CARNA BIOSCIENCES

News Release

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Carna Biosciences, Inc.

Carna Presented AS-1763 Posters at the 2022 American Association for Cancer Research (AACR) Annual Meeting

On April 11, 2022, Carna Biosciences, a clinical-stage biopharmaceutical company focusing on the discovery and development of innovative therapies to treat serious unmet medical needs, presented two posters highlighting the drug discovery and the result of the SAD part of Phase 1 study for AS-1763, an investigational small molecule drug designed to non-covalently inhibit Bruton's tyrosine kinase (BTK) in a highly selective manner, at the American Association for Cancer Research (AACR) 2022 Annual Meeting in New Orleans, Louisiana.

Details of the poster presentations are as follows:

Abstract Number:	1400
Poster Title:	AS-1763: a highly potent, noncovalent and next generation BTK inhibitor for the treatment of patients with B-cell malignancies having C481S mutation in BTK
Session:	High-throughput Screening, Drug Design, and Natural Products in Cancer
Presenter:	Wataru Kawahata, Tokiko Asami, Takao Kiyoi, Takayuki Irie, Shigeki Kashimoto, Hatsuo Furuichi, Kyoko Miyamoto, Akinori Arimura, Masaaki Sawa

Summary of the poster presentation:
BTK is a non-receptor tyrosine kinase known to have a crucial role in B cell antigen receptor (BCR) signaling during B cell development and activation and has been recognized as a validated therapeutic target for B-cell malignancies including chronic lymphocytic leukemia (CLL). First generation covalent BTK inhibitors including ibrutinib are key therapeutic options for patients with B-cell malignancies. However, patients are reported to develop resistance during the treatment due to substitution of cysteine residue at 481 position with serine (C481S mutation) in BTK, which prevents the covalent binding of the first generation irreversible BTK inhibitors. Therefore, there is a high unmet medical need for new therapeutic approaches to overcome the BTK C481S-mediated resistance.

In order to generate a novel BTK inhibitor targeting BTK C481S mutant with potent anti-proliferative efficacy in OCL-Ly10 cells, we implemented the structural optimization study of our lead compounds. After extensive lead optimization, AS-1763 was identified as a potent and highly selective inhibitor of both the wild type and C481S mutant BTK.

The poster detailed the following results:

- Structural optimization of a lead compound was performed to obtain AS-1763.

- AS-1763 strongly inhibited both the wild type and C481S mutant BTK in recombinant enzyme assay and cell-based assay.
- AS-1763 demonstrated an excellent kinase selectivity in a panel of 291 kinase assays.
- In phenotypic screening using human primary cell-based systems (BioMAP™ Diversity PLUS™) , treatment with AS-1763 only affected on B-cell related biomarker readouts, supporting its high selectivity in vivo.
- AS-1763 demonstrated significant antitumor efficacy in two xenograft mouse models bearing OCI-Ly10 and BTK[C481S] knock-in OCI-Ly10 cells.
- In IND-enabling safety studies, Ames test and an in vitro micronucleus test revealed no mutagenic nor clastogenic effects. No effects on the central nervous system, the respiratory function and the cardiovascular system were observed.
- In the 28-day repeat dose toxicity studies performed in mice (at dose levels up to 500 mg/kg/day) and in dogs (at dose levels up to 200 mg/kg/day), no AS-1763 treatment-related toxicologically were found. Therefore, the No Observed Adverse Effect Level (NOAEL) for the mouse study was set at 500 mg/kg/day, and the NOAEL for the dog study was set at 200 mg/kg/day.
- Based on its in vitro potencies, PK profiles, in vivo efficacies, and the safety profiles, AS-1763 was selected as drug candidate and currently under phase 1 clinical trials.

Abstract Number:	CT137
Poster Title:	Safety, pharmacokinetics, and pharmacodynamics of AS-1763, a highly selective, orally bioavailable, non-covalent BTK inhibitor, in healthy volunteers
Session:	Phase I Clinical Trials 1
Presenter:	Akinori Arimura, Kyoko Miyamoto, Maria Velinova, Marieke van den Dobbelsteen, Katsuhiro Mihara, Robert M. Miller, Masaaki Sawa

Summary of the poster presentation:

B-cell receptor (BCR)-BTK signaling plays a critical role in proliferation and survival of normal and malignant B cells. Covalent BTK inhibitors such as ibrutinib are approved for the treatment of patients with B-cell malignancies, but their long-term efficacy is limited due to their toxicity (i.e., on-target and off-target inhibition of kinases) and acquired resistance.

AS-1763 is a highly selective, orally bioavailable, non-covalent inhibitor of both wild-type and C481S-mutant BTK 2) that strongly inhibits the proliferation of B cell lymphoma cell line OCI-LY10 carrying wild-type and C481S-mutatant BTK in vitro and in vivo. AS-1763 is expected to be a promising treatment option for patients with chronic lymphocytic leukemia (CLL) and other B-cell malignancies who have failed or are intolerant to a covalent BTK inhibitor. Carna presented the result of the Phase 1 study in healthy volunteers (EudraCT number 2020-005599-37) at the poster presentation.

The poster detailed the following results:

<Study Design>

- FIH, double-blind, placebo-controlled, randomized, single-center, single-ascending dose Phase 1 study (SAD part) followed by open label relative bioavailability study comparing AS-1763 100-mg tablet and solution.
- In the SAD part, two cohorts of 8 subjects, males and females between 18 and 64 years of age, each were alternately dosed with single ascending doses of AS-1763 solution (5, 25, 100, 300, 500, 600 mg) or placebo to investigate safety and tolerability, pharmacokinetics (PK), and pharmacodynamics (PD; B cell CD69 upregulation) in blood.
- In the BA part, another cohorts of 8 subjects were dosed with a single dose of AS-1763 100 mg tablet to evaluate the PK and the relative bioavailability was compared with AS-1763 solution.

<Results>

- In the SAD part, AS-1763 was well-tolerated after single dose administration up to the maximum dose level (600 mg).
- No serious adverse events (AEs) were reported during the trial.
- Two Grade 2 AEs were reported in one subject, which were considered not related to trial medication.
- Other AEs reported were of mild intensity and showed no apparent dose-relationship in frequency.
- No clinically relevant changes from baseline were observed in all other safety parameters assessed (12-lead safety ECGs, vital signs, or physical examinations).
- After a single-dose oral administration, plasma concentration of AS-1763 rapidly reached the maximum and then declined in a biphasic manner across the dose range (median t_{max} between 0.5 and 1.5 hours; mean $t_{1/2}$ between 8.4 and 12.1 hours).
- Mean AS-1763 exposures generally increased with dose up to 500 mg.
- Inhibition of B cell CD69 upregulation was observed for 5 mg onwards.
- Maximum inhibition (arbitrarily defined as ≥80%) was observed at 1-2 hours post-dose from 100 mg to 600 mg, and the duration of inhibition was dose-dependent with values of 2, 6, 8 and 8 hours for 100, 300, 500, and 600 mg, respectively.
- Based on a PK/PD correlation analysis, the IC_{50} value of AS-1763 on CD69 upregulation was calculated to be 10.5 ng/mL.
- In the BA part, 100 mg tablet and the solution showed almost the similar PK profile while the exposure of 100 mg tablet was slightly lower than the that of the solution.
- The PK/PD data and favorable safety profile in healthy volunteers support a planned Phase 1b clinical study with AS-1763 tablet twice daily dosing in relapsed/refractory CLL and B-cell NHL.

About AS-1763

AS-1763 is a highly selective, orally bioavailable, non-covalent inhibitor of both the wild type and C481S mutant Bruton's tyrosine kinases (BTK) for the treatment of chronic lymphocytic leukemia (CLL) and other B cell malignancies. First generation covalent BTK inhibitors including ibrutinib are key therapeutic options for patients with B cell malignancies. However, patients are reported to develop resistance during the treatment due to substitution of cysteine residue at 481 position with serine (C481S mutation) in BTK, which prevents the covalent binding of the first generation irreversible BTK inhibitors. In in vitro experiments, AS-1763 significantly abrogates cell proliferation in both wild type and C481S mutant BTK lymphoma cells, strongly suggesting AS-1763 will be a new therapeutic option for treating patients with B cell malignancies both having wild type and C481S mutation in BTK.

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