dangerous heart-rhythm changes.

c. Drugs that are close to approval by regulatory agencies.

In this regard, it is noteworthy development of the compound "dapagliflozin" (an inhibitor of renal cotransporter sodium / glucose SGLT2). This compound is in phase III clinical development and is expected to have information in the coming months on progress in its development. The drug is being developed by Bristol-Myers Squibb and AstraZeneca. Its interest lies on the fact that it would be the first drug aimed at anti-diabetic SGLT2 inhibition.

3.2.- Development of drugs for the management of weight control.

The pharmaceutical industry is pursuing many novel drug targets for the treatment of obesity. Although this view is probably not justified, the tribulations of rimonabant and other compounds have created a perception that the regulatory bar for the approval of antiobesity drugs has been raised. Although >5% of placebo-subtracted weight loss maintained over 1 year is the primary efficacy end-point, it is improvements in cardiovascular risk factors that the Food and Drug Administration (FDA) and European Medicines Agency (EMEA) require to grant approval. Safety aspects are also critical in this indication. Many companies are now switching development of their antiobesity drug candidates into other metabolic disorders. Type 2 diabetes is accepted by the industry and FDA, but not EMEA, as the most appropriate alternative. On the other hand, improvements in plasma lipids produced by antiobesity drugs are moderate compared with established therapies, suggesting dyslipidaemia is not a viable development option. Metabolic Syndrome is not accepted by FDA or EMEA as a discrete disease and the agencies will not licence antiobesity drugs for its treatment.

Guides in the development of anti-obesity drugs.

Before initiating phase 3 clinical trials, the pharmacokinetics and dose-response profiles of a new weight-management product should be well-characterized. Because excess adiposity may influence a product's metabolism and disposition, the pharmacokinetics profile of a weight-management product should be examined in patients with a broad range of BMIs (e.g., 27 kg/m2 to 35 kg/m2) (Cheymol 2000). To increase the likelihood of identifying the most appropriate dose for the pivotal clinical trials, early phase clinical studies should include a range of doses and be designed to identify no-effect and maximally tolerated doses. Studies should be designed to differentiate the efficacy of all the active doses versus placebo. The duration of the phase 2 trials should be sufficient to capture the maximal or near-maximal weight loss effects of the active doses. Forethought should be given to whether the product will be ultimately used in a fixed-dose or dose-titration scheme, as this dosing decision will also influence the size and duration of the studies.

Patients included in the early phase efficacy and safety studies generally should have BMIs greater than or equal to 30 kg/m2 or greater than or equal to 27 kg/m2 if accompanied by comorbidities. The primary efficacy endpoints should be a comparison of the mean absolute or percent change in body weight between the active-product and placebo-treated groups and the proportion of patients in each treatment group who lose greater than or equal to 5 percent of baseline weight. The effects by dose of the weight-management product on common weight-related comorbidities also should be examined and taken into account when choosing the most appropriate dose for the phase 3 studies.

a. Drugs that have been suspended by regulatory agencies or that they have been withdrawn.

In February 2011, the FDA decided to reject the application for its drug company Orexigen "Contrave" active bupropion and naltrexone) for their potential cardiovascular safety concerns after chronic administration. In this sense, the FDA asked Orexigen to conduct a double-blind, randomized placebo-controlled of

sufficient size and duration in order to demonstrate that the risk of adverse cardiovascular events after administration of "Contrave" does not affect adversely risk-benefit profile of the drug. The rejection of this anti-obesity drug adds to the rejection of anti-obesity drugs 2 conducted by the FDA in the last year: "lorcaserin" (for a possible link to cancer ", and" Qnexa "due to cardiovascular problems.

b. New drugs approved by regulatory agencies.

- In June 2012, FDA approved the weight loss drug Belviq (before lorcaserin) (Arena Pharmaceuticals). Belviq, known chemically as lorcaserin, was one of three experimental weight-loss treatments seeking FDA approval after initial rejections by the agency.

. In July 2012, FDA approved the weight loss drug Qsymia (before known as Qnexa) (Vivus) for sale on the U.S. market. The pill is only for clinically obese people, and, if approved, would be the most effective legal, non-surgery weight loss method, with trial patients losing about 10% of their weight over a year, the drug manufactuer claims. Qsymia is a combination of the drugs phentermine, a drug currently approved for weight loss, and topiramate, which is used for the treatment of seizures. It was rejected once by the same committee of doctors in 2010 because of numerous possible side effects, including heart problems and birth defects.

c.Drugs that are close to approval by regulatory agencies.

Table 1 provides a list of antiobesity drug candidates that are in clinical development. These include the centrally-acting monoaminergic food intake regulators,e.g. locaserin (already apprived by FDA), tesofensine, ATHX-105 and PRX-07034, and the peripheral lipase inhibitor, cetilistat. Also listed are candidates targeted at hypothalamic neuropeptides, e.g. obinepitide, gut hormones, e.g. TKS 1225, and various combination products, e.g. Qnexa® (already apprived by FDA), Empatic®, Contrave® and pramlintide/metreleptin.

Biotechnology companies located in France, Portugal and Spain with an interest in drug development in obesity / diabetes.

We have identified the following biotechnology companies interested in drug development in obesity / diabetes:Located in Portugal:

- Gene PREDIT. A biotechnology company founded in 2006 and focuses on developing innovative strategies, identification of novel biomarkers and novel applications of pharmaceutical compounds for diseases with high incidence such as obesity and diabetes. André Faustino (andre.faustino @ genepredit.com.pt) is the contact person in the company named above. Located in Castanhede (Biocant).

Located in Spain:

- Genmedica Therapeutics. A biotechnology company focused on the search for new drugs in type 2 diabetesde. Alec Mian is the CEO of that company, which is located in Barcelona (PCB).

- Allinky Biopharma. This company is focused on the discovery and development of small molecular weight drugs to treat chronic inflammatory conditions, degenerative diseases associated with aging, and cancer. Located in the PCM. Miguel Vega is the CEO of that company.

- Genzyme Spain. A company interested in rare metabolic diseases. Fernando Castillo's Trade Commissioner, Division LSD, E-mail: fernando.castillo @ genzyme.com.

Located in France:

- GlaxoSmithKline Research Center-France. The Unit "Lipid Metabolism DPU" is a drug discovery center looking for new therapies in metabolic diseases, including obesity, type 2 diabetes and dyslipidemia. Location: Centre de recherche, 25 avenue du Québec ZA Courtaboeuf.

- Physiogenex (CRO). Company specializing in the provision of services in relación with metabolic diseases. Located in Toulouse.- Poxel. Located in Lyon, the company develops compounds in the field of metabolic diseases and in particular type 2 diabetes.

Table 1. Clinical development pipeline of antiobesity drugs.

Compound	Status	Mode of action	Company
Cetilistat	Phase III	Lipase inhibitor	Alizyme/Takada
Locaserin	Phase III	5-HT_{2C} agonist	Arena
Qrnexa	Phase III	Topiramate + phentermine	Vivus
Tesofensine	Phase III	Triple uptake inhibitor	Neurosearch
Contrave	Phase III	Naltexone SR + bupropion SR	Orexigen
Empatic	Phase IIb	Zonisimide SR + bupropion SR	Orexigen
S-2367	Phase IIb	Neuropeptide Y_5 inhibitor	Shionogi
Obinepitide	Phase IIa	Y_2 + Y_4 agonist	7TM
TM30339	Phase IIa	Y_4 agonist	7TM
ATHX-105	Phase II (on hold)	5-HT_{2C} agonist	Athersys
Pramlintide/metreleptin	Phase II	Amylinomimetic/leptin	Amylin
KRP-204	Phase II	Selective b_3-agonist	Kyorin
SLx-4090	Phase II	Mitochondrial transfer protein inhibitor	Surface Logix
PRX-07034	Phase Ib	5-HT_6 antagonist	Epix
Remogloflozinetabonate (GSK 189075)	Phase I	Sodium glucose transporter-2 (SGLT-2) antagonist	GSK
V24343	Phase I	CB_1 antagonist	Vernalis
Amylin analogue	Phase I	Amylinomimetic	Amylin
AZD 1175/2207	Phase I/II	CB_1 antagonists	AstraZeneca
AZD 1656	Phase I	Glucokinase activator	AstraZeneca
TKS 1225	Phase I	Oxyntomodulin analogue	Thiakis