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<tr>
<td><strong>SUBMITTER’S NAME</strong></td>
<td>Alexei Pushechnikov</td>
</tr>
<tr>
<td><strong>SUBMITTER’S EMAIL</strong></td>
<td><a href="mailto:apushechnikov@torreypinesinv.com">apushechnikov@torreypinesinv.com</a></td>
</tr>
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<td>Discovery of a highly selective, orally bioavailable, brain-penetrant LRRK2 Inhibitor</td>
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<td>Brenig Therapeutics</td>
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<p>| <strong>AUTHORS</strong>          |                                         |
| <strong>NAME</strong>             | Christian-Johannes Gloeckner            |
| <strong>EMAIL</strong>            | <a href="mailto:Johannes.Gloeckner@dzne.de">Johannes.Gloeckner@dzne.de</a>              |
| <strong>AFFILIATION INSTITUTION</strong> | German Center for Neurodegenerative Diseases (DZNE) |
| <strong>CITY</strong>             | Tübingen                                |
| <strong>COUNTRY</strong>          | Germany                                 |</p>
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<tr>
<td>G. Guaitoli</td>
<td>Giambattista Guaitoli</td>
<td><a href="mailto:Giambattista.Guaitoli@dzne.de">Giambattista.Guaitoli@dzne.de</a></td>
</tr>
<tr>
<td>G. Guaitoli</td>
<td>Guaitoli</td>
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<tr>
<td>R. Karapetian</td>
<td>Ruben Karapetian</td>
<td><a href="mailto:rk@chemdiv.com">rk@chemdiv.com</a></td>
</tr>
<tr>
<td>G. Guaitoli</td>
<td></td>
<td><a href="mailto:Giambattista.Guaitoli@dzne.de">Giambattista.Guaitoli@dzne.de</a></td>
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| CITY                             | San Diego           |
| STATE                            | California          |
| COUNTRY                          | USA                 |

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<tr>
<td>N. Savchuk</td>
<td>Nikolay Savchuk</td>
<td><a href="mailto:nsavchuk@torreypinesinv.com">nsavchuk@torreypinesinv.com</a></td>
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<tr>
<td>I. Dukes</td>
<td>Iain Dukes</td>
<td><a href="mailto:DukesI@OrbiMed.com">DukesI@OrbiMed.com</a></td>
</tr>
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<td>Stepan Mochalov</td>
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<tr>
<td>NAME</td>
<td>Benjamin Riebenbauer</td>
</tr>
<tr>
<td>EMAIL</td>
<td><a href="mailto:benjamin.riebenbauer@medizin.uni-tuebingen.de">benjamin.riebenbauer@medizin.uni-tuebingen.de</a></td>
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</tr>
<tr>
<td>EMAIL</td>
<td><a href="mailto:bernadette.dahl@medizin.uni-tuebingen.de">bernadette.dahl@medizin.uni-tuebingen.de</a></td>
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<td>EMAIL</td>
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OBJECTIVE

Development of a LRRK2 inhibitor drug candidate for both idiopathic and LRRK2[G2019S]-associated PD.

BACKGROUND

- Leucine-rich repeat kinase 2 (LRRK2) is a signaling protein that is a key therapeutic target in Parkinson's disease (PD).
- Gain-of-function mutations, e.g. LRRK2[G2019S], that increase LRRK2 kinase activity have been identified in a large number of PD patients
- Recently, an increased LRRK2 kinase activity was observed among a population of idiopathic PD patients
- Thus, combined genetic and biochemical evidence supports a hypothesis that the LRRK2 kinase function is causally involved in the pathogenesis of sporadic and familial forms of PD.
- Inhibition of the LRRK2 kinase activity is under clinical investigation and is demonstrating dose-dependent reduction of biomarkers of LRRK2 activity in CSF and urine while showing good tolerability and safety.
- Complete systemic inhibition of LRRK2 must be avoided. Total suppression of LRRK2 protein is associated with adverse effects in kidney and lung.
METHODS

Balanced PK approach focusing on less potent but more brain-penetrant molecules to have reduced tox effects in lungs/kidneys due to a different distribution.

RESULTS

- The lead molecules exhibit nanomolar potencies against LRRK2[WT] and the [G2019S] mutation.
- Achieved 1000x selectivity against other kinases and >500x selectivity against other targets from the safety panel.
- Demonstrated favorable pharmacokinetics, ADME, and safety profile for oral administration.
- Demonstrated a correlation between the in vivo unbound fraction exposure and the phospho-S935LRRK2/total LRRK2 ratio as a biomarker for activity.

CONCLUSION

We describe lead molecules with superior kinome selectivity compared to the publicly known best references. Our lead molecules demonstrate outstanding rodent in vivo PK and a high Brain(unbound)/Plasma(unbound) ratio.