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MEETING REPORT

RECENT DISCLOSURES OF CLINICAL CANDIDATES (SMR AWARD LECTURE)

HIGHLIGHTS FROM THE SOCIETY FOR MEDICINES RESEARCH SYMPOSIUM, HELD ON DECEMBER 5TH 2012 AT THE NATIONAL HEART & LUNG INSTITUTE (NHLI), LONDON, UK

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SUMMARY

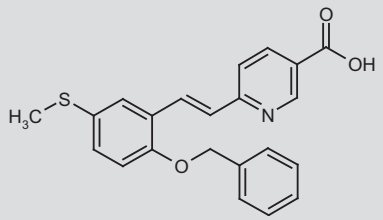
On December 5th, 2012 the Society for Medicines Research (SMR) held a 1-day meeting entitled Recent Disclosures of Clinical Candidates. This symposium, organized by Mike Brunavs, Phillip Cowley, Simon Ward and Peter Weber, brought together a panel of international speakers to present on the discovery and development of agents that are progressing through clinical trials. The meeting included the presentation of the 2012 SMR Award for Drug Discovery to Dr. Peter Mueller as the representative of Vertex Pharmaceuticals, Inc. for the discovery of telaprevir.

Key words: Glucokinase activators – Asthma – Diabetic nephropathy – Telaprevir – Cancer – Diabetes –Cognitive impairment

PROPERTY-BASED DESIGN IN THE OPTIMIZATION OF BENZAMIDE GLUCOKINASE ACTIVATORS: FROM HTS TO CLINICAL CANDIDATE AZD-1656

Dr. Darren McKerrecher (Associate Director, Medicinal Chemistry, AstraZeneca) began his presentation by describing the role of glucokinase (GK) in regulating blood glucose levels via glucose phosphorylation in the liver and the glucose-sensitive release of insulin in the pancreas. Hence, a GK activator ought to attenuate glucose levels and help control type 2 diabetes.

High-throughput screening (HTS) hit **1** was iterated several times to arrive at GKA-60 (**2**), a molecule with much improved bioavailability and increased half-life (1). However, it still contained the pyridinecarboxylic acid motif, and this was shown to be responsible for testicular toxicology through potent retinoic acid receptor-α (RAR-α) antagonism. The AstraZeneca team replaced this moiety with thiazole, which led to reduced solubility, but regained this lost ground in replacing the 3,5-difluorophenoxy group with 4-(sulfonylmethyl)phenoxy, as in compound **3** (2).



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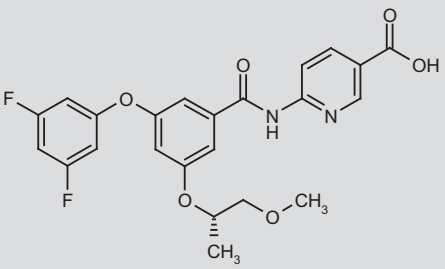

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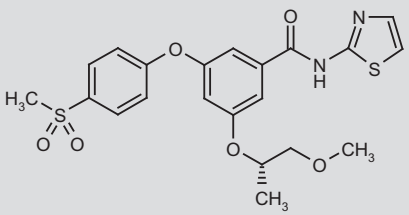

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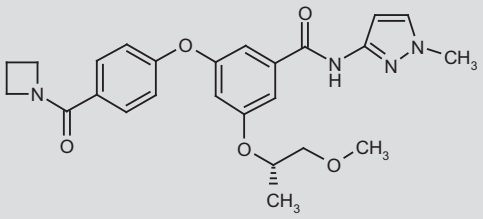

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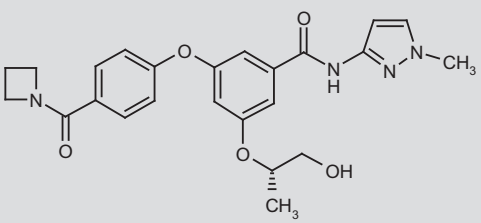
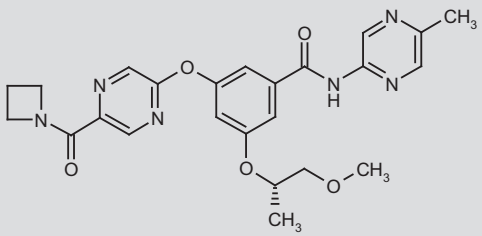


AZD-1092



AZD-1656

However, just as RAR-α activity was removed, a liability against the voltage-gated potassium channel K_V11.1 (hERG) then emerged. Detailed investigations regarding the physical property profiles of the molecules made thus far were carried out in an effort to determine the optimal characteristics that would reduce this new problem and retain the desired profile. LogD < 3 was found to be necessary for good solubility, but logD > 2 was needed for acceptable permeability. This "sweet spot" narrowed further when it was recognized that logD > 2.5 often led to a poor hERG profile (3).

Virtual library creation and subsequent in silico triage by physical properties identified 60 molecules expected to match the "sweet spot" criteria. A total of 36% of these targets achieved good exposure and solubility, with hERG affinity abolished, and a considerable improvement on the 6% achieved through random targeting. One such molecule was **4**, which fulfilled all criteria apart from its physical state, defying all attempts at crystallization and remaining amorphous. Demethylation of the terminal methoxy solved this issue to create the first clinical candidate, **AZD-1092**, albeit at the cost of lowering logD to 1.8 and slightly reducing bioavailability.

In pursuing a second candidate, the AstraZeneca team wanted to improve bioavailability, and although no amide hydrolysis was detectable in AZD-1092, it was known that the potential metabolite 1-methyl-3-amino-1,2-pyrazole was Ames-positive. Replacing the pyrazole would remove this issue, and in addition, the likely increase

in logD ought to improve permeability, but this risked the reintroduction of an hERG problem if not done in a controlled manner. Recapping the hydroxyl would also help, but ran the same risks.

To offset these factors, the team explored an increase in polarity in the pendant phenoxy ring. Virtual libraries involving Ames-negative aminoheterocycles to replace the pyrazole, ethers to replace the hydroxylated side chain and aza-heterocycles to replace the pendant phenoxy motif were created. This approach led to **AZD-1656**, which was superior to AZD-1092 in all respects (4). AZD-1656 was well tolerated in man, but failed to meet undisclosed internal AstraZeneca criteria at the end of phase IIb clinical trials. AstraZeneca is not progressing this asset at this time.

DISCOVERY OF SETIPIPRANT (ACT-129968), A CRTH2 ANTAGONIST FOR THE TREATMENT OF ASTHMA AND ALLERGIC RHINITIS

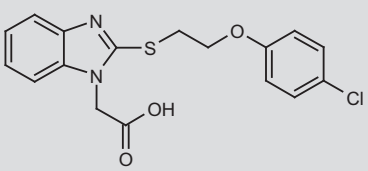
Dr. Heinz Fretz (Actelion Pharmaceuticals, Ltd.) opened his talk with an overview of the worldwide nature of asthma and the costs it creates. In reviewing the new mechanisms by which the disease is being addressed, Dr. Fretz drew attention to prostanoid DP_2 (CRTH2) receptor antagonism.

PGD_2 is a major prostanoid secreted during allergic reactions and induces chemotaxis and chemokines in T helper type 2 (Th2) cells, eosinophils and basophils, resulting in downstream airway hyperresponsiveness, lung inflammation and lung eosinophilia. Blockade of the CRTH2 receptor halts this pathway, and the CRTH2 antagonist ramatroban (BAY-u-3405) has been shown to inhibit PGD_2-induced eosinophil migration in vitro (5). The fact that CRTH2 is phylogenetically distinct from other prostanoid receptors gives rise to the possibility of non-prostanoid antagonist structures.

HTS at Actelion provided two hits, **5** and **6**. The progression of **5** has been published elsewhere (6) and was not discussed in this presentation. Compound **6** was attractive due to its potency (< 1 μM in both FLIPR and binding assays), but it contained structural features of concern. Initial structure–activity relationship (SAR) studies showed that alkylation of the amide nitrogen improved potency, and that substitution at the indole 4- and 5-positions was tolerated, whereas at the indole 6- and 7-positions it was not. Modeling revealed significant planarity, so a ring closure strategy was considered to retain that geometry and remove the undesirable α,β-unsaturated nitrile motif. This proved fruitful, as compound **7** had an IC_{50} of 145 nM. The IC_{50} for the corresponding urea, made to remove the chiral center, was 430 nM.

Settling on a tetrahydro-γ-carboline core, the team now searched for better acyl groups. A breakthrough was made in creating compound **8**, the unsubstituted benzamide, with an affinity of 17 nM. Further substitution in the "permitted" areas of the indole portion led to compound **9**, with an affinity of 2 nM.

Most single aromatic rings, and even naphthalenes, could be tolerated on the amide without seriously impacting solubility, but a number of compounds had low exposure/high clearance issues. The team substituted variously around the core in the search for molecules which did not suffer from these setbacks, and ACT-129968 (**setipiprant**; 6 nM) was one such compound.



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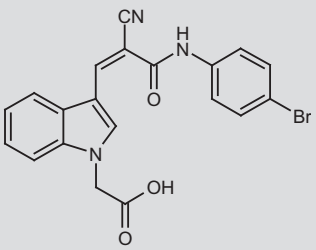

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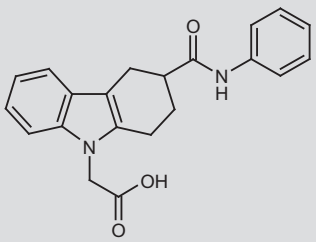

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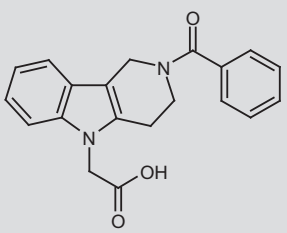

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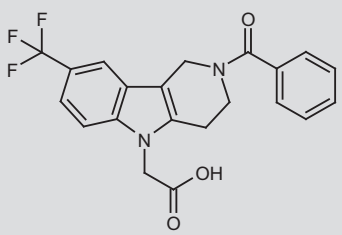

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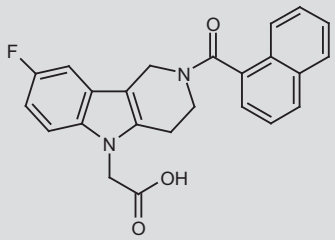


Setipiprant

Setipiprant proved highly selective against other prostanoid receptors, CNS targets generally and cytochrome P450 enzymes. It was of low clearance, high exposure, had no hERG liability and no adverse cardiovascular effects were seen in the spontaneously hypertensive rat. The rat half-life was 6 hours. The molecule demonstrated all the expected preclinical in vivo pharmacology with high activity.

Actelion took setipiprant forward to the clinic. In phase I, doses up to 2 g were well tolerated, safe and did not accumulate. Exposure was slightly less than dose-proportional but this did not prevent progression to phase II. Here, statistically significant reductions in allergen-induced late allergic reactions in patients with mild to moderate asthma were noted, but no effects were seen against early allergic reactions. Good effects were recorded against allergen-induced airway hyperresponsiveness and the compound proved effective in patients with mild to moderate allergic asthma and seasonal allergic rhinitis.

However, the molecule did not translate from phase II to phase III. No efficacy in phase III was seen, and so development was halted. Actelion is now bringing forward a molecule 10 times more potent, but no further details were disclosed.

MCP-1/CCL2 INHIBITOR NOX-E36 – A MIRROR-IMAGE OLIGONUCLEOTIDE DEVELOPED FOR DIABETIC NEPHROPATHY

Dr. Dirk Eulberg (VP Project Management, Noxxon Pharma AG) described the discovery, preclinical characterization and early clinical development of NOX-E36, a synthetic L-stereoisomer oligonucleotide targeted against monocyte chemotactic protein 1 (MCP-1, also referred to as CCL2). MCP-1 plays an important role as a chemokine that amplifies an inflammatory reaction by recruitment of monocytes to sites of inflammation. MCP-1 is an attractive target in the context of diabetic nephropathy, where it has been implicated in the development of structural and functional renal alterations through its direct effects on monocytes, mesangial cells and podocytes (7).

The discovery of NOX-E36 was based on Noxxon's proprietary SELEX platform, an evolutionary process that generates optimized L-RNAs (spiegelmers) as specific polynucleotide ligands (aptamers) to target proteins (8). Spiegelmers are able to adopt complex three-dimensional structures comparable to proteins and can bind targets with an affinity and selectivity similar to antibodies or recombinant proteins, while being biologically stable and lacking immunogenicity.

To generate a spiegelmer against MCP-1, a D-stereoisomer of the protein was synthesized and incubated with a library of 10^{15} D-RNA molecules. After a binding and elution step, RNAs with affinity for the target protein were amplified by PCR and the resulting pool of aptamers was again tested, separated and amplified in multiple rounds, leading to the generation of specific and selective ligands. Once optimized, a high-affinity aptamer was sequenced and synthesized as a spiegelmer to bind to the naturally occurring L-polypeptide drug target.

NOX-E36 is composed of 40 L-nucleotides and a 5′-PEG modification to improve pharmacokinetic (PK) properties. In biochemical studies, NOX-E36 bound to human MCP-1 with a K_d of 1.4 nM and also interacted with the chemokines MCP-2 and eotaxin with high affinity. In cellular assays, NOX-E36 inhibited chemotaxis at subnanomolar concentrations. Across species, NOX-E36 showed similar affinity for cynomolgus, pig and dog MCP-1; however, it did not bind to the rat, mouse or rabbit protein. Preclinical pharmacology studies were therefore conducted with a surrogate murine-specific spiegelmer (mNOX-E36). This molecule provided efficacy in seven different rodent inflammation models, including models of diabetic nephropathy (9) and lupus nephritis. In preclinical safety studies in mice and cynomolgus monkeys, NOX-E36 was well tolerated (dosing in cynomolgus monkeys up to 3 months), paving the way for clinical trials.

Since entering the clinic, NOX-E36 has been tested in three different phase I studies and appeared to be safe and well tolerated. The PK were dose–linear in healthy volunteers and patients with type 2 diabetes. Furthermore, a trial in patients with mild renal impairment did not show any issues with regard to the impact of renal function on PK. Pharmacodynamic (PD) data showed that compound levels were sufficient to affect the number of peripheral monocytes. Also, data from the phase Ib study suggested antiinflammatory and renoprotective effects in patients. A multicenter, double-blind, placebo-controlled phase II study in type 2 diabetic patients is ongoing and will report interim data in mid-2013.

SMR AWARD LECTURE: THE DISCOVERY AND DEVELOPMENT OF TELAPREVIR

The 2012 SMR Award for Drug Discovery was presented to Dr. Peter Mueller (Chief Scientific Officer and Executive Vice President, Vertex Pharmaceuticals, Inc.), as the representative of Vertex for the discovery of telaprevir (trade name Incivec® in the U.S., Incivo® in Europe). Telaprevir is an inhibitor of the hepatitis C virus (HCV) NS3/4A serine protease complex that is used in combination with pegylated interferon alfa (peginterferon alfa) and ribavirin (RBV) to treat chronic hepatitis C genotype 1 infection.

In his plenary lecture, Dr. Mueller initially outlined Vertex's approach to utilizing a global R&D network and focus on diseases with a high unmet need with the aim of bringing transformational medicine to patients. One of these diseases with a high unmet need is hepatitis C, a major medical problem with over 170 million people infected worldwide. Of these, patients infected with genotype 1 of the HCV virus are the hardest to treat. Until recently, the standard of care consisted of 48-week treatment with peginterferon alfa and RBV, a regimen that cured only approximately 40-50% of patients and caused substantial treatment-limiting side effects.

Dr. Mueller then described the various challenges faced in the HCV NS3/4A drug discovery program (10). The project was started with

the rationale that inhibitors of the viral NS3/4A protease should prevent viral replication and potentially restore innate immunity. The combination of these two mechanisms was thought to amplify the antiviral effect of HCV protease inhibitors and eliminate HCV from the body. However, an HTS campaign was unlikely to yield promising hits and biological assays useful for drug discovery were not available at the time. The team decided to follow a de novo design approach (the crystal structure was solved by Vertex in 1996) and initially optimize compounds using a biochemical enzyme assay, while seeking to build or acquire a means of assessing cellular and in vivo potency. Enzymology studies with peptide substrates and crystal structures of the NS3/4A active site showed that the design of potent small ligands would be challenging due to the low affinity of the protease to peptidic substrates and the shallow binding site of the enzyme. An approach was chosen that started from the natural substrate to a P1-P4 aldehyde inhibitor and included the exploitation of a pocket that formed upon inhibitor binding (11). These efforts resulted in the discovery of telaprevir, a slow, tight-binding inhibitor of NS3/4A with a K_i of 3 nM. In a newly developed genotype 1a infectious HCV virus assay in primary human hepatocytes, telaprevir inhibited viral replication with an IC_{50} of 290 nM.

The first phase I trial was conducted with telaprevir as a single agent to assess safety and investigate PK properties and the impact on viral kinetics. Multiple dosing of telaprevir for 14 days was well tolerated in HCV patients and the compound caused a rapid and dramatic antiviral response. However, breakthrough and emergence of resistant variants was observed, suggesting that the drug would need to be used in combination. In a second trial, telaprevir was therefore dosed with pegylated peginterferon alfa and RBV, leading to a sustained decrease in viral RNA in HCV patients over 28 days without severe adverse events. This trial also established the active dose of telaprevir, as well as dose frequency.

Subsequent trials aimed to examine the sustained virological response (SVR) rate. Eventually, telaprevir was registered on the basis of three large phase III studies. In summary, those trials showed that telaprevir therapy in combination with peginterferon alfa and RBV shortened treatment duration in the majority of treatment-naive patients by half while achieving high response rates. The compound also significantly increased cure rates in hard-to-treat patients. At the same time, adverse events were consistent, manageable and reversible.

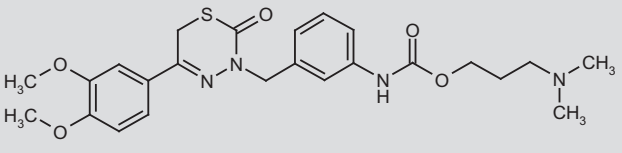
In the final part of his talk, Dr. Mueller covered the Chemistry, Manufacturing, and Controls (CMC) aspects of telaprevir and outlined how, despite the challenging properties of telaprevir, approaches like differential scanning calorimetry (DSC) and spray-drying enabled the development of a formulation that allowed the advancement of telaprevir through clinical trials to registration. For manufacturing, Vertex established a global supply chain that includes partners in the U.S., Europe and Asia. Telaprevir was fully approved for use in the U.S. in May 2011.

DISCOVERY AND EARLY CLINICAL DEVELOPMENT OF A HIGHLY SELECTIVE C-MET INHIBITOR, EMD-1214063

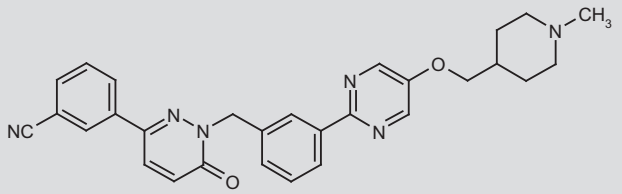
Dr. Friedhelm Bladt (Merck Serono) described the role of the tyrosine-protein kinase Met (c-Met), the receptor for hepatocyte growth factor (HGF), which is important for cell survival, proliferation, motility and migration. Constitutive activation of the HGF/c-Met pathway in animal models leads to tumor development and progression, while activating point mutations of c-Met have been identified in human malignancies, including renal carcinoma and lung cancer.

An HTS campaign using the recombinant kinase domain of c-Met led to the identification of **EMD-94283** as a novel inhibitor. This compound class was taken into an optimization campaign using enzymatic and cellular assays of the primary target, while improving selectivity, safety and PK parameters, leading to the identification of **EMD-1214063**. The optimized compound showed subnanomolar enzyme activity, with an IC_{50} of 6 nM in a cell-based assay, and was highly selective against a panel of kinases. The compound acted as a reversible competitor for adenosine triphosphate (ATP), with a well characterized mode of binding. EMD-1214063 showed a good safety and PK profile, with compound concentrations in tumor higher than those in plasma, leading to a prolonged PD profile in mice with c-Met inhibition to more than 4 days after a single dose. In vitro, EMD-1214063 interfered with survival, anchorage-independent growth and HGF-induced migration of tumor cells by blocking HGF-dependent and constitutive phosphorylation of c-Met. The compound also brought about tumor regression in HGF-dependent and -independent c-Met-addicted xenografts following oral administration in mouse models, comparing favorably with other c-Met inhibitors in these studies.

A first-in-man dose-escalation study is in progress, with the maximum tolerated dose (MTD) yet to be reached. To date, the compound has been well tolerated in patients with advanced solid tumors not amenable to standard therapy when dosed once a day. PK analysis revealed dose linearity and pharmacodynamic analysis of phospho-c-Met levels in tumor biopsies showed target inhibition in seven of nine patients. Initial indications of antitumor activity were also noted in the clinical studies to date; further development is ongoing.



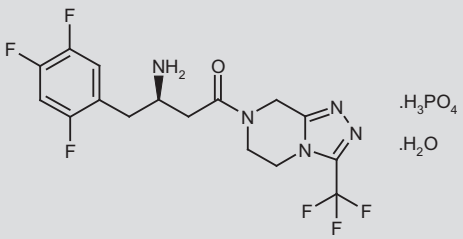
EMD-94283



EMD-1214063

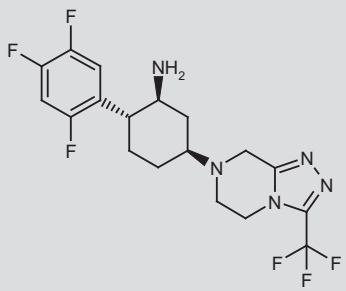
MK-3102: A NOVEL ONCE-WEEKLY DPP IV INHIBITOR FOR TYPE 2 DIABETES

Dr. Tesfaye Biftu (Merck) presented on the discovery and early clinical development of MK-3102, a dipeptidyl peptidase 4 (DPP IV) inhibitor which is currently in phase III clinical studies for the treatment of diabetes. The compound is the output of a second-generation program based around Januvia™ (**sitagliptin phosphate monohydrate**), which was the winner of the 2009 Society for Medicines Research Award for Drug Discovery. The objective of this program was to identify a long-acting DPP IV inhibitor suitable for once-weekly dosing, so as to improve convenience for patients.



Sitagliptin phosphate monohydrate

The starting point for the project was based on analysis of the X-ray crystal structure of sitagliptin bound to the DPP IV enzyme, which suggested that the central linker could be replaced with a more restrained cyclohexylamine moiety, leading to compound **10**. This prototype-restrained compound retained comparable potency (IC_{50} = 21 nM) to sitagliptin, with a good PK and in vivo efficacy profile. This lead was taken into an optimization program to further refine properties, leading to the identification of **omarigliptin** (IC_{50} = 1.6 nM). This compound showed excellent selectivity, in vivo efficacy comparable to sitagliptin, and importantly, had a PK profile that was predictive of a human half-life of 51 hours based on allometric scaling.



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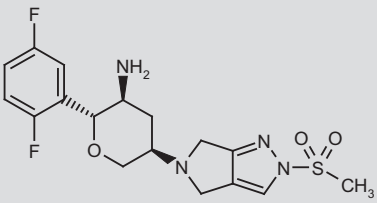
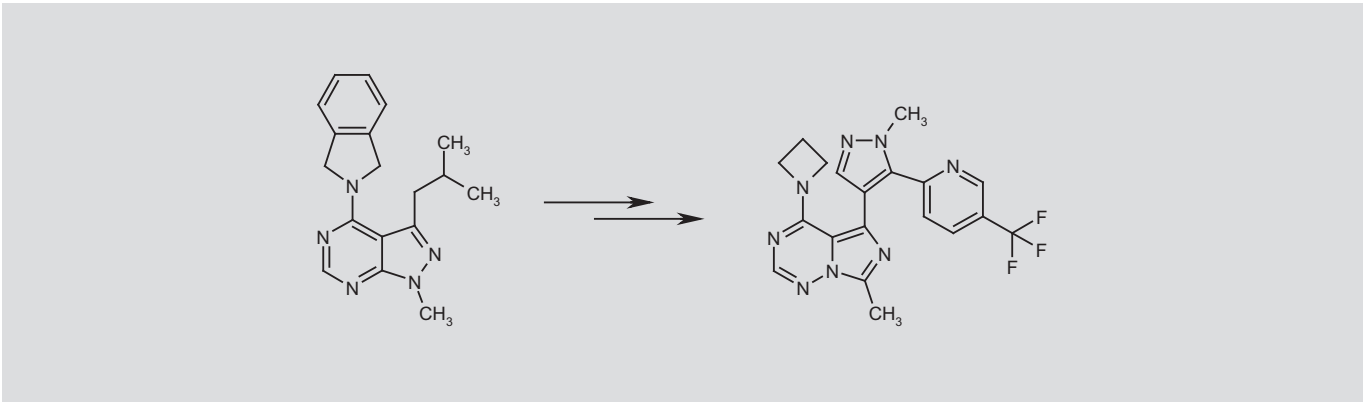


Omarigliptin

In clinical studies, omarigliptin dosed at between 10 and 100 mg once weekly showed sustained DPP IV inhibition comparable to sitagliptin dosed at 100 mg/day. In a phase IIb study, omarigliptin (25 mg once weekly for 12 weeks) showed a robust reduction in baseline HbA1c levels of 0.57% compared to a gain of 0.14% in the placebo group. The compound was taken into phase III development based on these data.

IDENTIFICATION OF A BRAIN-PENETRANT, HIGHLY SELECTIVE PHOSPHODIESTERASE PDE2A INHIBITOR CLINICAL CANDIDATE FOR TREATING COGNITIVE IMPAIRMENT: IN VIVO EFFICACY AND HUMAN PK DATA

Dr. Chris Helal (Pfizer) gave a presentation on the discovery project that ran at Pfizer to identify selective inhibitors of the phosphodiesterase PDE2A subtype. PDE2A is highly expressed in both limbic and basal ganglia brain regions (areas of neuronal circuitry which are defective in schizophrenia) and functions by hydrolyzing both cAMP and cGMP. At the point the project was initiated, all known inhibitors showed a low potential to be effective chronic drugs for CNS indications (supplemented by use of Pfizer's myeloperoxidase [MPO] analysis) (12, 13), so an HTS was run to identify improved chemical starting points. The output delivered a number of molecules, which were ranked according to MPO scores, ligand efficiency and synthetic tractability. Initial lead optimization led to molecules with good PK properties but insufficient selectivity across the PDE family, which was the presumed cause of cardiovascular effects seen at high concentrations. Subsequent optimization to enhance selectivity for PDE2 resulted in molecules, which when tested in functional and tissue cardiovascular safety models were well tolerated, giving confidence that despite the peripheral expression of PDE2, the target was of potential value for a CNS drug. Further development of the series relied on greater understanding of the strengths of H bonds from the various 5,6-heterocycles to PDE2, and using SAR from the original Bayer inhibitor BAY-60-7550, the series was developed into a set of precandidates. A set of molecules with acceptable drug-like properties were advanced into preclinical toxicology studies, with small structural differences resulting in wildly varying levels of tolerability. The result of this profiling was the identification of a clinical candidate which demonstrated activity in in vivo electrophysiology, attenuated glutamatergic-induced deficits in rats and amplified dopamine D_1 receptor



signaling in rodents (impaired dopamine prefrontal cortex signaling seen in schizophrenia). The molecule also demonstrated relevant activity in cognition models. Phase I assessment showed that the molecule was well tolerated, with a PK profile that was improved by a controlled-release formulation.

DISCLOSURES

S.E. Ward states no conflicts of interest. M. Brunavs is an employee of Lilly Research Centre, P. Cowley is an employee of TPP Global Development and P. Weber is an employee of Vertex Pharmaceuticals (Europe).

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