IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

To Understand The Discovery Of Drugs Process Through Study Of Development Process Of Sitagliptin

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Abstract: Sitagliptin is one who is a gliptin class of antidiabetic medications. Its method of action is through Dipeptidyl peptidase-4 inhibition (DPP-4), an acting enzyme to degrade and inactivate glucagon-like peptide-1 (GLP-1). The elevated GLP-1 level in reaction to sitagliptin results increased release of insulin after meals, and improved glucose tolerance. This quality, along with lack of weight gain with treatment, has resulted in increased use of sitagliptin as a second-tier a course of treatment for type 2 diabetes. The beginning of the treatment for type 2 diabetes was motivated by the development of glucagon-like peptide 1 (GLP-1) as a well-validated strategy and the preclinical validation of dipeptidyl peptidase IV (DPP-4) inhibition as a substitute, oral approach to GLP-1 therapy of a DPP-4 inhibitor program at Merck in 1999. The program was launched with the in-licensing of the the DPP-4 inhibitors threo- and allo-isoleucyl thiazolidide were developed, however testing on rats and dogs revealed they were extremely hazardous. Because both substances inhibit the related proline DPP8 peptidase and DPP9, significant toxicities in preclinical species may result from inhibiting either of these enzymes.

Index Terms **- Sitagliptin,Antidiabetic, DPP-4, GLP-1,Diabetes Mellitus.**

I. INTRODUCTION TO DRUG RESEARCH PROCESS

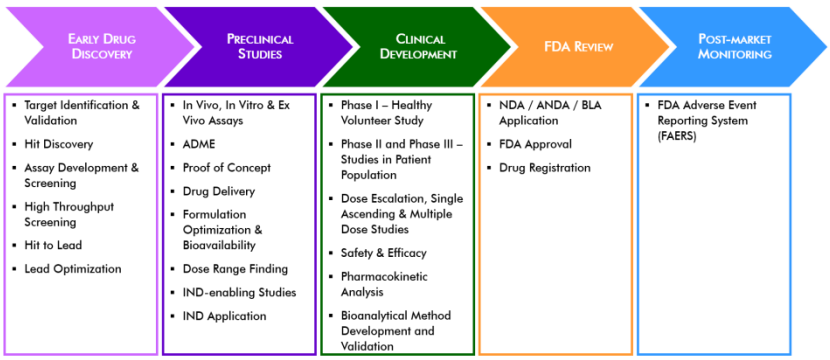

Figure 1: Drug Research Process

The complexity of developing new drugs has grown preclinical testing, investigational new drug (IND) submissions, and other procedures throughout the previous 40 years, completed clinical testing before marketing approval from the FDA. Generally, applications for biologics licenses or new drug applications (NDAs) are reviewed comprehensively before approval, and then drug performance is resubmitted to regulatory agencies for post-marketing studies.

The main objective is to provide patients with more effective and safe treatments as soon as possible following a careful medical evaluation.

Phases Stages: There are five critical steps in the U.S. drug development process, including many phases and stages within each of them. We will discuss these different phases and stages to develop an in-depth understanding of the entire process. The five steps are –

First step : Discovery and Development
Second step: Preclinical Research
Third step: Clinical Development
Fourth step: FDA Review
Fifth step: FDA Post-market Safety Monitoring

II. EARLY DRUG DISCOVERY PHASE OF DPP4 INHIBITOR - SITAGLIPTIN:

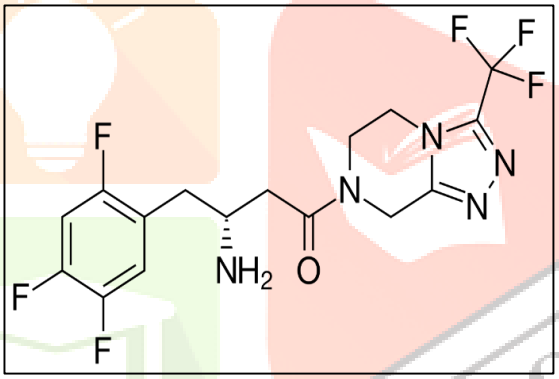

Figure 2: Sitagliptin

Active Substance-

The active substance is sitagliptin as monohydrate phosphate salt and its chemical name is 7-[(3R)-3-Amino-1-oxo-4-(2, 4, 5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-[3-(trifluoromethyl)-1,2,4-Triazolo [4, 3-a] pyrazine phosphate (1:1) monohydrate based on the IUPAC terminology. A white to off-powder substance called sitagliptin and exhibits pH dependent aqueous solubility.

Mechanism of action: The DPP-4 sitagliptin drug inhibitor, which is believed to exert its actions those who have type 2 diabetes by slowing the inactivation of incretin hormones. Concentrations of Sitagliptin increases the amount of active intact hormones, extending and enhancing the action of these hormones. Incretin hormones, such as glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), are generated by the gut throughout the day, and levels rise in response to a meal. These hormones are rapidly inactivated by the enzyme, DPP-4. The incretins are part of an endogenous system taking part in the physiologic control of the homeostasis of glucose. GLP-1 and GIP stimulate insulin production and release from pancreatic beta cells by intracellular signaling pathways including cyclic AMP when blood glucose levels are normal or increased. GLP-1 also reduces pancreatic glucagon secretion , leading to reduced hepatic glucose production. Sitagliptin enhances insulin release while boosting and extending active incretin levels and decreases glucagon levels in the circulation in a glucose-dependent manner. At concentrations that are similar to those from therapeutic doses, sitagliptin exhibits selectivity for DPP-4 and does not block DPP-8 or DPP-9 action in vitro.

Hit Discovery: The emergence of GLP-1, or glucagon-like peptide 1. as a well validated approach to addressing type 2 diabetes and preclinical validation DPP IV dipeptidyl peptidase (DPP-4) inhibition as an alternate, oral approach to GLP-1 therapy prompted the initiation of an inhibitor of DPP-4 program at Merck in 1999. The program was launched using the DPP-4 inhibitors threo- and allo-isoleucyl thiazolidide, but development was halted due to extreme toxicity in rats and dogs safety studies. Due to the fact that these substances inhibit the related proline peptidases DPP8 and DPP9, it has been suggested that preclinical species may exhibit severe toxicities when DPP8 and/or DPP9 are inhibited. The reported toxicities were indeed recapitulated by a selective dual DPP8/9 inhibitor but not by a selective DPP-4 inhibitor. The goal of medicinal chemistry was to find a clinically viable, highly selective DPP-4 inhibitor. Due to a lack of selectivity, early work on an a-amino acid series related to isoleucyl thiazolidide was abandoned; nevertheless, SAR analyses on two screening leads resulted in the discovery of a highly selective compound ß-amino acid piperazine series. A number of bicyclic derivatives were created in an effort to stabilize the piperazine moiety, which was heavily metabolized in vivo. This led to the discovery of a powerful and selective triazolopiperazine series. These analogs often displayed superior pharmacokinetic characteristics in preclinical animals, unlike their monocyclic counterparts. Optimization development of Sitagliptin, a highly selective DPP-4 inhibitor for the treatment of type 2 diabetes, was made possible by this study.

Table 1: Activity of DPP4

Serial No	**Assay/Activity**	**Use**	**Sitagliptin activity**	
1	DPP4 inhibitor assay	Activity of synthesised molecule	18 nM	Preserve the level of GIP and GLP- 1
2	DPP8/9	Selectivity assay	50 μM	No significance result
3	DPP6/10	Selectivity assay	No activity at several fold concentration	Influence potassium channel function

In-vitro screening assay: Inhibiting dipeptidyl peptidase-4 (DPP-4) is one method for treating diabetes, thus it's intriguing to carry out virtual screening experiments to look for new DPP-4 inhibitors. In this investigation, a virtual screening was conducted utilizing the crystal structure of DPP-4 and a subset of compounds from the ZINC database. We used some physicochemical characteristics, location at the three DPP-4 binding sites, molecular interactions, and ADME-Tox features to filter this compound subset. A consensus analysis with additional methods (AutoDock and GOLD) was used to examine the conformations of ligands produced from AutoDock Vina. The substances chosen through virtual screening were put through biological tests utilizing the "DPPIV-Glo protease assay". Tests for cytotoxicity were also carried out. At the binding site, one potential chemical (ZINC1572309) developed contacts with critical residues. ZINC1572309's ADME-Tox prediction outcomes were contrasted with those of a reference medication (sitagliptin). The Using the XTT short-term cytotoxic test, the cytotoxicity of sitagliptin and ZINC1572309 was assessed in order to monitor the cellular response to both normal and malignant cell lines inhibitor treatment at different genetic bases. The reference medicine sitagliptin and the chosen compound ZINC1572309 both suppressed DPP-4 activity, indicating intriguing pharmacological effects of the chosen chemical at non-cytotoxic concentrations. Therefore, a possible DPP-4 inhibitor was found via in vitro and virtual experiments; it can be structurally modified to obtain the desired action and pharmacokinetic profiles.

III. PRECLINICAL STUDIES –SITAGLIPTIN

Pharmacokinetics-The Sitagliptin's pharmacokinetics is similar in healthy individuals and in T2DM patients. It is Orally well absorbed with an 87% bioavailability. In human beings, the protein binding of Sitagliptin, as determined by ultracentrifugation is 34-46%. Among wholesome volunteers and for those with T2DM of different ethnic background, the tolerability of different doses as once or twice daily is good. The most important pharmacokinetic factors (Tmax, Cmax and t1/2) measured in studies were similar at baseline and in the steady state after longer administration. The current plasma concentration of Sitagliptin is reached after 3 days later with terminal half-life of 10-12 hours at doses of 25-100 mg. The elimination and excretion is mainly renal (75- 80% of an oral drug is found in urine as unchanged drug) and the rest is metabolised via cytochrome CYP3A4 and CYP2C8.

Dose- The most beneficial dose for several glycaemic indices is Sitagliptin 100 mg daily, which is the highest permitted and recommended amount. The Sitagliptin administration is independent of meals.

Toxicology-

• **Single dose toxicity-** Single dose studies with sitagliptin were performed in rats and mice. The highest non-lethal dose in mice was 1000mg/kg (122 times the human exposure according to AUC). In rats the highest non-lethal dose was 2000mg/kg for females and 3000 mg/kg for males (271 and 182 times the human exposure based on AUC respectively).

• **Repeat dose toxicity (with toxicokinetics)-** Toxicity tests on multiple doses were performed in mice (up to 93 days), rats (up to 184 days) and dogs (up to 365 days). The maximum non-lethal dose was 750 mg/kg/day for mice (approximately 80 times the human exposure based on AUC), 500 mg/kg/day for rats (48 times the human exposure based on AUC), and = 50 mg/kg/day for dogs (= 22 times the human exposure based on AUC). In rats mortality was greater in males than females, while in mice it increased in females. In both Rats and mice renal toxicity was observed at systemic exposure values above 58 times the human exposure levels, while the no-effect level was found at 19 times the human exposure level. In mice it consisted of dilatation within the renal pelvis (associated with variable loss of papillary, medullary, and cortical tissue) and increases in relative kidney weights.

• **Genotoxicity-** Sitagliptin did not exhibit any genotoxic effects in in vitro or in vivo tests for mutagenicity (Ames test), direct DNA damage (in vitro test in primary rat hepatocytes), or clastogenicity (in vitro chromosome aberration test) in Chinese hamster ovary cells in vivo.

• **Carcinogenicity-** In mice and rats, the carcinogenic risk of sitagliptin was assessed. In the two-year mouse carcinogenicity study, no organ showed any increase in tumor incidence due to therapy, tested doses (50, 125, 250, 500 mg/kg/day). Both sexes experienced treatment-related non-cancerous alterations, such as centrilobular hepatocellular hypertrophy at a dose of 500 mg/kg/day and hydronephrosis at =250 mg/kg/day. At 500 mg/kg/day, there was a slight, but not significant decrease in survival due to an increased incidence of hydronephrosis. Based on the results of these, the NOEL for induction of neoplasia was >500 mg/kg/day and the NOEL for non-neoplastic changes 125 mg/kg/day in male and female mice.

•**Immunotoxicity** - Inhibition DPP-4 by sitagliptin does not seems to play a major part in T cell dependent immune responses. Animal data on the part DPP-4 plays in T cell immune response showed no consistent changes after inhibition/knock out of DPP-4. In vitro studies showed that the required sitagliptin concentrations to evoke noticeable effects about T cells are sufficiently far above the maximal plasma concentration, which is reached after a therapeutic dose of 100 mg in humans. In the repeated-dose toxicity studies, there was no suggestion of an immunosuppressive effect of sitagliptin, and there was no evidence of allergenicity in the test for local lymph nodes in mice (section on local tolerance).

IV. CLINICAL DEVELOPMENT-

The next phase of research is clinical medication development, which involves volunteer studies and clinical trials to finetune the drug for human use.

Phase 1-Healthy Volunteer Study

This phase is the initial time the drug is tested on humans; less than 100 volunteers will help researchers assess security and pharmacokinetics, absorption, metabolic, and elimination effects on the body, in addition any side effects for safe dosage ranges.

Phase 2 and Phase 3- Patient Population Studies

Phase II evaluates the safety and effectiveness of the therapy in an additional 100–500 patients, some of whom may also receive a standard medication or a placebo. While adverse events and dangers are being documented, schedules are made with the aid of analysis of the ideal dose strength. Phase III enrols 1,000–5,000 patients, allowing for the creation of medicine labels and usage guidelines. Trials in phase III demand a lot of cooperation, organization, and Independent Ethics Committee (IEC) or Institutional Review Board (IRB) coordination and regulation in anticipation of full-scale production following drug approval.

Findings of Clinical Study of Sitagliptin-

Clinical trials have examined sitagliptin, an oral, once-daily DPP-4 inhibitor, as a monotherapy, an add-on therapy, or as part of an initial combination therapy with metformin. Sitagliptin provided efficient postprandial and fasting glucose control in a variety of type 2 diabetic patients. ß-cell function markers (HOMA-ß and proinsulin/insulin ratio) were improved with sitagliptin treatment. Sitagliptin was generally well tolerated in these clinical trials, with a total incidence of side effects equivalent to placebo and a low risk of hypoglycemia or gastrointestinal adverse experiences, and a body-neutralizing effect weight. The patient population who took part in each clinical trial for up to a year is the only one whose outcomes are covered in this study. Future clinical studies should evaluate if this group of drugs has the capacity to either stop type 2 diabetes from developing or to reduce its progression.

Conclusions- Sitagliptin has demonstrated efficacy and well-tolerated in various treatment regimens and may be considered for both initial therapy and as supplemental treatment for people with type 2 diabetes.

Dose Escalation, Single Ascending and Multiple Dose Studies-

Methods- In research 1, 66 healthy individuals participated in a single-dose escalation research that was double-blind, randomized, placebo-controlled, and used sitagliptin as a treatment as a positive open-label control. Sitagliptin 12.5, 25, 50, 100, 200, or 400 mg was given to forty-four patients in seven cohorts; 12 subjects received a placebo. The positive control was sitagliptin 100 mg, which was given to the remaining ten individuals. For the pharmacokinetic study and measurement of plasma levels of insulin, glucose, active glucagon-like peptide-1, and plasma dipeptidyl peptidase-4 inhibition, blood, urine, and feces were collected. In Study 2, 14 healthy volunteers were divided into two groups and given a single oral dosage of sitagliptin 100 mg either before or after a high-fat meal. There was a 14-day washout interval in between treatments. To assess how diet affects the pharmacokinetics of sitagliptin, blood samples were taken.

Results: Sitagliptin was quickly absorbed after a single oral dose, with a median time to maximum concentration of 1.0-3.25 h. The terminal half-life was much longer than that of sitagliptin, ranging between 25.8 and 41.3 h. Between 25 mg and 400 mg, the plasma concentration-time curve's area under the curve was roughly dose proportional, while the increase in maximum concentration was more than dose proportionate. The medication was primarily eliminated in urine in its unaltered form. (27.2–46.2% of dose) and minimally via the faeces (1.4% of dose). Increased levels of active glucagon-like peptide-1, suppression of dipeptidyl peptidase-4, and a slight decrease in blood glucose were observed, whereas insulin was not significantly altered when compared with placebo. The weighted average Sitagliptin 100 mg inhibits dipeptidyl peptidase-4 was

higher than that mediated by sitagliptin 100 mg. Sitagliptin was well-accepted up to a solitary dosage of 400 mg. Food had no noticeable effects.

Conclusions-Sitagliptin increased levels of active glucagon-like peptide-1, decreased plasma dipeptidyl peptidase-4 activity, and was well tolerated at single doses up to 400 mg, with no dose-limiting harm in healthy individuals. The pharmacokinetics of sitagliptin were unaffected by food.

Safety and Efficacy-

Methods-Patients on a sulfonylurea and metformin with HbA1c levels of 7.5% and 10.5% were randomly assigned to either sitagliptin 100 mg/day or a placebo for 24 weeks. Patients in the placebo group transitioned to pioglitazone 30 mg/day at Week 24, and both groups kept taking it for an additional 30 weeks.

Results- 339 (79.4%) of the 427 randomly assigned participants finished the study. At Week 24, sitagliptin considerably outperformed the placebo group in terms of mean HbA1c reductions from baseline (-0.84% vs -0.16%, P 0.001), 2-h post-meal glucose (-2.0 vs -0.2 mmol/L, respectively) with fasting blood sugar (-0.7 vs 0.3 mmol/L, respectively). At 54th week, improvements glucose under control continued. Because hypoglycemia occurred more frequently with sitagliptin than with placebo at Week 24, the incidence of adverse events (AEs) was quantitatively higher with sitagliptin. A increased frequency of hypoglycemia and edema in the placebo/pioglitazone group after Week 24 was the main reason for the equal incidence of AEs at Week 54 between the two groups. At Week 54, the placebo/pioglitazone group's weight was the only one to show a significant change.

Conclusions- In this trial, sitagliptin 100 mg/day, when added to the regimen of sulfonylurea and metformin in patients with T2DM, was generally well tolerated and improved glycemic control.

V. FDA REVIEW-

Once the new drug has been formulated for its best efficacy and safety, and the results from a clinical trial is available, it's advanced forward for wholistic FDA review. At this time, the FDA reviews and approves, or does not approve, the drug application submitted by the drug development company.

IND Application-

IND applications are submitted with the FDA before starting clinical trials. If a clinical trial is ready to be conducted, and an FDA has not responded negatively about the drug, developers may start the trials.

NDA/ANDA/BLA Applications-

An NDA abbreviated New Drug Application (ANDA), or BLA is submitted with the FDA after clinical trials demonstrate the safety of drugs and efficacy. The FDA reviews study data and decides whether to grant approval or not. Additional research or a team of experts to advise may be required before a final decision is made.

FDA Approval- This study investigates the potential using sitagliptin to treat pediatric diabetes mellitus type 2 (T2DM) patients, aged 10 to 17 years.

The prevalence of T2DM among pediatric patients is increasing, concurrent with the obesity epidemic.However, the only non-insulin therapy authorized for use in T2DM children 10 years of age and older is metformin. Metformin's effectiveness is restricted by gastrointestinal side effects and, frequently, the requirement for multiple daily doses. Furthermore, because diabetes is a progressive condition, patients may require more antidiabetic medication in addition to metformin to obtain sufficient glycemic control. Based on the reduced risk of hypoglycemia and oral delivery, sitagliptin might offer a helpful additional therapy option for young T2DM patients. Adolescents should take sitagliptin 100 mg daily, according to a single-dose trial that evaluated the drug's pharmacokinetics, safety, and tolerability. Because it is unclear whether sitagliptin's effects on adults and children are sufficiently similar, its effectiveness must be proved in the pediatric population. Given that the protocols for sitagliptin pediatric clinical research include stringent

inclusion and hyperglycemic rescue criteria as well as diet, exercise, and diabetic education, the use of placebo is morally acceptable.

Studies of T2DM patients under ten years of age, including neonates, are impossible or highly impractical because few of these patients require pharmacologic therapy.

• Clinical studies:

Study 1: a double-blind, randomized, placebo- and active-controlled, safety- and effectiveness study study of the effect of sitagliptin on haemoglobin A1c (HbA1c) in children with T2DM aged 10 to 17 years (inclusive) who are not on treatment with a diabetes medication for =12 weeks before screening and have poorly controlled blood sugar (HbA1c = 7.0% and =10.0%). The trial must have a screening phase, a single-blind run-in phase lasting one week, a 20-week active- and placebo-controlled Phase "A," and at least a 32-week active-controlled Phase "B." Glycemic rescue and unique patient discontinuation criteria must be stated in the protocol.

• Objectives of the study:

• To evaluate the effect of sitagliptin treatment compared to placebo at 20 weeks on the change from baseline in HbA1c in Phase A
• To assess sitagliptin's long-term safety in the pediatric population during Phase B

•Patients to be examined-

The study will be conducted on the following age group: age group of 10 to 17 patients
- At least 30% of randomized patients must be 10-14 years old
- At least 30% of randomized patients must be female
- Amount of patients expected randomized: At least 360 total with roughly same numbers of patients randomized to each of the three treatment groups
- There may not have been any patients who took an AHA for at least 12 weeks previous to randomization
.- Poor glycemic control (HbA1c between 7.0% and 10.0%).

VI. POST-MARKET MONITORING-

Following drug approval and manufacturing, the FDA requires drug companies to keep an eye on safety of its drug using the FDA Adverse Event Reporting System (FAERS) database. FAERS helps FDA implement its post-marketing safety surveillance program. Through this program, producers, medical experts, and customers report problems with medicines that have been approved.

Results- 270 adverse drug reactions (ADRs) occurred in 207 (6.3%) of the 3265 individuals whose safety was assessed. Hypoglycemia (17 patients, 0.52%) was the most prevalent ADR, occurring in 58 patients overall (53 non-serious, 5 serious), making metabolism and nutrition problems the most prevalent class of ADRs. In people with eGFR more than 90 mL/min/1.73 m2, at baseline (mean ± SD, 106.42 ± 18.11 mL/min/1.73 m2, n = 584), eGFR declined by 11.83 ± 17.53 mL/min/1.73 m2

(P < 0.0001; n = 360) over the observation period whereas eGFR appeared to be relatively maintained when patients have lower baseline eGFR levels. In this Japanese population, cardiovascular events were uncommon (occurring in 4 of 84 (4.76%) patients at high cardiovascular risk), lacked any distinguishing characteristics, and had a cumulative incidence similar to that shown in sitagliptin-related studies (8.42% (3.12-21.70) at 36 months; n = 32).

The average change in HbA1c among patients who underwent efficacy testing was mean SD - 0.68 1.34% (P 0.0001, n = 2070). Younger patients and patients with higher body mass index (BMI) and HbA1c readings at the start of medication tended to experience bigger reductions in HbA1c.

VII. CONCLUSION-

In the context of ordinary clinical practice, long-term sitagliptin administration is linked with good effectiveness, including as monotherapy, and poses no new safety concerns.

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