



Fact Sheet

Bayer Schering Pharma Development Projects

Business Unit: Hematology/Cardiology

Development candidate BAY 58-2667 – Potential for an effective treatment option in acute decompensated heart failure

- Activation of soluble guanylate cyclase as a novel principle of action
- No evidence of the development of tolerance

Status: June 2007

<p>Project description</p> <p>BAY 58-2667 is a novel substance that is undergoing clinical trials for the treatment of acute decompensated heart failure. BAY 58-2667 activates soluble guanylate cyclase (sGC), a key enzyme in a signal cascade with central significance in the regulation of the cardiovascular system. In preclinical and clinical studies to date, BAY 58-2667 showed efficacy and tolerability. There has been no evidence of developing tolerance to the substance.</p> <p>In June 2007, results of a Phase II study in patients with an acute decompensated heart failure were published. This study confirmed the therapeutic potential of BAY 58-2667 in this indication. The response rate to the drug ranged from 53% after two hours and 83% after four hours to 90% after six hours. The administration of BAY 58-2667 led to distinctive arterial and venous vasodilatation and resulted in a clear reduction of the burden on the heart.</p>	<p>At a glance</p>
	<p>Name of the active substance</p> <p>sGC activator (BAY 58-2667)</p>
	<p>Type of substance</p> <p>Low molecular weight substance (small molecule)</p>
	<p>Targeted Indication</p> <p>Acute decompensated heart failure</p>

<p>A Phase IIb study in this indication is planned to start this year.</p>	<p>Administration form Intravenous infusion</p>
<p>The medical and physiological background Soluble guanylate cyclase (sGC) is a key enzyme in a signal cascade that has central significance in the regulation of a large number of physiological processes. It is activated by the endogenously formed gas nitrogen monoxide (NO) and in its active form catalyzes the formation of cyclic guanosine monophosphate (cGMP). This neurotransmitter cGMP acts as a "second messenger" and leads, for example, to the dilatation of vessels, has a blood pressure-lowering effect and mediates tissue-protective effects. Limited bioavailability of NO or reduced sensitivity to endogenous NO play a role in various diseases, e.g. cardiovascular diseases and pulmonary hypertension.</p>	<p>Mode of action Activation of the enzyme soluble guanylate cyclase in a signal cascade that leads to vasodilatation</p>
<p>The therapy options for cardiovascular diseases, in which this signal path (NO → sGC → cGMP) is adversely affected or disturbed, are limited. They include the administration of NO donors, e.g. in the form of glyceryl trinitrate (nitroglycerin) or substances that prevent the breakdown of cGMP (inhibitors of the enzyme phosphodiesterase). The direct NO-independent activation of the enzyme soluble guanylate cyclase is a novel principle. To date, no drugs based on this principle are available.</p> <p>Acute heart failure Acute heart failure is the most common cause of hospital admissions in patients over 65 years of age. There is an urgent need for improved therapy options for patients with acute heart failure, as both morbidity and mortality in the disease are very high. After clinical treatment for the first time, 20% of patients are readmitted to hospital after one month, 60% after six to twelve months. 10% of the patients die within a month, 20-40% in a period between six and twelve months.</p>	<p>Status</p> <ul style="list-style-type: none">▪ Phase IIa study completed (Proof of Concept)▪ Start of a Phase IIb study planned for 2007

Active substance

The sGC activator BAY 58-2667 is a novel low molecular weight substance in clinical development that acts directly on the enzyme soluble guanylate cyclase in the signal pathway $\text{NO} \rightarrow \text{sGC} \rightarrow \text{cGMP}$ (see above). As a result of the binding of BAY 58-2667 to the enzyme sGC, this is activated and causes the formation of the second messenger cGMP, which can mediate the known vasodilator, blood pressure lowering and tissue-protective effects. BAY 58-2667 is able to bind to sGC when the enzyme is altered due to disease, i.e. when a certain component of the enzyme, the iron-containing haem group, is not present or is present only in oxidized form. This property is of central significance for the therapeutic potential of BAY 58-2667, as normally the endogenous or therapeutically administered signal molecule NO binds to the reduced haem group. Preclinical studies have shown that the activation of sGC takes place independently of the availability of NO.

sGC activators

sGC activators are substances that act directly on the enzyme soluble guanylate cyclase in the signal pathway $\text{NO} \rightarrow \text{sGC} \rightarrow \text{cGMP}$ (see above) and activate this. Whereas the sGC stimulants stimulate the normally functioning enzyme and increase the effect of NO on the enzyme, the sGC activators are able to activate the enzyme when it is altered due to disease and NO can no longer act on this enzyme.

Bayer HealthCare

Bayer HealthCare, a subsidiary of Bayer AG, is one of the world's leading, innovative companies in the healthcare and medical products industry and is based in Leverkusen, Germany. The company combines the global activities of the Animal Health, Consumer Care, Diabetes Care and Pharmaceuticals divisions. The pharmaceuticals business operates under the name Bayer Schering Pharma and as Bayer HealthCare

Pharmaceuticals in the US and Canada. Bayer HealthCare's aim is to discover and manufacture products that will improve human and animal health worldwide.

Bayer Schering Pharma

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Research and Development at Bayer Schering Pharma

Bayer Schering Pharma concentrates its R&D activities on innovative treatment approaches for diseases with a high unmet medical need to improve patients' quality of life and prolong lives. In this context, Bayer Schering Pharma focuses on its core competencies and its many years of experience. Thus, Bayer Schering Pharma holds a leading position in many therapeutic fields: for example, in the treatment of hemophilia and multiple sclerosis, in contrast media and oral contraception. We are also striving for a leading position in oncology. With new approaches in cancer therapy, for cardiovascular diseases, gynaecological therapies and in molecular imaging, Bayer Schering Pharma aims to become an innovation leader in these fields. In addition, Bayer Schering Pharma further develops products already on the market in order to improve their application and/or extend their range of indications.

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Forward-looking statements

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