Multi-center, randomized, double-blind, placebo-controlled phase 2 study to assess the safety, tolerability and early signs of efficacy of tid orally administered BAY63-2521 in adult deltaF508 homozygous Cystic Fibrosis patients

Published: 09-07-2015
Last updated: 19-04-2024

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Congenital and hereditary disorders NEC
Study type	Interventional

Summary

ID

NL-OMON42435

Source
ToetsingOnline

Brief title
Early signs of efficacy study with Riociguat in homozyg. deltaF508 CF pat.

Condition

- Congenital and hereditary disorders NEC
- Congenital respiratory tract disorders

Synonym

mucoviscidosis

Research involving
Human

Sponsors and support

Primary sponsor: Bayer HealthCare AG
Source(s) of monetary or material Support: Bayer HealthCare AG

Intervention

Keyword: cystic fibrosis, homozygous deltaF508

Outcome measures

Primary outcome

To assess the safety and tolerability of oral administration of

BAY63-2521versus placebo in homozygous deltaF508 Cystic Fibrosis patients

To assess early signs of efficacy of BAY63-2521 versus placebo in homozygous

deltaF508 Cystic Fibrosis patients as observed by change from baseline in sweat

chloride content

Secondary outcome

To assess early signs of efficacy of BAY63-2521 versus placebo in homozygous

deltaF508 Cystic Fibrosis patients as observed by change from baseline in nasal

potential difference (NPD), lung clearance index (LCI) and forced expiratory

volume in 1 second (FEV1)

To assess the pharmacokinetics (PK) of BAY63-2521 and its main metabolite M1

(BAY60 4552) in homozygous deltaF508 Cystic Fibrosis patients

Additional objective is to evaluate further biomarkers to investigate the drug

(i.e. mode-of-action-related effect and/or safety) and/or the pathomechanism of

the disease.

Study description

Background summary

Cystic Fibrosis, also termed as mucoviscidosis, is one of the most prevalent genetic disorders. Cystic Fibrosis is an autosomal recessive inherited disease and is affecting 1 out of 2,500 to 3,000 newborns with a prevalence of around 60,000 to 70,000 patients worldwide. Cystic Fibrosis patients have a substantially reduced quality of life, facing high morbidity and mortality with an overall survival age of only 40 years. Cystic
Fibrosis is caused by several mutations of a single gene, the Cystic Fibrosis transmembrane conductance regulator (CFTR) gene, which encodes for a chloride ion channel. There are different mutations of the CFTR gene characterized, however approximately 80-90% of Cystic Fibrosis patients are carrying the deltaF508- mutation, a deletion of phenylalanine (F) in position 508 of the CFTR channel. The deletion of residue 508 in deltaF508 CFTR prevents the mature protein from correct processing and folding. This misfolded CFTR is degraded and cannot, or cannot completely, exit the endoplasmatic reticulum and traffic to the plasma membrane. The reduced number of channels (and associated reduction in ion channel activity) finally leads to a substantial reduction of the airway surface liquid layer. Under these conditions the mucus becomes dehydrated, viscous and can no longer be cleared by cilia. Reduction of mucociliary clearance results in chronic inflammation and infection of the lungs and a progressive decline of lung function. Therefore, correction and potentiation of the CFTR channel
function, which is the basal defect, could become a disease modifying treatment option in Cystic Fibrosis with significant impact.
Currently, only two disease modifying therapies are available. Ivacaftor (VX-770, Kalydeco), a CFTR channel potentiator, is approved for patients with the G551D - mutation, which comprise about 4% of the total patient population, and for a few other rare (gating) mutations. In July 2015, Ivacaftor+Lumacaftor (Orkambi), a therapy combining a CFTR channel potentiator with a CFTR channel corrector (Lumacaftor) has been approved by US FDA for patients homozygous for the DF508 mutation.For the vast majority, no disease modifying therapy is available.

Riociguat is approved in the United States and Canada for chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension (PAH) under the trade name Adempas. Preclinical data indicate that BAY63-2521 (Riociguat) might be able to act as a disease modifier by correcting deltaF508-CFTR function. The magnitude of effects observed with sGC stimulators in preclinical models may translate in a significant clinical benefit in Cystic Fibrosis patients. BAY63-2521 (Riociguat) has already been tested in healthy volunteers and patients with
pulmonary arterial hypertension and chronic thromboembolic pulmonary

hypertension. Clinical results showed that Riociguat was e.g. able to improve the 6- minute walk distance and exercise capacity in patients with pulmonary arterial hypertension. A positive risk-benefit assessment has been established in these two indications.

Study objective

The aim of this trial is to test in a first clinical study the above mentioned hypothesis that BAY63-2521 can at least partially correct deltaF508-CFTR function. Therefore, we plan to include patients with Cystic Fibrosis, who are homozygous for the deltaF508-CFTR
mutation.
Parameters, which are considered to reflect CFTR function (sweat chloride test and NPD) and different aspects of lung function (lung clearance index [LCI] and FEV1), will be used as read outs for pharmacodynamics effects (signs of efficacy, surrogate efficacy marker). As this is a first *early signs of efficacy* study, the study has been powered for the primary endpoint *change in sweat chloride content compared to baseline* only.

An additional aim is to evaluate the pharmacokinetic (PK) properties of BAY63-2521 in these patients in order to allow for investigation of pharmacokinetic/ pharmacodynamics (PK/ PD)-relationship and appropriate dose finding studies in later stages of clinical development.

Treatment doses in this study have been selected based on the experience in earlier studies in the above mentioned indications PAH and CTEPH.

Study design

This study is a phase 2, randomized, double-blind, placebo-controlled, sequential group, multi-center, international study designed to investigate safety, tolerability, early signs of efficacy and PK of BAY63-2521 in adult Cystic Fibrosis patients.

Intervention

The study will consist of part 1 and 2.
In the first part patients will be randomized using a 1-to-2 randomization to either placebo or one treatment arm (= lower dose cohort). Within the placebo arm only placebo will be given. Within the active treatment arm, patients will start on 0.5 mg BAY63-2521 for 14 days. The dose will be increased to 1 mg BAY63 2521 for an additional 14 days, if this is considered safe and tolerable on the basis of the available data for a given patient.
After all patients of part 1 have finished the treatment period, an independent Data Safety Monitoring Board (DSMB) will decide * based on safety and tolerability data - whether the second part of the trial can be started.

In the second part a second cohort of patients will be randomized using a 1-to-2 randomization to either placebo or one treatment arm (= higher dose cohort). Within the placebo arm only placebo will be given. Within the active treatment arm patients will start on 1 mg BAY63-2521 for 14 days. The dose will be increased to 2 mg BAY63 2521 for an additional 14 days, if this is considered safe and tolerable on the basis of the available data for a given patient.
For all patients the first two intakes of study medication will take place at the study site for safety reasons. The patient will be discharged after a safety monitoring period of four hours after the second intake. The same precautions will apply at Visit 6 when the dose is planned to be increased.

Study burden and risks

The study involves 7 visits to the study center and two telephone calls and the patients will take part in the study for maximum 9 weeks. The two visits where the study medication is given for the first time (visit 3) or up-titrated (visit 6) will require a stay at the study center for at least 12,5 hours. For the other visits a duration of 3-4 hours is estimated. At the visits measurements of NPD (optional), LCI and FEV1 will be performed as well as blood pressure, heart rate be monitored, blood samples taken (not more than 300 mL, i.e. approx. 21 table spoons over the whole study), oxygen concentration measured and sweat tests performed. Additionally, patients will be asked to complete a Cystic Fibrosis Questionnaire about their quality of life and to document the intake of the study medication in a paper diary.

An overview of all study visits and all related study procedures can be found in the protocol in table 14-1, 14-2, 14-3 and 14-4. A description of all study procedures is written in section 7 of the protocol.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Signed informed consent available before any study specific tests or procedures are performed
2. Patients must be at least 18 years of age at time of inclusion (i.e. upon signature of informed consent)
3. Patient diagnosed with Cystic Fibrosis according to standard criteria (i.e. either elevated sweat chloride content above 60 mmol/ L and/ or genetic testing)
4. Patient is homozygous for the deltaF508 mutation
5. Patient has a mild-to-moderate stage of lung disease as determined by FEV1 (FEV1 between 40 and 100% predicted)
6. Patient has a stable condition of lung disease (no ongoing or recent pulmonary exacerbation and no change in current treatment) within the last 4 weeks prior to screening
7. Ability and willingness to understand and follow study procedures for the entire Study
8. Patients do not smoke. Patients with a history of smoking can be included, if they have refrained from smoking for the last 3 months. If a patients starts smoking during the study participation, he/ she needs to be excluded and considered to be a drop-out
9. Body mass index (BMI): * 16 and * 32 kg/ m² (calculated by dividing the patient*s weight by the square of his/ her height [kg/ m2])
10. Women of childbearing potential must agree to use adequate contraception when sexually active. *Adequate contraception* is defined as one highly effective form of contraception (intrauterine devices [IUD], contraceptive implants or tubal sterilization) or a combination of methods (hormone method with a barrier method). If a partner*s vasectomy is the chosen method of contraception or if a partner has documented azoospermia, a hormone or barrier method must be used in combination. Adequate contraception is required from the
signing of the informed consent form up until 4 weeks after the last study drug administration.

Exclusion criteria

1. Patients with Cystic Fibrosis with any background other than homozygous deltaF508 mutation
2. Patients receiving treatment with Ivacaftor
3. Active state of hemoptysis or pulmonary hemorrhage, including those events managed by bronchial artery embolization. Also any history of moderate hemoptysis within the 3 months prior to inclusion
4. Any history of pneumothorax, bronchial artery embolization or massive hemoptysis. Massive hemoptysis being defined as acute bleeding >240 mL in a 24-hour period or recurrent bleeding >100 mL/ d over several days
5. A positive sputum culture for Burkholderia cenocepacia, Burkholderia dolosa, and/ or Mycobacterium absessus either currently or within the previous year.
6. Active allergic broncho-pulmonary aspergillosis
7. Current pulmonary exacerbation
8. Known history of solid organ transplantation
9. Known history of any form of pulmonary arterial hypertension;11. Known or suspected malignant tumors or a history of malignant tumors
12. Unstable liver disease as indicated by
a. bilirubin >2 times upper limit normal (ULN) and/ or hepatic transaminases >5 times ULN
b. signs of severe hepatic insufficiency (e.g. impaired albumin synthesis with an albumin < 32g/ L, hepatic encephalopathy > Grade 1a)
13. Patients with severe hepatic impairment (Child Pugh C) should be excluded
14. Recent evidence (within 12 months prior to inclusion) of distal intestinal obstruction syndrome.
15. Patients with creatinine clearance <15 mL/ min or on dialysis need to be excluded.
16. Known history of cardiovascular disease unless stable and without therapy changes in the previous 3 months
17. Known history of clinically relevant arterial hypotension or clinically relevant orthostatic reactions (e.g. as indicated by syncopes, dizziness)
18. Venous/ arterial thromboembolic diseases (particularly deep vein thrombosis, pulmonary embolism, stroke, myocardial infarction)
19. Known current thyroid disorders which require treatment (patients with an euthyroid struma who do not need any treatment can participate)
20. Known hypersensitivity to the study medication (active substances or excipients of the preparations)
21. Documented severe or clinically significant allergic reactions including anaphylaxis or hives
22. Intolerance to lactose requiring strictly lactose-free diet and restriction to lactose-free oral medicines (hereditary galactose intolerance, galactose-glucose malabsorption, lactase deficiency)
23. Recent history (i.e. in the last 12 months prior to screening) of severe hypoglycemic events in patients with severe Cystic Fibrosis diabetes
24. Any medical disorder, condition, or history of such that would impair the patient's ability to participate or complete this study in the opinion of the investigator

25. Smoking (former smokers who have stopped smoking at least 3 months prior to the first screening visit may be included)
26. Suspicion of drug or alcohol abuse or recent (i.e. within 2 years) history of drug, medicine or alcohol abuse
27. Donation of blood or plasmapheresis after or within 4 weeks of signing the informed consent form
28. Concomitant use of the following medication: nitrates or nitric oxide donors (such as amyl nitrite) in any form, PDE 5 inhibitors (such as sildenafil, tadalafil, vardenafil), strong multi pathway CYP and p-gp/ BCRP inhibitors such as azole antimycotics (e.g. ketoconazole, itraconazole) or HIV protease inhibitors (e.g. ritonavir).
29. Clinically relevant ECG findings in screening ECG
30. Systolic blood pressure below 95 or above 160 mmHg (after at least 10 min in supine position) at screening
31. Diastolic blood pressure below 50 or above 100 mmHg (after at least 10 min in supine position) at screening
32. Heart rate below 45 or above 100 beats/ min (after at least 10 min in supine position) at screening
33. Clinically relevant findings in the physical examination, which in the opinion of the investigator prevents patients from safe participation in the study
34. Positive urine pregnancy test
35. Positive cotinine test in conjunction with current tobacco smoking. In case cotinine positivity refers to oral/nasal nicotine consumption only and current smoking is excluded, the patient may be enrolled.
36. Positive results for hepatitis B virus surface antigen (HBsAg), hepatitis C virus (HCV) antibodies, anti- or human immune deficiency virus (HIV 1+2) antibodies
37. Clinically relevant deviations of the screened laboratory parameters from reference ranges outside of expected changes for Cystic Fibrosis patients, especially a hemoglobin value below 110 g/L or a creatinine clearance based on the Cockcroft-Gault formula < 15 ml/ min
38. Pregnant women (i.e. positive pregnancy test or other signs of pregnancy), or breast feeding women
39. Patient is in custody by order of an authority or a court of law
40. Exclusion periods from other studies or simultaneous participation in other clinical studies/ participation in another clinical study during the preceding 6 weeks (i.e. last treatment from previous study to first treatment of new study)
41. Previous assignment to treatment (e.g. randomization) during this study (allowing previously randomized patients to be re-included into the study may lead to bias)
42. Close affiliation with the investigational site (e.g. a close relative) or persons working at the study site
43. Patient is an employee of Bayer HealthCare or Bayer Pharma AG or of Theorem CR (the acting contract research organization)
44. Criteria which in the opinion of the investigator preclude participation for scientific reasons, for reasons of compliance, or for reasons of the patient*s safety.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-03-2016
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Adempas
Generic name:	Riociguat
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	09-07-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-10-2015
Application type:	First submission

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-12-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-12-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-03-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-03-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2013-004595-35-NL
ClinicalTrials.gov	NCT02170025
CCMO	NL53573.078.15