Financial Results
FY2021 Q3
(January to September 2021)

Carna Biosciences, Inc.

Stock Code: 4572

FY2021 Q3 Key Highlights

- Announced positive results for AS-0871 Phase 1 Single Ascending Dose study. (July)
- Completed dosing in Phase 1 Single Ascending Dose study of BTK inhibitor AS-1763. (July)
- Bought back and canceled Series 18th Subscription Rights to Shares. (July)
- Issued Series 19th Subscription Rights Shares. (July)
- The board resolved to apply for the listing on the Growth Market under the new market segment of Tokyo Stock Exchange.(September)
- The research paper on the discovery of AS-1763 was published in *Journal of Medicinal Chemistry*. (September)
- The research paper on the discovery of AS-0141 was published in *Journal of Medicinal Chemistry*. (October)

Robust Drug Pipeline

<Oncology>

Compound	Target	Indication	Discovery/Preclinical	Clinical	Partner
AS-0141	CDC7/ASK	Cancer			
Small Molecule	Kinase	Immuno-Oncology			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			Sumitomo Dainippon Pharma
AS-0871	BTK	Immune-inflammatory diseases			
Small Molecule	N/A	Malaria			
Small Molecule	STING	Immune-inflammatory diseases			

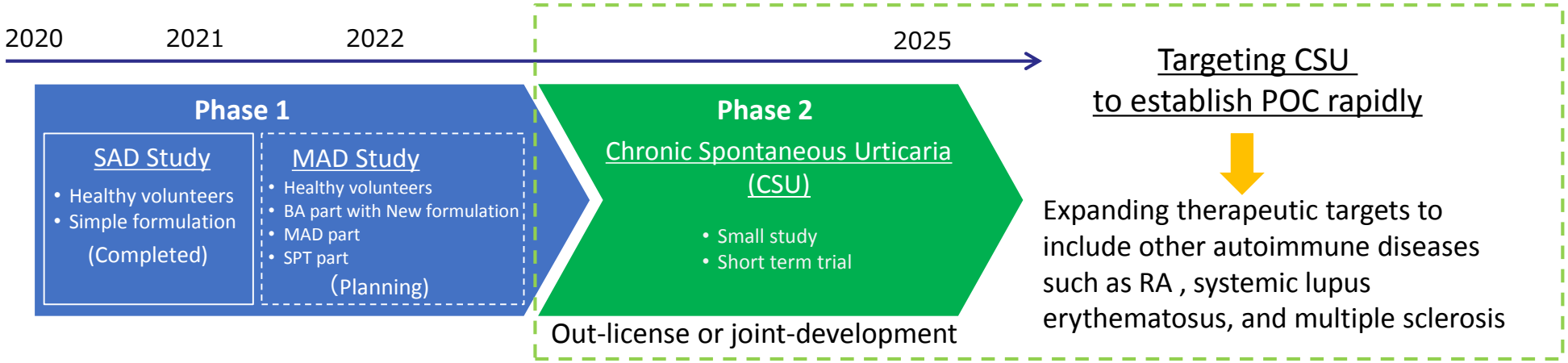
✓We are actively pursuing early discovery programs to create next wave of pipeline.

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
- Find a partner to conduct further development after completing Phase 1 study



POC：Proof of Concept

AS-0871: Phase 1 Clinical Trial Underway

Phase 1 Single Ascending Dose (SAD) study: *Completed*

- ✓ The SAD study in healthy volunteers was initiated in H2 2020 in the Netherlands
- ✓ Safe and well-tolerated at all dose levels tested from 5 mg to 900 mg

Favorable Pharmacokinetic Profile

- ✓ Demonstrated a favorable pharmacokinetic profile with dose-dependent exposures (Cmax and AUC)
- ✓ Elimination half-life ranging 7-9 hours after administration at 100 mg or above

Promising Pharmacodynamic effects

- ✓ Demonstrated a dose-dependent and marked inhibition of basophil and B-cell activation

Clinical Development Plan

- ✓ Plan to initiate a Multiple Ascending Dose (MAD) study consisted of three parts with a new formulation
  - ➢ BA part: To evaluate the bioavailability (BA) of capsule and tablet formulations
  - ➢ MAD part: To evaluate the safety, tolerability, PK and PD in the 2-week multiple ascending dose (MAD) part
  - ➢ SPT part: To evaluate the effect on allergen-induced skin reaction in the skin prick test (SPT) to assess the potential of AS-0871 for the treatment of Chronic Spontaneous Urticaria (CSU), a disease with high unmet needs
- ✓ The bioavailability (BA) part in human with the capsule formulation will be conducted in H2 2021 and the GMP production of the drug product is underway
- ✓ New tablet formulation is under development, and the BA part is also planned
- ✓ Plan to initiate the MAD part with the new formulation based on the BA studies

AS-0871: Excellent Kinase Selectivity

◆ 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

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Journal of Medicinal Chemistry

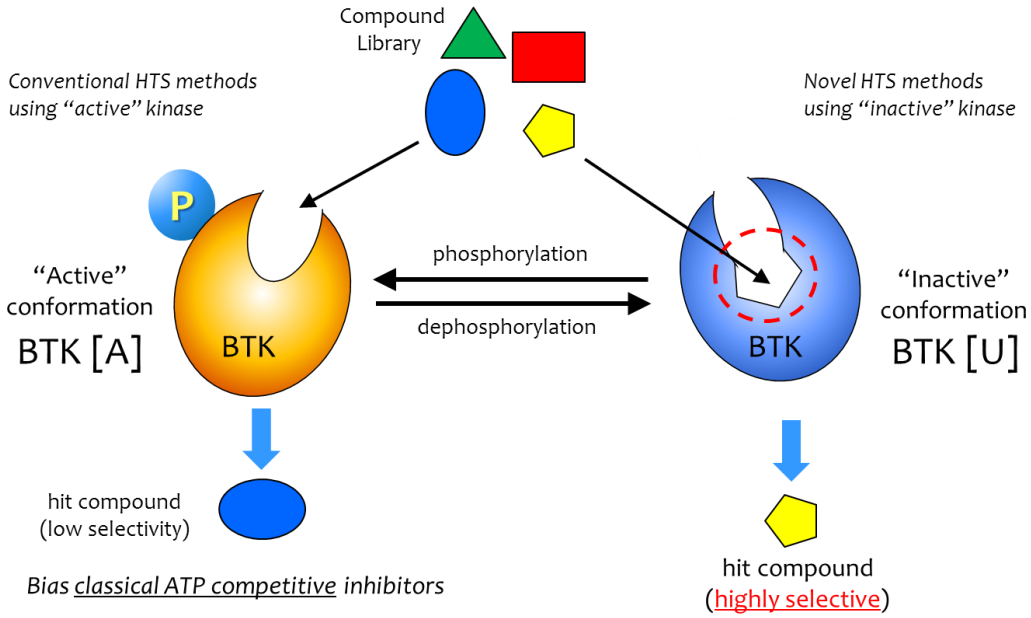
Article

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

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

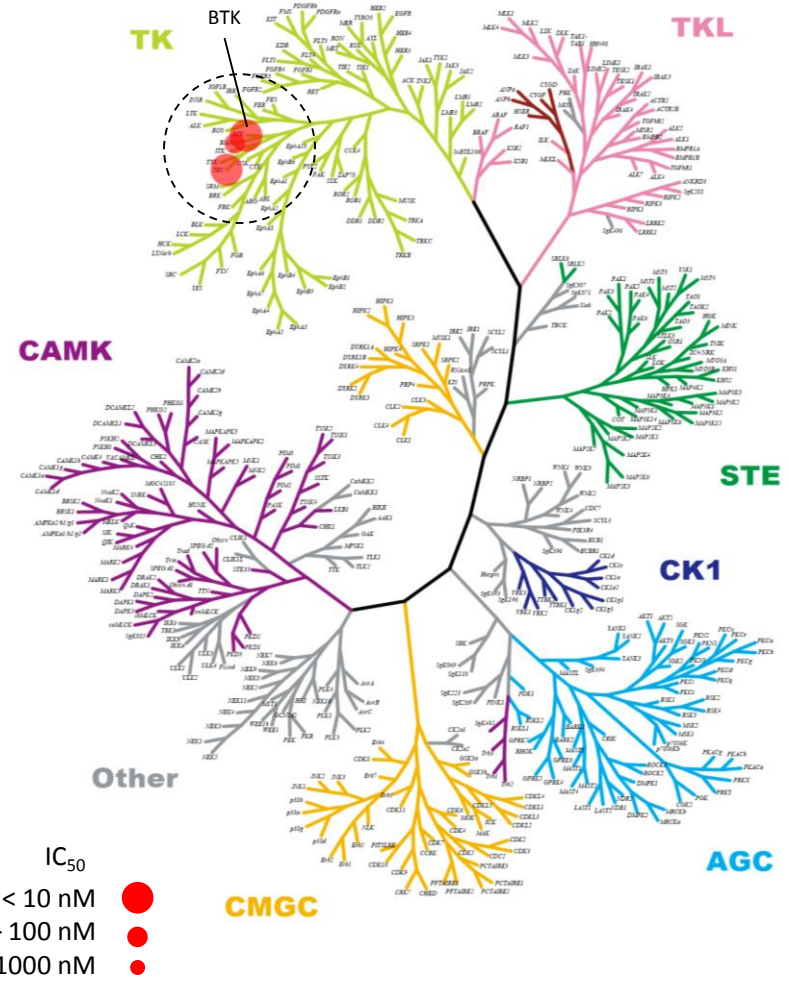


Bias classical ATP competitive inhibitors

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

◆ Kinase Selectivity Profiling

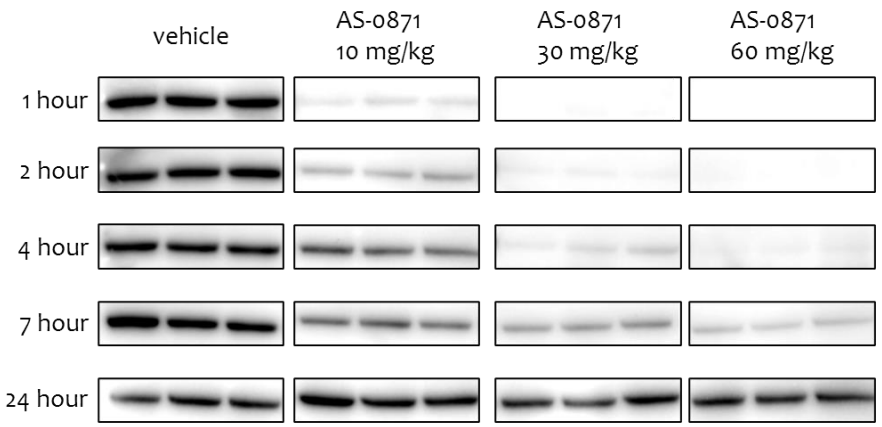
Only inhibited 2 other kinases in a total of 312 kinases tested at 0.3 μM concentration.

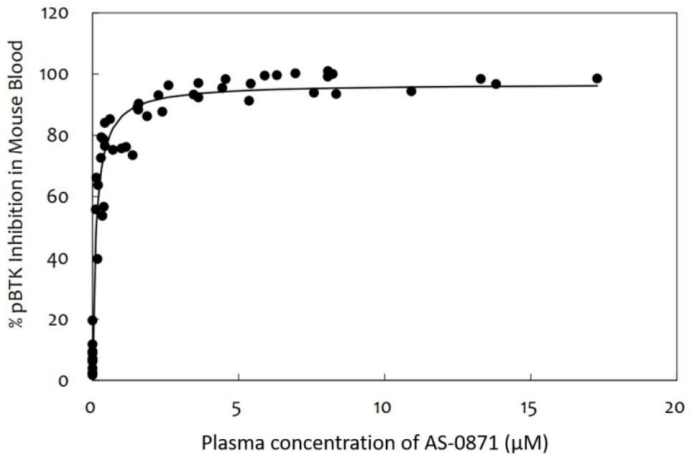


AS-0871: In Vivo Therapeutic Efficacy

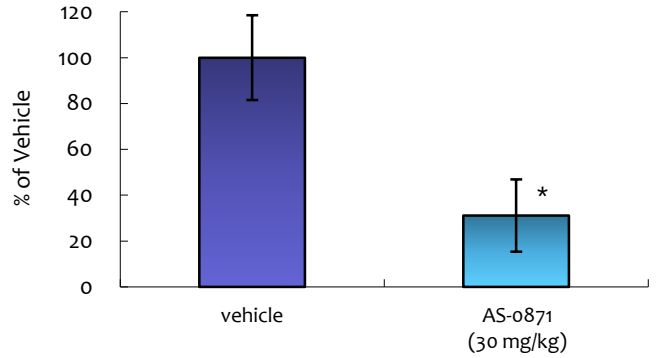
- PK/PD Study

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

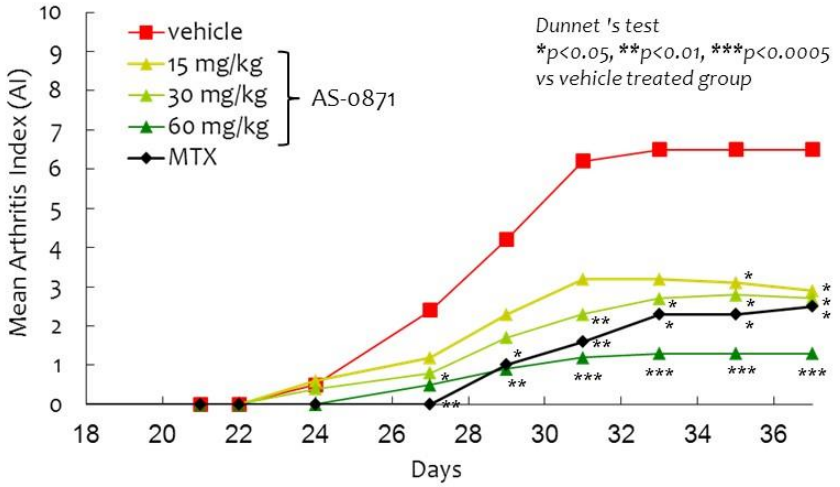




- Passive cutaneous anaphylaxis (PCA) mouse model (n=5)



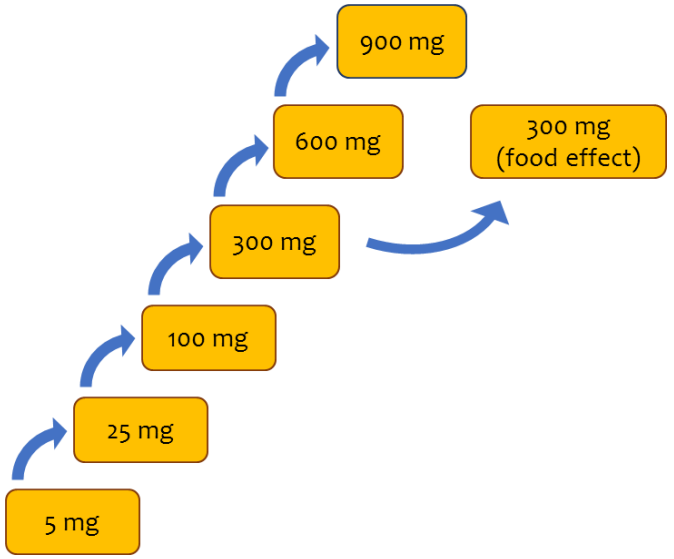
- Collagen-induced arthritis (CIA) mouse model (n=10)



AS-0871: FIH study

SAD Part (Completed)

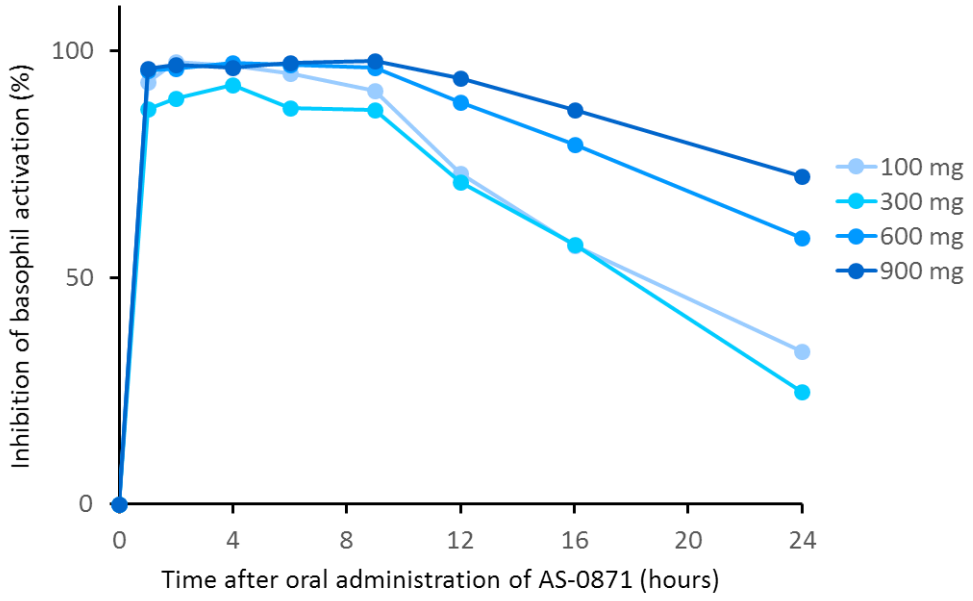
Step 1 Single Ascending Dose Study (SAD)	Step 2
• 6 dose levels (8 subjects/cohort) • Placebo controlled (6 active / 2 placebo) • Safety and tolerability • Pharmacokinetics and pharmacodynamics	• Food effect

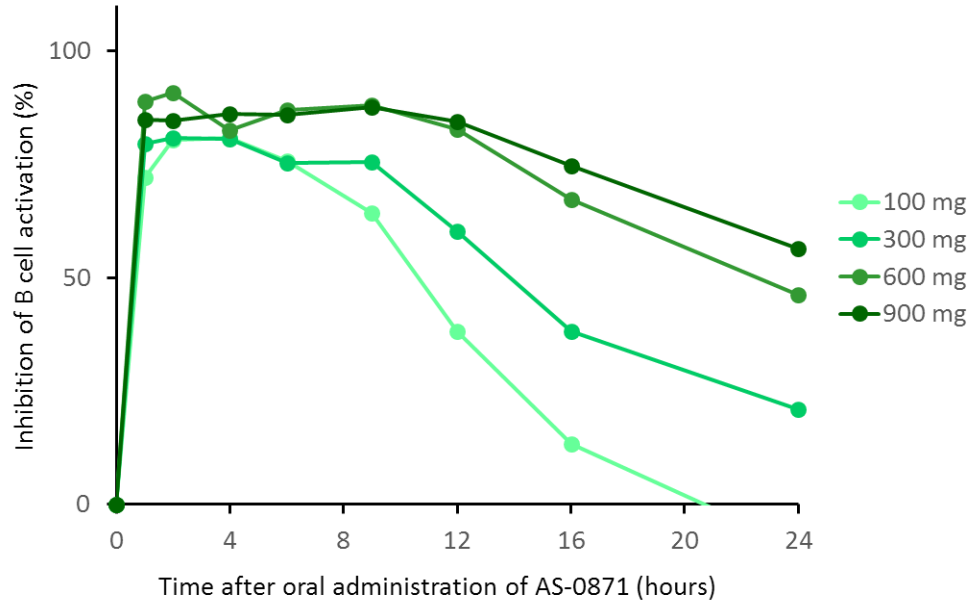


- ✓ AS-0871 is well-tolerated without any safety concerns.
- ✓ Favorable pharmacokinetic profile.
- ✓ Blood samples to assess PD effects were analyzed for evaluation of the B-cell and basophil responses. Administration of AS-0871 at 100mg or above resulted in strong inhibition of B-cell and basophil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



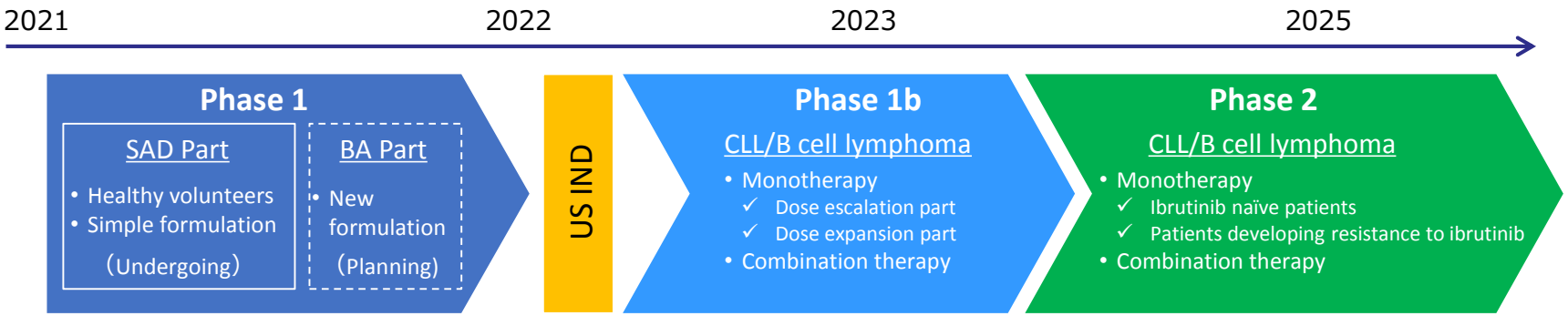


AS-1763：Next Generation BTK Inhibitor Targeting Blood Cancer

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
- Potential applications for autoimmune diseases
- Plan to accelerate the clinical studies utilizing the clinical data of BioNova, the licensee in Greater China



BA: Bioavailability
IND: Investigational New Drug application

AS-1763 : Phase 1 Clinical Trial Underway

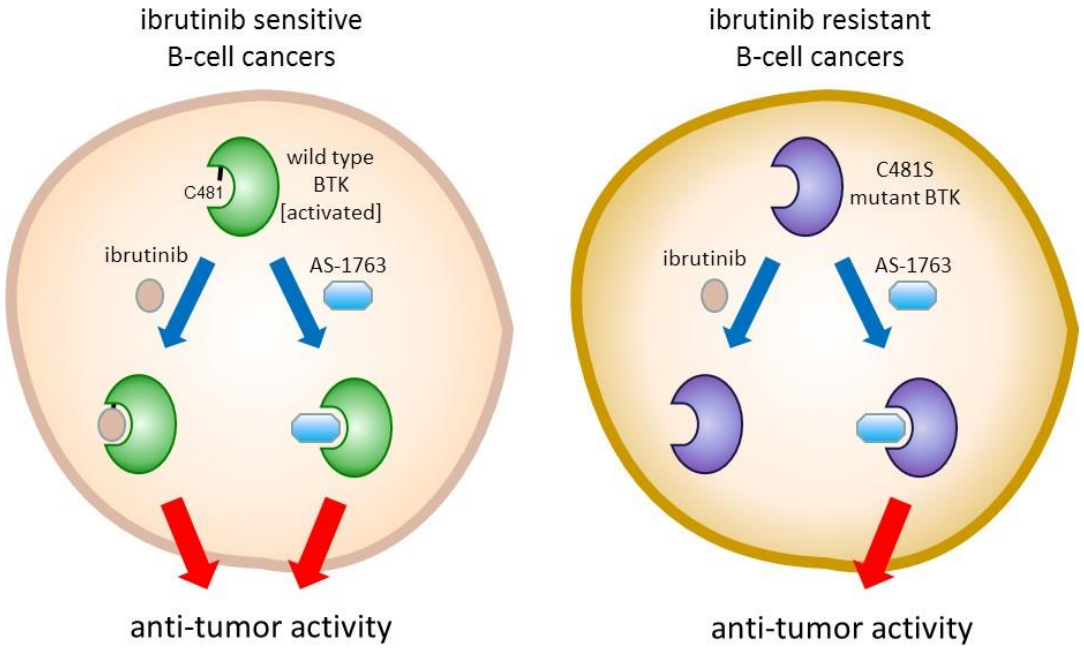
Phase 1 Study in healthy volunteers

- ✓ The Phase 1 study in healthy volunteers was initiated in the Netherlands in H1 2021
- ✓ Dosing in the SAD part was completed
- ✓ Well-tolerated without any safety concerns
- ✓ Pharmacokinetic profile was also found favorable

Clinical Development Plan

- ✓ New formulation has been developed and the GMP production is underway
- ✓ The BA part in the Phase 1 using new formulation will be conducted in H2 2021
- ✓ Plan to initiate Phase 1b study in patients with chronic lymphocytic leukemia (CLL)/B cell lymphoma in the U.S. in 2022
- ✓ Request a pre-IND (Investigational Drug Application) meeting with FDA
- ✓ Aim to conduct clinical studies efficiently, collaborating with BioNova

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

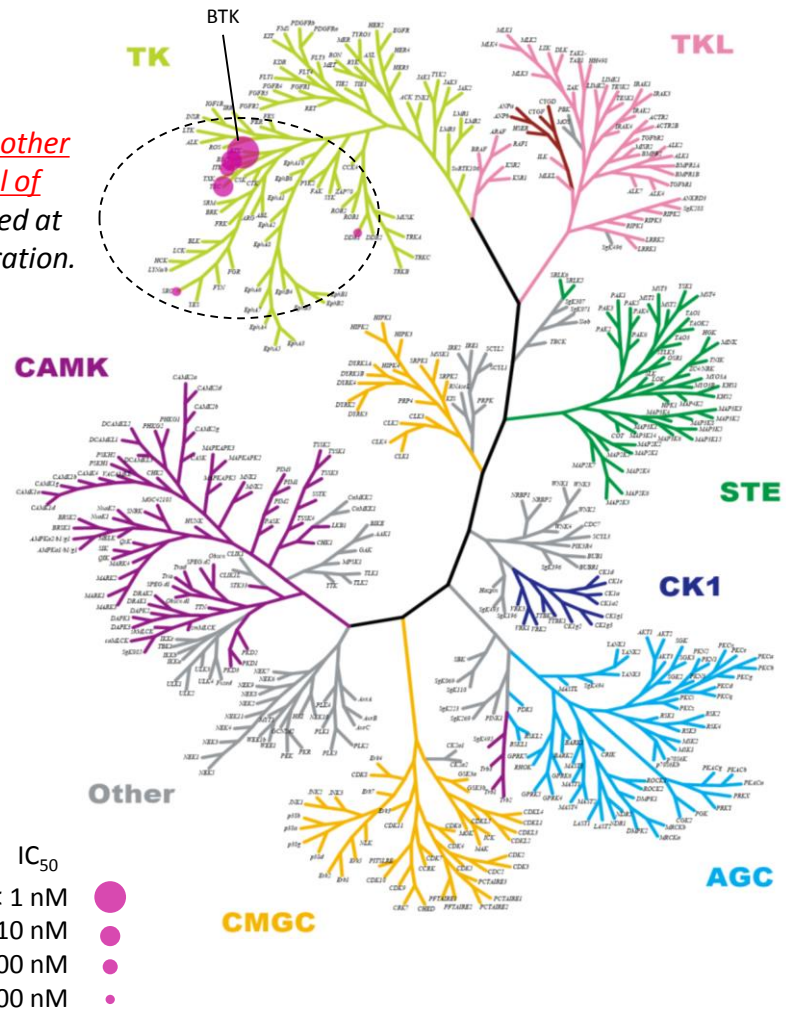
50-fold Stronger activity

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.

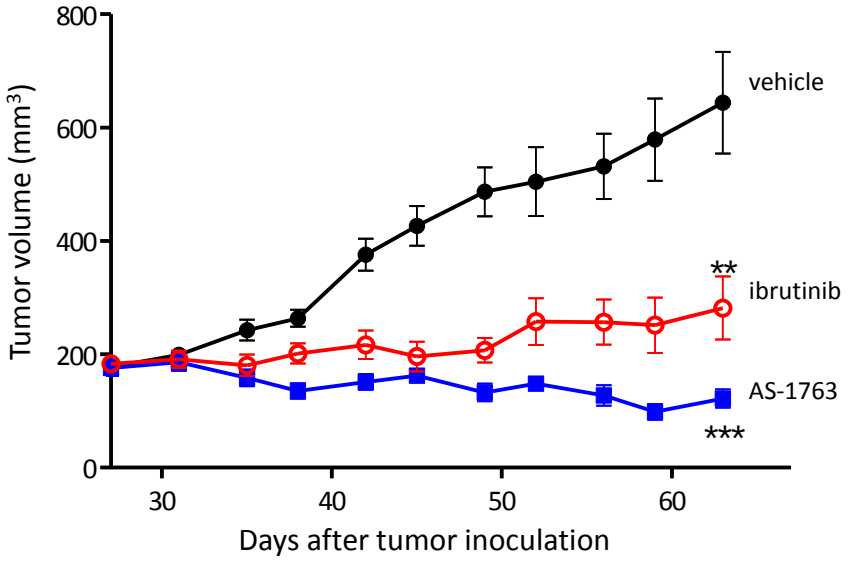
◆ Kinase selectivity profiling

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

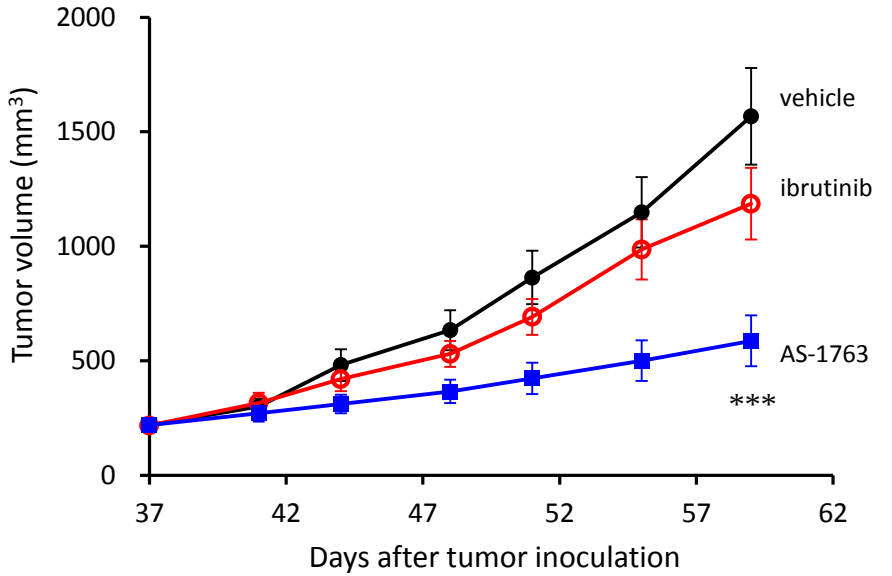
- In vivo antitumor effects of AS-1763 on human B-cell non-Hodgkin lymphoma cell line, OCI-LY10 tumor xenograft mouse model (n=8-10)



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

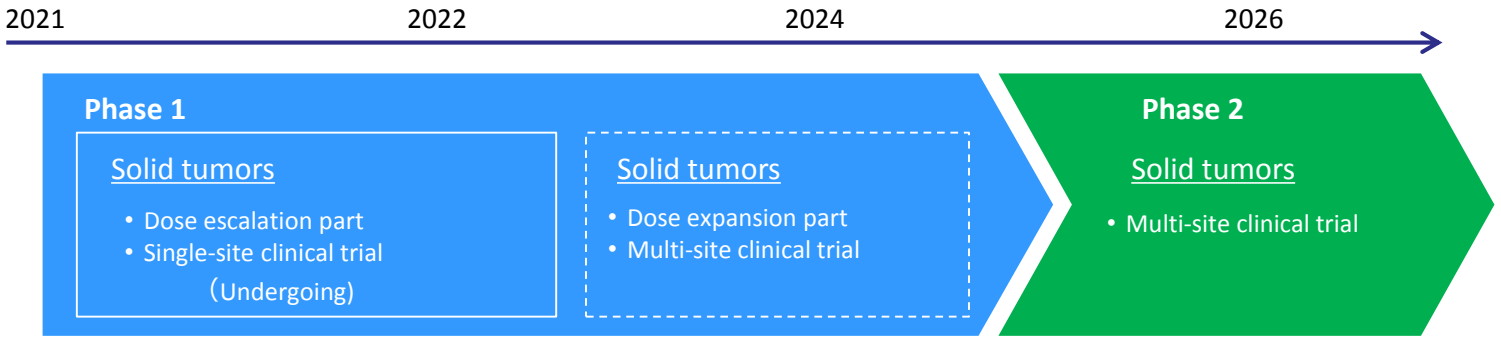
J Med Chem. 2021 Oct 14;64(19):14129-14141.

AS-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 Underway

Phase 1 Study in patients

- ✓ The Phase 1 study in 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 dose escalation part is ongoing
- ✓ No dose-limiting toxicity (DLT) has been observed so far
- ✓ Approved dose escalation to Cohort 3 (dose level 3)

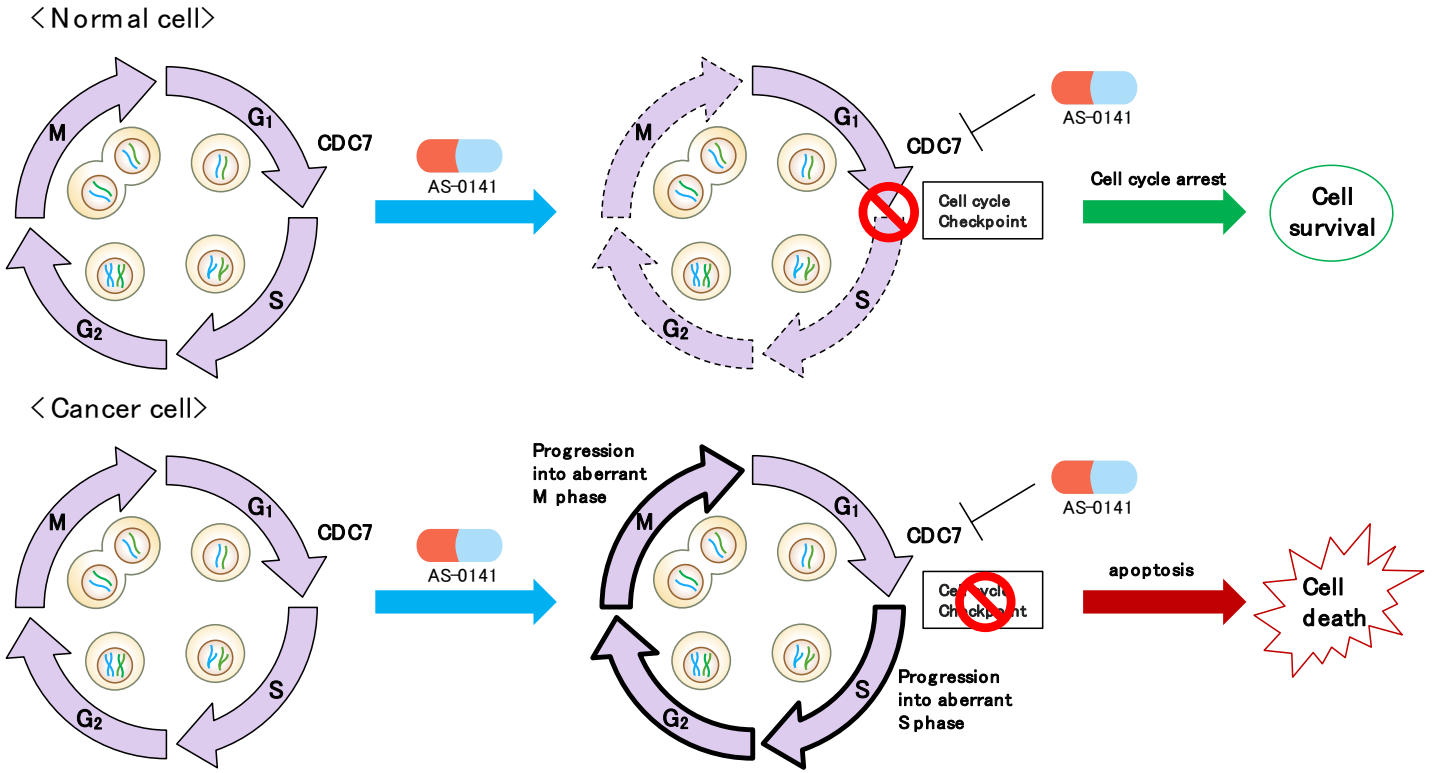
Clinical Development Plan

- ✓ Continuing dose escalation
- ✓ Select dose level for expansion phase
- ✓ Exploring multiple types of solid tumors

AS-0141: Highly Selective CDC7 Inhibitor

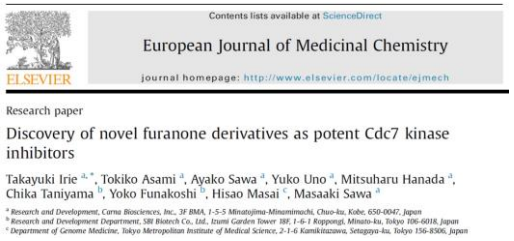
■ CDC7 kinase inhibitor

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]

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[c] Department of Genome Medicine, Tokyo Metropolitan Institute of Medical Science, 2-1-6 Kamikitazawa, Setagaya-ku, Tokyo 156-8506, Japan


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

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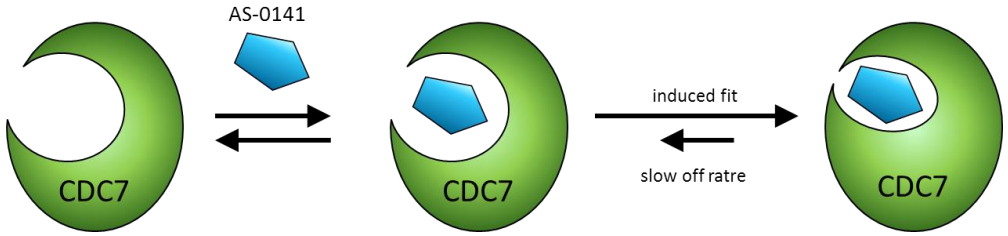


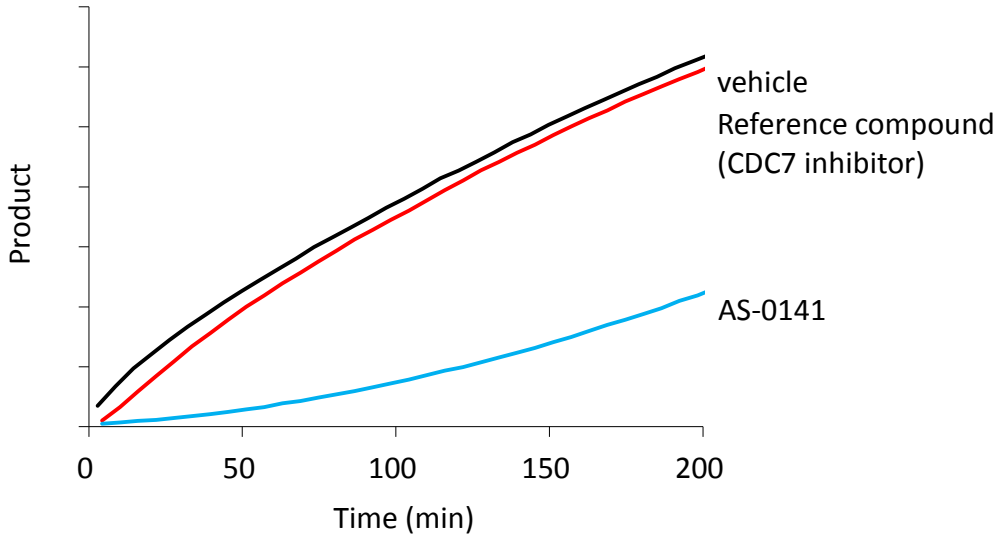
Inhibitory potency (IC_{50}) for CDC7 in the presence of 1 mM ATP

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

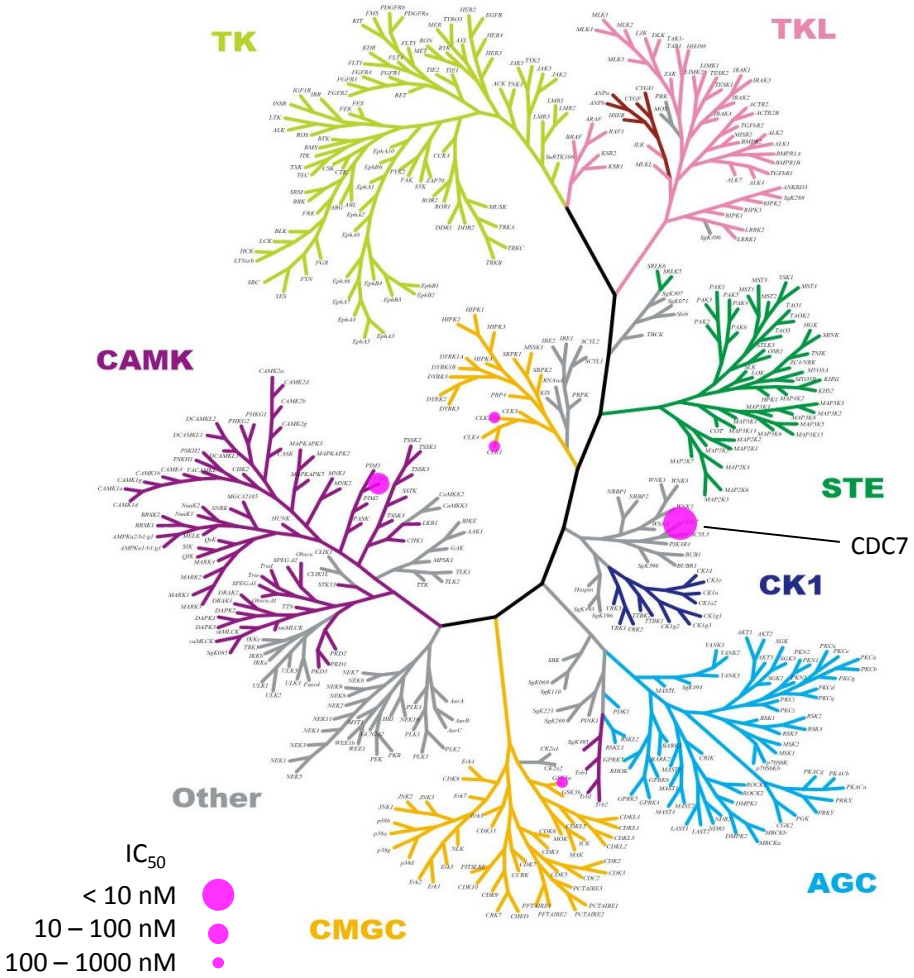
Rapid dilution assay for Cdc7 inhibitors. Recovery of enzymatic activity was monitored by formation of the phosphorylated product.



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)	
	Preincucabation	
	-	+
CDC7	503	2.4
	210-fold	
PIM1	30	34
CLK1	212	206
CLK2	270	227
GSK3α	189	251

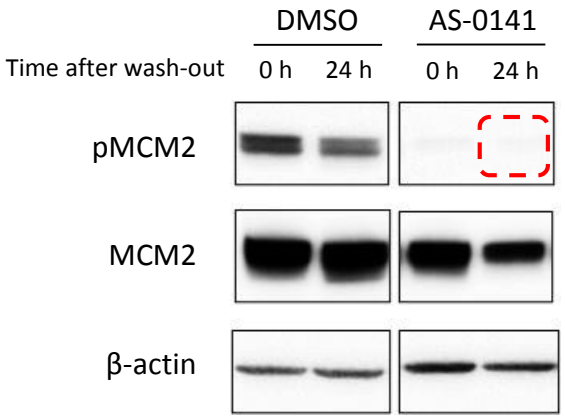
CDC7 is the only kinase that shows preincubation effect

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

AS-0141: Strong Cellular Activity

◆ Prolonged inhibition in cells

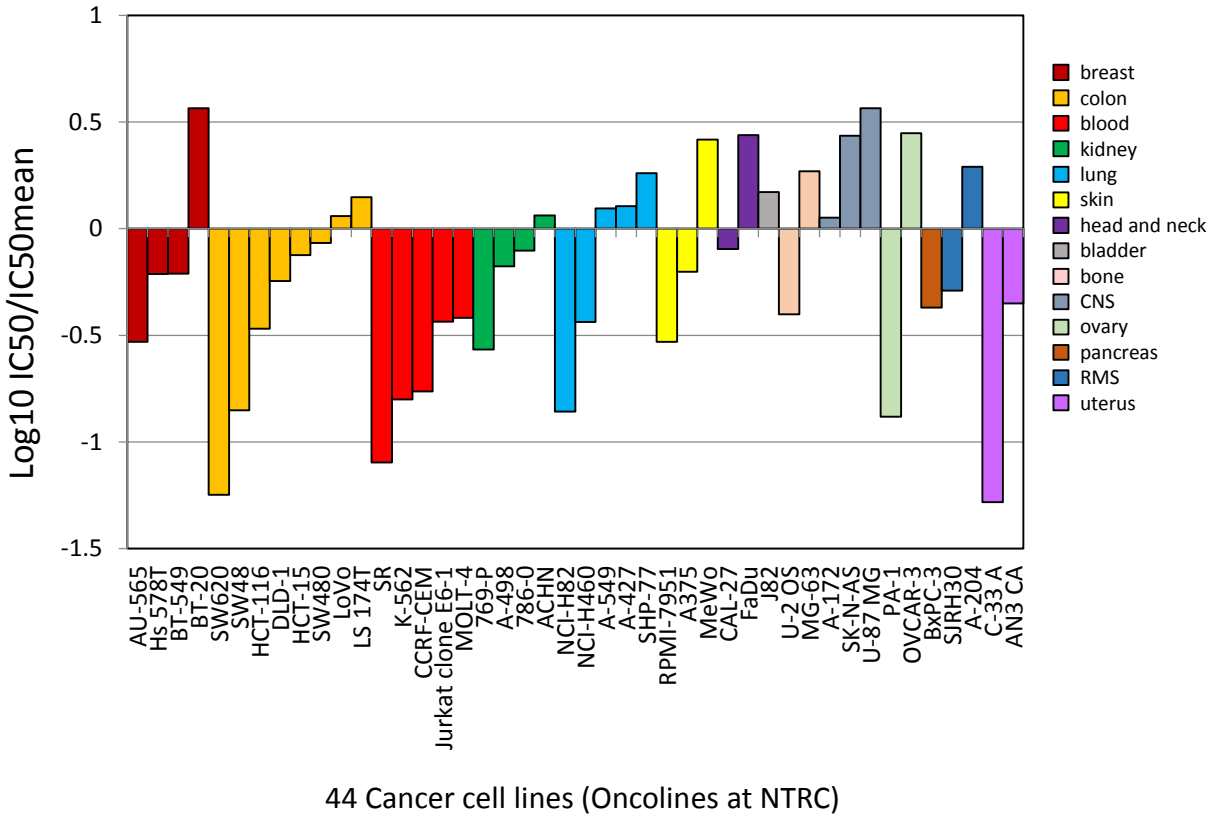
Human colon cancer cell line, Colo-205 cells were treated with DMSO control or AS-0141. After washout of the inhibitor, the cells were further incubated in the same media for 0 or 24 h and subjected to western blot analysis.



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

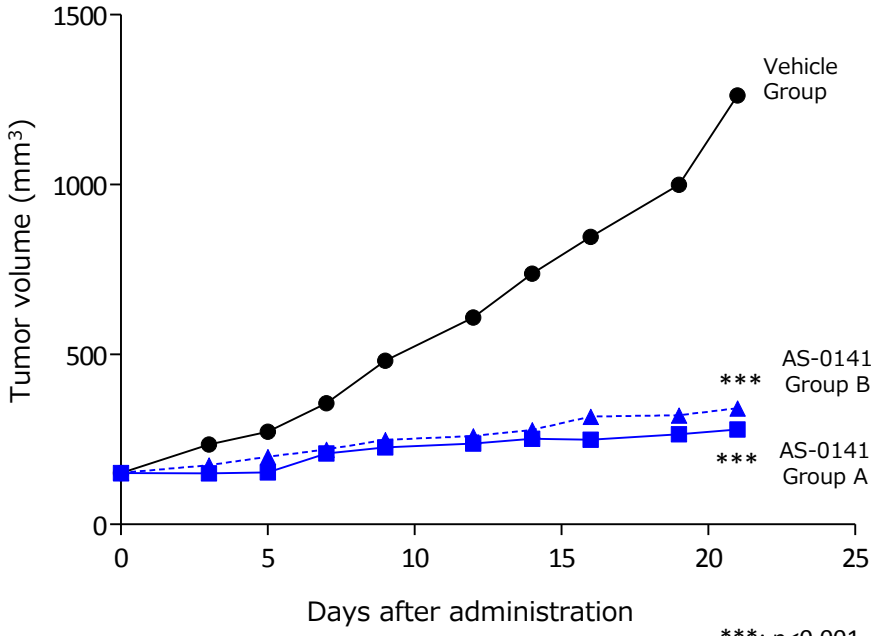


44 Cancer cell lines (Oncolines at NTRC)

AS-0141: Robust In Vivo Antitumor Efficacy

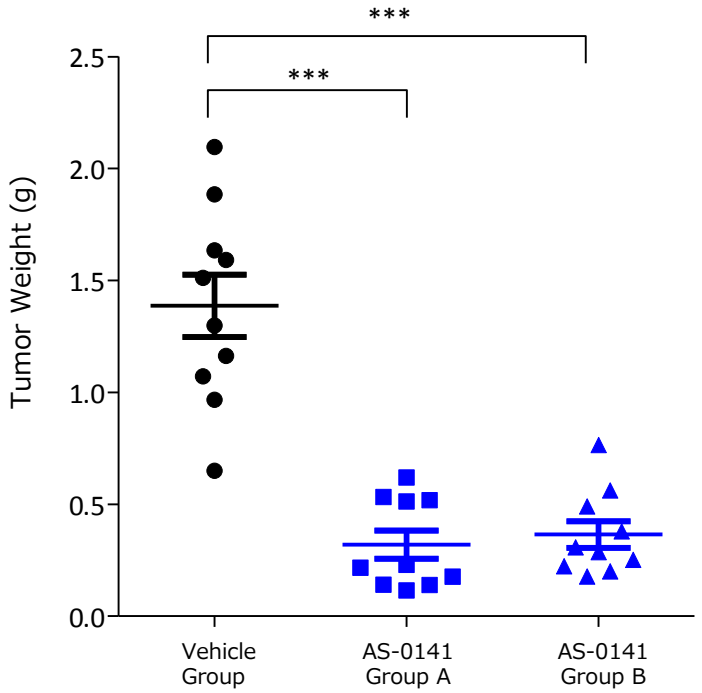
- In vivo antitumor efficacy of AS-0141 in a SW620 (human colon cancer) xenograft mouse model

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 Q3 Key Highlights

- At Drug Discovery Support business, sales in Q1-3 were slightly behind the full year plan while operating profit was stronger than expected.
  - ✓ In North America, sales declined yoy but they were stronger than expected thanks to sales to Gilead.
  - ✓ In Japan, sales of kinase proteins were strong while profiling service and agent business (cell-based assay and X-ray crystallography) were weaker than expected. Weak agent business sales had limited impact on operating profit as the profitability of the agent business is relatively low.
  - ✓ Sales of Cell-based assay service using NanoBRET™ technology were strong. Launched a full-panel assay service (192 kinds of kinases) aiming to boost sales further.
  - ✓ In China, orders from the agent were strong. However, sales in September and October were temporarily affected by the delay in the import custom clearance due to COVID-19. Working closely with the agent to deliver products as soon as possible.
- Focusing on the growth areas to achieve full year sales target.
  - ✓ Increase sales from newly established biotech companies in the U.S.
  - ✓ Increase sales of custom kinase proteins only Carna can offer.
  - ✓ Conduct wet lab work for AI drug discovery companies to increase profiling sales.

FY2021 Q3 Consolidated Financial Results

(JPY million)	FY2020 Q3 Actual	**FY2021 Q3 Actual**	YoY Change	FY2021 Plan	
Sales	847	**636**	-211 -24.9%	923	-Slightly behind the FY sales plan due to weaker than expected sales in Japan. -Received an upfront payment from licensing in Q1 FY2020.
Operating Profit/Loss	(615)	**(1,169)**	-553	(1,811)	
Ordinary Profit/Loss	(625)	**(1,171)**	-546	(1,816)	
Net Profit/ Loss	(649)	**(1,178)**	-528	(1,825)	
R&D Cost	941	**1,310**	+368 +39.1%	1,981	-Investment in clinical studies.

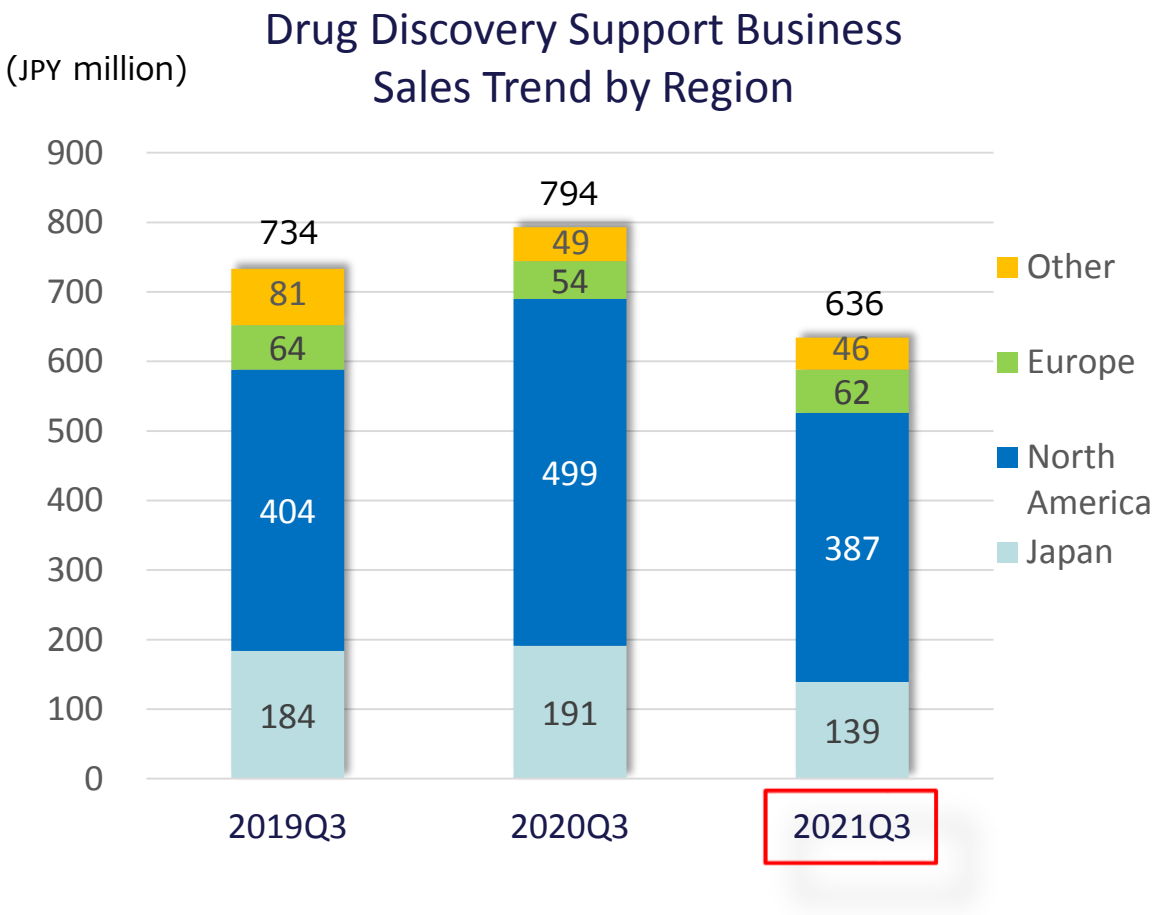
Note 1: Rounded down to the nearest million yen.
Note 2: YoY change % for Operating Profit/Loss, Ordinary Profit/Loss, and Net Profit/Loss are not presented since losses were recorded.
Note 3: FY2021 plan was disclosed on February 12, 2021.

FY2021 Q3 Results by Business Segment

(JPY million)	FY2020 Q3 Actual	**FY2021 Q3 Actual**	YoY Change	FY2021 Plan	vs. FY Plan	
Total Sales	847	**636**	-211 -24.9%	923	69.0%	
ddSP business	794	**636**	-158 -19.9%	923	69.0%	Slightly behind the FY sales plan due to weaker than expected sales in Japan.
ddRD business	53	—	-53	—	—	Received an upfront payment from licensing in Q1 2020.
Total Operating Profit/Loss	(615)	**(1,169)**	-553	(1,811)	—	
ddSP business	347	**199**	-148 -42.7%	207	95.8%	Sales of high-margin kinase proteins were robust.
ddRD business	(963)	**(1,368)**	-404	(2,019)	—	Investment in clinical studies.

Note 1: Rounded down to the nearest million yen.
Note 2: YoY change % for consolidated operating profit/loss and ddRD operating profit/loss are not presented since since losses were recorded.
Note 3: FY2021 plan was disclosed on February 12, 2021.
Note 4: ddRD: Drug Discovery R&D business, ddSP: Drug Discovery Support Business

FY2021 Q3 Discovery Support (ddSP) Business Sales by Region



- Japan: Decreased 26.8% YoY
  - Sales of profitable kinase proteins were robust, offsetting weak profiling sales.
  - Agent business (cell-based assay service and X-ray crystallography) were weak but the impact on the operating profit was limited as its profitability is relatively low.
- North America: Decreased 22.4% YoY
  - Contribution from sales to Gilead continued.
  - NanoBRET assay service showed strong growth.
  - Agent business (cell-based assay service) were weak.
- Europe: Increased 13.6% YoY
  - Kinase proteins, profiling service and NanoBRET assay service were robust.
- Other: Decreased 5.2% YoY
  - Orders from Chinese agent were robust.
  - Sales in September and October were temporarily affected by the delay in the import custom clearance in China.

Balance Sheet

(JPY million)	As of Dec. 31, 2020	As of Sep. 30, 2021	Change	Reason for changes
Current assets	4,708	4,084	-624	
Cash and deposits	4,299	3,790	-508	
Non-current Assets	127	127	+0	
Total assets	4,835	4,211	-624	
Current liabilities	727	584	-142	
Non-current liabilities	284	147	-136	Long term loans payable -105 Bonds payable -28
Total liabilities	1,011	731	-279	
Total net assets	3,824	3,479	-344	Capital stock and capital surplus +810, Retained earnings -1,178
Total liabilities and net assets	4,835	4,211	-624	

Shareholders' equity ratio	79.0%	82.4%
BPS	308.0 yen	264.4 yen
PBR	3.9x	4.2x
Share price of Carna	1,212 yen	1,099 yen

Note: Share price is the closing price of the term end.

"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

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