

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/342475148>

press release : PNB-VESPER covid-19 clinical trial

Conference Paper · June 2020

CITATIONS

0

READS

257

1 author:



[Eric Lattmann](#)

PNB Vesper Life Science

88 PUBLICATIONS 1,025 CITATIONS

[SEE PROFILE](#)

Some of the authors of this publication are also working on these related projects:



Furanones -butenolides [View project](#)



CCK antagonists as CNS agents [View project](#)

A small step for PNB-Vesper and a big step for mankind:

PNB-001 is re-positioned from IBD (inflammatory bowel disease) to inflammation of the lung in the Covid-19 pandemic

Project Molecule

Background

The potential investee is a Kochi (India) based, techno-entrepreneur driven Company, formed in 2011. The Company's promoters have been contracting its preclinical research, drug development and clinical trials with various reputed academic and commercial organizations in UK, US, Thailand, and India.

Business

The Company currently has 6 molecules under development, 4 NCE in preclinical phases – 2 in clinical phase

- CCK-B antagonist, for the treatment of inflammatory pain and inflammatory bowel disease, IBD.
- a CCK-C isoform-selective antagonist is being developed for the treatment of colon and pancreatic cancer,
- A CCK-A antagonist for the treatment of pancreatitis and opiate management
- a pan CCK antagonist, is in late discovery stage for the treatment of CCK-gastrin cancers such as lung , liver and brain cancer

All the above molecules have been patented and the related Intellectual Property Rights (IPRs) have been secured by the Company in the US, Europe and Rest of World.

Stage of Business

The first two key molecules entered and continue clinical trials in due course. PNB-001 is in phase 2 clinical trials, phase 1, SAD and MAD were completed earlier this year. PNB-028 will enter Phase 1 clinical trial in patients later this year. The clinical protocols for the cancer molecule PNB-028 were approved by the Drug Controller General of India (DCGI) in January 2019.

PNB Vesper is a CLINICAL STAGE research based Biopharmaceutical Company with a vision to “***work towards a healthier World by developing novel, safe, and affordable medicines to prevent and treat unmet medical needs***”.

Vesper has 6 molecules in various development stages. PNB-001, a CCK₂ antagonist, is under development for the treatment of inflammatory pain and inflammatory bowel disease.

Now, a pilot trial is launched and PNB Vesper submitted the application for phase 2 this week and the trials will be completed within 60 days. PNB-028, a CCK isoform-selective antagonist is being developed for the treatment pancreatic and colon cancer, while a CCK₁ antagonist, PNB-081, is in late discovery stage for the treatment of pain in conjunction with opioids. PNB-291 is in the late discovery stage for neuroendocrine cancers.

PNB molecules pipeline overview

	Molecular target Most relevant	Therapeutic indication	Stage of development
PNB-001	CCK ₂ CCK-B Gastrin	Inflammatory pain IBD Dysmenorrhea	Clinical Phase 1 SAD completed MAD completed
PNB-028	CCK _C	Pancreatic cancer Colon cancer	Preclinical development completed Phase 1 / phase 2 trial approved for colon- and pancreatic cancer
PNB-081	CCK ₁ CCK-A	Opiate potentiation / Opiate tolerance Pancreatitis	PK completed, preclinical development Rat toxicology
PNB-101	CCK ₂ CCK-B	Gastric cancer Lung cancer , small cell lung cancer only	Preclinical development PK completed, proof of concept
PNB-291	Pan-CCK CCK ₁ , CCK ₂ CCK _C	Brain cancer Lung / liver cancer	Preclinical development Discovery

CORE MOLECULES IN PNB-VESPER'S PIPELINE

Baladol® (PNB-001) was found extremely safe in a PHASE 1 clinical trials with expected pharmacokinetics, leading to subsequent phase 2 trials in Covid-19 patients

Abstract

PNB-001, Baladol®, was tested now in 74 healthy subjects in clinical phase 1. Following a SAD study with 42 subjects Baladol® was tested in MAD, (multiple ascending doses) at low, medium and high doses over a period of 14 days in 32 healthy subjects. Overall, Baladol® was tested safe and with an efficient therapeutic window. From 32 subjects 30 completed the MAD trial and only 2 adverse reactions were observed. 1 AE was vomiting in a female subject and at a high dose a >2.5-fold increase of ALT was identified. In pre-clinical models PNB-001 is highly efficient in inflammation and the inflammation data were completed by results from Dengue fever studies, in which PNB-001 was tested highly efficient. A pilot trial is launched in Covid-19 patients and a clearly defined cohort will be enlarged until NDA (new drug application) is obtained within months.

COVID-19 Corona SARS-2 pandemic

According to The Journal of Clinical Investigation [130 (5), 2020] Covid-19 is the pandemic coronavirus infectious disease (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The new form of the current virus is rapidly spreading across the globe. Increased cytokine levels (IL-6, IL-10, and TNF- α), are associated with severe COVID-19. Overall, according to this study COVID 19 in its final form is characterized by a cytokine storm in severe COVID-19.

Various **treatment targets** are established for SARS CoV-2. In summary, viral attachment and entry are inhibited by e.g. chloroquine. Viral proteolysis is inhibited by e.g. Lopinavir and viral replication is affected by e.g. remdesivir. The host cytokine response is blocked by biological e.g. tocilizumab.

Viral attachment, viral proteolysis and viral replication are not targeted by PNB-001. The potent anti-inflammatory agent is acting on the inhibition of the host cytokine response, similar to the pathway blocked by biologicals (monoclonal antibodies). The foundation in form of clinical evidence was made public in the most recent [Dexamethasone Welcome Recovery Trial](#).

In this recent trial with >2100 Covid-19 patients on a low dose of dexamethasone, the death rate in ventilated patients was reduced by 1/3 and reduced by 1/5 in patients receiving oxygen only.

PNB-001 was better in preclinical studies testing inflammation better than the prednisolone steroid standard and it is anticipated that PNB-001 will be superior in phase 2 trials, too.

Mode of action of PNB-001, role of TLR-4

Studies in mice highlighted the important role and influence of PNB-001 on the immune system. Schwarzmenn et al gave support for this hypothesis with respect to the underlying mode of action and the unique role of the gastrin related peptide receptors, Downstream the toll-like receptor (TLR)-4 modulates the migration of neutrophils towards viral infections, as well as cancerous cells, thus, making PNB-001 the **first in class experimental agent** to act on pain & inflammation, pyrexia and the supporting role of the immune system.

Planned clinical trials to gain market authorisation in India & NDA application:

A randomised COVID trial is launched (phase 2a) using only one oral dose of 100 mg TD with initially 16 patients; followed by a phase 2b trial with a group size of 240 infected patients with moderate symptoms. For the recently launched **pilot trial**, 12 patients will be on active drug product and 4 patients on the best standard of care. The drug dose could be narrowed down to only one dose for the phase 2 trials (2a/2b) for patients with moderate symptoms. Sufficient data will be obtained to grant NDA approval in India and worldwide.

Based on the outcome of the phase 1 trial only 1 dose, 100 mg, TD is required for the duration of up to 10 days. Patients will be included on criteria with a body temperature $T > 38^{\circ}\text{C}$, lung inflammation visualised by x-ray, requiring oxygen, but no ventilator. Patients are able to administer the drug product orally, and they show elevated IL-6 inflammation marker. Clinical outcomes will be the reduction of lung inflammation monitored by x-ray, increase of oxygen level from 94% towards 100%, reduction of pyrexia, analgesia and the reduction of volume of oxygen gas in a hospital setting.

Vesper's clinical COVID-19 programme is reviewed by the US-FDA and the BARDA funding is currently at stage 2. In India the COVID-19 programme is supported at the accelerated stage with the highest priority in a combined BIRAC / DTB initiative.

For further information please contact:

Dr. Eric Lattmann, VP-Research
PNB-Vesper Life Science
Mobile: 07 456 650 332 UK
E-mail: lattmane.e@gmail .com
WWW.pnbvesper.com

PN Balaram
Managing Director
PNB-Vesper Life Science
E-mail: PNBalaram@cybelelife.com
WWW.pnbvesper.com

PNB-001 for the Treatment of Lung Inflammation & Pyrexia

Therapeutic target	Cholecystokinin/gastrin receptor, CCK-B, CCK ₂
Therapeutic indication	Lung Inflammation (pneumonia), COVID-19
Secondary indications	Pyrexia

Background about target The peptide cholecystokinin (CCK) was originally discovered in the gastrointestinal tract and has been shown to mediate pancreatic secretion and contraction of gallbladder. CCK was then described in the mammalian central nervous system (CNS) as a gastrin-like immune reactive material. Two types of CCK receptors (type A, “alimentary”, and type B, “brain”) have been distinguished. CCK-A and CCK-B receptor types have been shown to differ by their relative affinity for the natural ligands, their differential distribution, and their molecular structure. Gastrin, a peptide hormone secreted by the parietal cells of the stomach, binds to CCK-B receptor and elicits its function. Upon binding to CCK₂, it releases histamine, which in turn plays a role in releasing hydrochloric acid/gastric acid. In addition, gastrin also plays important roles in cell proliferation and has a role in the immune response via toll like receptors. Gastrin is also produced in excess in gastrinoma or gastric cancers. In Dengue fever death rate in man and in mice correlated with the degree of inflammation. Inflammation and death rate were reduced in the viremia mouse model by PO administration of 10 mg/kg PNB-001 up to 80%. Current corona SARS-2 pandemic is terminal as inflammatory disease and key to treatment is the reduction of the cytokine storm, monitored by biomarker IL-6.

Preclinical studies: PNB-001 is an isoform-selective antagonist that binds to CCK₂ at 20 nM. In an isolated tissue assay, using CCK-5 as agonist the antagonizing properties were confirmed. L-365,260 was used as best CCK₂ gastrin antagonist standard and PNB-001 was 10 times more potent and of much higher magnitude.

PNB-001 was tested in a rat model of indomethacin-induced IBD and was compared to positive control, prednisolone. PNB-001, at 5 mg/kg and 20 mg/kg p.o. was extremely effective in reducing the inflammation- and IBD-dependent damage to various gastrointestinal tissues and organs. Gross pathological changes and histopathological observations demonstrating IBD and Crohn’s disease in this animal model were completely reversed by PNB-001. The anti-inflammatory effect is general and in the rat paw oedema test PNB-001 is highly efficient at 10 mg/kg. In mice PNB-001 showed in the Baker’s yeast model at 10 mg/kg a potent antipyretic effect.

In the hotplate model and the tail flick assay 0.5 mg/kg PNB-001 is analogue to 40 mg/kg tramadol was administered to mice and the latency period in a tail flick assay was measured. The analgesic effect along with its anti-pyretic activity will position PNB-001 in the market as new treatment in viral infections, such as Covid-19. Subsequently, we then evaluated the efficacy of PNB-001 analog in a more complex model of pain. Rats were grouped and a dose response curve of PNB-001 analog (P.O. or i.p.) was performed and compared to morphine in a formalin induced neuropathic (phase I) and inflammation pain (phase II) models. PNB-001 was extremely effective in this model of pain. The formalin test and the carrageenan oedema are classical inflammatory assays and carrageenan induced swelling is mediated by cytokines. In a Dengue fever viremia model PNB-001 was tested for efficacy in Dengue fever using NMRI mice. At a dose of 10 mg /kg death rate is reduced by 70-80% and inflammation marker IL-6 is reduced accordingly. Mice were injected with unadapted Dengue virus, resulting in a dose-dependent transient viremia lasting several days. Increased levels of pro-inflammatory cytokine IL-6 was measured to provide experimental evidence of the key involvement of inflammation.

Oral administration of the gastrin antagonist PNB001, led to a reduction of splenomegaly and proinflammatory cytokine levels and most importantly death. The results validate the experimental agent to be studied clinically in viral diseases, in which death is triggered by inflammation, such as COVID-19.

Preclinical development studies: PNB-001 has a short half-life of 1.20 min in rat liver microsome and approximately 12 min in dogs and human liver microsome. Subsequent studies were performed to determine the pharmacokinetic (PK) properties of PNB-001. Rats were administered orally with 20 mg/kg PNB-001 to determine the circulating concentration. PNB-001 peak concentration was achieved at 40 min. PNB-001 had a half-life of 9 hrs and had a relatively low bioavailability. Considering the bioavailability in a species with rapid liver metabolism, we expect PNB-001 to have a manifold bioavailability in humans.

PNB-001 was evaluated in various ADME studies, including cytochrome P450 enzyme inhibition, plasma protein binding, and CaCo2 permeability. PNB-001 did not inhibit Cyp3A4, Cyp2C9, and Cyp1A2 up to 10 μ M and Cyp2C19 until 3 μ M. With 97% of PNB-001 bound to rat and human plasma, the amount of free unbound PNB-001 is comparable to some of the marketed drugs. CaCo2 permeability studies indicated that PNB-001 has high permeability and is not effluxed in the B>A direction.

Regulatory toxicology and safety pharmacology studies (acute toxicity studies in rats and mice, 7 day dose range finding studies in rats and dogs, 28 days toxicology studies in rats and dogs, PK studies in rats and dogs, safety pharmacology studies (cardiac, renal, respiratory, and neuro), chromosomal aberration and mutagenesis studies) conducted with PNB-001 under GLP environment and in accordance with ICH guidelines demonstrate extremely high levels of safety and tolerability. Doses selected were 50 to 100 fold above the efficacy dose.

Synthetic chemistry: PNB-001 synthetic schema has been established both in non-GMP and in GMP conditions. Moreover, synthetic chemistry efforts are optimized to synthesize PNB-001 one a multi kg scale.

Formulation studies: Formulation development, stability, and physicochemical characterization of PNB-001 were conducted. The studies demonstrated that PNB-001 was highly stable with ideal physicochemical properties.

Phase I clinical trials: Phase I SAD clinical trial protocols have been completed and PNB-001 was found extremely safe over the dose range from 25-1500 mg. PNB-001, Baladol®, was tested now in 74 healthy subjects in clinical phase 1. Following a SAD study with 42 subjects Baladol® was tested in MAD, (multiple ascending doses) at low, medium and high doses over a period of 14 days in 32 healthy subjects. Overall, Baladol® was tested safe and with an efficient therapeutic window. From 32 subjects 30 completed the MAD trial and only 2 adverse reactions were observed.

Ongoing studies: The indication inflammation with application in IDB is currently extended to cancer. The newly established mechanism will allow immediate clinical studies after completion of MAD studies in gastrin related cancers.

Current formulation studies are ongoing to develop a parenteral administration form, essential for the treatment of severe COVID-19 patients. These patients can only benefit from the injectable drug administration.

Intellectual property of PNB-001 and structurally related molecules are well protected with patents filed in the US, Europe, and rest of the World. Examination by the PTO office in Washington DC did not find any infringement issues with this series of molecules. USPTO has issued the patent on December 28, 2014. An Indian patent was filed in May 2020 and a full examination was requested.

For further information please contact:

Dr. Eric Lattmann
Vice-President Research
PNB-Vesper Life Science
E-mail: lattmane.e@gmail.com
WWW.pnbvesper.com

PN Balam
Managing Director
PNB-Vesper Life Science
E-mail: PNBalam@cybelelife.com
WWW.pnbvesper.com