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Clinical Trial Highlights – Kinase Inhibitors

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Introduction

Protein kinases are a group of molecules that play a crucial role in regulating several cellular functions by modulating various protein structures. Kinases mainly act by phosphorylating specific amino acids of the target protein utilizing adenosine triphosphate (ATP) as a phosphate source. This brings about a conformational change turning the target proteins from inactive to active [1]. Such changes alter the signaling cascades, thus bringing the desired effect. Abnormal kinase activation is associated with the pathogenesis of various diseases, with most of the work done in oncology [2]. Preclinical and human studies have demonstrated the abnormal activity of various kinase systems playing a role in Parkinson's disease (PD) pathogenesis [2]. There are many kinase proteins implicated in PD pathogenesis like c-Jun N-terminal kinases, glycogen synthase kinase 3β, colony-stimulating factor 1 receptor, Leucine-Rich Repeat Kinase 2 (LRRK2), and Abelson Murine Leukemia Viral Oncogene Homolog 1(c-Abl), to name a few [2]. Targeting kinase inhibition as disease modification in PD has garnered increasing interest in the scientific community. Appraising all kinase systems is beyond the scope of the current review, and as such, the focus will be on LRRK2 and c-Abl kinases based on the molecules currently in trial.

Mutations in the LRRK2 gene are linked to the most common autosomal dominant cause of familial PD. LRRK2 is a large multi-domain protein expressed heavily in the immune cells, lungs, and kidneys in addition to the brain. It has two main enzymatic domains, kinase and GTPase, along with other protein interaction domains. In addition to directly regulating proteins via phosphorylation, LRRK2 also modulates cellular processes like autophagy, vesicular trafficking, inflammation, and mitochondrial functions indirectly via a distal downstream effect [3]. While the exact pathogenic pathway is not well understood, increased LRRK2 kinase activity is central to the majority of disease-associated mutations and variants.

Additionally, increased LRRK2 activity is associated with sporadic PD as well [4]. As such, achieving LRRK2 inhibition may result in reduced neuronal degradation. However, developing direct inhibitors has been challenging as LRRK2 expression is not just limited to the brain. Safety concerns exist due to renal and lung histological changes reported in animal studies [5,6]. The molecules studied have been ATP-competing LRRK2 inhibitors, speculated to alter vesicular transportation negatively [7]. This has raised concerns regarding the long-term safety of such inhibition. A proposed solution includes targeting GTP-binding and potential allosteric inhibition of LRRK2 instead [7]. DNL201 and DNL151 are two small molecule LRRK2 inhibitors that have been moved into human trials. LRRK2 inhibition is also being targeted via the antisense oligonucleotide (ASO)

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against specific LRRK2 mutations to reduce the increased protein expression and the kinase activities. BIIB094 is one such ASO that has been moved into clinical trials.

c-Abl is another kinase system that plays an essential role in normal cellular functioning and maintains a minimally active state at baseline. Preclinical studies demonstrate increased alpha-synuclein aggregation and neuronal degradation in response to aberrant c-Abl activation. While c-Abl acts via multiple pathways, two main interactions are central to neurodegeneration related to increased alpha-synuclein aggregation and reduced clearance. The changes in response to c-Abl activation include increased phosphorylation of alpha-synuclein leading to increased alpha-synuclein aggregation, and phosphorylation of parkin leads to reduced synuclein clearance [3,4,8]. c-Abl molecules on the market were developed for oncology, not central nervous system (CNS) indications, so low blood-brain barrier (BBB) penetrance poses a challenge for PD therapeutics.

Nilotinib is currently approved to treat Philadelphia chromosome-positive chronic myeloid leukemia in the USA. Though not the most penetrant among other c-Abl inhibitors, Nilotinib has been shown to reduce synuclein pathology across different animal models and ostensibly also targets other kinases like discoidin domain receptors (DDR), which has also been linked to PD pathogenesis [9]. Two recently concluded Phase 2 studies of Nilotinib in PD have established a reasonably safe drug profile when tested in a carefully selected population [10,11]. Though both the studies had similar effects, the two have diverged paths in regard to decision for future trials due to target engagement evidence interpretation. Nilotinib studies have been published and, as such, will not be included in this review [10,11]. A few c-Abl inhibitors are currently being developed for neurodegenerative disorders with attention to CNS exposure, which will be discussed in this review.

Kinases play an intricate role in PD pathogenesis, and kinase inhibition presents as a promising target. Among other challenges to developing effective therapy, CNS penetration and selective or preferential kinase inhibition to avoid arresting multiple cellular functions are of prime concern.

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Overview of clinical trials for kinase inhibitors

ORGANISATION	DRUG	MECHANISM OF ACTION	PHASE	COMPLETION DATE
LRRK2 inhibitors				
Biogen	BIIB094	LRRK2 Antisense oligonucleotide	1	September 2023
Denali Therapeutics Inc.	DNL151	LRRK2 inhibitors	1	March 2021
c-Abl inhibitors				
II-Yang Pharm. Co. Ltd	Radotinib	Bcr-Abl kinase inhibitor	2	April 2022
Sun Pharma Advanced Research Company Ltd.	K0706 or SCC-138 or Vodobatinib	Bcr-Abl kinase inhibitor	2	March 2023
1st Biotherapeutics, Inc.	FB-101	c-Abl kinase inhibitor	1	June 2020
Inhibikase Therapeutics, Inc.	IkT-148009	c-Abl Kinase inhibitor	1	March 2021

LRRK2 inhibitors

Despite the relatively high profile of LRRK2 in the PD research field, there are only three programs at the clinical stage of development for LRRK2 inhibitors, one from Biogen (BIIB094) and two from Denali Therapeutics (DNL151 and DNL201). All three programs are in phase 1.

BIIB094 is an ASO to the mRNA of LRRK2, aimed at reducing the production of LRRK2. It is being developed by Biogen in collaboration with Ionis Pharmaceuticals. IONIS-HTTRx has demonstrated safety, tolerability, and target engagement of the ASO Ionis technology platform in Huntingdon's disease and is now in a phase 3 trial in collaboration with Roche [1].

DNL151 and DNL201 are orally-delivered selective brain penetrant small molecule inhibitors of LRRK2. Denali has conducted two phase 1 trials each for DNL151 and DNL201. The first set of studies evaluated safety, tolerability, and pharmacokinetics/pharmacodynamics in healthy volunteers. The DNL201 study (NCT04551534) completed in August 2018 and the DNL151 version (NCT04557800) is still in progress and recruiting. The second is a phase 1b design in people with Parkinson's (PwP) to evaluate the same parameters. The DNL201 study finished in December 2019 (NCT03710707) and that for DNL151 ended in December 2020 (NCT04056689). The number of dose levels in the Denali healthy volunteer studies is not specified; the phase 1b study of DNL151 in PwP evaluated three dose levels while the same trial design for DNL201 tested two levels.

Safety and tolerability data from phase 1 studies have shown that both molecules meet the criteria set for progression to the next stage. Denali released top line conclusions in August 2020 following an interim review of data from the first 162 volunteers in the DNL151 Phase 1 [3]. Based on these data, DNL151 appears to have an acceptable safety and tolerability profile, and has met the target engagement goals. DNL151 will be moved forward to two phase 2 trials in 2021, as it has pharmacokinetic properties that provide more flexible dosing compared to DNL201. One phase 2 study will recruit patients with LRRK2 mutations, and the other will recruit patients with idiopathic PD. Biogen and Denali are collaborating on the future development of DNL151 [2].

Biogen's ASO BIIB094 study is a combination of single ascending dose (SAD) and multiple ascending dose (MAD), evaluating six dose levels in the SAD stage and three in the MAD. The drug is administered by intrathecal injection.

The Biogen study is recruiting PwP of up to seven years' duration with a Hoehn & Yahr (H&Y) score ≤3. Both Denali phase 1b trials also required a H&Y score of up to three. The completed DNL201 phase 1b also required a sub-group of PwP with a LRRK2 mutation and one without, as does the Biogen BIIB094 phase 1.

Biogen's phase 1 study is assessing adverse events up to 253 days from baseline. The phase 1 study of DNL201 had a treatment duration of 10 days, extended to 42 days in the phase 1b. Both DNL151 studies extended treatment to 42 days, and both active molecules are being tested at two dose levels. Establishing safety of LRRK2 inhibitors is even more important than usual, given preclinical data in PD models raised toxicity issues [4].

The preclinical pipeline is more reflective of the research interest in the LRRK2 pathway. Arrien Pharma, E-Scape Bio, GSK, Merck, Neubase, and Neuron 23 all have LRRK2 inhibitor programs in the preclinical stage. In addition, Cerevel Therapeutics, Lead Discovery Center, and Servier (in partnership with OncoDesign) have discovery programs under way.

c-Abl tyrosine kinase inhibitors

Four companies have c-Abl inhibitor projects at the clinical stage. Sun Pharma Advanced Research Company Limited (SPARC)'s K0706 (vodobatinib/SCC-138) and Il Yang's radotinib are in phase 2, while 1st Biotherapeutics' 1st-101 (FB101) and Inhibikase's IkT-148009 are both in phase 1. All four experimental treatments are taken orally.

K0706 is a small molecule, brain penetrant, and orally available c-Abl inhibitor that has successfully completed phase 1 [5]. It is now being evaluated in the PROSEEK phase 2b study. Radotinib is already approved for use in Chronic Myeloid Leukaemia (CML), and K0706 is in phase 2 for CML.

K0706 has successfully completed two phase 1 studies with no significant adverse events in either (NCT02970019 and NCT03445338). Preliminary pharmacokinetic data indicate the presence of active drug in cerebrospinal fluid (CSF), suggesting BBB permeability, an important parameter for c-Abl inhibitors, given the issues in previous studies of Nilotinib [6]. Radotinib is also reported to be brain penetrant. A phase 2 study in Dementia with Lewy bodies (DLB) is under way for K0706 in collaboration with Georgetown University in the USA (NCT03996460).

The PROSEEK study is evaluating two dose levels of K0706 versus placebo in a large study of 504 PwP, with outcome measures focused on early efficacy defined as a change in MDS- UPDRS Part II+III over a 40-week intervention period. The trial is recruiting PwP yet to start dopaminergic treatment, and an H&Y score of ≤2. The treatment period is 40 weeks, a relatively short period for disease-modifying trials. The age criterion is for PwP over the age of 50.

The Radotinib phase 2a is a smaller study with 40 PwP, focusing on safety and pharmacokinetic parameters. There are secondary measures of efficacy at a six-month timepoint, again a relatively short duration, but complemented by a series of biomarker assessments. The age criteria for recruitment are broader at 40-80 years, with an H&Y score ≤2.5.

As would be expected in phase 1 studies, the outcome measures for FB-101 and IkT-148009 relate to safety, tolerability, and pharmacokinetics. IkT-148009 will also be evaluated for brain penetrance through CSF measurements. FB-101 will be tested in 48 healthy subjects between the ages of 18 and 55. IkT-148009 will be tested in 112 healthy volunteers between the ages of 55 and 70.

Treatment-emergent adverse events will be measured after seven days of treatment with FB-101 and after 14 days with IkT-148009. Both studies will measure similar pharmacokinetic parameters with measurements in single ascending dose (SAD) and multiple ascending dose (MAD) protocols.

We were not able to identify any other c-Abl inhibitors in the preclinical pipeline

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LRRK2 Inhibitors

Biogen BIIB094

Background: BIIB094 is an ASO to the mRNA of LRRK2, aimed at reducing the production of LRRK2. Similar to IONIS-HTTRx in Huntington's disease [1], the objective is to reduce the gain-of-function activity produced by variants of LRRK2, as well as targeting the primary pathology in patients with no mutations in the LRRK2 gene. It is being developed by Biogen in collaboration with Ionis Pharmaceuticals.

Title: A phase 1 single- and multiple-ascending dose study to assess the safety, tolerability, and pharmacokinetics of BIIB094 administered intrathecally to adults with Parkinson's disease (REASON).

Phase: 1

Objective: To evaluate the safety and tolerability of single and multiple doses of BIIB094 administered via intrathecal injection to participants with PD. The secondary objective of this study is to evaluate the pharmacokinetic (PK) profile of BIIB094.

Status: Recruiting.

Clinicaltrials.gov ID: NCT03976349

Sponsor: Biogen

Collaborators: Ionis Pharmaceuticals

Estimated Enrolment: 82 participants

Estimated Completion Date: September 2023

Study Design: The study is double-blind, randomized, placebo-controlled, sequential allocation, and multicenter at 16 sites in the USA, Canada, Israel, Norway, Spain, and the UK. The age range for recruitment is between 35 and 80. Patients must be less than seven years since diagnosis, have an H&Y score of ≤3, and be free of major motor fluctuations or dyskinesia. Standard exclusionary criteria apply.
The single ascending dose (SAD) is evaluating six dose levels of BIIB094, and the multiple ascending dose (MAD) will test three dose levels. The study is planned to complete in September 2023.

Outcome Measures: There are one primary and six secondary outcome measures. The primary one is the number of participants with adverse events (AEs) and serious adverse events (SAEs). The SAD will be conducted from screening (day -42) up to day 85. The MAD will run from screening (day -77) up to day 253.

Secondary outcomes are:

1. Serum concentrations of BIIB094.
2. Area under the concentration-time curve from time zero extrapolated to infinity (AUCinf).
3. Area under the concentration-time curve from time zero to last quantifiable concentration (AUClast).
4. Maximum concentration (Cmax).
5. Time to reach maximum concentration (Tmax).
6. Terminal elimination half-life (t1/2).

The timeframe for each of the secondary outcomes for the SAD is pre-dose through day 57; and for the MAD, pre-dose through day 169.

Comments:
BIIB094 is the first ASO drug to reach the clinical phase of development for PD. The ultimate goal is to attempt to modify the course of PD, slowing or even stopping the progression. Establishing safety and tolerability parameters with a relatively new technology are thus crucial.

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Denali DNL151

Background: Four phase 1 trials have been conducted on DNL151 and DNL201, summarized in the table below.

	DNL151		DNL201	
NCT number	NCT04557800	NCT04056689	NCT04551534	NCT03710707
Phase	1	1b	1	1b
Status	Recruiting	Complete	Complete	Complete
Recruitment	200 healthy volunteers	25 PwP	122 healthy volunteers	28 PwP
Objective	Safety, tolerability, PK/PD	Safety, tolerability, PK/PD	Safety, tolerability, PK/PD	Safety, tolerability, PK/PD

Denali reported that DNL151 has completed dosing of 162 healthy volunteers in an ongoing Phase 1 study, and completed a phase 1b in 25 PwP [1]. Denali is currently completing further dose escalation cohorts in an expanded Phase 1 and an additional cohort in the Phase 1b study to define the full therapeutic window. Based on the clinical data to date, DNL151 appears to have an acceptable safety and tolerability profile, and has met desired target engagement goals.

DNL201 successfully completed a Phase 1 study in 122 healthy volunteers (NCT04551534) in August 2018 and a Phase 1b study in 28 PwP (NCT03710707) December 2019. Results are yet to be published, but the company has stated that DNL201 has been generally safe and well tolerated in the doses tested and met target engagement and biomarker goals.

Denali has decided that, while DNL201 meets the criteria for progression into further clinical studies, the development will be put on hold in favor of moving DNL151 into two phase 2 studies based on pharmacokinetic properties that provide additional dosing flexibility. The phase 1 study of DNL151 in healthy volunteers is described in more detail below.

Title: A phase 1, randomized, placebo-controlled, double-blind study to determine the safety, tolerability, pharmacokinetics, and pharmacodynamics of DNL151 in healthy volunteers.

Phase: 1

Objective: The study focuses on establishing the drug's safety and tolerability profile along with PK and pharmacodynamics parameters.

Status: Recruiting.

Clinicaltrials.gov ID: NCT04557800

Sponsor: Denali Therapeutics Inc.

Estimated Enrolment: 200 participants

Estimated Completion Date: March 2021

Study Design: The study is a double-blind, randomized, placebo-controlled, single ascending dose (SAD), multiple ascending dose (MAD), and 28-day safety study in healthy volunteers.

Outcome Measures: There are seven primary and two secondary outcome measures. The primary ones are:

1. Incidence of treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs) and discontinuations due to TEAEs.
2. Maximum observed concentration (Cmax) in plasma.
3. Time to maximum observed concentration (Tmax) in plasma.
4. The area under the concentration-time curve from time zero extrapolated to infinity (AUC0-∞) in plasma (SAD only).
5. Area under the concentration-time curve from time zero to the time of last quantifiable concentration (AUC [0-last]) in plasma.
6. The area under the concentration-time curve over a dosing interval (AUC0-τ) in plasma (MAD only).
7. Apparent terminal elimination half-life (t1/2) in plasma.

The timeframe for the measures above is up to 42 days.

Secondary outcome measures are the concentration of DNL151 in CSF (following selected single and multiple doses) up to 13 days from initiation; and the pharmacodynamics of DNL151 in whole blood as measured by the percent change from baseline in pS935, up to 42 days.

Comments: This study is a large, classic design phase 1 safety study in healthy volunteers. Inclusion and exclusion criteria are straightforward. The trial has been conducted in parallel with a phase 1b in 25 PwP (NCT04056689), producing data to support progression into the next phase.

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c-Abl inhibitors

Radotinib

Background: Radotinib is an oral, second-generation, selective bcr-Abl tyrosine kinase inhibitor [1]. Though structurally similar to Nilotinib, Radotinib has superior brain penetrance [2,3]. In sporadic PD animal models using the alpha-synuclein preformed fibrils to induce neurodegeneration, Radotinib was noted to reduce c-Abl activation, neuroinflammation, lewy body aggregation, dopaminergic neuronal and striatal dopaminergic terminal loss [2]. Additionally, the degree of improvement in such a model was more significant than that observed for Nilotinib, possibly due to its difference in brain penetrance [2]. However, Radotinib did not reduce the alpha-synuclein level when used in transgenic mouse models [3]. While reasons like the choice of animal model, dose, and duration could account for the difference in the result, the preclinical data does lay the foundation to support human studies. Radotinib is an approved second-line treatment for CML in South Korea. The drug is well tolerated with a manageable safety profile, established from the CML clinical trials in Asian populations [4]. The ongoing first in human PD clinical trial is discussed here.

Title: A Randomized Double-blind Placebo-controlled Multicenter Study to Assess Safety, Tolerability, Pharmacokinetics and Efficacy of Radotinib in Parkinson's Disease

Phase: 2

Objective: This is a Phase 2, randomized and placebo-controlled study to assess the safety, tolerability, pharmacokinetics, and efficacy of Radotinib in individuals with PD.

Status: Not yet recruiting

Clinicaltrials.gov Identifier: NCT04691661

Sponsor: II-Yang Pharm. Co. Ltd

Estimated Enrolment: 40 participants

Estimated Primary Completion Date: April 13, 2022

Study Design: This is a Phase 2, randomized, parallel assigned, double-blind, placebo-controlled study. The outcome is focused on the safety, tolerability, pharmacokinetics, and efficacy of Radotinib in PwP. The 40 individuals will be randomized to 4 dosing groups. In each dosing group, eight individuals will receive Radotinib, and two will receive matching placebo. The dose will be administered once daily for six months at each escalating dose level. The Radotinib doses being studied include 50mg/day, 100mg/day, 150mg/day and 200mg/day. The data monitoring committee will decide if the individual can be escalated to the next dose level.

The study will include dopaminergic drug naïve PwP between 40-80 years of age with Hoehn and Yahr stage of ≤ 2.5. They will utilize the MDS clinical diagnostic criteria with a positive DAT scan for inclusion. In addition to standard exclusionary criteria, individuals on certain drugs will be excluded. The comprehensive list of exclusionary drugs includes strong CYP3A4 inhibitors and inducers, P-glycoprotein inducers, and medications that prolong QT interval.

The study is being conducted across seven centers in France.

Outcome: The primary outcome measure focuses on safety assessment by measuring the incidence and severity of adverse events 12 months after dose administration.

The secondary outcome measures assess the effect in two main domains, pharmacokinetic and clinical.

1. Pharmacokinetic assessments will be done at 14 days after dose administration, and measurements include peak observed drug concentration, time to reach peak drug concentration, trough plasma concentration, the area under plasma concentration-time curve, elimination half-life, apparent total drug clearance, and apparent volume distribution.
2. Clinical assessment will include
   a. Change in MDS-UPDRS parts I-III at 6 months.
   b. Time to initiation of dopamine replacement therapy assessed at 6 months
   c. Patient reported outcome will include a change in the quality of life via PDQ-39 and the subject's clinical global impression scale at 12 months.

Other outcome measures will include the following:

a. Change in Brain DaT SPECT scan
b. CSF concentration of the following at 6 months: alpha-synuclein, Tau, phospho-Tau (p-181), beta-amyloid peptide 1-42.
c. CSF and plasma concentration of Radotinib
d. Serum concentration of NF-L

Comments:
Radotinib is a potential c-Abl inhibitor alternative drug for PD owing to its superior brain penetration [2,3]. The current study is exploring doses lower than the approved dose for CML. Compared to other kinase inhibitors, Radotinib exerts its effect via c-Abl inhibition only [3]. It is undetermined whether the road to effective alpha-synuclein reduction is via multiple or selective kinase inhibition. While there is conflicting preclinical data regarding Radotinib efficacy, whether this translates to human efficacy is yet to be seen.

References:

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K0706 (Vodobatinib/SCC-138) - PROSEEK TRIAL

Background: Sun Pharma is developing K0706 or SCC-138 or Vodobatinib, a well-tolerated bcr-Abl inhibitor. In addition to PD, it is simultaneously being evaluated for CML and Dementia with Lewy Bodies [1,2]. Two Phase 1 studies, NCT03445338 and NCT02970019, in healthy volunteers and PwP have been completed. The

results have not been made available, but according to the company website, there were no significant adverse events. The preliminary data indicate the presence of the drug in CSF [2]. The drug has since been moved into the Phase 2 PROSEEK trial.

Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of K0706 in Subjects With Early Parkinson's Disease

Phase: 2

Objective: To evaluate the efficacy, safety, and tolerability of K0706 in individuals with early PD.

Status: Recruiting

Clinicaltrials.gov Identifier: NCT03655236

Sponsor: Sun Pharma Advanced Research Company Limited

Estimated Enrolment: 504 participants

Estimated Completion Date: March 2023

Study Design: This is a Phase 2 multicentre, randomized, double-blind, placebo-controlled study evaluating the efficacy, safety, and tolerability of K0706 among individuals with early PD. The study plans to include dopaminergic drug naïve individuals aged 50 years and above with a clinical diagnosis of probable PD using the MDS clinical diagnostic criteria. The PwP should be projected to not require dopaminergic medications for nine months. Only MAO-B inhibitor usage is allowed at the time of inclusion. Standard exclusionary criteria apply.

The drug is administered orally once-daily, and participants will be assigned to one of the three arms:
1. Low dose K0706
2. High dose K0706
3. Placebo

The study visits will include at least 1 screening visit, 10 study treatment visits, and 1 follow-up visit 4 weeks post final study visit. The study is being conducted across 79 centers in the USA and Europe

Outcome: The primary outcome measure is the change from baseline in the sum of MDS-UPDRS parts II and III at 40 weeks.

The secondary outcome measure will assess the change at 40 weeks from baseline in the following:
1. MDS-UPDRS
2. Time to initiation of symptomatic treatment
3. Health-related quality of life as measured by the European quality of life questionnaire 5 level version
4. Clinician global impression severity
5. Parkinson's disease- autonomic questionnaire
6. Level of K0706

The study will also include other exploratory measures, including effect of the drug on the DaT Scan, Skin biopsy, blood, and CSF levels of K0706. Following exploratory measures will be included:

1. Effect of the active drug on Dopamine Transporter Single Photon Emission Computed Tomography (DaT SPECT)
2. CSF K0706 levels of progression

Comments: No preclinical data specifically for K0706 or Vodobatinib were found in the literature. According to the company press release, phase 1 studies report a safe profile and CNS presence. We await the efficacy data from the ongoing trial.

References:

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[2] Sparc.life, Research Programs SCC-138 (n.d.). https://www.sparc.life/research-programs/scc-138. Accessed February 13, 2021.

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FB-101

Background: FB-101 is a c-Abl inhibitor being developed by 1st Biotherapeutics, Inc. According to the 1st Biotherapeutics press release from Oct 2017, the molecule will be co-developed with Neuraly Inc., a subsidiary of D&D Pharmatech company [1,2]. Neuraly Inc have listed NLY02 as a "proprietary BBB penetrating kinase inhibitor targeting glial activation" [2]. The 1st Biotherapeutics website suggests superior brain penetration and selective inhibition, although no preclinical data are available for this molecule [1]. The molecule is currently in Phase 1 clinical trial in healthy subjects.

Title: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single-Ascending Dose and Multiple-Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Oral FB-101 in Healthy Subjects

Phase: 1

Objective: To assess the safety, tolerability, and pharmacokinetics of single and multiple ascending doses in healthy individuals.

Status: Recruiting

Clinicaltrials.gov Identifier: NCT04165837

Sponsor: 1st Biotherapeutics, Inc.

Estimated Enrolment: 48 participants

Estimated Completion Date: June 2020

Study Design: This is a Phase 1, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and pharmacokinetics of the active drug, FB-101. The study has two parts where the drug will be administered in single and multiple ascending doses. 48 healthy adults aged between 19 to 55 years will be included. Standard inclusion and exclusionary criteria apply. The study is being conducted in Baltimore, USA.

Outcome: The primary outcome measures the number and severity of treatment-emergent adverse events seven days after the last dose. The secondary outcome will measure the peak plasma concentration and area under the curve of FB-101.

Comments: FB-101 is another c-Abl kinase inhibitor being introduced to the gamut of kinase inhibitors. There is a lack of available preclinical data at this time. The molecule is still in the early stages. The current study is a phase 1 trial in younger healthy volunteers with no assessment of BBB penetrance. Safety, tolerability, and efficacy in the PD population are yet to be explored. The study is listed to have been completed in June 2020, but no updates have been provided on clinicaltrials.gov or the company website. The delay could have been in the setting of the COVID-19 pandemic. Further news and data are awaited.

References:

[1] 1ST BIOTHERAPEUTICS, INC – 퍼스트바이오, 테라퓨틱스, 1stbio, (n.d.). Research and pipeline. http://www.1stbio.com/#press. Accessed February 28, 2021.
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[3] Safety, Tolerability, and Pharmacokinetics of Oral FB-101 in Healthy Subjects - Full Text View - ClinicalTrials.gov, (n.d.). https://clinicaltrials.gov/ct2/show/NCT04165837. Accessed February 28, 2021.

IkT-148009

Background: IkT-148009 is another c-Abl kinase inhibitor being developed by Inhibikase Therapeutics. No preclinical data for this molecule is available to review. According to the company website, in animal models, IkT-148009 was demonstrated to reduce PD pathology in the brain and GI tract [1]. As such, the molecule has been moved into human trials. The Phase 1 study in healthy subjects is discussed here.

Title: A Phase I, Randomized Single Ascending Dose (SAD) and Multiple Ascending Dose (MAD) Study to Determine the Safety, Tolerability, and Pharmacokinetics (PK) of IkT-148009 in Elderly Subjects

Phase: 1

Objective: To evaluate the safety, tolerability, and pharmacokinetics of IkT-148009 in elderly healthy participants.

Status: Not yet recruiting

Clinicaltrials.gov Identifier: NCT04350177

Sponsor: Inhibikase Therapeutics, Inc.

Estimated Enrolment: 112 participants

Estimated Completion Date: March 2021

Study Design: This is a phase 1, randomized, placebo-controlled study designed to evaluate the safety, tolerability, and pharmacokinetics of IkT-148009. The study will include elderly, otherwise healthy individuals between the age of 55 to 70 years. The study will have two parts. In part A, single ascending dose, there will be 8 participants in each cohort. Six will receive the investigational drug, and two will receive placebo. Participants will be observed for four days. In part B, cohorts will consist of 12 participants, of which nine will be assigned to the investigational drug. Sentinel dosing will be employed for each cohort, and dose escalation will be undertaken after reviewing the preceding dose's safety data.

Outcome: Primary outcome measures focus on safety and measure vital signs, clinical laboratory data, electrocardiogram, Columbia suicide severity rating scale, adverse events. Pharmacokinetic measurements will include maximum concentration, time to reach maximum concentration and half-life. An exploratory measure will look at the CSF drug concentration for multiple ascending doses.

Comments:
IkT-148009 is another c-Abl kinase inhibitor being developed as a potential disease-modifying agent for PD. The molecule is still in the early phase and is being evaluated for safety and tolerability at this time. Unlike FB-101, this molecule is being evaluated in elderly otherwise healthy individuals. The study will also assess brain penetrance of the drug by CSF measurement.

References:
[1] IkT-148009 for Parkinson's Disease and GI complications : Inhibikase Therapeutics, Inc. (IKT), (n.d.). https://www.inhibikase.com/pipeline/ikt-148009-for-parkinsons-disease-and-gi-complications. Accessed February 28, 2021
[2] A Study to Assess Single and Multiple Doses of IkT-148009 in Healthy Elderly Participants - Full Text View - ClinicalTrials.gov, (n.d.). https://clinicaltrials.gov/ct2/show/NCT04350177?term=ikt148009&draw=2&rank=1. Accessed February 28, 2021