GLIFLOZINS, a new anti-diabetic drug- a preview into drug development

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Introduction:

Type 2 Diabetes mellitus is a metabolic disorder which is characterized by increased levels of blood glucose, elevated HbA1c levels and deranged lipid profile, all this is attributed to insulin insufficiency or insulin insensitivity. Till date there are scores of anti-diabetic medications discovered. Of these different classes of anti-diabetes drugs, the sodium-glucose co-transporter 2 (SGLT2) inhibitors or Gliplozins are the newest additions to this arsenal for treating type 2 diabetes mellitus. These agents help regulate blood glucose levels by blocking the reuptake of filtered glucose in the proximal tubule, leading to significant excretion of glucose via the urine, which is a novel and insulin-independent approach[1].

Introduction to SGLT2 inhibitors:

SGLT2 is a high-capacity, low-affinity transporter when compared to SGLT1, it is mainly present in early segment of proximal convoluted tubule in nephrons. This SGLT2 is responsible for 90% of active glucose absorption[2]. Once the glucose molecule enters the cells in proximal convoluted tubule, it is diffused into the circulation via facilitative glucose transporters (GLUTs) present at the baso-lateral membrane. In diabetes the blood glucose levels increases to high such high levels that the transporters present at luminal surface are unable to absorb any more glucose, hence extra being excreted in urine. In time gradually the SGLT2 genes are activated and the number of SGLT2 are increased at luminal surface. But at certain limit when further increase in receptor number is no more possible, glucosuria is seen[2].

Mechanism of action of SGLT2 inhibitors:

Gliflozins are reversible potent selective competitive inhibitor of SGLT2. They have 5000 times more affinity to SGLT2 receptors when compared to other SGLT receptors. SGLT2 is highly expressed in the kidney, whereas expression in other tissues is absent or very low. In type 2 diabetes a large portion of glucose is filtered and reabsorbed at proximal convoluted tubule, this Gliflozins specifically inhibit these SGLT2 receptors and prevent the re-absorption of glucose back into the plasma. Thereby increasing the excretion of free glucose from the urine which simultaneously causes the lowering of plasma glucose[3] details are depicted in the figure1 mentioned below.

Benefits of SGLT2 inhibitors:

SGLT2 inhibitors, by increasing the excretion of glucose, thereby decrease the plasma glucose concentrations, which further attributes to additional benefit of reducing body weight. The mechanism of action of this class of drug does not depend on the presence of insulin, so its effect would not be affected by insulin resistance or insulin impairment[4]. Also risks related to hypoglycemic events is low, due to its non-impairment of endogenous

response to hypoglycaemia or on insulin release[5-6]. Finally SGLT2 has potential to be used in combination with other anti-diabetic medications to improve glycemic control[4].

Drawbacks of SGLT2 inhibitors:

Since the SGLT2 inhibitors depend on the filtration and delivery of glucose to the proximal tubule at nephron level, they are not effective in patients with moderate to severe renal impairment[7-8]. Also long term excretion of high glucose in urine predisposes the patient for genital and urinary tract infections[4].

The details of various under development SGLT2 inhibitors are captured in the table.1 mentioned below[4].

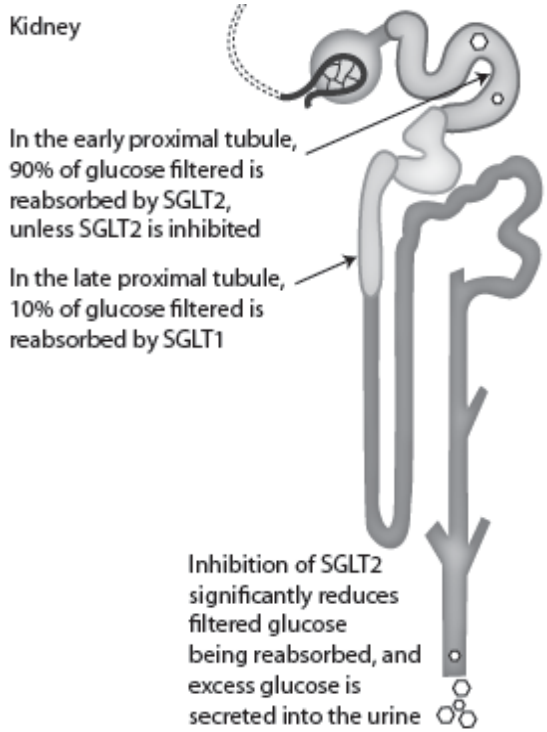

Figure 1. Anti-diabetic mechanism of SGLT2 inhibitors[2]

Table. 1: SGLT2 Inhibitors in Development

Compound Company	**Compound Company**
Dapagliflozin	Bristol-Myers Squibb/AstraZeneca
Canagliflozin	Johnson & Johnson/Mitsubishi Tanabe
Empagliflozin	Boehringer Ingelheim/Eli Lilly
Ipragliflozin	Astellas
LX4211	Lexicon Pharmaceuticals
PF-04971729	Pfizer

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GLIFLOZINS DRUG DEVELOPMENT PLAN WITH WHAT SRC CAN CONTRIBUTE

snl	Steps involved	Activities involved	Results achieved
1.	Step 1	**Drug development** – this step involves the manufacture of drug (SGLT-2) at an approved GMP facility. At first a test batch is produced for in-vitro and animal testing. And during a clinical trial a large scale production can be started. **SRCs Role**: *We can help in developing the study drug at our drug development facility and provide gap analysis and market entry strategy for the study drug.*	Drug product which is stable and ready for animal testing.
2.	Step 2 (both studies can be done in parallel)	**In-vitro studies** - to test the potency and specificity of our drug to block SGLT-2 receptors in animal models/ tissue. **SRCs Role**: *our team can help in procuring these details.* **Preclinical studies** - animal model studies like using Zucker diabetic fatty (ZDF) rats, different doses of drug or vehicle (placebo) will be tested to find a dose-dependent increases in urine glucose excretion, and a month's treatment of study drug/ placebo will be tested to check the levels of fasting plasma glucose (FPG) and HbA1c, and improved glucose tolerance in response to glucose challenge in the study animals. Animals will also be tested for total body water, protein content and fat content loss. Conduct of cytotoxicity and genontoxicity studies[2]. **SRCs role**: *Can conduct these studies on behalf of client, preparation of Investigators Brochure (IB) for the study drug, Chemistry Manufacturing and Control (CMC) data generation along with conduct of stability studies.*	The effectiveness of the study drug in effectively reducing the blood glucose levels. Dose estimation of study drug for next phase. Generation of cytotoxicity and genontoxicity data.
3.	Step 3 (Phase I)	**Phase I** will designed to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of single escalating doses of our study drug. During this phase the drug absorption, $t_{1/2}$, plasma distribution and drug elimination will be measured. The total amount of glucose excreted over 72 hours increased with dose and plasma glucose levels will be measured. The number of subjects experiencing an adverse event (AE) will be recorded for safety concerns.	The probable dose of study drug which might be suitable to test for next phase.

snl	Steps involved	Activities involved	Results achieved
		SRCs role: *Study Design, Regulatory approval, conduct of study, analysis of study and generation of clinical study report.*	
4.	Step 4 (Phase II)	**Phase II** safety and exploratory efficacy study. A randomized, double-blind, placebo-controlled trial will be conducted to evaluate the efficacy, safety, tolerability, and pharmacokinetics of selected doses of study drug in patients with type 2 diabetes over 12 weeks. A decreases in FPG and HbA1c that will be measured along with patient weight and urine glucose. One more model being treatment on glomerular filtration rate under controlled conditions of euglycaemia and hyperglycaemia in subjects with type 1 diabetes mellitus with or without renal hyperfiltration and to characterize the safety and efficacy of study drug as add on therapy to insulin in patients. **SRCs Role**: *Preparation of Development safety Update Report (DSUR), site selections globally for the conduct of study, procurement of regulatory approval and generation of Clinical Study Report (CSR).*	The safety profile of the study drug and steady state concentration in the patient's blood plasma. Effect of Drug on patient population.
5.	Step 5 (Phase III) pre marketing	**Phase III** efficacy and benefit–risk assessment study. Often pivotal study, which will provide the evidence for the safety and efficacy of the drug needed to gain its approval for marketing. This phase may involve single study drug or as FDC along with an approved therapy. Blood FPG and HbA1c will be monitored for a period of year at least. This phase will include the patients with various co morbid conditions (renal impairment, CKD stage 1 &2 patients) along with the disease under study, to evaluate the effect of study drug on various other conditions. **SRCs Role**: *preparation of DSUR, Periodic Safety Update Report (PSUR), updating of the IB based on the results available from clinical trials. Preparation of New Drug application (NDA) application for procuring marketing authorization approval.*	Data for the study drug is generated which can be used for applying to marketing authorization.
6.	Step 6 (post marketing study and beyond the	As per recent directions from FDA drugs blocking on SGLT2 needs to show effect on cardiovascular system. Hence long term study may be warranted in indications like coronary artery disease, effect of study drug in controlling hypertension, effect on insulin sensitivity and improvement/ further deterioration of renal function test and diabetic nephropathy.	Safety and efficacy of study is established in various other indications and

snl	Steps involved	Activities involved	Results achieved
	indication studies)	Many cases the FDA also requests for drug-drug interaction studies. Which becomes important part of study drug approval. Also the sponsor needs to provide post marketing surveillance reports for the study drug for various duration of time. **SRCs Role**: *Conduct of Post marketing studies, reporting of the additional safety updates to regulatory authorities and Pharmacovigilance. Updating of the PSURs and IB on timely manner.*	safety is established in patient population without any exclusion criteria.

Drug Development Process Summary:

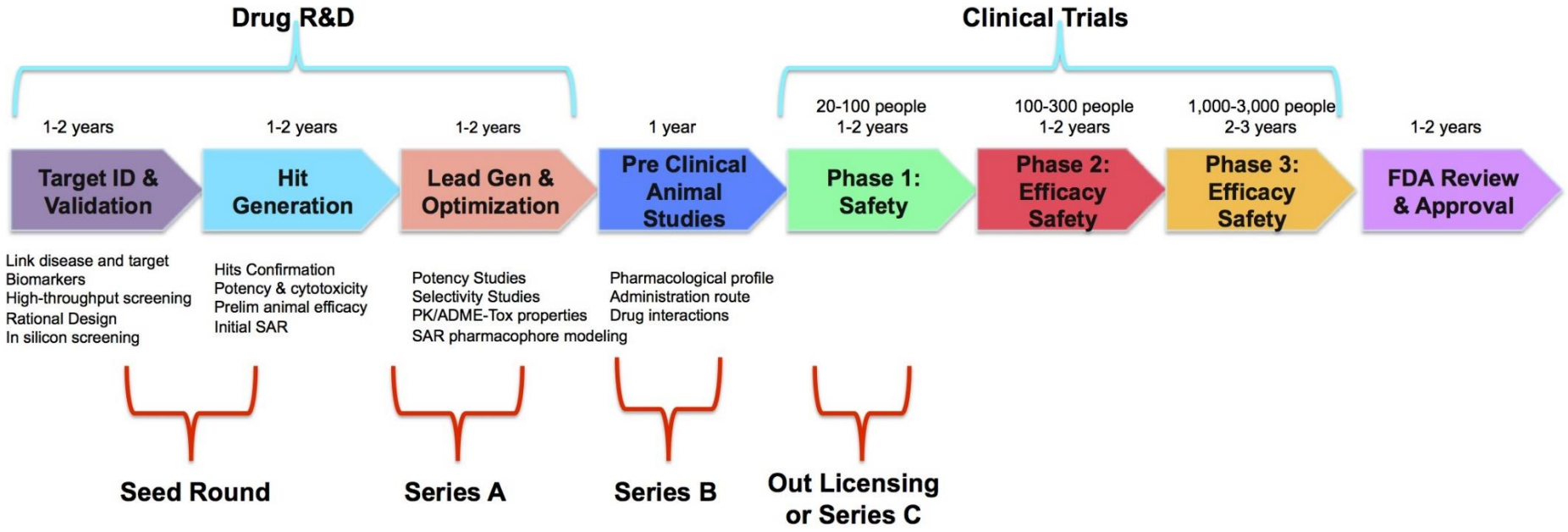

Figure 2: Drug development process[9]

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