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IC-351 (GF-196960), an inhibitor of phosphodiesterase 5 (PDE5) from ICOS Corp, is in phase II trials for the treatment of mild to moderate erectile dysfunction (ED) [274568], [296831]. A randomized, placebo-controlled, crossover study assessed the safety and physiological effects of IC-351 in patients with ED [274568]. Enrollment was completed in April 1998 [284935]. Results from the trial showed that IC-351 demonstrated significant benefit over placebo [311566]. In October 1998, ICOS entered into a joint venture agreement with Eli Lilly for the development and commercialization of IC-351 for the treatment of sexual dysfunction [300118], [310951]. IC-351 is also in development for the treatment of female sexual dysfunction [321995].

In March 1998, the company announced that the compound was in preclinical evaluation for the treatment of hypertension [284638].

A collaboration with Glaxo Wellcome (GW) was terminated in March 1997 [240438] and intellectual property rights were assigned to ICOS. This left ICOS to develop the compounds with royalties payable to GW. Although GW reserved the right to pursue its own program, it does not appear to be doing so.

In February 1999 Deutsche Bank predicted sales of $200 million in 2002 rising to $400 million in 2003 for IC-351 [316821].

Licensees Eli Lilly & Co

Status Phase 2 clinical

Indication Sexual dysfunction, hypertension

Action PDE5 inhibitor

Synonyms GF-196960, GG-960

Introduction

The development of selective inhibitors of GMP specific phosphodiesterases has received a vast amount of attention following the recent launch of the selective PDE5 inhibitor sildenafil (Viagra) by Pfizer for the treatment of ED. Although this drug had originally been intended as an anti-anginal drug, the profile in early clinical trials indicated its ability to induce erections and resulted in a repositioning for ED and launch, with much hype, in 1998.

The rapid uptake of this drug in the US market led to forecasts of first year sales in excess of $1 billion. Although concerns about cardiovascular safety and reimbursement have blunted the growth, the first year sales, at $788 million, were close to projections. Certainly this is the most dramatic success for a newly launched pharmaceutical product, particularly considering it was not available in most international markets outside the US.

Although it represents a major breakthrough in ED management, as the first truly-effective oral treatment, it may not be ideal therapy, but is substantially more convenient for the patient than earlier treatments for this condition. Sildenafil has only modest selectivity for PDE5 over PDE6 and may inhibit other isozymes at the relatively high plasma levels achieved, particularly at the highest (100 mg) dose. The drug is also contraindicated in angina patients taking, or likely to take, nitrates. The onset of action (approx 1 h) is also considered by many to be less than optimal. Overall, it is theoretically possible to improve on the overall clinical profile of sildenafil by pharmacodynanic or pharmacodynamic manipulations. ICOS was one of the earliest companies to also seek to develop selective PDE5 inhibitors for this indication and IC-351 was a compound that resulted from its earlier collaboration with Glaxo Wellcome.

Synthesis and SAR

In the absence of information on the identity of IC-351 it is not possible to discuss the synthesis or SAR. However, all the available patents describe compounds with potencies of 2 to 10 nM as PDE5 inhibitors, comparable to sildenafil, which has a K_i value of 4 nM.

The collaboration had used the chemical expertise of Glaxo France with patents being filed describing pyrazino-(2',1':6,1)-pyrido-(3,4-b)indole-1,4-diones (WO-09519978) and claiming their use for the treatment of impotence (WO-09703675). ICOS now appears to be synthesizing a structurally-distinct class of PDE5 inhibitors (WO-09743287).

Pharmacology

ICOS has yet to publish any pharmacological data on IC-351. Glaxo France, its former collaborators, has described the activity of the novel selective PDE5 inhibitor 1,3-dimethyl-6-(2-propoxy-5-methanesulfonylamidophenyl)-pyrazolo(3,4d)-pyrimidin-4-(5H)-one (DMPPO) [210793], [225926], [295703]. The compound is a potent inhibitor of the enzyme with a K_i value of 3 nM [210793], and an effective vasodilator both *in vitro* [295703] and *in vivo* at 5 mg/kg po [225926].

Whilst it is unlikely that DMPPO is IC-351, it is reasonable to assume that IC-351 displays enhanced *in vivo* potency and possibly *in vitro* potency.

Clinical Development

Phase I

Phase I studies were initiated in 1995 [191529] and have been reported as free from adverse reactions to IC-351 [298769], [311566].

demonstrated significant efficacy in stimulating a sexual response. This confirmed the reported effects in an earlier 44 patient study [298769].

Current Opinion

The initial indication of PDE5 inhibitors was intended to be the treatment of cardiovascular disease and Pfizer initially developed sildenafil for that indication. The observation of pronounced penile vasodilation and consequent erections led to the development of sildenafil as the first orally-administered agent for the treatment of ED (impotence). Whether the overall clinical profile can be improved upon with the design of more selective PDE5 inhibitors remains to be determined, but the race is certainly on. Since gaining FDA approval in the US, sildenafil has displayed a dramatic sales growth and some analysts are predicting it has a global sales potential that could exceed $10 billion per annum.

IC-351 is the only other selective PDE5 inhibitor known to be in advanced clinical development and therefore has the activity). If the market for PDE5 inhibitors develops as analysts forecast, then IC-351 has the potential to make ICOS into a major pharmaceutical company. The only caveat would be if restrictions, on the use of such agents, were enforced due to their potential to induce heart failure, because of excessive vasodilation, as has currently been reported for a small number of patients with sildenafil.

The decision by Glaxo Wellcome to abandon its collaboration with ICOS now appears, in hindsight, injudicious given the rapid development of this market. There is no evidence that Glaxo Wellcome is currently developing an alternative molecule. However, it was no surprise that another major company, Eli Lilly, was prepared to step in and fund the development of IC-351 through the creation of a joint venture. Until more information is forthcoming on the biological effects of IC-351 it is not possible to decide whether it should prove therapeutically superior to sildenafil but IC-351 is believed to have an improved profile of activity.

Licensing

Eli Lilly & Co

ICOS and Lilly entered into an agreement in October 1998 for the joint development and commercialization of PDE5 inhibitors for the treatment of male and female sexual dysfunction. ICOS will receive an initial payment of $ 75 million, followed by milestone payments as IC-351 progresses through clinical development [300118].

Development History

DEVELOPER	COUNTRY	STATUS	INDICATION	DATE	REF
Glaxo Wellcome plc	UK	DX	Inflammation	01-APR-97	240438
Glaxo Wellcome plc	UK	DX	Asthma	01-APR-97	240438
Glaxo Wellcome plc	UK	DX	Impotence	01-APR-97	240438
Glaxo Wellcome plc	UK	DX	Angina	01-APR-97	240438
Glaxo Wellcome plc	UK	DX	Cardiac failure	01-APR-97	240438
ICOS Corp	UK	DR	Sexual dysfunction	02-OCT-98	300118
Eli Lilly & Co	US	DR	Sexual dysfunction	02-OCT-98	300118
ICOS Corp	US	DR	Hypertension	01-MAR-98	284638
ICOS Corp	Western Europe	C2	Impotence	13-JAN-98	274568
ICOS Corp	UK	C1	Impotence	13-NOV-95	191529
ICOS Corp	UK	C1	Angina	13-NOV-95	191529
ICOS Corp	UK	C1	Cardiac failure	13-NOV-95	191529

Biology: References which disclose aspects of the drug's pharmacology in animal models.
Metabolism: References that discuss metabolism, pharmacokinetics and toxicity.
Clinical: Reports of clinical phase studies in volunteers providing, where available, data on the following: whether the experiment is placebo-controlled or double- or single-blind; number of patients; dosage.

Clinical

EFFECT STUDIED	MODEL USED	RESULT	REF
Efficacy in ED.	Phase II, randomized placebo-controlled, crossover study to assess the safety and physiological effects of IC-351 in patients with mild to moderate ED.	Announcement of initiation of phase II trial.	274568
Efficacy in ED.	Phase II trial in 44 patients assessing the safety and efficacy of IC-351 for the treatment of ED.	IC-351-treated patients showed significant improvement relative to placebo-treated patients in the primary endpoint ($p < 0.001$) and all secondary endpoints.	298769
Safety and pharmacokinetics.	Phase I trials of IC-351 in healthy volunteers.	IC-351 was well-tolerated.	298769

Associated patent – WO-09519978

Title Tetracyclic derivatives, process of preparation and use.

Assignee Labs Glaxo SA

Publication WO-09519978 27-JUL-95

Priority GB-1090 21-JAN-94

Inventors Daugan AC

Abstract

Novel tetracyclic derivatives are claimed which have PDE inhibitory activity. The compounds are claimed for the treatment of cardiovascular disorders including angina, hypertension, pulmonary disease and congestive heart failure, and inflammatory diseases, stroke, bronchitis, asthma and rhinitis. Inhibition of cGMP-PDE activity was measured using a one-step assay adapted from Wells *et al* (*Biochem Biophys Acta* (1975) **384**:430). IC_{50} values were in the range 10 nM to 10 μM. An *in vivo* antihypertensive test in rats is also described. 119 Compounds are exemplified by syntheses. Seven formulatory examples are given. (6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-(3,4-methylenedioxy-phenyl)-pyrazino(2',1':6,1)pyrido (3,4-b)indole-1,4-dione is one of 11 compounds specifically claimed.

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