CLX-104

CLX-104: A NOVEL MOLECULAR CONJUGATE OF ESLICARBAZEPINE AND EICOSAPENTAENOIC ACID FOR THE TREATMENT OF EPILEPSY

- A novel pro-drug conjugate of Eslicarbazepine and Eicosapentaenoic acid (EPA)
- Designed for slow sustained release of the actives
- Host enzyme mediated release of the actives
- Eslicarbazepine and EPA can have beneficial synergistic pharmacological effects in controlling seizures and neuronal stabilization
- Expected to be more efficacious than eslicarbazepine in the treatment of epilepsy
- Preclinical studies are ongoing.
- Robust patent estate

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1. Opportunity Overview

CLX-104 is a novel molecular conjugate of eslicarbazepine with Eicosapentaenoic acid (EPA). In this conjugate, eslicarbazepine is chemically linked with EPA utilizing CellixBio's proprietary patented Synergix platform technology. Eslicarbazepine is linked with EPA through simple ester linkage. The ester bond undergo hydrolytic cleavage by the host hydrolytic enzymes present in the intestine/plasma/liver microsomes. The hydrolytic cleavage of ester bond in the molecule is expected to control the release profile of eslicarbazepine and EPA to ensure a slow and sustained release of the active moieties.

CLX-104 is designed to provide superior pharmacokinetic, pharmacodynamic and safety advantages over the currently approved product of eslicarbazepine in the treatment of epilepsy. EPA is approved as a drug by US FDA. In addition to its effect in controlling TG levels, EPA is reported to have several beneficial effects in the nervous system that include anti-inflammatory, modulation of ion channels, growth and differentiation, controlling oxidative stress, stabilization of neuronal membranes, modulation of gene expression, neurotransmission and learning and memory (Taha A.Y. et al., 2010), which are expected to provide synergistic pharmacological effect with eslicarbazepine. EPA is also reported to be effective in various in-vitro models as well as in controlling seizures in patients with epilepsy (Taha A.Y. et al., 2010).

So far, we have completed biopharmaceutical assessment and a preliminary pharmacokinetic study in the rodents. Studies that are ongoing/planned include: clinical formulation development, safety and efficacy studies in animal models of disease such as drug resistant epilepsy. The expected target product profile/differentiation opportunities of CLX-104 include:

- ✓ Oral route of administration
- ✓ Slow sustained absorption of the actives, translating to improved safety
- ✓ Superior efficacy than eslicarbazepine in approved indications

- ✓ Potential for new indications such as drug resistant epilepsy.

2. Market Description

The global market for epilepsy yielded $4.2 billion in sales during 2012 and $4.5 billion in 2014. The introduction of novel antiepileptic drugs and increased access to therapies is expected to drive market growth. By 2022, global sales are expected to rise to $5.4 billion, with more than 50%, or $2.7 billion of those sales in the U.S. Although there are many generic drugs for the treatment of epilepsy, the current focus is to develop safe adjunctive therapies for refractory patients (Gohil K., *et al*., 2014).

3. Unmet Medical Need

Epilepsy:

Even though seizures are well-controlled with currently available anti-epileptic drugs (AEDs), seizures persist in a substantial proportion (approximately 30%) of epilepsy patients, who do not respond to any of two to three first line AEDs, despite administration in an optimally monitored regimen (Remy S and Beck H., 2006). It is apparent that there are more than 7.5 million people in the world are with refractory complex partial seizures (Treiman D.M., 2011). Overall, seizures in approximately, 30% to 40% of patients with epilepsy fail to respond to antiepileptic drugs or other treatments. While much has been made of the risks of new drug therapies, not enough attention has been given to the risks of uncontrolled and progressive epilepsy (Laxer *et al*., 2014).

Despite the advantage of simple dose titration schedule, once-daily dosing and good tolerability in the patients with refractory seizures, its efficacy data revealed the median relative reduction in seizure frequency was only 35% and 39% (placebo: 15%) at 800 and

1200 mg and the responder rate was 36% and 44% (placebo 22%) at 800 and 1200 mg respectively, and the seizure freedom at the 1200 mg was only 8%.

- Integrated analysis of pooled data from double-blind phase III clinical studies on the efficacy and safety of eslicarbazepine acetate (ESL) as add-on treatment in patients with focal-onset seizures revealed the median relative reduction in seizure frequency was respectively, 35% and 39% (placebo15%) at 800 and 1200 mg and the responder rate was 36% and 44% (placebo 22%) at 800 and 1200 mg (Gil-Nagel A., *et al., 2013).*

- During the 18-week double-blind treatment period, median reductions in standardized seizure frequency occurred with ESL 1200 mg (36.1%) and ESL 1600 mg (47.5%). The responder rates (a 50% or greater reduction in seizure frequency from baseline) during the 18-week double-blind period and the monotherapy period, respectively, were 35.2% and 38.9% for ESL 1200 mg, and 46.0% and 46.0% for ESL 1600 mg (Jacobson M.P *et al*., 2015).

Hence there is unmet need in the epilepsy treatment is to achieve improved efficacy in patients in terms of improved median relative reduction in seizure frequency, increase in the responder rate and seizure freedom in more number of patients.

CLX-104 could potentially offer to reduce the incidence of drug resistance in epilepsy due to its synergistic pharmacological effects with EPA for patients who are on treatment with various drugs.

4. Scientific Rationale

Eslicarbazepine acetate (ESL) is a novel voltage-gated sodium channel (VGSC) blocker that is chemically related to carbamazepine, but with differences in metabolism that may result in lower drug interaction potential and a favorable safety profile (Ben-Menacham et al., 2010). Eslicarbazepine binds and stabilizes the inactive form of sodium channels, preventing its reversion to the resting form and limiting sustained repetitive neuronal firing (Verrotti A., *et al.*, 2014). The half-life of eslicarbazepine in healthy subjects and epileptic adults is compatible with once-daily administration and consistent with an effective half-life of 20 to 24 h at steady-state plasma concentrations.

EPA is shown to modulate ion channels, inhibit chemical/electrical excitatory signals in rat hippocampal slices, inhibit CA3 evoked AP in brain slices, stabilize the neuronal membranes and suppress Na+ and Ca+ channels. Mixed results are reported in efficacy studies animal models of epilepsy (Taha A.Y. *et al.*, 2010; Voskuyl R.A. *et al.,* 1998). Recent clinical studies with omega-3 fatty acids show strong POC in drug resistant epilepsy (DeGiorgio CM *et al*, 2015).

The clinical studies suggested that n-3 PUFA may have potential therapeutic use in patients who suffer from epilepsy (DeGiorgio *et al.*, 2014, Schlanger S., *et al.* 2002; Yuen A.W. *et al.* 2005). A summary of clinical trials which utilized EPA in combination with DHA for the control of seizures is presented below.

Clinical trial	Duration in weeks	Nature of trial	EPA doses used	Findings
Schlanger S et al., 2002	24	Open-label	900 mg: EPA 2300 mg: DHA 50 mg: LA	Reduced seizure frequency by >50% in all patients (5/21) that completed the study

Yuen A.W et al., 2005	12	Double-blind, RCT	1000 mg/day of EPA 700 mg/day of DHA	Transiently reduced seizure frequency
DeGiorgio et al., 2014	42	Double-blind, 3 period crossover RCT	648 mg of EPA 432 mg DHA	Low dose fish oil showed reduction in seizure frequency

CLX-104 could potentially offer to reduce the incidence of drug resistance in epilepsy due to its synergistic pharmacological effects with EPA for patients who are on treatment with various drugs.

5. Preclinical Summary

Several preclinical investigations were carried out with CLX-104 in order to assess the biopharmaceutical and pharmacokinetic properties.

The biopharmaceutical properties of CLX-104 (solubility, physico-chemical properties and stability in simulated intestinal fluids) are suitable for developing a delayed and extended release oral dosage form for optimal delivery. Additionally, *in vitro* stability studies showed that eslicarbazepine-EPA conjugate was stable in simulated gastric fluid while undergoes enzymatic hydrolysis in the plasma or liver microsomes. This condition is ideal for developing an extended release formulation that could potentially improve the GI tolerability or adverse event profile. Additionally, CLX-104 undergoes rapid cleavage in plasma or liver microsomes of rat, dog and human, thereby minimizing the systemic exposure to the conjugate *per se*.

Oral (gavage) pharmacokinetics of eslicarbazepine-EPA conjugate was studied in rats (at equivalent dose of eslicarbazepine in 75 mg/kg eslicarbazepine acetate). The key results (analyte: Eslicarbazepine) are summarized below.

- A substantial reduction in C_{max} in comparison with the eslicarbazepine acetate
- Prolonged T_{max} in comparison with the eslicarbazepine acetate
- Relative bioavailability was approximately 100% in comparison with eslicarbazepine acetate administration.
- The systemic exposure to EPA was higher in the Eslicarbazepine-EPA conjugate dosed group (AUC_{0-t}: 9.6 µg.h/mL) as compared to the rats that received eslicarbazepine acetate (AUC_{0-t}: 5.26 µg.h/mL); back ground plasma level of EPA in rats.

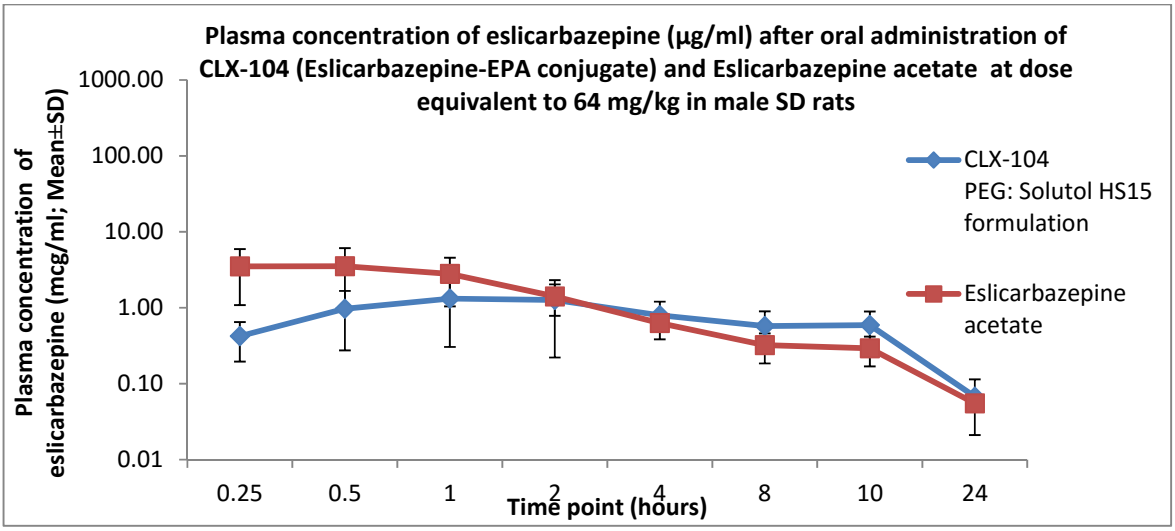

Figure-1: Plasma concentration of eslicarbazepine at various time-points following single dose oral administration of (S)-CLX-SYN-G4-C01a-EPA equivalent to eslicarbazepine acetate at 75 mg/kg (eslicarbazepine dose: approximately 64 mg/kg). CLX-104: Emulsion formulation of *(S)*-CLX-SYN-G4-C01a-EPA with Solutol HS and PEG-300 dispersed in Milli-Q water; Eslicarbazepine acetate in 0.5% HPMC.

Further studies that are being planned:

- *Comparative efficacy study in appropriate models of drug resistant epilepsy animal models*
- *Comparative safety study in animal models for motor in coordination*

8. References

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