Carna Biosciences, Inc.

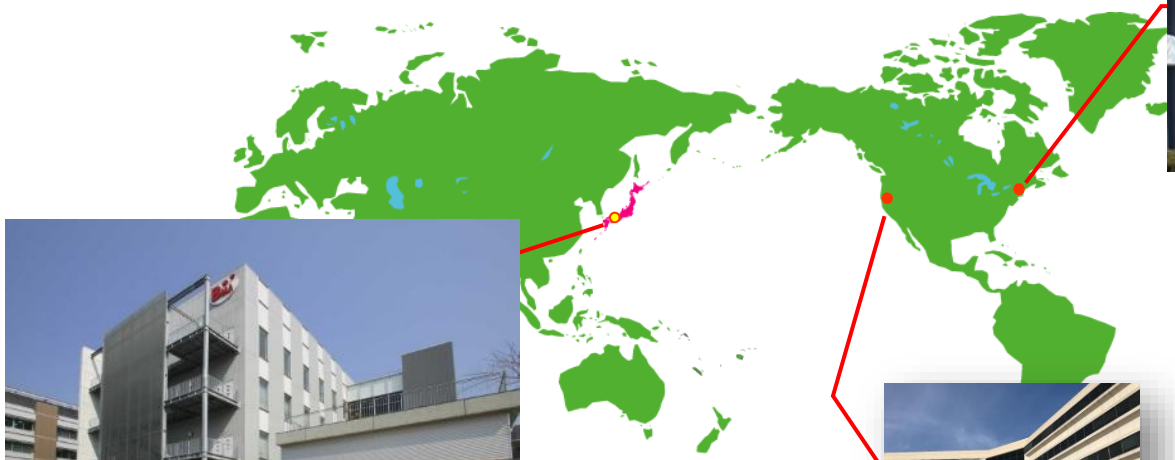
February 10, 2023

Stock Code: 4572

Company Overview

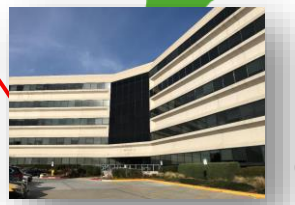
Company Overview

- Founded in April 2003 (spin-out company from N.V. Organon [MSD])
- Initial Public Offering (JASDAQ 4572) in March 2008
- 81 people
- Offices:
  - Carna Biosciences, Inc. - Kobe, Japan;
  - CarnaBio USA, Inc. - Natick, MA
  - Clinical Development Office – South San Francisco, CA



CarnaBio USA
(Natick, MA)

Carna Biosciences, Inc.
(Kobe, Japan)



Clinical Development Office
(SSF, CA)

(As of February 1, 2023)

Our Mission

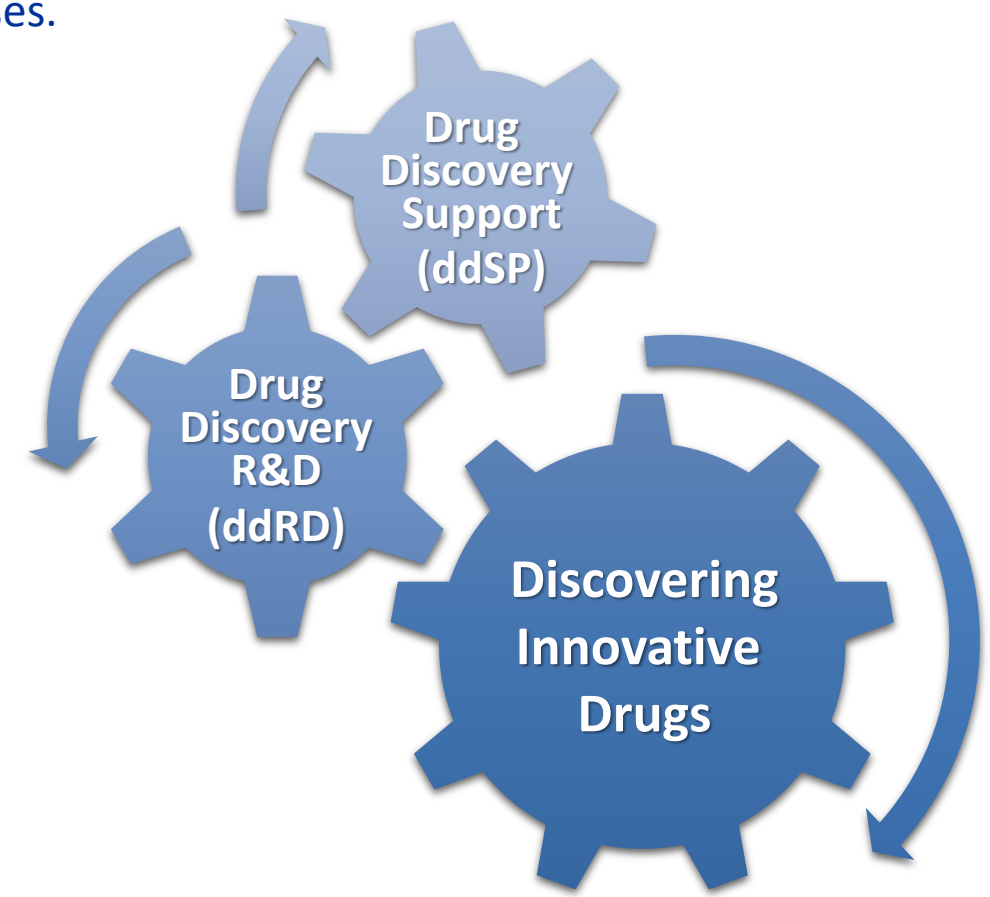
Discover and develop significant medical values that will provide therapeutic solutions for improving human health

Carna's powerful drug discovery engine invents a drug from scratch and drives our pipeline expansion

Continuously deliver innovative therapies for patients to treat serious unmet medical needs

Business Model to Drive Growth

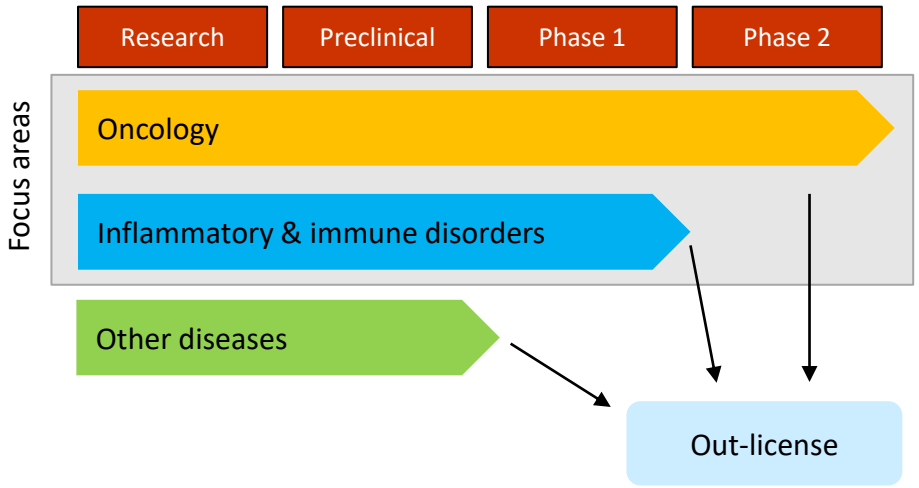
- Drug Discovery Support (ddSP) business provides pharmaceutical companies with the new tools to drive their kinase research. The stable income from the support business helps the drug discovery business to invest in R&D.
- Our small but powerful team with talented professionals at the Drug Discovery Research & Development (ddRD) business are focused on the research and development of innovative therapies targeting oncology and autoimmune diseases.



Business Model of Drug Discovery R&D (ddRD) Business

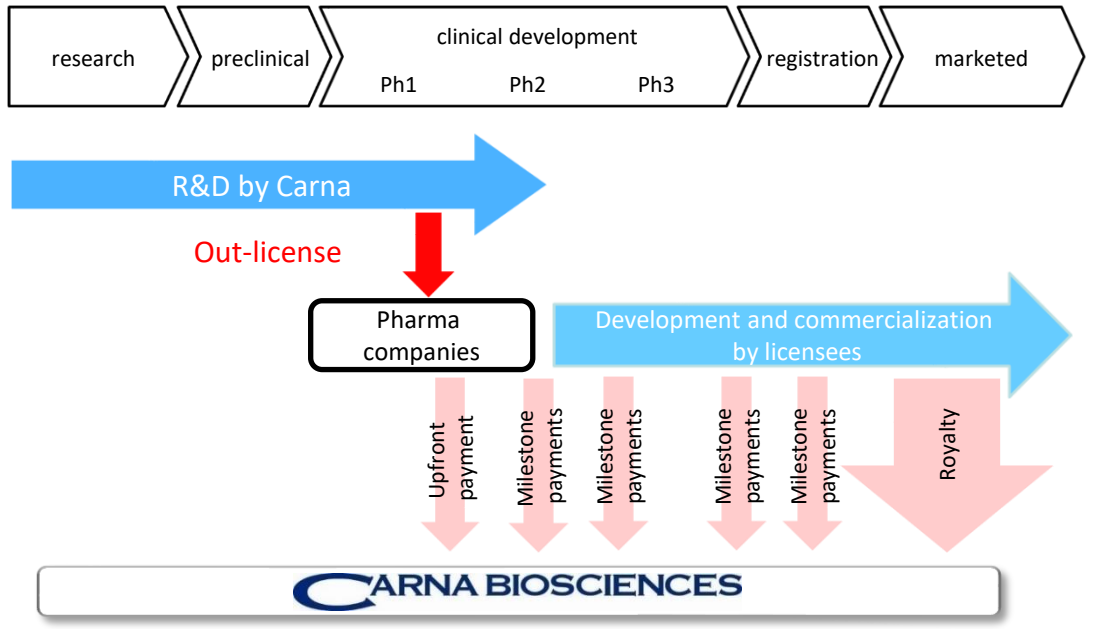
<R&D focus areas>

- ddRD business conducts research and development of innovative small molecule drugs including kinase inhibitors, focusing on oncology and inflammatory and immune disorders.
- We develop our oncology drug pipelines up to Phase 2 to maximize the potential values.
- For non-oncology pipelines, we basically license out at early stage before entering Phase 2 study to mitigate the development risk.



<Earnings model>

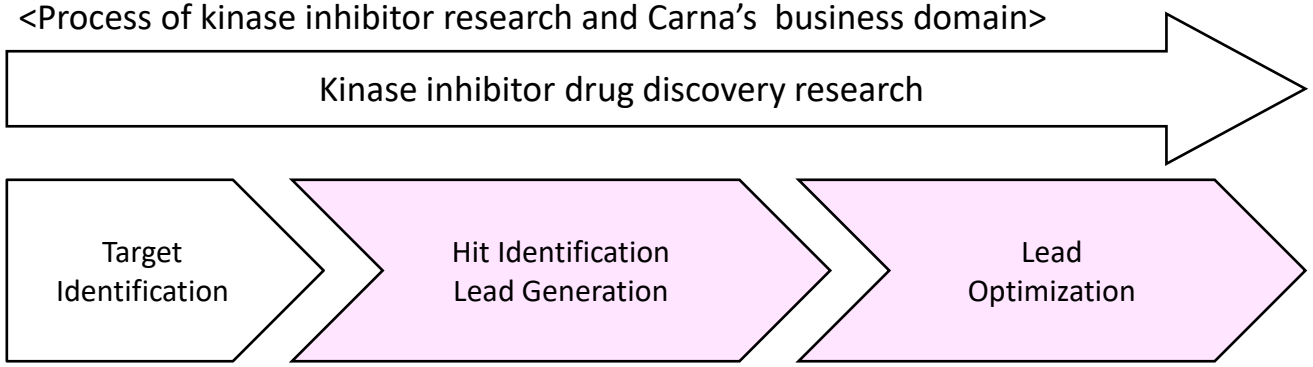
- We license our drug pipelines to pharma companies to generate revenue through upfront payments, milestone payments, and royalties on the resulting product sales.
- We intend to build long-term value by developing our own drug pipelines up to Phase 2 clinical trial on a fully burdened cost or in collaborations with development partners.



Business Model of Drug Discovery Support (ddSP) Business

- ddSP business develops and offers research tools for drug discovery, leveraging our proprietary kinase research technology, to generate stable cash flow. We apply the cash flows from ddSP business to ddRD business for the development of our own drug pipelines and the continued discovery of promising drug candidates in the future.

<Process of kinase inhibitor research and Carna's business domain>



Kinase proteins	Kinase proteins
Kinase Assay development Kinase Assay kits	Kinase Profiling service
Kinase Profiling service	Kinase Cell-based assay service
Kinase Screening service	X-Ray crystallography
Kinase Cell-based assay service	

Carna's products and services

Kinase proteins

Kinase Assay kits

Kinase Profiling and screening service

Drug Discovery R&D (ddRD) Business

Drug Discovery R&D: Pursuing Sustained Growth

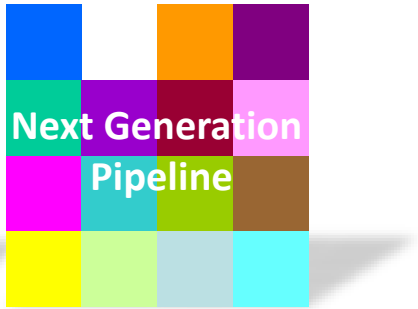
Robust Drug Pipeline

Cancer

- **AS-1763**
- **AS-0141**
- **GS-9911** — GILEAD
- **BN102** (AS-1763 Greater China) — BioNova Pharmaceuticals

Immune-inflammatory diseases

- **AS-0871**
- **FRTX-10** — fresh tracks THERAPEUTICS
- **Joint Research** — Sumitomo Pharma



Extensive Expertise in Drug Discovery

Selected Publications

nature COMMUNICATIONS

ARTICLE

Received 28 Jan 2016 | Accepted 14 Jul 2016 | Published 26 Aug 2016 DOI: 10.1038/ncomms12586 OPEN

TNIK inhibition abrogates colorectal cancer stemness

Mari Masuda[1], Yuko Uno[2], Naomi Ohbayashi[3,*], Hirokazu Ohata[4,*], Ayako Mimata[1,*], Mutsuko Kukimoto-Niino[3], Hideki Moriyama[2], Shigeki Kashimoto[2], Tomoko Inoue[2], Naoko Goto[1], Koji Okamoto[4], Mikako Shirouzu[3], Masaaki Sawa[2,*] & Tesshi Yamada[1,*]

SCIENTIFIC REPORTS

OPEN

Development of Highly Sensitive Biosensors of RAF Dimerization in Cells

Received: 27 July 2018
Accepted: 30 November 2018

Kyoko Miyamoto[1] & Masaaki Sawa[1,2]

Journal of Medicinal Chemistry

Article

Cite This: J. Med. Chem. 2018, 61, 8917−8933 pubs.acs.org/jmc

Design and Synthesis of Novel Amino-triazine Analogues as Selective Bruton's Tyrosine Kinase Inhibitors for Treatment of Rheumatoid Arthritis

Wataru Kawahata,* Tokiko Asami, Takao Kiyoi, Takayuki Irie, Haruka Taniguchi, Yuko Asamitsu, Tomoko Inoue, Takahiro Miyake, and Masaaki Sawa

scientific reports

OPEN

A cell-free assay implicates a role of sphingomyelin and cholesterol in STING phosphorylation

Kanoko Takahashi[1], Takahiro Niki[2,4], Emari Ogawa[2], Kiku Fumika[2], Yu Nishioka[3], Masaaki Sawa[3], Hiroyuki Arai[2], Kojiro Mukai[1,5] & Tomohiko Taguchi[1,5]

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

ELSEVIER

Research paper

Discovery of novel furanone derivatives as potent Cdc7 kinase inhibitors

Takayuki Irie [a,*], Tokiko Asami [a], Ayako Sawa [a], Yuko Uno [a], Mitsuharu Hanada [a], Chika Taniyama [b], Yoko Funakoshi [b], Hisao Masai [c], Masaaki Sawa [a]

Journal of Medicinal Chemistry

pubs.acs.org/jmc Drug Annotation

Discovery of AS-1763: A Potent, Selective, Noncovalent, and Orally Available Inhibitor of Bruton's Tyrosine Kinase

Wataru Kawahata,* Tokiko Asami, Takao Kiyoi, Takayuki Irie, Shigeki Kashimoto, Hatsuo Furuichi, and Masaaki Sawa

Journal of Medicinal Chemistry

pubs.acs.org/jmc Drug Annotation

Discovery of AS-0141, a Potent and Selective Inhibitor of CDC7 Kinase for the Treatment of Solid Cancers

Takayuki Irie,* Tokiko Asami, Ayako Sawa, Yuko Uno, Chika Taniyama, Yoko Funakoshi, Hisao Masai, and Masaaki Sawa

EXPERT OPINION

Review

Targeting the Wnt signaling pathway in colorectal cancer

Masaaki Sawa, Mari Masuda & Tesshi Yamada†

over 40 publications (papers, reviews and books)

Strong Science Background in both Biology and Medicinal Chemistry

Robust Drug Pipeline

<Oncology>

Compound	Target	Indication	Discovery/Preclinical	Clinical	Partner
AS-0141	CDC7/ASK	Cancer			
Small Molecule	DGKα	Immuno-Oncology	Licensed to Gilead		GILEAD
AS-1763	BTK	Blood Cancer			BioNova Pharmaceuticals *
Small Molecule	ALK5	Immuno-Oncology			
Small Molecule	CDK1	Cancer			

*Greater China only

<Other Therapeutic Areas>

Compound	Target	Indication	Discovery/Preclinical	Clinical	Partner
Small Molecule	Kinase	Psychiatry & neurology	Joint research with Sumitomo Pharma		Sumitomo Pharma
AS-0871	BTK	Immune-inflammatory diseases			
Small Molecule	N/A	Malaria			
Small Molecule	STING (antagonist)	Immune-inflammatory diseases	Licensed to Fresh Tracks Therapeutics (Rebranded from Brickell Biotech)		fresh tracks THERAPEUTICS

✓ As of February 2023

✓ We are actively pursuing early discovery programs to create next wave of pipeline.

Potential Revenue from Out-licensed Programs

- Carna is in license agreements with the pharmaceutical companies listed below and eligible to receive milestone payments upon achievement of certain development and commercial milestones. Carna will also receive royalties on future net sales.

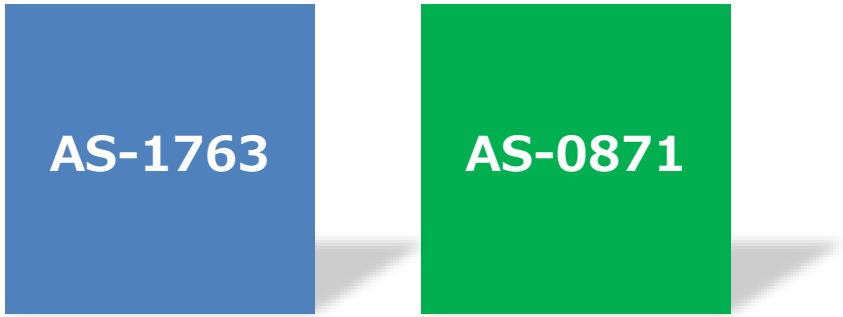
< License/joint research agreements with pharmaceutical companies >

Partner	Compound (Target)	Upfront payment	Total milestone payments expected	Royalty	Region	Contract date	Milestones received
Sumitomo Pharma (Joint research)	Kinase inhibitor (Psychiatric and neurological disorders)	JPY80M (including research milestone)	JPY10.6B	Undisclosed	Worldwide	Mar. 2018	
Gilead Sciences (Out-license)	GS-9911 (Immuno-oncology)	$20M	$450M	Undisclosed	Worldwide	Jun. 2019	$10M (Dec. 2021)
BioNova Pharmaceuticals (Out-license)	AS-1763(BN102) (Blood cancer)	Undisclosed	$205M	Up to two digits %	Greater China	Mar. 2020	$0.5M (Mar. 2022)
Fresh Tracks Therapeutics (Out-license)	FRTX-10 (Immune-inflammatory diseases)	$2M	$258M	Up to 10%	Worldwide	Feb. 2022	

* The amount and timing of milestone payments as well as royalty rates are not disclosed due to the agreements with the partners.

BTK Inhibitor

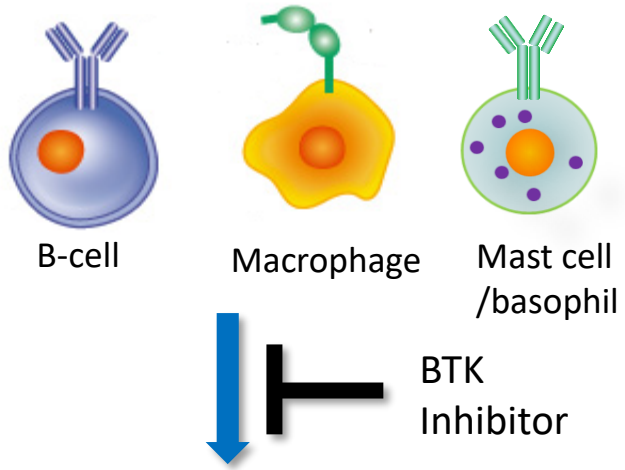
AS-1763 (Blood cancer)
AS-0871 (Immune-inflammatory diseases)



BTK Inhibitor Program

Bruton's Tyrosine Kinase (BTK)

- ✓ BTK is one of the crucial kinases for the B-cell maturation and macrophage activation
- ✓ BTK has been recognized as a validated therapeutic target since the success of Ibrutinib, the first FDA approved BTK inhibitor
- ✓ The expected peak sales of Ibrutinib is > $10 billion*



<Sales of BTK inhibitors in market>

Launch	Product	Company	Target	2021	2026 Est.
2013	Ibrutinib	AbbVie/J&J	Blood cancer	$8.2B*1	$10.8B*2
2017	Acalabrutinib	Astra Zeneca	Blood cancer	$1.2B*1	

- In January 2019, Loxo Oncology, developing kinase inhibitors including non-covalent BTK inhibitor LOXO-305, was acquired by Eli Lilly for $8.0 billion.
- In December 2019, ArQule, developing non-covalent BTK inhibitor ARQ 531, was acquired by Merck for $2.7 billion.

→ High potential of non-covalent BTK inhibitors for sizable license deals

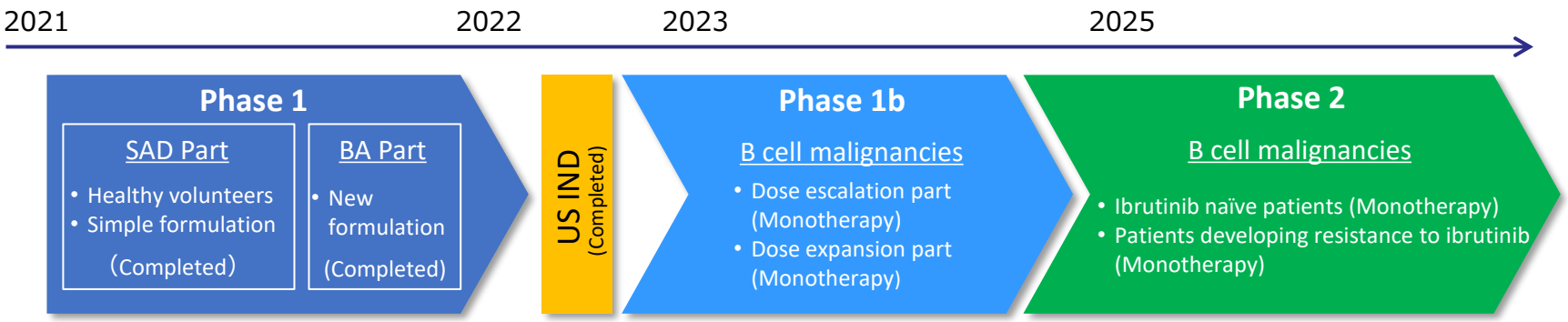
Source: 1. Company data
2. Evaluate Pharma

AS-1763: Next Generation BTK Inhibitor Targeting Blood Cancer

AS-1763：Targeting Blood Cancer

- Small molecule BTK inhibitor
- Non-covalent/reversible
- High kinase selectivity
- Inhibits both BTK wild type and ibrutinib resistant BTK C481S mutants
- Orally available

- Displayed strong anti-tumor effects in lymphoma model with both wild type and C481S mutant BTK
- Displayed efficacy in immuno-oncology model
- Completed an IND application process in the U.S.
- FPI in the U.S. is expected in Q1 2023.
- Plan to accelerate the clinical studies utilizing the clinical data of BioNova, the licensee in Greater China



IND application: Investigational New Drug application
FPI: First Patient In
BA: Bioavailability
B-cell malignancies: Chronic Lymphocytic Leukemia (CLL), Small Lymphocytic Lymphoma (SLL), and B-cell non-Hodgkin Lymphoma (B-cell NHL), etc.

AS-1763: Phase 1 Clinical Trial in Progress

Phase 1 in the Netherlands (Healthy volunteers)

Completed

SAD part Evaluate the safety, tolerability and PK using simple formulation

- ✓ Completed dosing in SAD part
- ✓ Safe and well-tolerated
- ✓ Favorable Pharmacokinetic Profile
- ✓ Promising Pharmacodynamic effects

BA part Evaluated comparative bioavailability using new formulation

- ✓ Pre-IND meeting
- ✓ IND submission

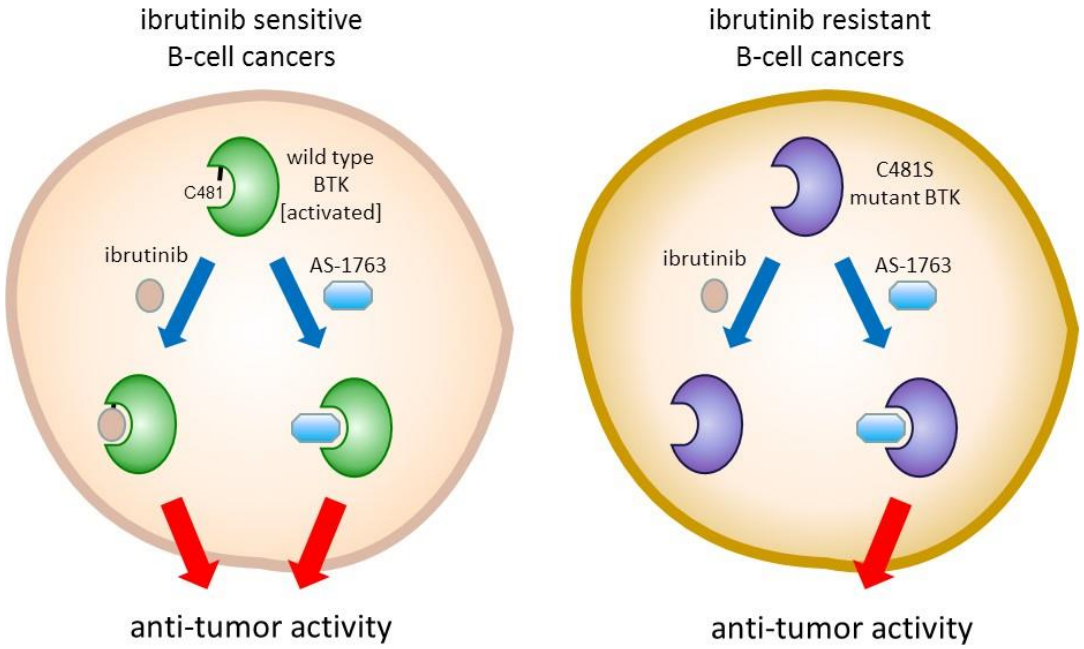
Completed

Phase 1b in the U.S. (Patients with CLL/SLL/B-cell NHL)

In preparation

- In May, Carna received an approval for an IND to initiate Phase 1 study in the U.S.
- FPI in the U.S. is expected in Q1 2023.

AS-1763: Potent Inhibitor of C481S mutant BTK



Journal of Medicinal Chemistry
pubs.acs.org/jmc
Drug Annotation

Discovery of AS-1763: A Potent, Selective, Noncovalent, and Orally Available Inhibitor of Bruton's Tyrosine Kinase

Wataru Kawahata,* Tokiko Asami, Takao Kiyoi, Takayuki Irie, Shigeki Kashimoto, Hatsuo Furuichi, and Masaaki Sawa

Cite This: *J. Med. Chem.* 2021, 64, 14129–14141 Read Online

- IC_{50} values of AS-1763 against wild-type and C481S-mutant BTK

	IC_{50} (nM)	
	BTK[A]	BTK^{C481S}
AS-1763	0.85	0.99

J Med Chem. 2021 Oct 14;64(19):14129-14141.

AS-1763: Strong Cellular Activity and High Kinase Selectivity

CARNA BIOSCIENCES

◆ In vitro pharmacological activities of AS-1763

	IC_{50} (nM)	
	AS-1763	ibrutinib
Autophosphorylation BTK (Ramos)	1.4	1.1
CD69 activation (Human whole blood)	11	8.1
Cancer cell growth OCI-Ly10 cells	1.8	0.75
Cancer cell growth OCI-Ly10 [BTK C481S] cells	20	1030
Normal cell growth HEL299 cells	6370	6870

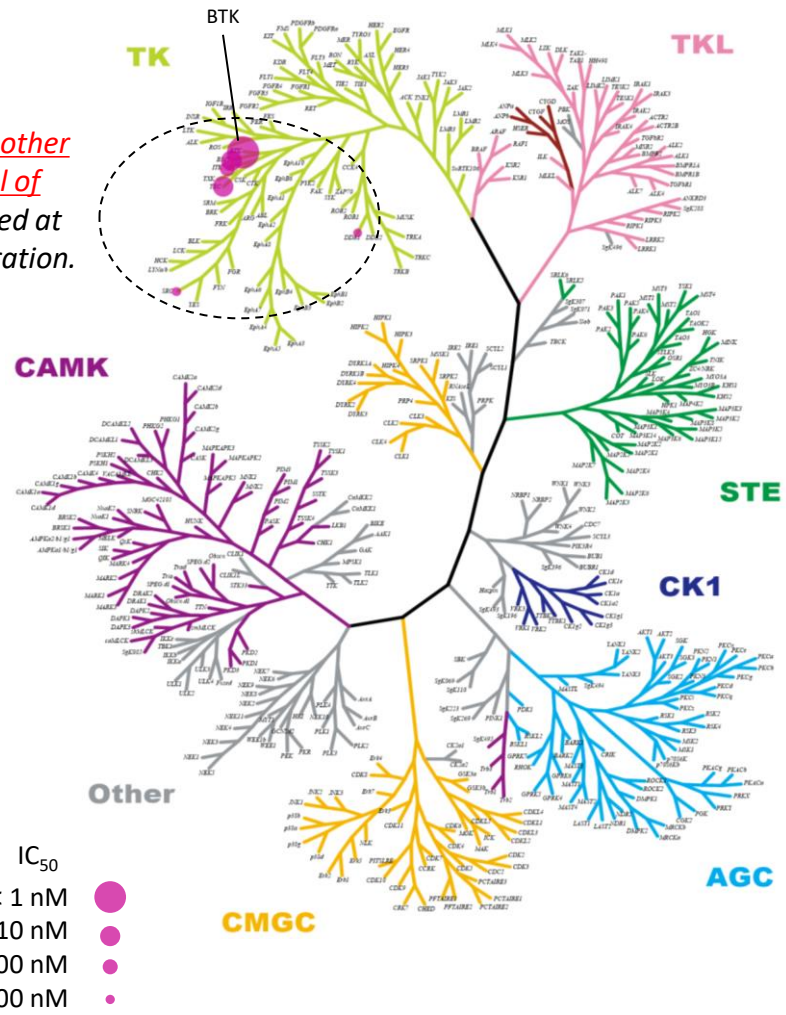
50-fold Stronger activity

Ramos: human Burkitt lymphoma cell line
OCI-Ly10: human B-cell non-Hodgkin lymphoma cell line
OCI-Ly10 [BTK C481S]: BTK[C481S] knock-in OCI-Ly10 cells
HEL299: human embryo lung cell line

J Med Chem. 2021 Oct 14;64(19):14129-14141.

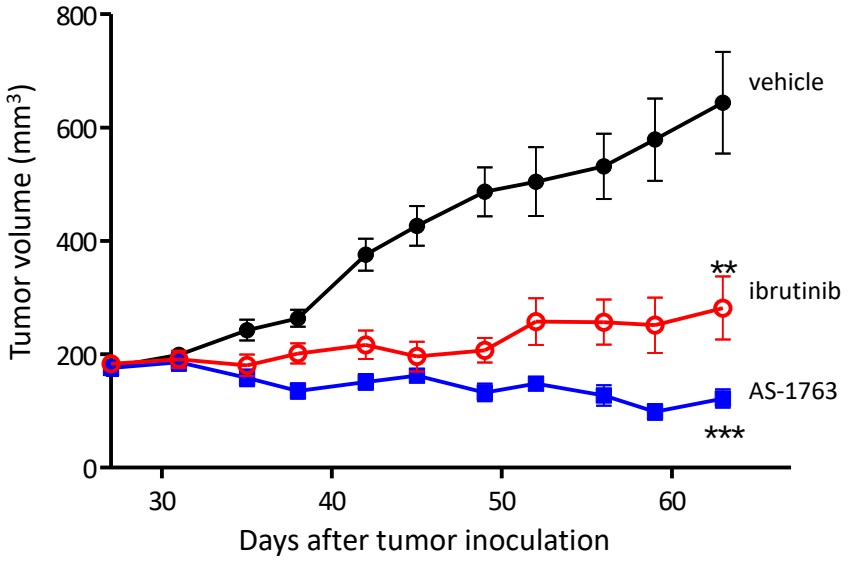
◆ Kinase selectivity profiling

Only inhibited 6 other kinases in a total of 291 kinases tested at 0.3 μM concentration.



AS-1763: In Vivo Antitumor Effect against BTK^{C481S} Mutant

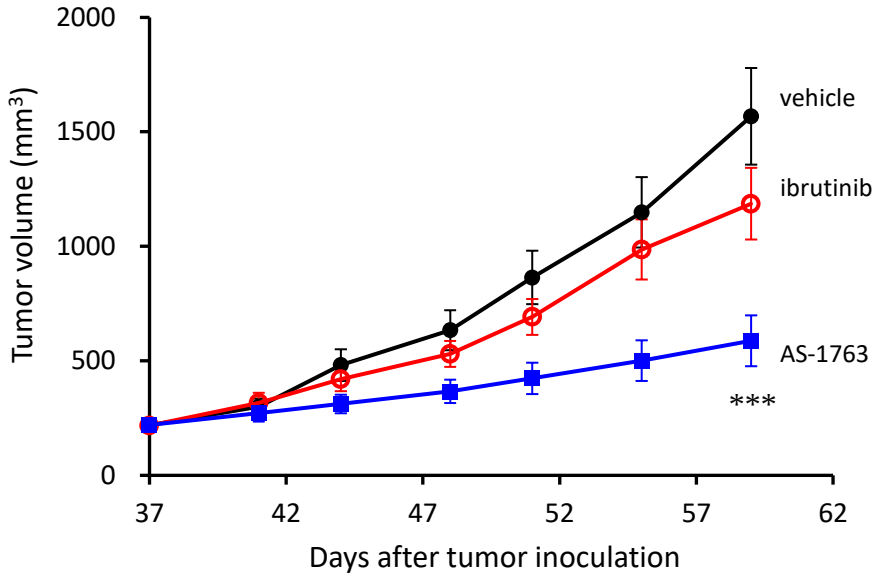
- In vivo antitumor effects of AS-1763 on human B-cell non-Hodgkin lymphoma cell line, OCI-LY10 tumor xenograft mouse model (n=8-10)



Ibrutinib: 25 mg/kg QD
AS-1763: 60 mg/kg BID

**: p<0.01
***: p<0.001

- In vivo antitumor effects of AS-1763 on ibrutinib-resistant BTK^{C481S} knock-in OCI-LY10 tumor xenograft mouse model (n=11)



Ibrutinib: 25 mg/kg QD
AS-1763: 60 mg/kg BID

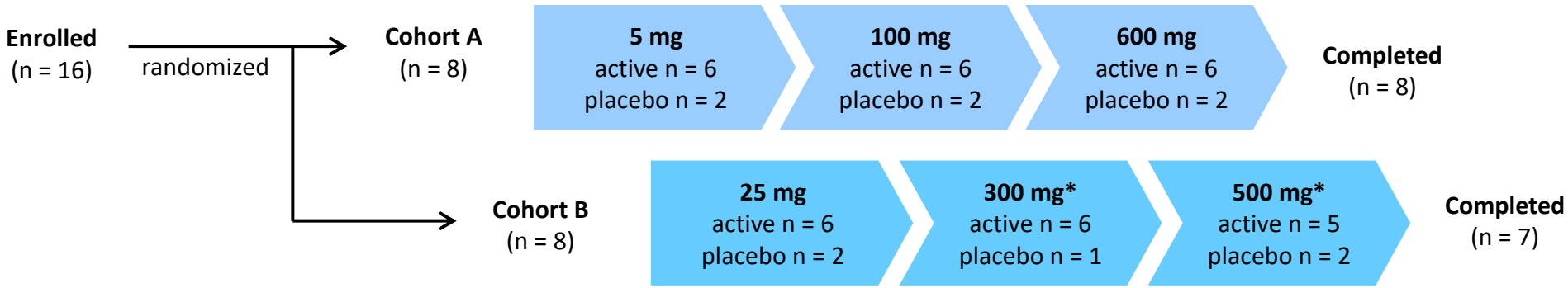
***: p<0.001

J Med Chem. 2021 Oct 14;64(19):14129-14141.

AS-1763: FIH Phase 1 Clinical Trial in Healthy Volunteers

Study Design

Step 1 SAD Part	Step 2 BA Part
• Double-blind, placebo-controlled, randomized FIH study • Simple formulation (solution) • 6 dose levels (8 subjects/cohort A, 8 subjects/cohort B) • 6 active / 2 placebo for each dose level • Safety and tolerability • Pharmacokinetics and pharmacodynamics (PD; CD69 upregulation on naïve B cells)	• Open label study • Another cohort of 8 subjects • The subjects were dosed with a single dose of AS-1763 100-mg tablet, and relative bioavailability with simple formulation was evaluated



*One subject was withdrawn from the study on Day 1 of 300-mg period before the intake of treatment medication (placebo) by physician's decision. This subject showed AEs (Grade 2 lymphocytosis and Grade 2 neutropenia) which were considered treatment-emergent but not trial medication-related. No replacement was done at 300-mg and the following 500-mg periods.

AS-1763: SAD Part

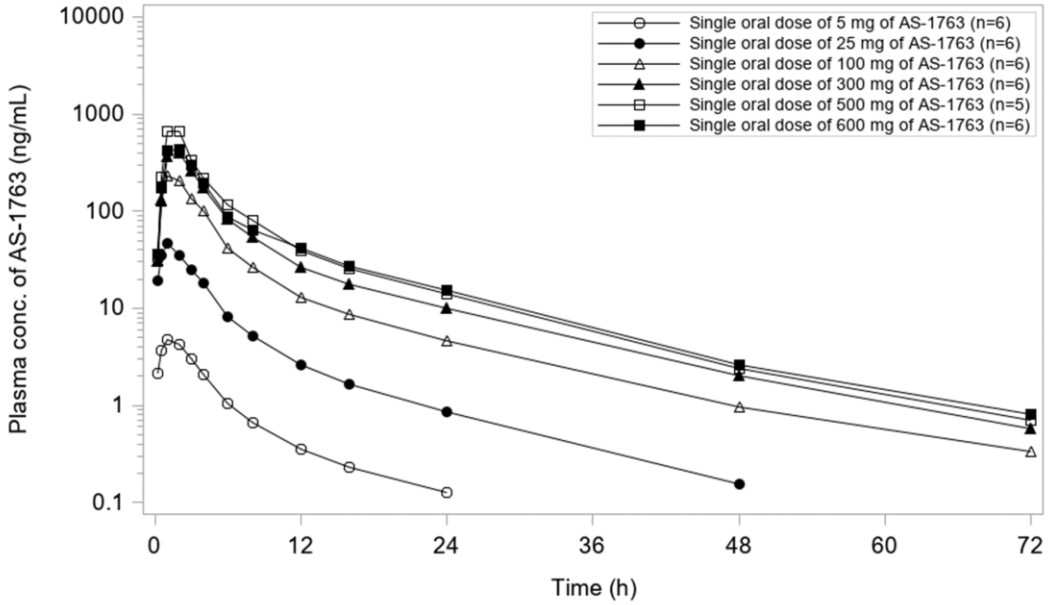
<Safety and tolerability>

- 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 (clinical laboratory, 12-lead safety ECGs, vital signs, or physical examinations).

<Pharmacokinetics >

- 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.

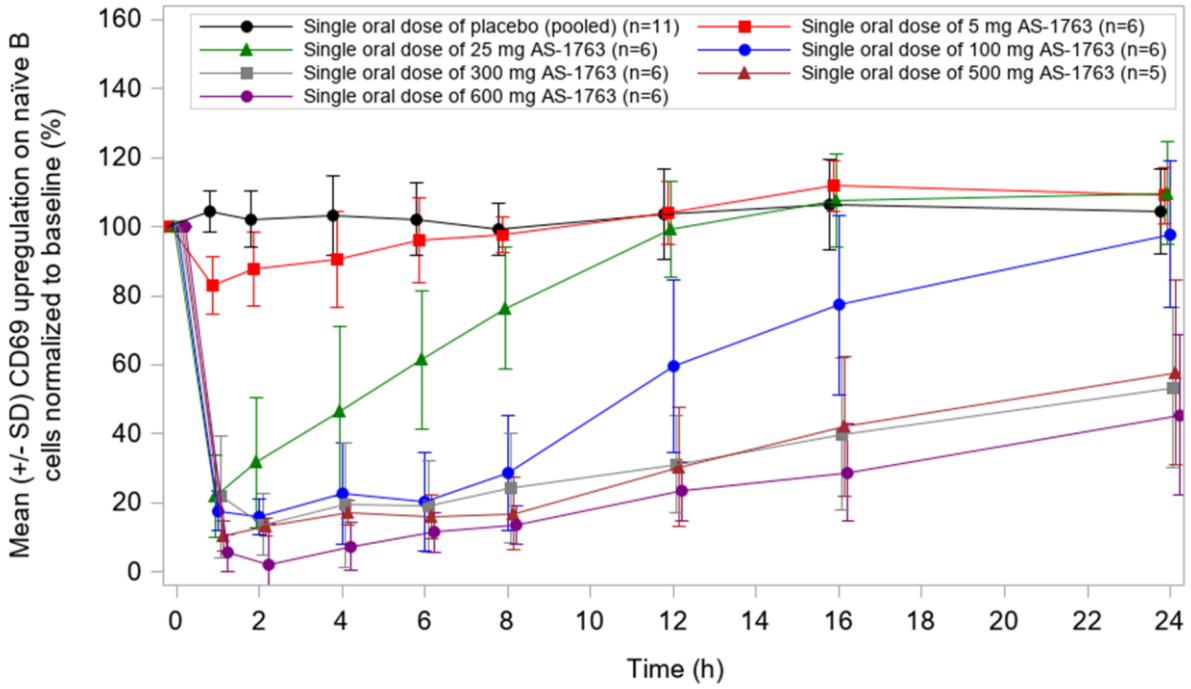
<Plasma concentration of a Single oral dose AS-1763>



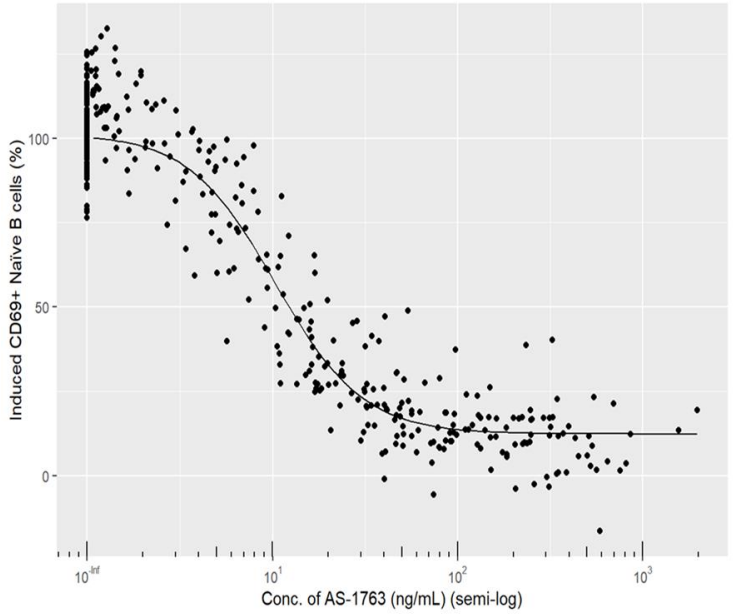
Pharmacodynamics of AS-1763

- 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 IC50 value of AS-1763 on CD69 upregulation was calculated to be 10.5 ng/mL.

<B cell CD69 Upregulation after a Single oral dose AS-1763>



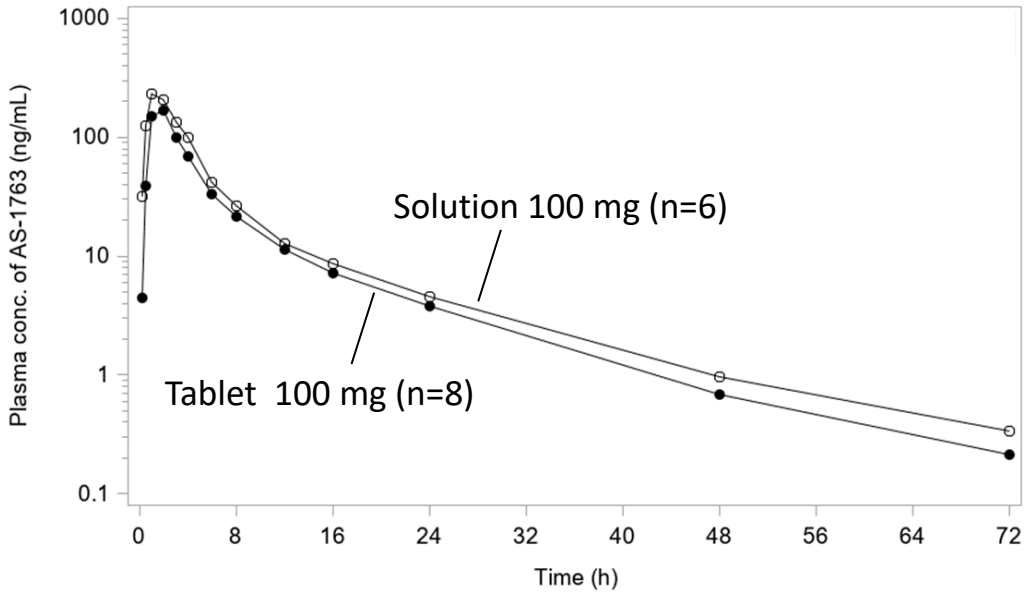
<PK/PD Correlation Analysis>



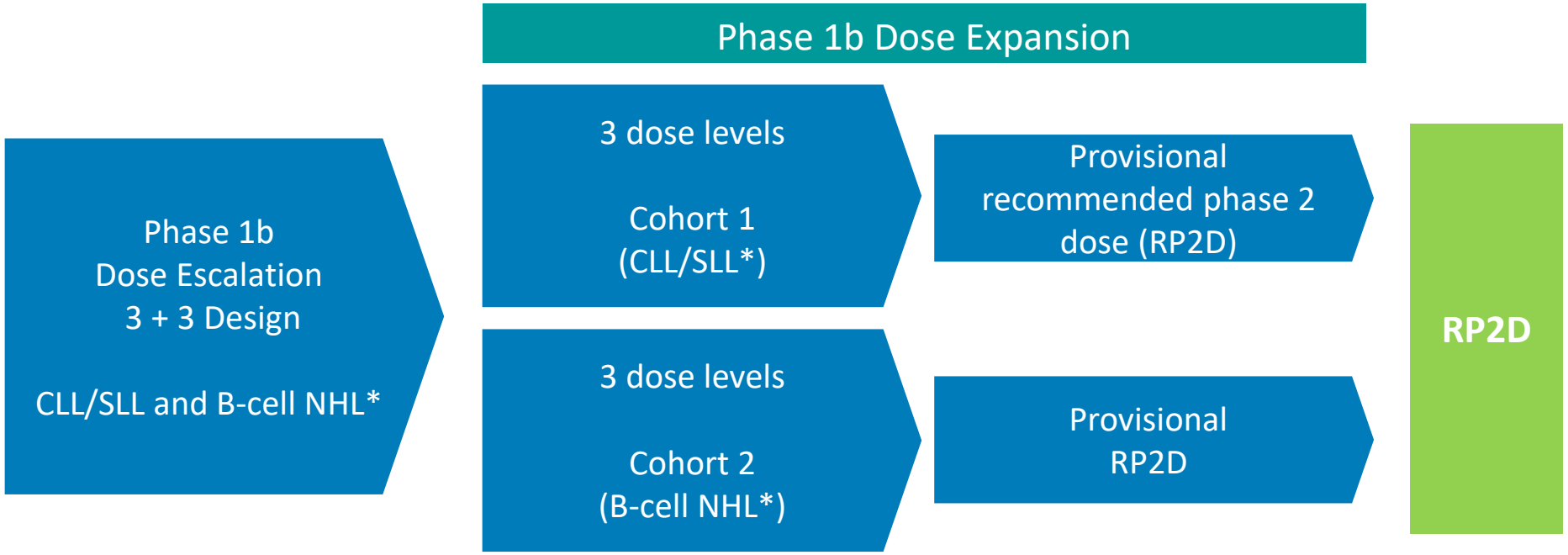
AS-1763: BA Part

- 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.

＜PK of Tablet vs Solution after a Single oral dose AS-1763>



AS-1763: Phase 1b Schema (US)



*Previously treated patients

- FPI in the U.S. is expected in Q1 2023.

BTK Inhibitors for Blood Cancers

- Covalent BTK inhibitors
  - ✓ Covalent BTK inhibitors including ibrutinib are key therapeutic options for patients with B cell malignancies including chronic lymphocytic leukemia (CLL).
  - ✓ Sales of BTK inhibitors, ibrutinib, acalabrutinib, and zanubrutinib, totaled over $9 billion in 2021. Sales of ibrutinib is expected to be over $10 billion according to an estimate by Evaluate Pharma.
  - ✓ However, patients are reported to develop resistance during the treatment as more BTK inhibitors are prescribed.

＜Sales of BTK inhibitors＞

($million)	Development/ Marketing	2019	2021	2026Est.
Ibrutinib	AbbVie + J&J	7,291	8,199	10,722
Acalabrutinib	AstraZeneca	164	1,238	n.a.
Zanubrutinib	BeiGene	1	217	n.a.

Source: Financial report of the companies for historical data. Estimate for 2026 is based on EvaluatePharma.

Non-Covalent BTK Inhibitors under Development Targeting Cancer

- Urgent need to develop novel BTK inhibitors to overcome the BTK inhibitor resistance
  - ✓ Patients treated with covalent BTK inhibitors are reported to develop resistance during the treatment due to substitution of cysteine residue at 481 position with serine (C481S mutation) in BTK, which reduces the efficacy of the covalent BTK inhibitors.
  - ✓ In January 2023, U.S. FDA approved pirtobrutinib, a non-covalent BTK inhibitor, for adult patients with relapsed or refractory Mantle Cell Lymphoma after at least two lines of systemic therapy including a BTK inhibitor.
  - ✓ However, the emergence of resistance mutations to pirtobrutinib has already been reported (ref. 1). Therefore, there is still a high unmet medical need for next-generation BTK inhibitors which have efficacy for such resistance mutations.
  - ✓ In preclinical studies, AS-1763 potently inhibited both wild type and mutant BTKs that confer resistance to BTK inhibitors including ibrutinib and pirtobrutinib. Carna is advancing development of AS-1763 as a next-generation BTK inhibitor.

Ref. 1. Wang E., et al., N. Engl. J. Med. 2022;386(8):735–743.

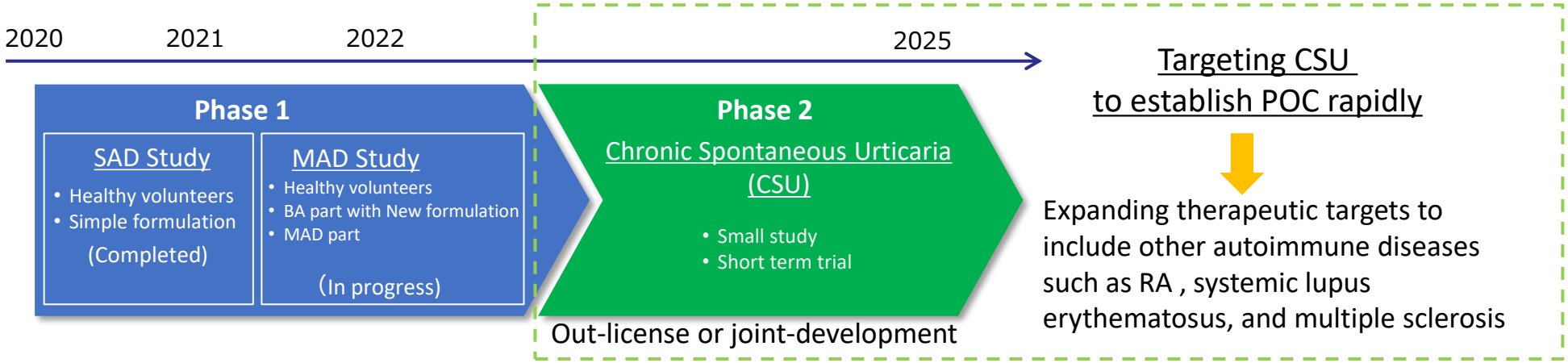
Compound	Company	Development Phase
pirtobrutinib (LOXO-305)	Lilly (Loxo)	Approved/P3
nemtabrutinib (ARQ 531)	Merck (ArQule)	P2
TT-01488	TransThera	P1
HMPL-760	HutchMed	P1

AS-0871: Non-covalent BTK Inhibitor Targeting Immune-inflammatory diseases

AS-0871：Targeting Immune-inflammatory diseases

- Small molecule BTK inhibitor
- Non-covalent/reversible
- High kinase selectivity
- Orally available

- Demonstrated significant efficacies in arthritis models
- Showed efficacy in systemic lupus erythematosus model
- Phase 1 MAD study is in progress
- Find a partner to conduct further development after completing Phase 1 study



SAD: Single Ascending Dose
MAD: Multiple Ascending Dose
BA: Bioavailability
POC：Proof of Concept

AS-0871: Phase 1 Clinical Trial in Progress

Phase 1 in the Netherlands SAD study (Healthy volunteers)

Completed

- ✓ Safe and well-tolerated at all dose levels
- ✓ Favorable Pharmacokinetic (PK) Profile
- ✓ Promising Pharmacodynamic(PD) effects
- ✓ Conducted using simple formulation

Developing multiple new formulations

Phase 1 in the Netherlands MAD study (Healthy volunteers)

Completed

BA part Evaluate the relative bioavailability of multiple new formulations to select the best formulation

Ongoing

MAD part Evaluate the safety, tolerability, PK and PD in the 2-week multiple ascending dose of AS-0871

*The protocol has been amended to skip the SPT (Skin Prick test) part based on the recent clinical outcomes of competing BTK inhibitor drug candidates, which enable us to predict the efficacy from the PD effects.

AS-0871: Excellent Kinase Selectivity

CARNA BIOSCIENCES

◆ Targeting Inactive Conformation of BTK


Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

TR-FRET binding assay targeting unactivated form of Bruton's tyrosine kinase

Tokiko Asami *, Wataru Kawahata, Masaaki Sawa

Carna Biosciences, Inc., BMA 3F, 1-5-5 Minatojima-Minamimachi, Chuo-ku, Kobe 650-0047, Japan

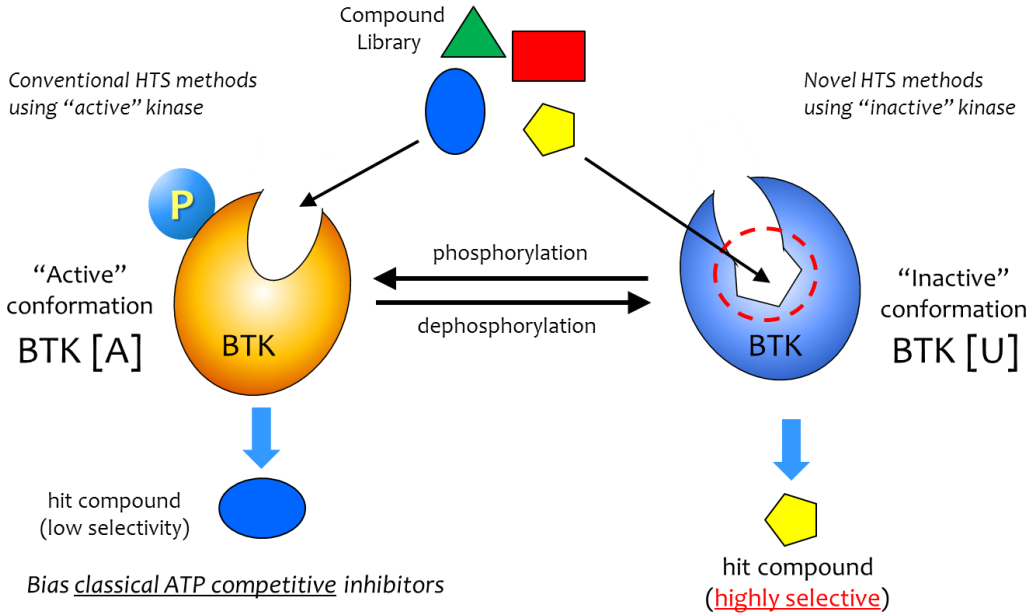

Journal of Medicinal Chemistry

Article

Design and Synthesis of Novel Amino-triazine Analogues as Selective Bruton's Tyrosine Kinase Inhibitors for Treatment of Rheumatoid Arthritis

Wataru Kawahata,* Tokiko Asami, Takao Kiyoi, Takayuki Irie, Haruka Taniguchi, Yuko Asamitsu, Tomoko Inoue, Takahiro Miyake, and Masaaki Sawa

Research and Development, Carna Biosciences, Inc., 3rd Floor, BMA, 1-5-5 Minatojima-Minamimachi, Chuo-ku, Kobe 650-0047, Japan

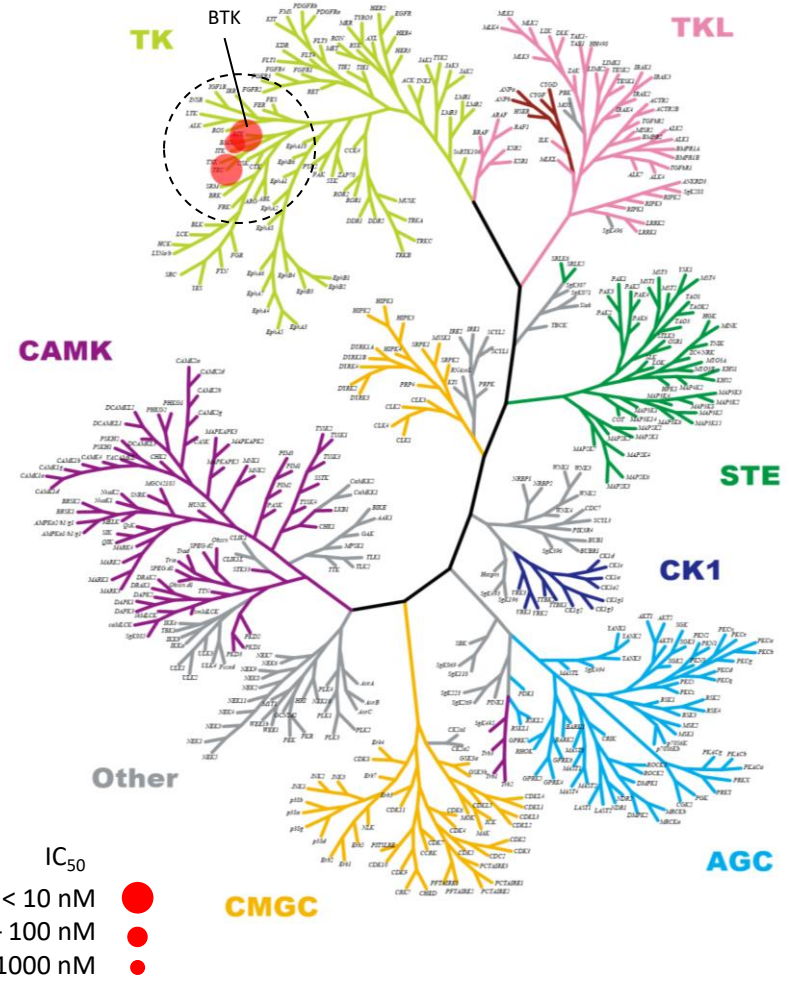


Bias classical ATP competitive inhibitors

	BTK IC_{50} (nM)	
	BTK [A]	BTK [U]
AS-0871	3.4	0.3

◆ Kinase Selectivity Profiling

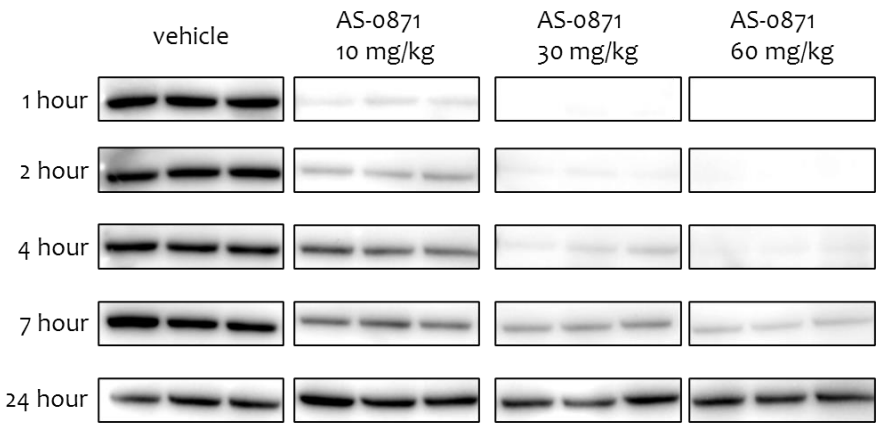
Only inhibited 2 other kinases in a total of 312 kinases tested at 0.3 μM concentration.

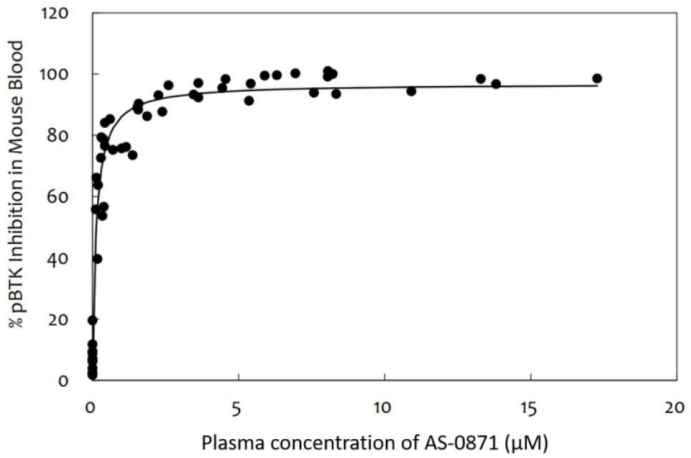


AS-0871: In Vivo Therapeutic Efficacy

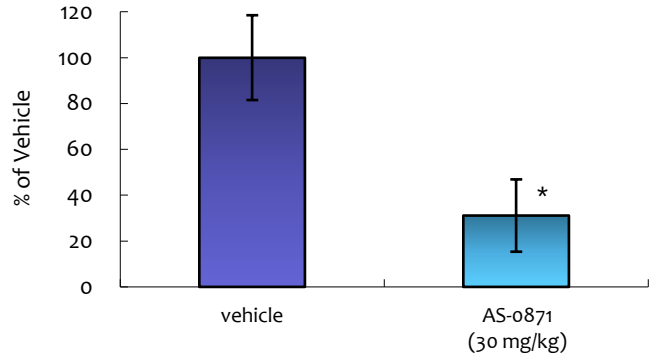
- PK/PD Study

Auto-phosphorylation status of BTK was measured following oral single administration of AS-0871

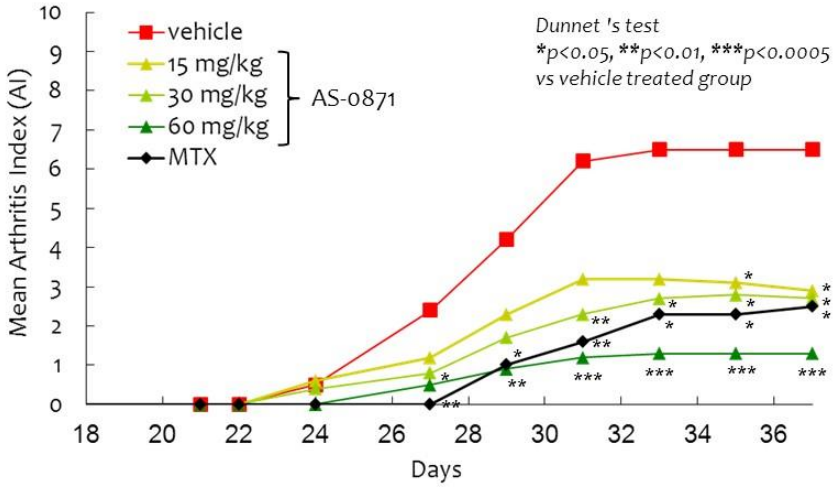




- Passive cutaneous anaphylaxis (PCA) mouse model (n=5)



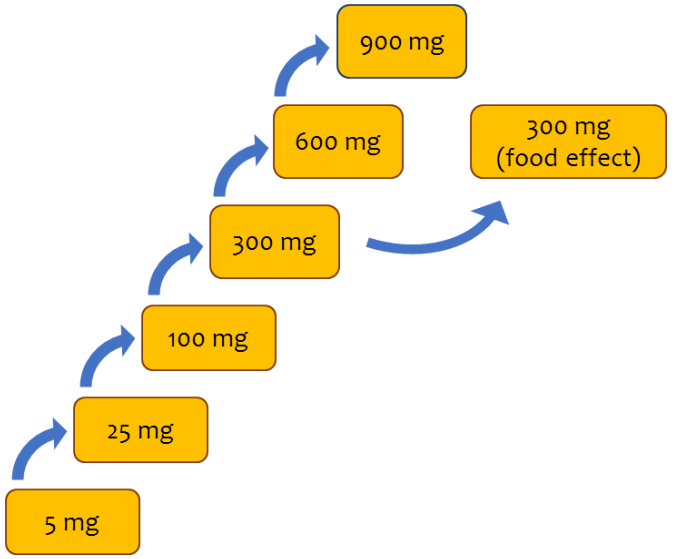
- Collagen-induced arthritis (CIA) mouse model (n=10)



AS-0871: FIH study

SAD Part (Completed)

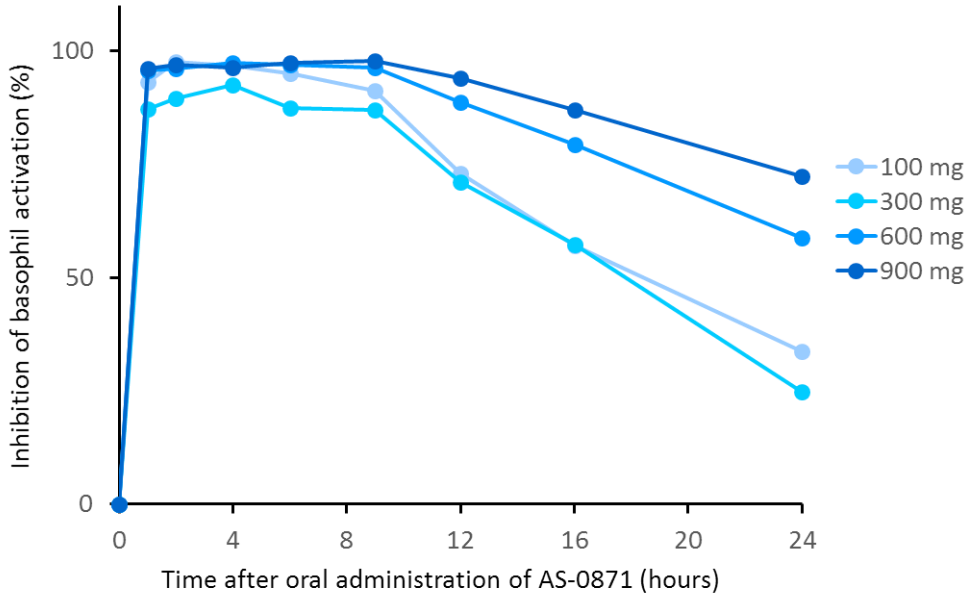
Step 1	Step 2
• 6 dose levels (8 subjects/cohort) • Placebo controlled (6 active / 2 placebo) • Safety and tolerability • Pharmacokinetics and pharmacodynamics	• Food effect

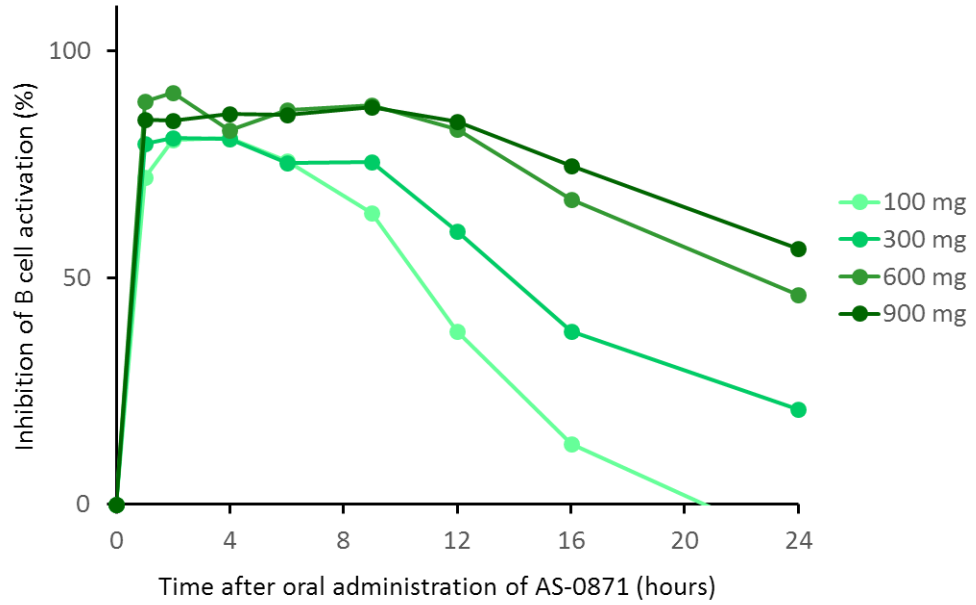


- ✓ AS-0871 is well-tolerated without any safety concerns.
- ✓ Favorable pharmacokinetic profile.
- ✓ Blood samples to assess PD effects were analyzed for evaluation of the B-cell and basophil responses. Administration of AS-0871 at 100mg or above resulted in strong inhibition of B-cell and basophil activation.
- ✓ Switching to a new formulation in the MAD study.

Pharmacodynamics of AS-0871

- ✓ Pharmacodynamic study demonstrated that subjects who received AS-0871 showed dose proportional inhibitions in basophil and B-cell activations, and significant and sustained inhibitory effects were observed at 100 mg and above.
- ✓ Oral administration of AS-0871 achieved therapeutic plasma levels needed to inhibit B cells and basophils activation, suggesting that AS-0871 has a potential to become a new treatment option for inflammatory diseases.

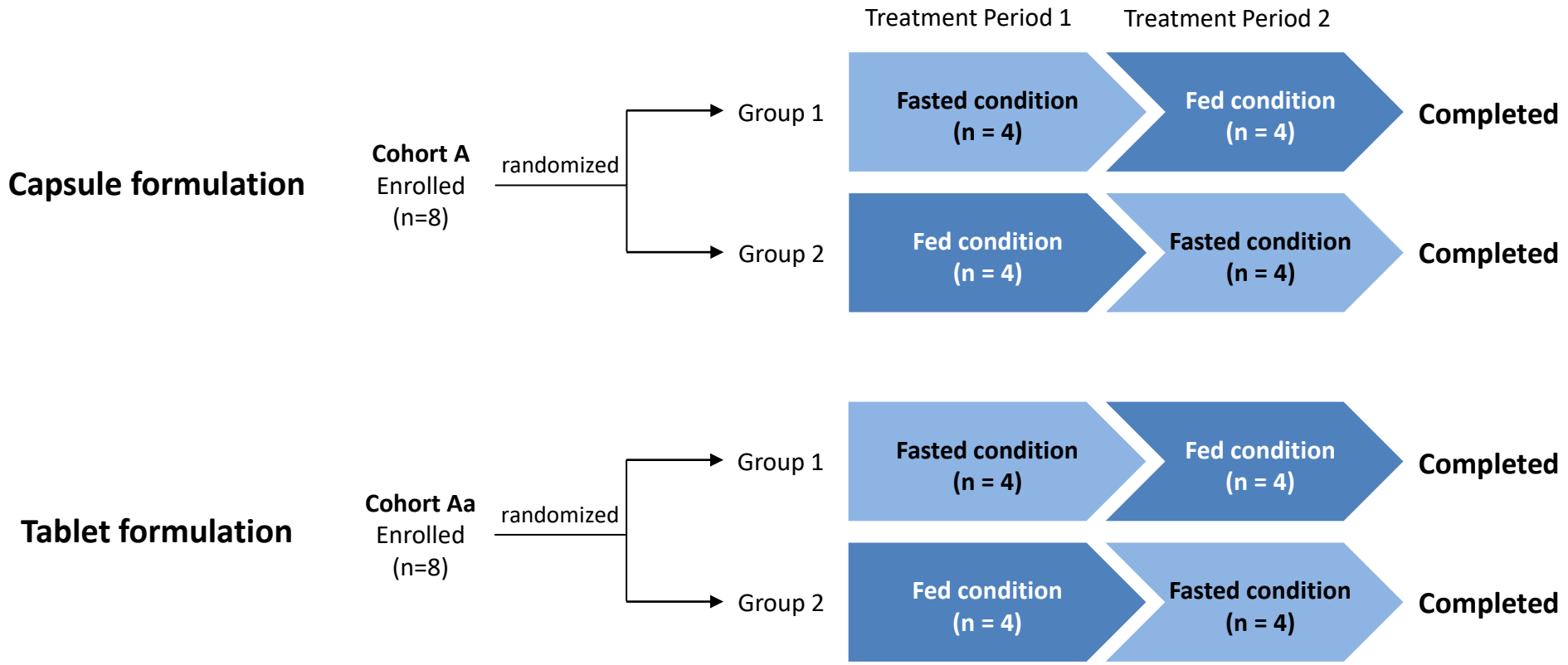




AS-0871: Phase 1 MAD Study: BA part

Study Design of rBA/FE part

PK, safety, and tolerability after single-dose oral administration of AS-0871, formulated as capsules or tablets, were be evaluated under fasted and fed conditions in an open-label, randomized, 2-period crossover design. Eight healthy subjects (Cohort A or Cohort Aa) were randomized to either Group 1 or Group 2 (4 subjects per group).

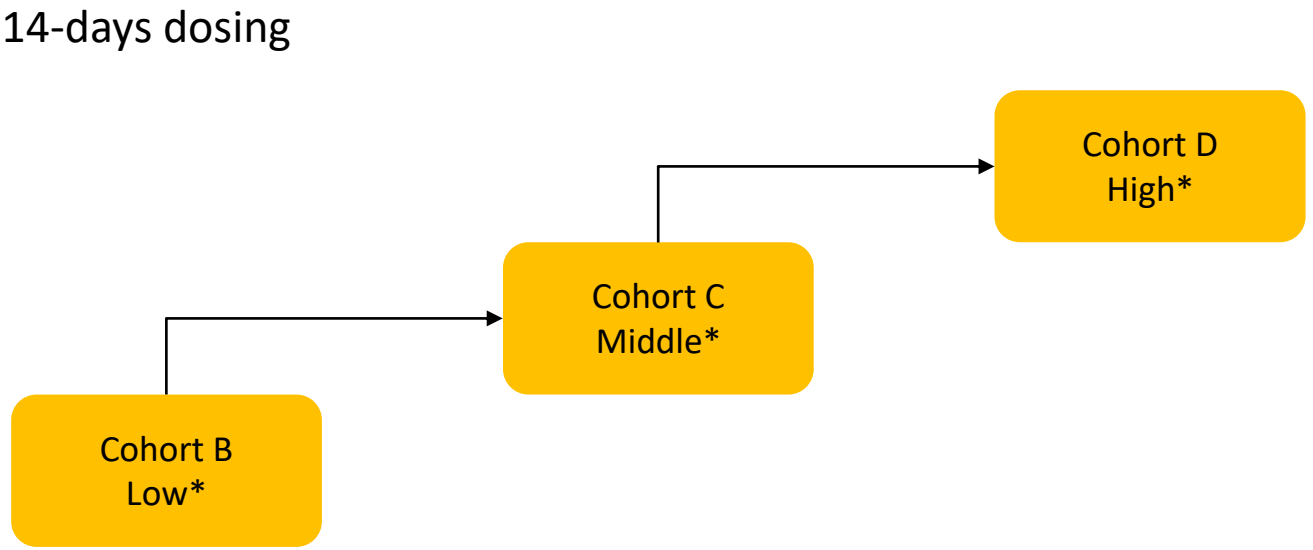


*One subject vomited after dosing (considered not related to study drug), excluded from the PK analysis.
**One subject withdrew from the study due to personal reasons before dosing.

AS-0871: Phase 1 MAD Study: MAD part

Study Design of MAD part

- In the MAD part, safety, tolerability, PK, and PD of 3 multiple ascending doses of AS 0871, following 14 day multiple dose oral administration of AS-0871, will be investigated using a double blind, placebo-controlled, randomized design in 3 cohorts of 8 healthy subjects each.
- Dosing will be completed in Q1 2023.
- The results are expected in H2 2023.



*The dose levels may be adjusted for the MAD part to match with projected exposure levels depending on the results of the BA part.

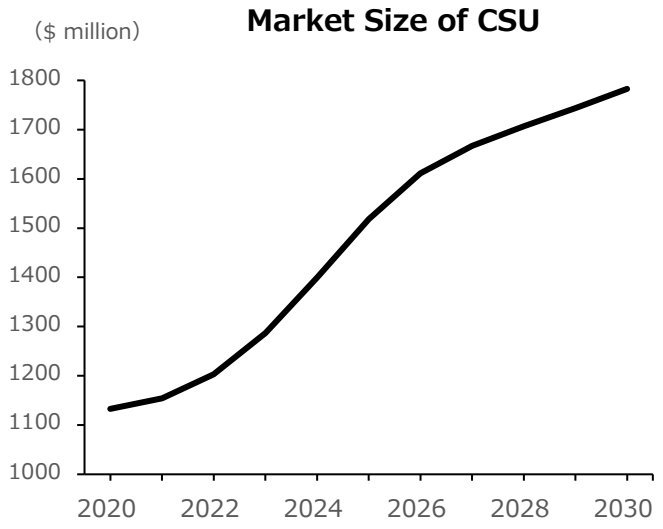
Non-covalent BTK inhibitors under development targeting autoimmune diseases

- Fenebrutinib is the only non-covalent BTK inhibitor under development targeting autoimmune diseases.
- No non-covalent BTK inhibitors under development targeting Chronic Spontaneous Urticaria.

Compound	Company	Development Phase
Fenebrutinib (GDC-0853)	Roche / Genentech	P3 Multiple Sclerosis

Chronic Spontaneous Urticaria

- ✓ Chronic Spontaneous Urticaria (CSU) is one of most frequent skin diseases with unmet medical needs since curative treatment is not available.
- ✓ CSU is a distressing skin disorder that characterized by itching and hives lasting for more than 6 weeks, which has major detrimental effects on quality of life with sleep deprivation and other conditions.
- ✓ An underlying cause is rarely detected and symptoms can be exacerbated by infectious diseases or stress.
- ✓ The lack of efficacy of approved standard therapy (antihistamines) in many patients is another major problems.
- ✓ Omalizumab, humanized anti-IgE anti IgE antibodies, has been approved as the third-line therapy, but the drug is very expensive ($1874 per 4 weeks on average).
- ✓ The market size of CSU in 2020 was estimated as $1,133 million in major seven countries. The market size excluding antihistamines was $1,062 million.
- ✓ The market size of CSU is expected to become $1,783 million in 2030 with launch of several humanized anti-IgE anti IgE antibodies competing with omalizumab.
- ✓ There are no approved BTK inhibitors targeting CSU.

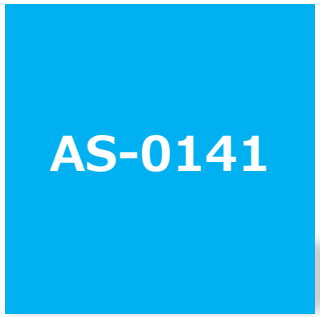


Source: DeleveInsight

*1 Market size of CSU is estimated by DeleveInsight.
*2 Major seven countries include US, Germany, France, Italy, Spain and Japan.

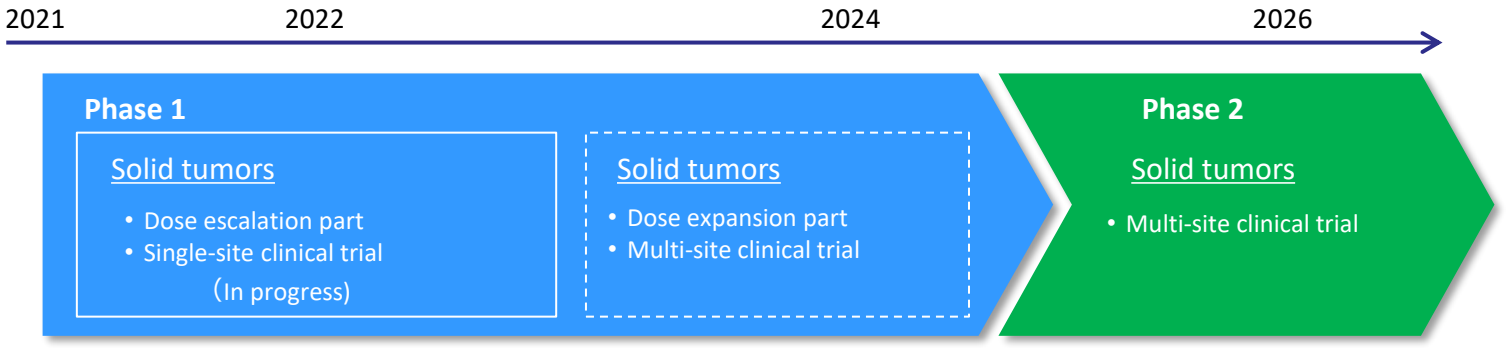
CDC7 Inhibitor

AS-0141 (Solid cancer)



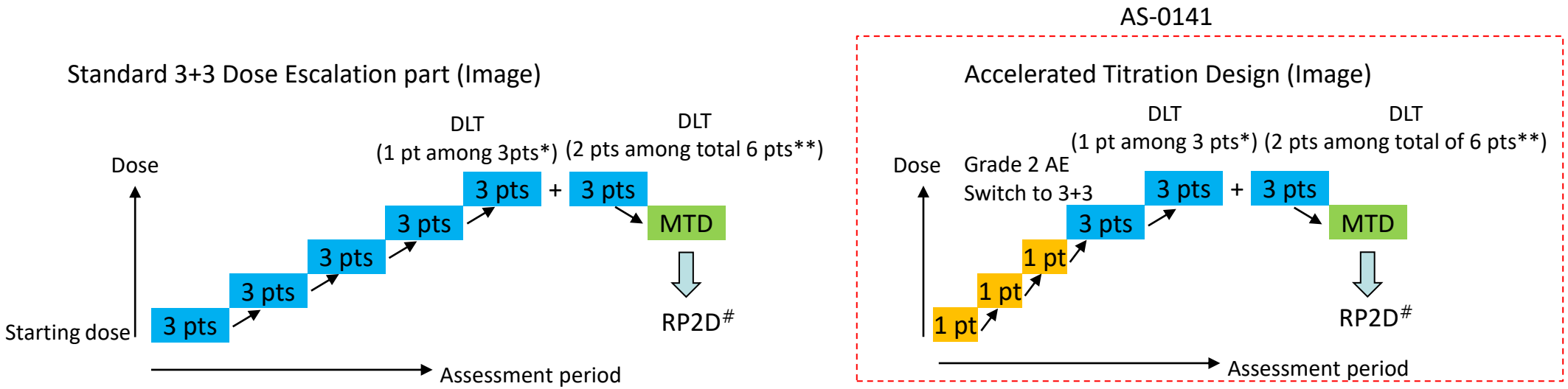
AS-0141: CDC7 Inhibitor

AS-0141：Targeting Cancer	
● Small molecule CDC7 inhibitor ● High kinase selectivity ● Potential First-in-class drug ● Orally available	● Potent anti-proliferative activity against various cancer cell lines ● Demonstrated strong anti-tumor activity in several human tumor xenograft models ● Conducting Phase 1 study in Japan targeting solid tumors



AS-0141: Phase 1 Clinical Trial

- Phase 1 study targeting cancer patients
  - ✓ Phase 1 study in patients with unresectable, advanced, recurrent, or metastatic solid tumors was initiated in Japan in H1 2021.
  - ✓ The study consists of two parts, a dose escalation and an expansion.
  - ✓ The primary objective is to assess safety, tolerability, maximum tolerated dose(MTD), preliminary anti-tumor activity, and PK / PD as well as to determine RP2D.
  - ✓ The dose escalation part employs accelerated titration design.
    - One patient is treated per cohort unless a Grade ≥ 2 AE occurs during dose limiting toxicity (DLT) assessment period.
    - Switch to 3+3 dose escalation design when any Grade ≥ 2 AEs are observed during DLT assessment period.



* No more patients will be added to this cohort if 2 pts among 3 pts experience DLT.
** If only 1 pt experiences a DLT among 6 pts, 3+3 design will be continued with higher dose levels.
# Recommended dose level will be determined at MTD or lower dose level.

pt/pts: patient(s)

AS-0141: Phase 1 Clinical Trial in Progress

- ✓ Favorable pharmacokinetic profile at dosage of 20 mg BID to 300 mg BID.
- ✓ The study was switched to 3+3 design as one Grade 2 AE was observed in Cohort 6 (300 mg BID).
- ✓ After switching to 3+3 design, 2 patients among 3 patients experienced dose-limiting toxicities (DLTs). The MTD is considered at the dose lower than 300 mg BID as 2/3 patients experienced DLTs.
- ✓ Additional patients will be enrolled at lower dose levels to determine MTD and recommended dose level.

- Ongoing Phase 1 Dose escalation part

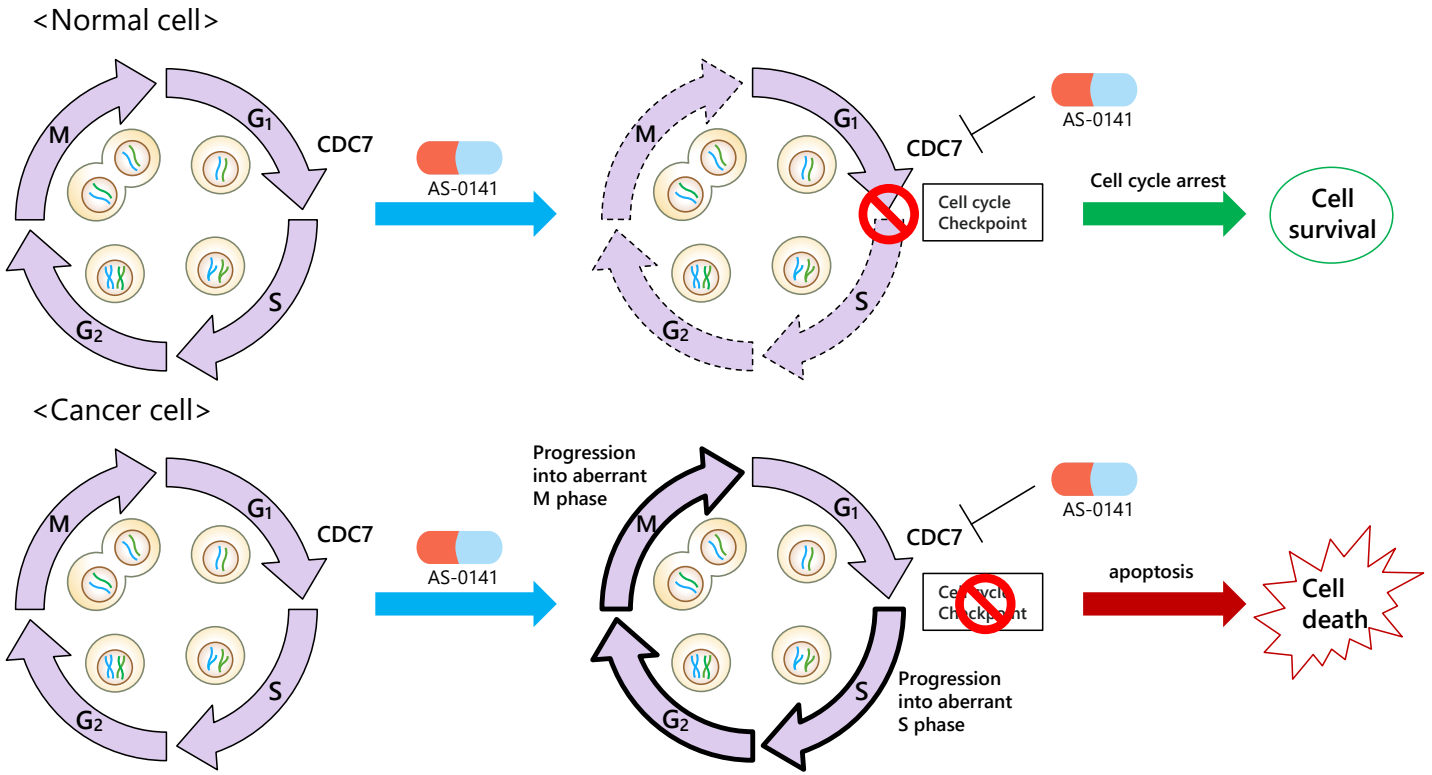
Cohort	Dose level (5d on/2d off)		Status
1	20 mg BID	N=1	No G2 AE/No DLT
2	40 mg BID	N=1	No G2 AE/No DLT
3	80 mg BID	N=1	No G2 AE/No DLT
4	150 mg BID	N=1	No G2 AE/No DLT
5	250 mg BID	N=1	No G2 AE/No DLT
6	300 mg BID (switched to 3+3 design)	N=3	DLT（2/3 pts）
	< 300 mg BID (3+3 design)		

*BID: Twice a day, 5d on/2d off: 5 days medication followed by 2 days drug holiday

AS-0141: Highly Selective CDC7 Inhibitor

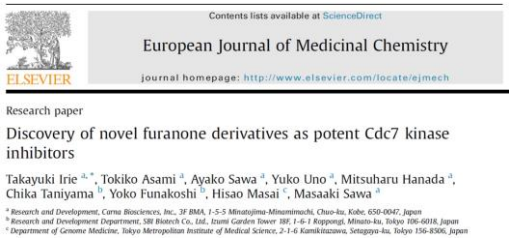
■ CDC7 kinase inhibitor

CDC7 (cell division cycle 7) is a serine-threonine kinase that plays a critical role in DNA synthesis and is required for the activation of DNA replication origins throughout the S phase of the cell cycle. Inhibition of CDC7 in cancer cells causes lethal S phase or M phase progression, whereas normal cells survive, most likely through induction of cell cycle arrest at the DNA replication checkpoint. It has been reported in the literature that CDC7 is overexpressed in many cancers. Therefore, CDC7 is an attractive target for cancer drug development.



AS-0141: Time-Dependent Inhibitor of CDC7

- AS-0141 has a unique inhibitory mechanism for CDC7 kinase (time-dependent inhibition)


Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Research paper

Discovery of novel furanone derivatives as potent Cdc7 kinase inhibitors

Takayuki Irie [a, *], Tokiko Asami [a], Ayako Sawa [a], Yuko Uno [a], Mitsuharu Hanada [a], Chika Taniyama [b], Yoko Funakoshi [b], Hisao Masai [c], Masaaki Sawa [a]


Journal of Medicinal Chemistry

pubs.acs.org/jmc

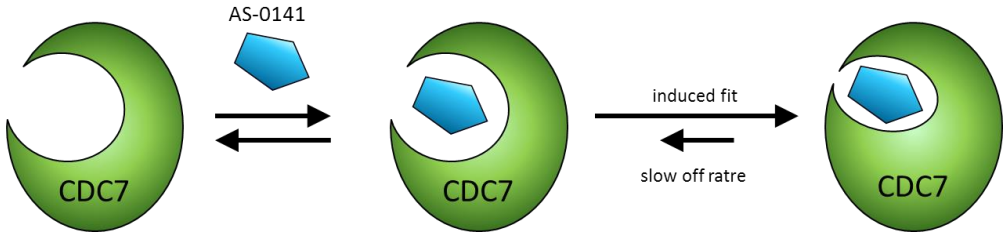
Drug Annotation

Discovery of AS-0141, a Potent and Selective Inhibitor of CDC7 Kinase for the Treatment of Solid Cancers

Takayuki Irie,* Tokiko Asami, Ayako Sawa, Yuko Uno, Chika Taniyama, Yoko Funakoshi, Hisao Masai, and Masaaki Sawa

Cite This: J. Med. Chem. 2021, 64, 14153−14164

Read Online



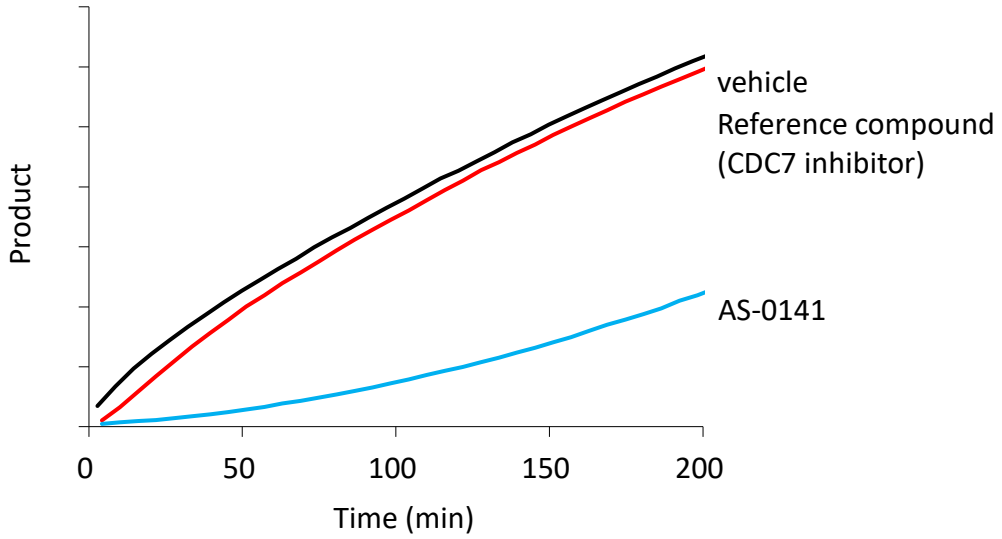
Inhibitory potency (IC_{50}) for CDC7 in the presence of 1 mM ATP

Without Preincubation	With Preincubation
503 nM	2.4 nM

J Med Chem. 2021 Oct 14;64(19):14153-14164.

- AS-0141 inhibits CDC7 in a reversible fashion but has a very slow off-rate

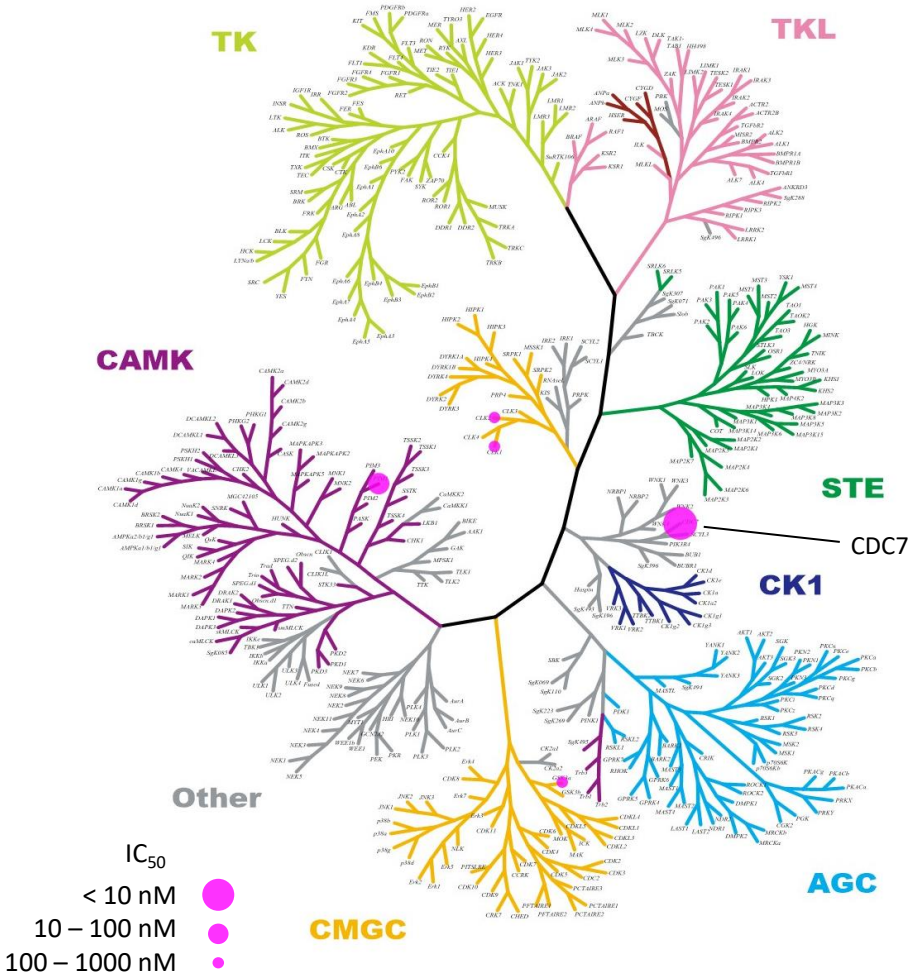
Rapid dilution assay for Cdc7 inhibitors. Recovery of enzymatic activity was monitored by formation of the phosphorylated product.



AS-0141: High Kinase Selectivity

◆ Kinase Selectivity Profiling

In the presence of 1 mM ATP with preincubation



◆ IC_{50} values of hit kinases （at 1 mM ATP）

	IC_{50} (nM)	
	Preincubation	
	-	+
CDC7	503	2.4
	210-fold	
PIM1	30	34
CLK1	212	206
CLK2	270	227
GSK3α	189	251

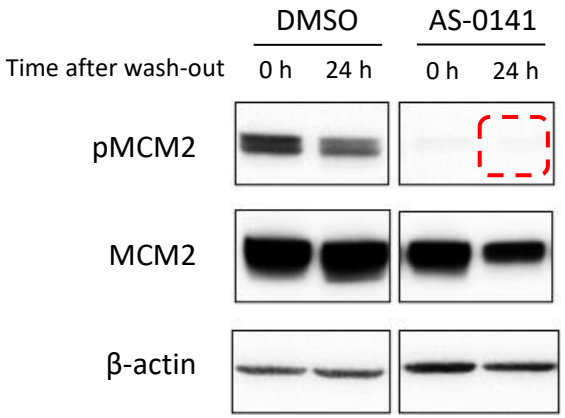
CDC7 is the only kinase that shows preincubation effect

J Med Chem. 2021 Oct 14;64(19):14153-14164.

AS-0141: Strong Cellular Activity

◆ Prolonged inhibition in cells

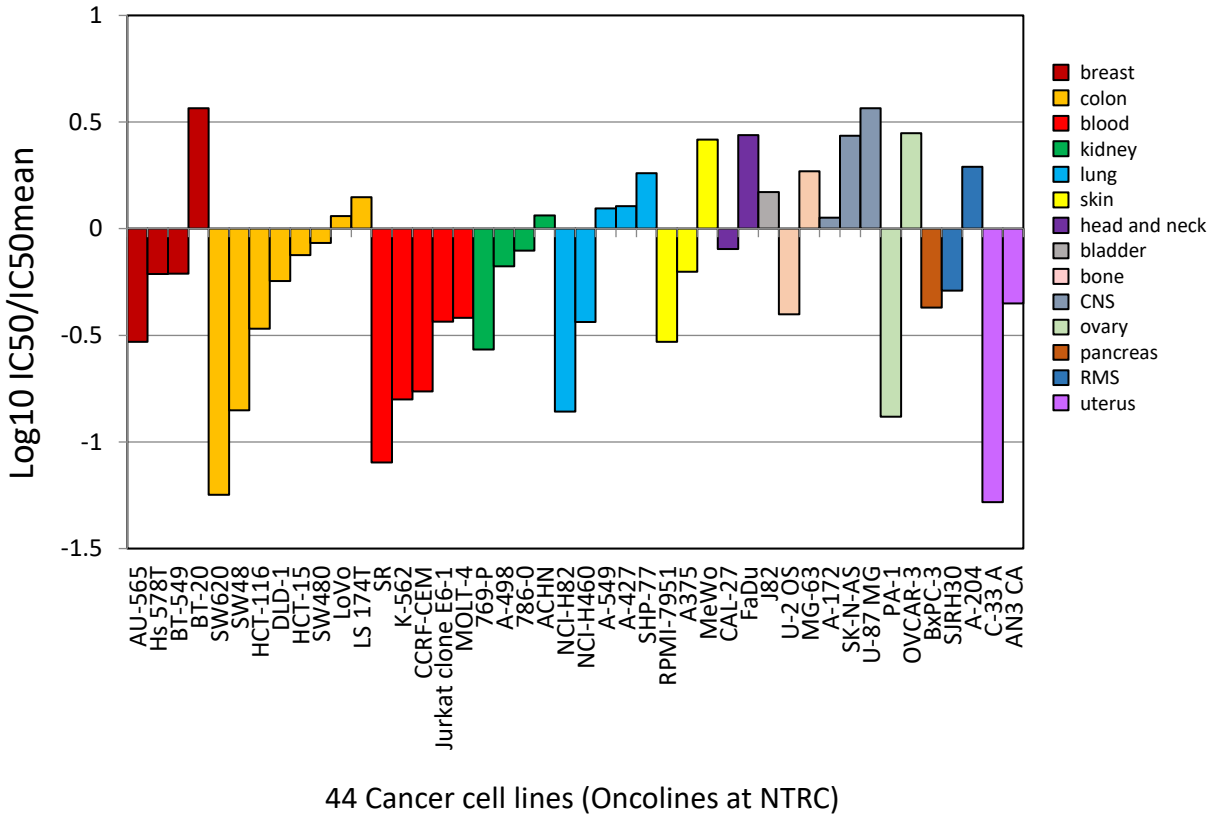
Human colon cancer cell line, Colo-205 cells were treated with DMSO control or AS-0141. After washout of the inhibitor, the cells were further incubated in the same media for 0 or 24 h and subjected to western blot analysis.



the inhibitory effect of AS-014 on the phosphorylation of MCM2 in cells continued up to 24 h after washing out

J Med Chem. 2021 Oct 14;64(19):14153-14164.

◆ AS-0141 potently inhibited growth in a wide range of tumor cell lines, including solid and hematological tumors

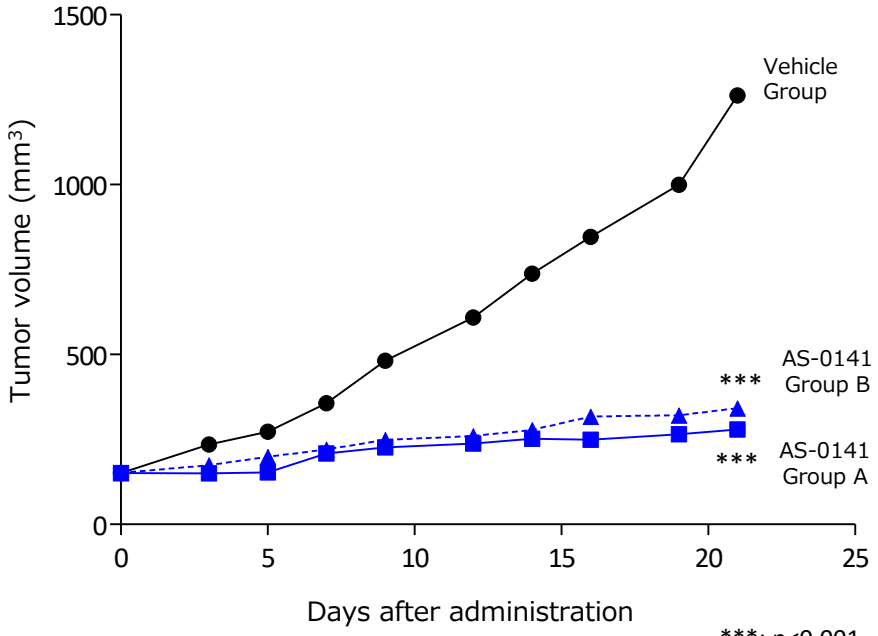


44 Cancer cell lines (Oncolines at NTRC)

AS-0141: Robust In Vivo Antitumor Efficacy

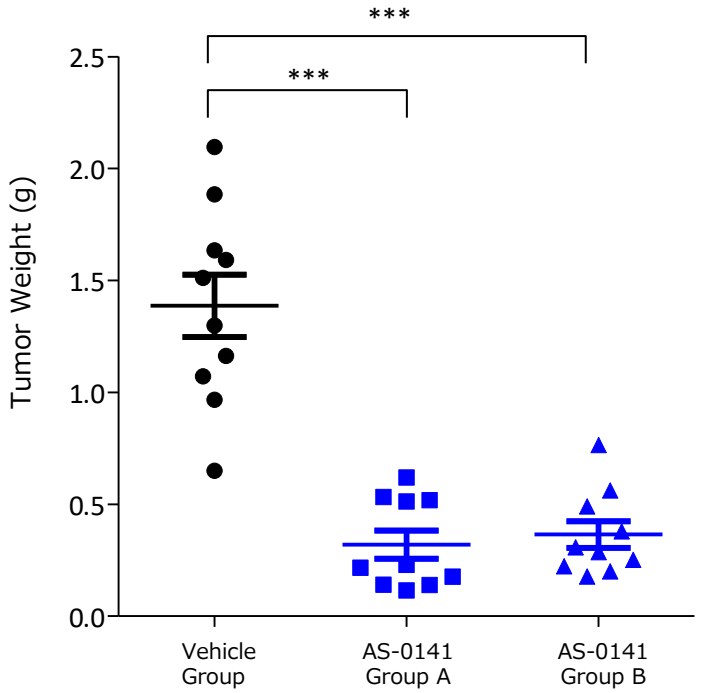
- In vivo antitumor efficacy of AS-0141 in a SW620 (human colon cancer) xenograft mouse model

Tumor Growth Curve (Mean, n = 10)



***: p<0.001

Final Tumor Weight of Each Mouse



***: p<0.001

AS-0141 group A: 60 mg/kg TID, 4d ON/2d OFF
AS-0141 group B: 120 mg/kg QD

J Med Chem. 2021 Oct 14;64(19):14153-14164.

Drug Discovery Support (ddSP) Business

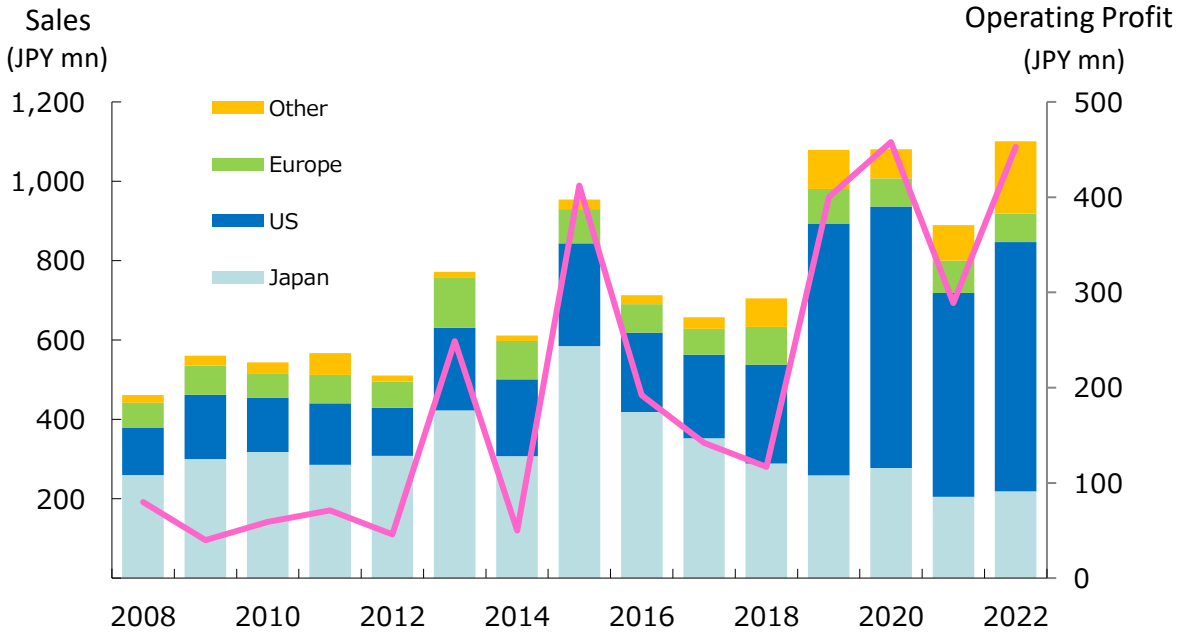
Drug Discovery Support (ddSP) Business

- ddSP business offers scientists worldwide key resources for their kinase inhibitor research including kinase proteins, assay kits, profiling and screening services, and cell-based assay services.
- Our customers include top 10 pharmaceutical companies and biotech companies worldwide.
- Our commitment to quality, including enzyme activity, purity, variability among others, leads to repeat orders and helps keeping our corporate image.

- High quality kinase proteins
  - ✓ *Lineup of 465 products that are important for drug discovery research*
  - ✓ *Biotinylated Kinases of 187 kinds.*
- Accurate profiling service
  - ✓ *Validated Kinase Panel that well cover the Human kinome (>330 kinases)*
- Assay kits and assay development that satisfy customer needs
- *Cell-based assay services that provide further support to customers*
  - ✓ *NanoBRET™ TE Intracellular Kinase Cell-Based Assay*
  - ✓ *ACD's Tyrosine Kinase Cell-Based Assay*
  - ✓ *NTRC's Oncolines™, panel of cancer cell lines*

Market Environment for Drug Discovery Support

- ✓ The demand for kinase inhibitor research services is strong in North America and China. More stable demand in Japan.
- ✓ Major competitors include Thermo Fisher Scientific(US), Eurofins(EU), SignalChem(Canada), and Reaction Biology(US) while no competitors exist in Japan.
- ✓ Carna is the only drug discovery support service provider specialized in kinase inhibitors.
- ✓ Carna is the only major player who offers biotinylated Kinases.
- ✓ Accurate assays, detailed technical support, and product development by researchers who have experiences in drug discovery.
- ✓ Focusing on cell-based assay services including NanoBRET™ TE Intracellular Kinase Assays, assay service licensed from Promega Corporation for which Carna recently launched a new full panel service.



Business Plan

Growth Strategy

➢ *Advance clinical trials of our innovative pipelines to maximize corporate value*

Started internal drug discovery activity	Demonstrated strong capabilities in drug discovery	Maximize the value of pipelines	Continue delivering profits
2010-2015	2016-2020	2021-2025 (Plan)	2026-2030 (Plan)
• Established in-house research capability • Established pipeline	• Out-licensed multiple programs • Initiated clinical trials	• Advance clinical trials of AS-0871, AS-1763, and AS-0141 • Earn revenue from new license deals • Receive milestone payments from the out-licensed programs and deliver profits • Initiate pre-clinical and clinical studies of new pipelines	• Receive milestone payments and royalty income from the out-licensed programs and expand profits • Earn revenue from new license deals • Initiate pre-clinical and clinical studies of new pipelines

<ddRD>
- ✓ Advance clinical trials of AS-0871, AS-1763, and AS-0141
- ✓ Create next wave of pipeline
- ✓ Receive milestone payments and royalty income from out-licensed programs

<ddSP>
- ● Expand sales of in-house developed products and services in North America and Asia
- ● Secure sustainable sales growth by launching new products and services and reaching out to new customers
- ● Generate cash to invest in ddRD

ddRD: Drug Discovery R&D business
ddSP: Drug Discovery Support Business

Business Plan

(JPY million)	FY2022 Actual	**FY2023 Plan**	**Outlook for 2024 - 2026**
Total Sales	1,386	**902**	
ddSP business	1,100	**902**	Maintain stable sales
ddRD business	286	**—**	Revenue from milestone payments and upfront payments
Total Operating Loss	(1,269)	**(1,890)**	
ddSP business	452	**221**	Maintain stable profit while investing in product developments
ddRD business	(1,722)	**(2,111)**	Continue to invest in R&D and deliver profits depending on the size of milestone payments and upfront payments
Ordinary Loss	(1,278)	**(1,911)**	
Net Loss	(1,349)	**(1,936)**	

(JPY million)	FY2022 Actual	**FY2023 Plan**	**Outlook for 2024 – 2026**
R&D Cost	1,882	**1,968**	Invest in R&D (JPY1 bn to 2.5 bn) for the future growth.
Capex	125	**6**	Invest in equipment for R&D and IT system (JPY20 mn to 100 mn)

- Business plan for FY2023 dose not include potential milestone payments or upfront payments as the timing or the amounts are difficult to predict.
- Numerical targets for 2024-2027 are not disclosed for the same reason.

ddRD: Drug Discovery R&D business
ddSP: Drug Discovery Support Business

Key Milestones for 2023

Business		Key Milestones		
		Milestones for 2022	Achievement in 2022	Milestones for 2023
ddRD	AS-0871	☐ Start partnering activity	☑ Started partnering activity	☐ Complete Ph1 MAD study ☐ Prepare a package for licensing
	AS-1763	☐ Initiate Ph1b (US)	☑ Completed IND (US) ☐ FPI is expected in Q1 2023	☐ Ph1b FPI (US)
	AS-0141	☐ Initiate Ph1 expansion part	☑ Switched to 3+3 design in Ph1 dose escalation part ☐ Plan to initiate Ph1 expansion part in H2 2023	☐ Initiate Ph1 expansion part
	Research program	☐ Bring one or more programs in preclinical stage or license a program.	☑ STING antagonist was licensed to FRTX	☐ Bring one or more programs in preclinical stage or license a program.
ddSP		☐ Expand sales of in-house developed products and services ☐ Expand line-up of protein kinase products ☐ Increase target kinases to expand profiling service ☐ Seek collaboration opportunities to boost Carna's business	☑ Strong sales in North America and Asia. ☑ Launched 36 new kinase protein products ☑ Added 5 new PIK3 mutant targets to profiling service and 12 new targets to 1 mM assay ☑ Started discussion with potential collaboration partners	☐ Expand sales of in-house developed products and services in North America and Asia ☐ Increase line-up of protein kinase products ☐ Expand sales of cell-based assay

FPI: First Patient In
ddRD: Drug Discovery R&D business ddSP: Drug Discovery Support Business

☑ Achieved
☐ Plan or to be achieved

Balance Sheet

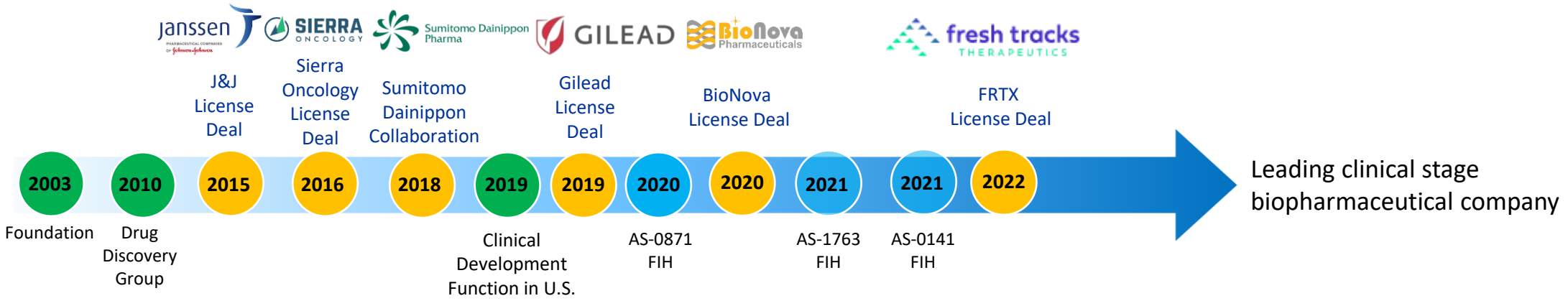
- In order to advance clinical trials, we aim to maintain adequate cash position by generating cash from Drug Discovery Support(ddSP) business and licensing, as well as by raising funds from capital markets.

(JPY million)	As of Dec. 31, 2021	As of Dec. 31, 2022	Change
Current assets	5,318	4,104	-1,214
Cash and deposits	3,817	3,379	-438
Non-current Assets	114	162	+48
Total assets	5,432	4,266	-1,166
Current liabilities	774	436	-338
Non-current liabilities	342	188	-154
Total liabilities	1,116	624	-492
Total net assets	4,315	3,641	-673
Total liabilities and net assets	5,432	4,266	-1,166

Appendix

Building Long-Term Value

Our goal is to deliver innovative therapies for patients suffering from serious diseases



2003 - 2021	2023 Plan	Long term plan
● Founding members who had expertise in kinase drug discovery technology spun out from Nippon Organon and established Carna. ● Started offering kinase proteins and screening services to pharmaceutical companies for kinase inhibitor drug discovery. ● In 2010, Drug Discovery Group was established to conduct internal drug discovery. ● Entered into four license agreements and one joint-development agreement with pharmaceutical companies. ● Initiated FIH study of BTK inhibitor AS-0871.	● Conducting Phase 1 studies of BTK inhibitor AS-0871, AS-1763, and CDC7 inhibitor AS-0141. ● Strengthening global clinical development capability. ● Advance research programs and initiate preclinical development.	● Advance clinical studies of AS-0871, AS-1763, and AS-0141 and earn upfront payments and milestone payments from out-licensing the pipelines. ● Receive milestone payments and royalties from licensees and strengthen financial position. ● Create next wave of pipeline.

FIH: First in Human

Management Team

Directors

Kohichiro Yoshino, Ph.D. **President & Chief Executive Officer, Representative Director**

Dr. Yoshino founded Carna Biosciences in 2003 as a spin-out venture from Nippon Organon, a subsidiary of N.V. Organon where he was the head of the Osaka Research Center. As a member of Organon Research Committee, Dr. Yoshino contributed to research and development of NV Organon. Before joining Nippon Organon, he engaged in the research and development of small molecule drugs at Kanebo Corporation Inc.
From 2004 to 2008, he was a Visiting Professor at Center for Advanced Science and Innovation, Osaka University.
He earned M.S. in Chemistry from the Graduate School of Tokyo Institute of Technology and Ph.D. from Kyoto University.

Norio Aikawa **Head of Drug Discovery and Support Business, Head of IP and Legal Department, Director**

Mr. Aikawa is one of the founding member of Carna Biosciences. Mr. Aikawa has a long and extensive experience in the area of intellectual property and has contributed to strengthening Carna's IP strategy. Before joining Carna in 2003, he was the head of Intellectual Property Department at Nippon Organon. Before that, he was the head of Intellectual Property Department at Kanebo Corporation.
He holds a bachelor's degree in Science from Hirosaki University.

Masaaki Sawa, Ph.D. **Chief Scientific Officer, Director**

Dr. Sawa built the current drug discovery group at Carna. Before joining Carna, he held positions at Sumitomo Dainippon Pharma.
Prior to that, he was a medicinal chemist at Nippon Organon, a subsidiary of N.V. Organon.
From 2004 to 2006, he was a visiting scientist at the Scripps Research Institute in San Diego.
Dr. Sawa was a Visiting Professor at Graduate School of Medicine, Kobe University from 2013 to 2015.
He received his Ph.D. from Kyoto University.

Emi Yamamoto **Chief Financial Officer, Director, President of CarnaBio USA, Inc.**

Ms. Yamamoto joined Carna Biosciences in 2004 after engaged in fund administration at CSK Venture Capital. She built Carna's accounting and business management group and held a responsible role in Carna's IPO. Since 2017, she leads administration group, in charge of accounting, finance, human resources, and corporate planning.
Ms. Yamamoto holds a bachelor's degree in Business Administration from Aoyama Gakuin University, and a Certified Public Accountant.

Management Team

Directors

Atsuo Arita **Outside Director**

Before joining the Board of Directors in 2020, Mr. Arita served as External Auditor of Carna Biosciences from 2004 to 2020, overseeing its management as a full-time company auditor. He held various responsible roles in accounting, finance, and sales management at Kanebo Corporation Ltd. and was the head of business management at Kanebo.
He holds a bachelor's degree in Business and Commerce from Keio University.

Tsuguo Ogasawara **Outside Director**

Mr. Ogasawara served as External Auditor of Carna Biosciences from 2005 to 2020 before joining the Board of Directors in 2020. He has brought Carna his extensive experience in international business. He was a Director at Chugai Pharmaceutical Co. Ltd., in charge of international business. Prior to that, he was engaged in business management, finance, and international business at Toray Industries, Inc.
He holds a bachelor's degree in Economics from Keio University.

Teruo Takayanagi, Ph.D. **Outside Director**

Dr. Takayanagi joined the Board of Directors of Carna Biosciences in 2015. He was the Director of Daiichi Pharmaceutical Co., Ltd. from 2001 to 2006 where he engaged in the R&D management and led post-marketing surveillance to promote proper use of its pharmaceutical products. He also held a responsible role in business integration with Sankyo. He was a full-time Auditor of Daiichi Sankyo Company, Limited from 2007 to 2011. Dr. Takayanagi is Board Member of Showa Pharmaceutical University and Auditor of Japanese Society of Drug Informatics.
Dr. Takayanagi received his Ph.D. from the University of Tokyo.

Takao Matsui **Outside Director**

Mr. Matsui served as External Auditor of Carna Biosciences since 2019 to 2020 before joining the Board of Directors in 2020. He has over 35 years of experience in financial audit and related advisory business. He served as Certified Public Accountant at KPMG AZSA LLC. from 1982 to 2018. Mr. Matsui also currently serves as Outside Director of AIR WATER, INC. He was a Specially Appointed Professor at School of Accountancy, Kansai University since April 2018 to March 2020. He is a part-time lecturer at Kansai University and School of Accountancy, Kansai University since April 2020.
Mr. Matsui holds a bachelor's degree in School of Business Administration from Kwansei Gakuin University, and a Certified Public Accountant.

"Carna" is a goddess of Roman mythology who takes care of human health, protecting the human heart and other organs as well as everyday life, and is said to be the root for the word "cardiac."

The word "biosciences" is derived from the words 'biology' and 'life sciences.'

Carna Biosciences has created contemporary Carna goddess with protein kinase.

Carna Biosciences, Inc.

Corporate Planning

BMA3F 1-5-5 Minatojia-Minaimachi,

Chuo-ku, Kobe 650-0047

https://www.carnabio.com/

ir-team@carnabio.com