Company Update

Striving to improve human health

April 2, 2019

NASDAQ **CNAT**

Conatus Pharmaceuticals

Forward-looking Statements

This presentation contains forward-looking statements. All statements other than statements of historical facts contained in this presentation, including statements regarding our future results of operations and financial position, business strategy, prospective products, product approvals, research and development costs, timing and likelihood of success, plans and objectives of management for future operations, and future results of current and anticipated products are forward-looking statements. These statements involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. These known risks and uncertainties are described in detail in our filings made with the Securities and Exchange Commission from time to time. Because forward-looking statements are inherently subject to risks and uncertainties, some of which cannot be predicted or quantified and some of which are beyond our control, you should not rely on these forward-looking statements as predictions of future events. The events and circumstances reflected in our forward-looking statements may not be achieved or occur and actual results could differ materially from those projected in the forward-looking statements.

All forward-looking statements are qualified in their entirety by this cautionary statement, which is made under the safe harbor provisions of the Private Securities Litigation Reform Act of 1995 and we undertake no obligation to revise or update this presentation to reflect events or circumstances after the date hereof.

Conatus at a Glance

Lead in-licensed compound emricasan has the potential to modify liver disease outcome

Two ongoing Phase 2b NASH cirrhosis trials reading out in mid-2019

Novartis partnership fully funds any further emricasan development

Lead internally developed compound CTS-2090 targeted for clinical testing 1H20

Capital at least sufficient to fund emricasan commitments and CTS-2090 IND-enabling studies

Emricasan – Targeting Unmet Need in Liver Disease

Profile

First-in-class pan-caspase inhibitor ideally suited to treat liver disease

Orally administered

Actively transported into the liver

Not metabolized in the liver

Addresses all etiologies of cirrhosis

Efficacy

Potent mechanism with multiple disease intervention points

Confirmed activity across broad spectrum of chronic liver disease

Signal of anti-fibrotic treatment effect using a histology endpoint in HCV

Clinically meaningful reductions in relevant cirrhosis endpoints

Safety

Administered to ~950 subjects (~700 with liver disease) across 19 clinical trials

Well tolerated with ~425 patient-years of exposure

Serious adverse event and adverse event profiles similar in placebo and emricasan treated patients

Phase 2b ENCORE-PH Trial

In NASH Cirrhosis Patients with Severe Portal Hypertension

EmricasaN, a Caspase inhibitOR, for Evaluation in Portal Hypertension

Design

~240 patients at ~70 sites across US and EU. Randomized 1:1:1:1 to receive placebo or emricasan at 5 mg, 25 mg, or 50 mg BID

NASH cirrhosis and severe portal hypertension
(HVPG ≥12 mmHg)

Double-blind, placebo-controlled

Primary Endpoint

Change from baseline to Week 24 in mean HVPG in each dosing group compared with placebo

Strong basis for HVPG as a surrogate endpoint in patients with severe portal hypertension

Extension

24-week treatment/placebo continuation

Following for liver function and clinical outcomes

Top-line HVPG results reported 4Q18
Extension results expected mid-19

Phase 2b ENCORE-LF Trial

Evaluating Clinical Outcomes in NASH Cirrhosis Patients with Impaired Liver Function

EmricasaN, a Caspase inhibitOR, for Evaluation in Portal Hypertension

Design

~210 patients at ~90 sites in US. Randomized 1:1:1 to receive placebo or emricasan at 5 mg, or 25 mg BID

Decompensated NASH cirrhosis

Double-blind, placebo-controlled

Primary Endpoint

Event-free survival, free from:

01 All-cause mortality

02 New decompensation events

03 ≥4 points MELD score progression

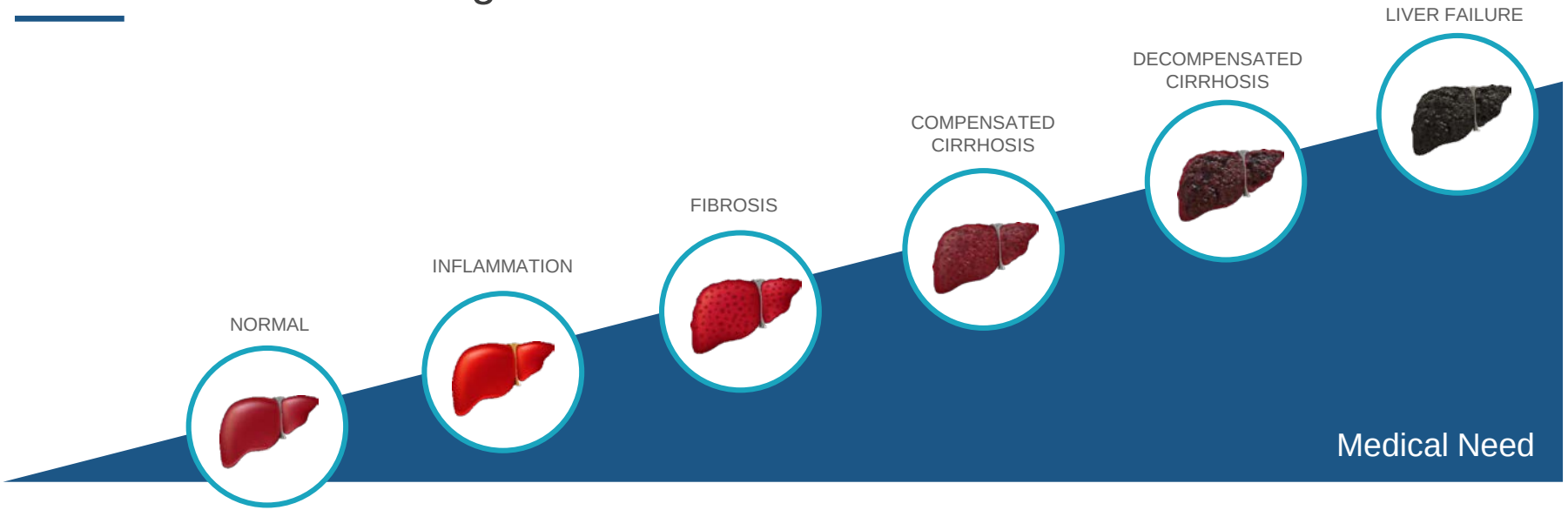
Top-line results expected mid-19

Phase 2b Trials Define Distinct Paths to NASH Cirrhosis Market

Potential Accelerated and Regular Approval Opportunities

Ongoing P2b Trial	Endpoint	Clinical Benefit	Market
ENCORE-PH Extension Compensated or early decompensated cirrhosis with severe portal hypertension	Liver Function Clinical Outcomes	Improve portal hypertension and improve liver function	Cirrhosis w/ Severe PH
ENCORE-LF Decompensated cirrhosis	Event-free Survival	Prevent decompensation event and improve liver function	Decompensated Cirrhosis

Medical Need and Diagnosis Rates Drive Value in Cirrhosis



2030 U.S. NASH PATIENT ESTIMATES			
US Patients	Early Fibrosis F0-F1	Advanced Fibrosis F2-F3	Cirrhosis F4
Prevalence*	12.9M	10.6M	3.5M
Diagnosed*	1.8M	1.8M	**2.9M**

Cirrhosis is an attractive market opportunity

- Unmet need recognized by doctors and patients
- Treatment value proposition recognized by payers
- NASH related is ~25% of market opportunity
- Safety and efficacy profile appropriate for disease state

*Estes C et al J Hepatol 2018 / analyst reports. Assumes diagnosis rate of 13% for early fibrosis, 17% for advanced fibrosis and 84% for cirrhosis.

CTS-2090

Inflammasome Diseases

Conatus Pharmaceuticals

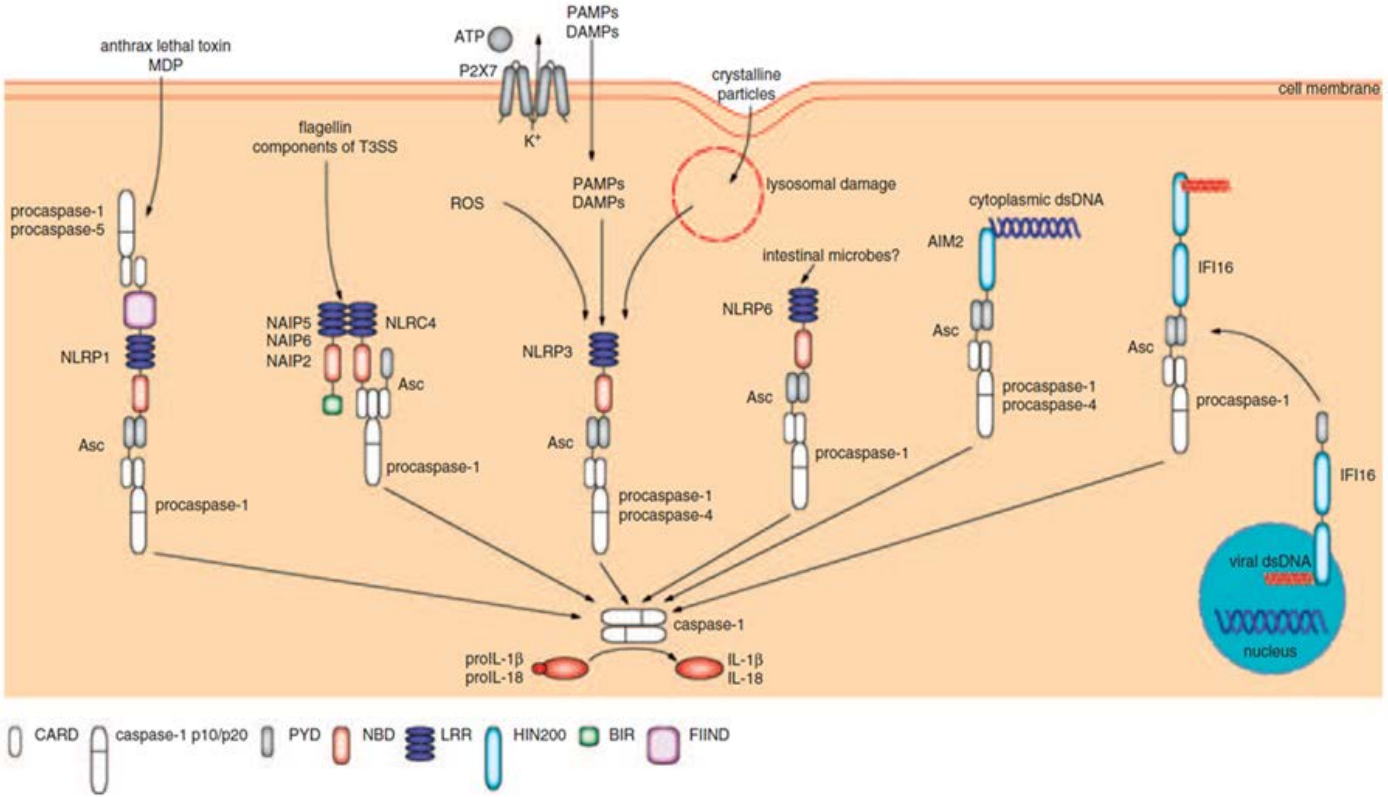
IL-1β Blocking Agents – Set the Stage for Next Generation Products

- Multiple approved biologic agents that block IL-1β
  - Canakinumab (Ilaris®)
  - Anakinra (Kineret®)
  - Rilonacept (Arcalyst®)

- Global sales of over $700 million in 2018

- Approved rare disease indications include Cryopyrin-Associated Periodic Syndromes, Familial Cold Autoinflammatory Syndrome, Muckle-Wells, Twin Anemia Polycythemia Sequence, Hyper-IgD Syndrome, Familial Mediterranean Fever

IL-1β - Driven by Multiple Inflammasomes



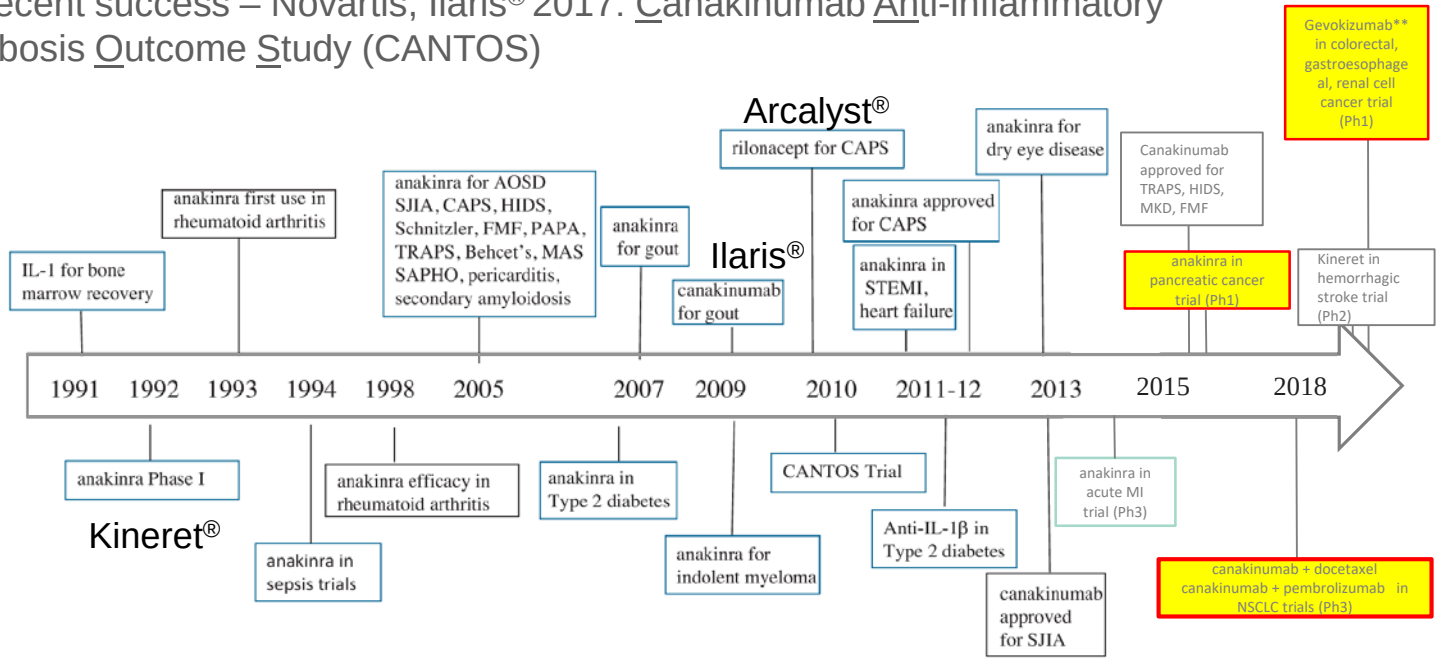
Solberger G, et al. Innate Immun. 2014, p115-125.

Disease Areas Implicated in the Inflammasome Pathway

Therapeutic areas	Disease Conditions				
Oncology	NSCLC	Breast Cancer	Melanoma		
Hepatology	NASH	Autoimmune Hepatitis	PSC (POLT)	α-ATTD	Alcoholic Hep
Respiratory	Steroid Resistant Asthma	COPD	IPF	Acute Lung Injury	
Renal	Polycystic Kidney Disease	Lupus Nephritis	Acute Kidney Injury		
Gastroenterology	Crohn's	Ulcerative Colitis			
Dermatology	Behcet Disease	Inflammatory Acne	Plaque Psoriasis	Dermatitis	
Ophthalmology	Retinal Detachment	Macular Degeneration	Retinitis Pigmentosa		
CNS/neuroinflammatory	Multiple Sclerosis	Parkinson's Disease	Multiple System Atrophy	Epilepsy	Huntington's Disease
Rheumatology	Osteoarthritis	Rheumatoid Arthritis	Psoriatic Arthritis	Gout	
Cardiovascular/Metabolic	Atherosclerosis	Myocardial Infarction	Type 2 Diabetes		
Autoinflammatory	Cryopyrin-Associated Periodic Syndromes	Muckle-Wells Syndrome	Schnitzler's Syndrome	Familial Mediterranean Fever	Macrophage Activation Syndrome
Audiology	Age-related Hearing Loss	Drug-induced Hearing Loss			

IL-1β Blocking Agents – Development Pathway Defined*

- Wide scope of clinical indications and therapeutic validation
- All agents given by injection (not orally active)
- Most recent success – Novartis, Ilaris® 2017: Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS)

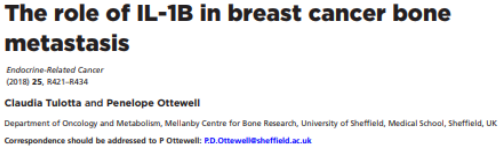


*Modified from Dinarello and van der Meer, Semin. Immunol, 2014. **NVS acquired gevokizumab from Xoma Aug 2017.

The Future of IL-1β Blocking May Be in Cancer


IL1 Receptor Antagonist Inhibits Pancreatic Cancer Growth by Abrogating NF-κB Activation

Zhuonan Zhuang, Huai-Qiang Ju, Mitzi Aguilar, Takashi Gocho, Hao Li, Tomonori Iida, Harold Lee, Xiaoqiang Fan, Haijun Zhou, Jianhua Ling, Zhongkui Li, Jie Fu, Min Wu, Min Li, Davide Melisi, Yoichiro Iwakura, Kesen Xu, Jason B. Fleming, and Paul J. Chiao

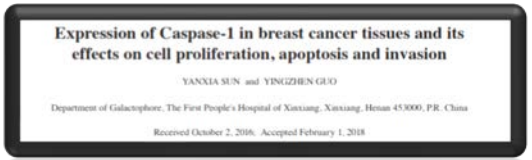

The role of IL-1B in breast cancer bone metastasis

Endocrine-Related Cancer
(2018) **25**, R421–R434

Claudia Tulotta and Penelope Ottewell

Department of Oncology and Metabolism, Mellanby Centre for Bone Research, University of Sheffield, Medical School, Sheffield, UK

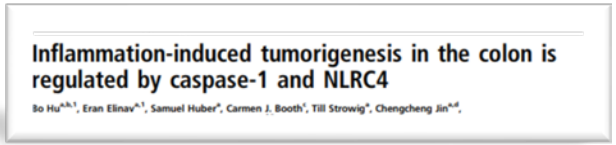
Correspondence should be addressed to P Ottewell: P.D.Ottewell@sheffield.ac.uk


Expression of Caspase-1 in breast cancer tissues and its effects on cell proliferation, apoptosis and invasion

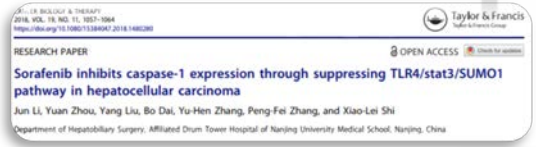
YANXIA SUN and YINGZHEN GUO

Department of Galactophore, The First People's Hospital of Xinxiang, Xinxiang, Henan 453000, P.R. China

Received October 2, 2016; Accepted February 1, 2018


Inflammation-induced tumorigenesis in the colon is regulated by caspase-1 and NLRC4

Bo Hu[a,b,1], Eran Elinav[a,1], Samuel Huber[a], Carmen J. Booth[c], Till Strowig[a], Chengcheng Jin[a,d],


Taylor & Francis

RESEARCH PAPER

OPEN ACCESS

Sorafenib inhibits caspase-1 expression through suppressing TLR4/stat3/SUMO1 pathway in hepatocellular carcinoma

Jun Li, Yuan Zhou, Yang Liu, Bo Dai, Yu-Hen Zhang, Peng-Fei Zhang, and Xiao-Lei Shi

Department of Hepatobiliary Surgery, Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China


SCIENTIFIC REPORTS

OPEN

Targeting inflammasome/IL-1 pathways for cancer immunotherapy

Received: 12 July 2016

Beichu Guo[1,2], Shunjun Fu[1], Jinyu Zhang[1], Bei Liu[1,2] & Zihai Li[1,2]

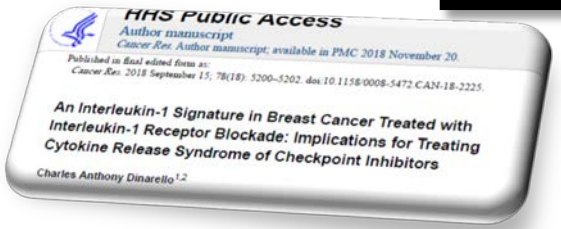

IL-1 is required for tumor invasiveness and angiogenesis

Elena Voronov*, Dror S. Shouval*, Yakov Krelin*, Emanuela Cagnano*, Daniel Benharroch*, Yoichiro Iwakura†, Charles A. Dinarello‡, and Ron N. Apte*§


Caspase-1 cleaves PPARγ for potentiating the pro-tumor action of TAMs

Zhiyuan Niu, Qian Shi, Wenlong Zhang, Yuxin Shu, Nanfei Yang, Bing Chen, Qingsong Wang, Xuyang Zhao, Jiajia Chen, Nan Cheng, Xiujing Feng, Zichun Hua, Jianguo Ji & Pingping Shen

Nature Communications **8**, Article number: 766 (2017) | Download Citation


HHS Public Access

Author manuscript

Cancer Res. Author manuscript; available in PMC 2018 November 20.

Published in final edited form as:

Cancer Res. 2018 September 15; 78(18): 5200–5202. doi:10.1158/0008-5472.CAN-18-2225.

An Interleukin-1 Signature in Breast Cancer Treated with Interleukin-1 Receptor Blockade: Implications for Treating Cytokine Release Syndrome of Checkpoint Inhibitors

Charles Anthony Dinarello[1,2]

Inflammasome Companies: Investor and Pharma Interest

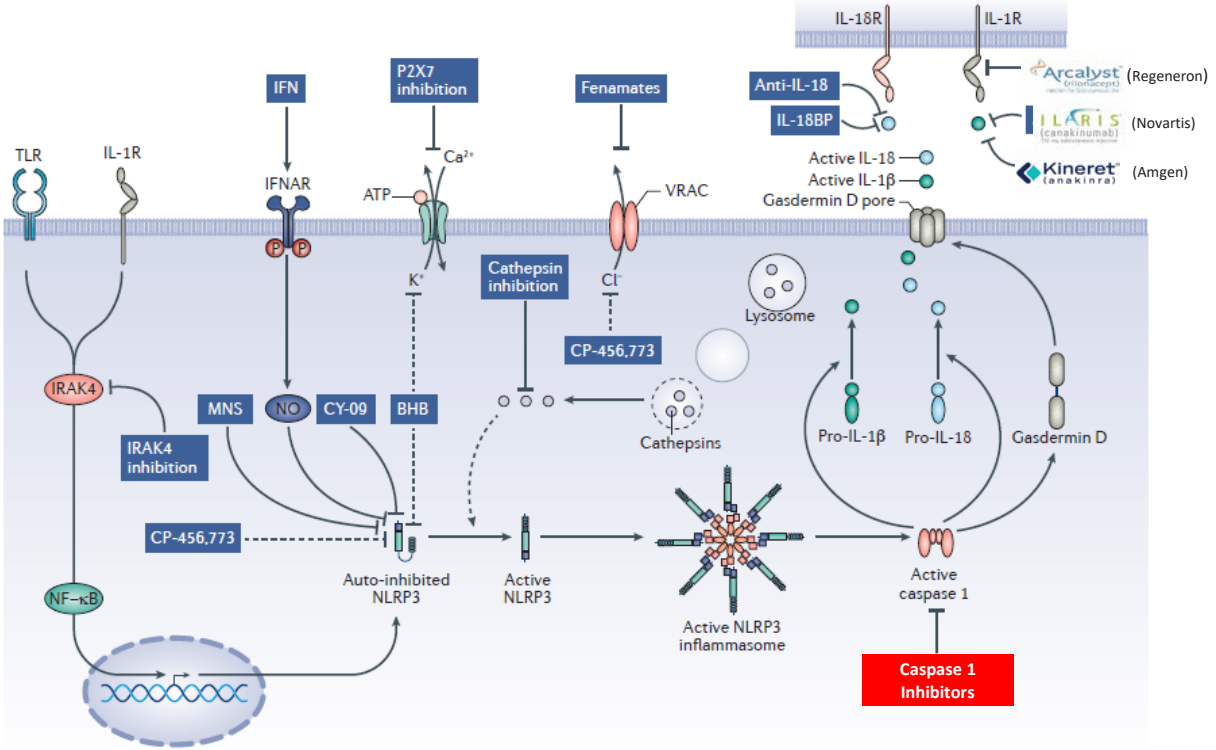
- Jecure Therapeutics raised a $30mm Series A from Versant in 2017. Acquired by Genentech in 2018.

- Inflazome closed a $17mm Series A in 2016 from Novartis Venture Fund and others. Recently closed a $46mm Series B to move compounds to POC. Investors included Forbion, Longitude, Novartis Venture Fund, and Fountain Healthcare Partners.

- IFM TRE raised a $31mm Series A in 2018 from Atlas, Abingworth, and BMS. Acquisition by Novartis announced April 2019 for $310M upfront (Phase 1) and up to $1.6B total.

Caspase 1 Inhibitors Target Inflammasome Pathway at Optimal Intervention Point

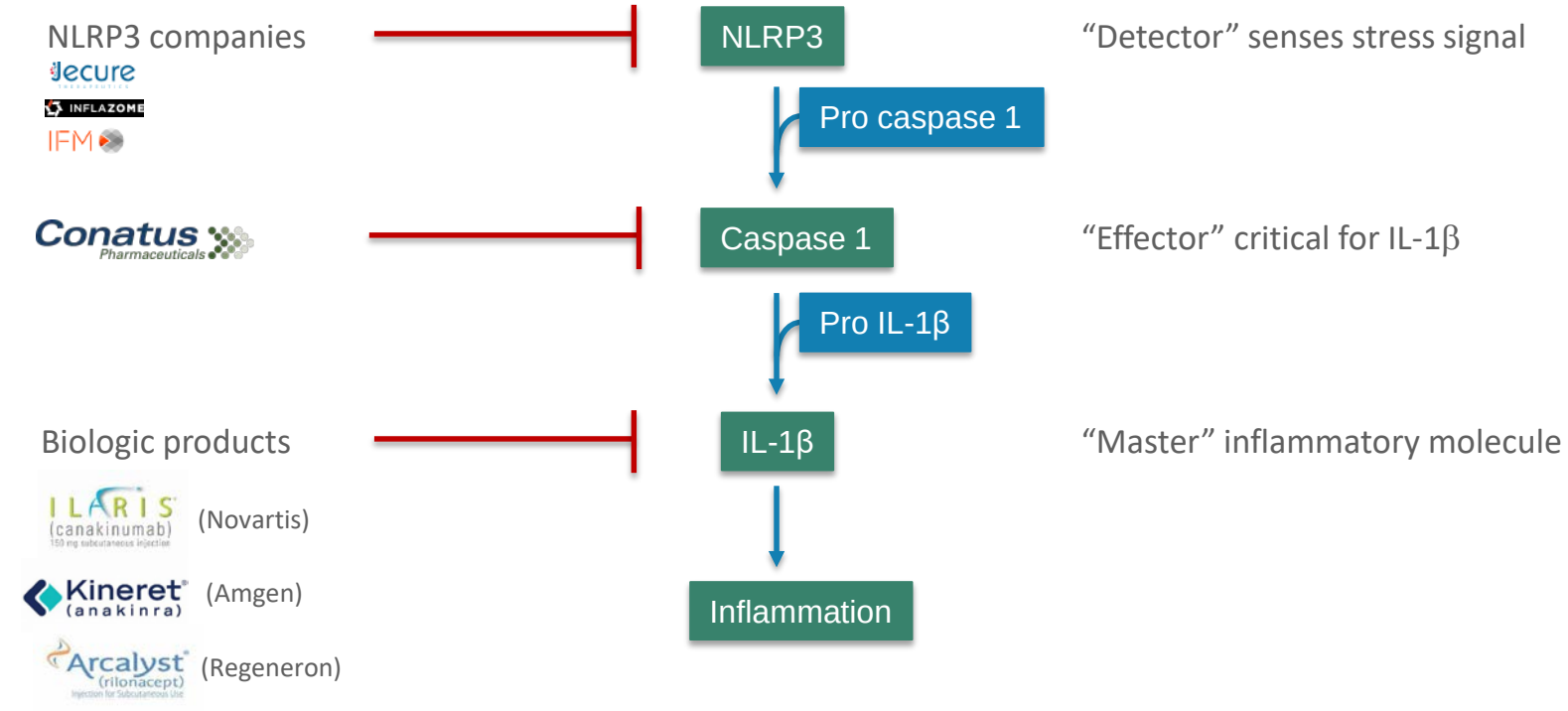
We believe a caspase 1 selective small molecule inhibitor can be a safe and efficacious agent for intervention in the inflammasome pathway



Modified from Mangan M et al. Nature Reviews Drug Discovery, 2018 p. 588-606.

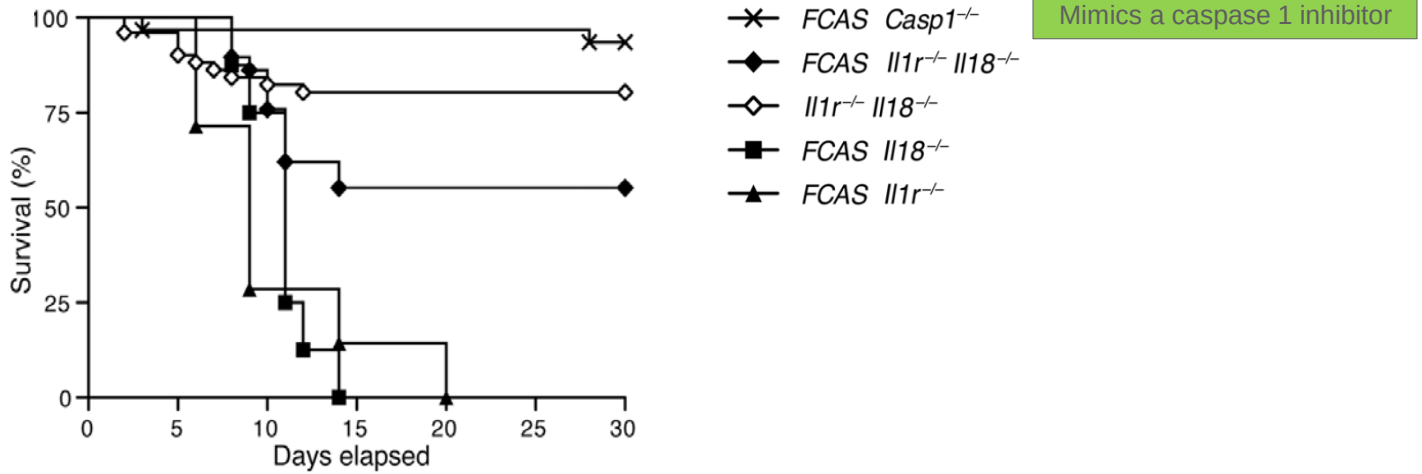
Targeting IL-1β and Inflammation via Caspase 1 Inhibition

IL-1β is a validated inflammatory target – high interest in the pathway



Caspase -1 Inhibition Improves Survival Better than Blocking IL-1β, IL-18 or Both

- Constitutively active NLRP3 (FCAS model) results in chronic activation of caspase 1
  - Leads to production of IL-1β and IL-18
  - Leads to pyroptotic cell death via gasdermin D cleavage
- Caspase -1 KO showed improved survival over IL-1β KO, IL-18 KO or both



Brydges SD, Broderick L, McGeough MD, Pena CA, Mueller JL, Hoffman HM. Divergence of IL-1, IL-18, and cell death in NLRP3 inflammasomopathies. J Clin Invest 2013;123:4695-4705.

Conatus Caspase 1 Inhibitor Portfolio

- Designed highly selective caspase 1 inhibitors
  - Incorporated novel chemistry to remove activity against apoptotic caspases
  - Maintained sub-nanomolar activity against caspase 1
  - Inhibits downstream IL-1β (a clinically validated target)

- Demonstrated functional activity and selectivity in cellular models
  - High potency in cell models of NLRP3 driven inflammation
  - Little to no activity in cellular models of apoptosis

- Demonstration of functional activity and selectivity in animal models
  - Orally active in animal model of NLRP3 driven inflammation
  - Potency similar to NLRP3 reference standard (MCC950)
  - Not active in a standard animal model of apoptosis

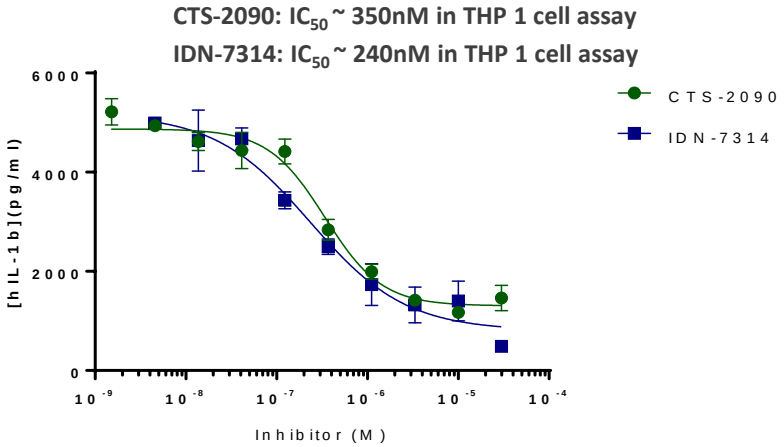
Conatus' Lead Caspase 1 Inhibitor: CTS-2090

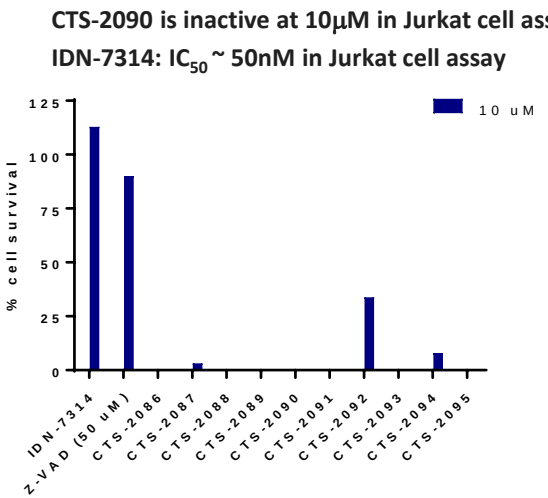
- **Potency**
  - Sub-nanomolar IC_{50} against human caspase-1
  - Sub-micromolar IC_{50} in THP 1 cells
- **Selectivity**
  - Broad panel of receptors and enzymes, >100,000 fold selectivity over caspase 1
  - No anti-apoptotic activity in cells at 10μM – enzyme selectivity reflected in cell-based functional assay
  - No anti-apoptotic activity *in vivo* at 10mg/kg – cellular functional selectivity translates *in vivo*
- **Oral Bioavailability**
  - Good oral bioavailability – ~10-fold higher than benchmark pan-caspase inhibitor in rodents[1]
- **Tissue Distribution**
  - Not specific for liver – AUC liver ~ AUC plasma.
- ***In vivo* activity**
  - Pathway inhibition in mouse model of LPS/urate crystal-induced IL-1β production – potency similar to MCC950

[1]Hoglen NC. Discovery of a First in Class Apoptotic Caspase Inhibitor Emricasan PF 03491390 IDN 6556. CRC Press 2009:211-224.

Caspase Selectivity Profile Validated in Cell-based Functional Assays

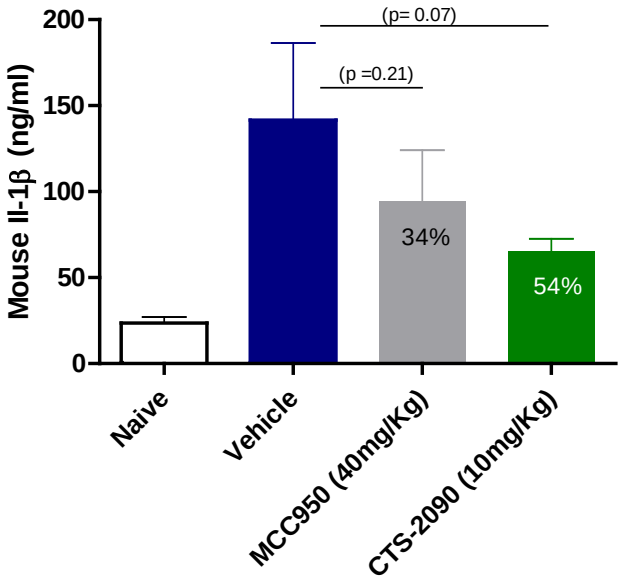
- CTS-2090 is a potent inhibitor of LPS-stimulated NLRP3 driven IL-1β production in THP 1 cells
  - IC $_{50}$ value similar to that of the potent pan-caspase inhibitor, IDN-7314
- CTS-2090 does not protect Jurkat cells from α-Fas – induced apoptosis (0% protection at 10μM)
  - Pan-caspase inhibitor IDN-7314 is protective with IC_{50} ~ 50nM (greater than 200-fold window of selectivity)
- Cellular profile confirms mechanistic potency and functional selectivity of CTS-2090





Pathway Inhibition in Mouse Gout Model of Crystal-induced IL-1β Production

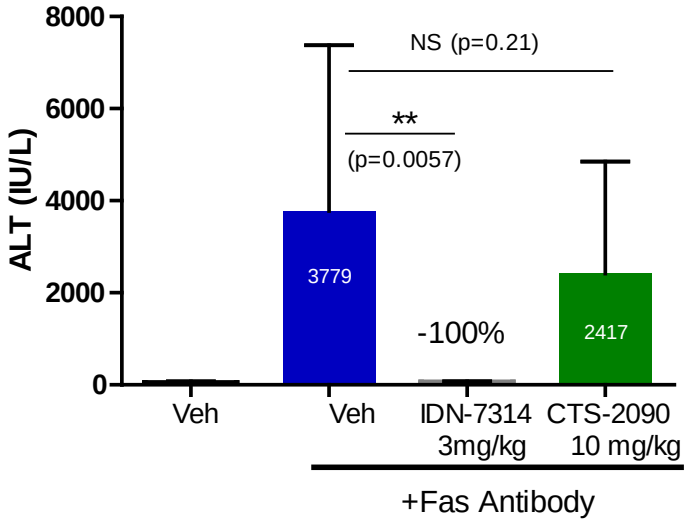
- Reduces IL-1β levels to the same extent and at a lower oral dose than the NLRP3 standard inhibitor MCC950 in the MSU model of gout
  - Oral administration of CTS-2090 at 10 mg/kg. Oral administration of MCC 950 at 40mg/kg



Unpaired t test

CTS-2090: Caspase 1 Selectivity Profile Validated *in vivo*

- Consistent with cellular and enzymatic selectivity profiles
  - CTS-2090 does not protect against αFas induced apoptosis in mice
    - Oral administration at 10mg/kg
  - IDN-7314 is fully protective against αFas induced apoptosis in mice
    - Oral administration at 3mg/kg

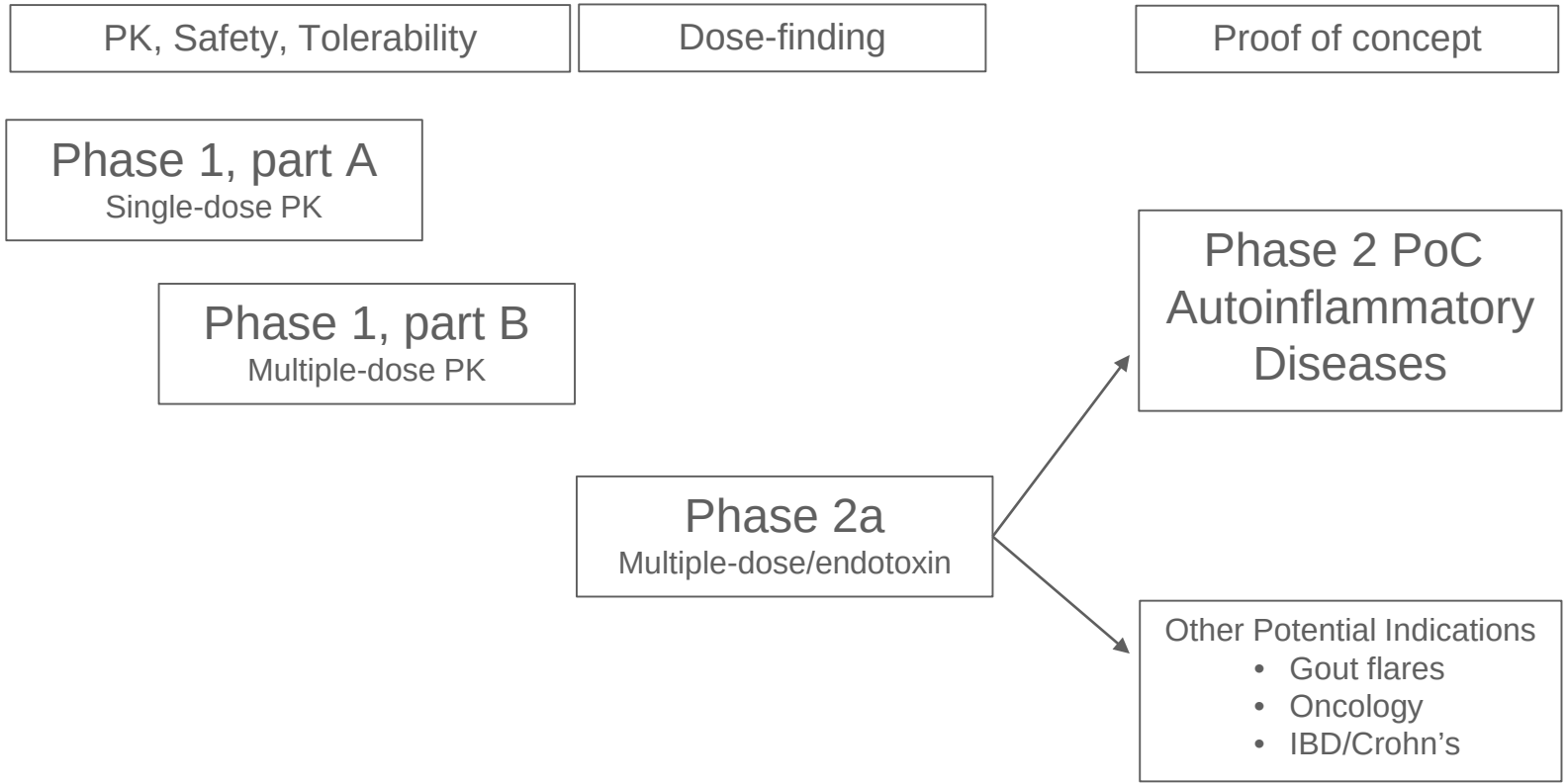


t test unpaired, one sided

Autoinflammatory Diseases as Initial Clinical Target for CTS-2090

- Single-gene mutations that activate inflammasomes and result in IL-1β production
- Spectrum of diseases with variable organ system involvement, severity and age of onset
  - Cryopyrin-associated periodic syndromes (CAPS)
    - Familial cold urticaria syndrome or familial cold autoinflammatory syndrome (FCAS)
    - Muckle-Wells syndrome (MWS)
    - Neonatal-onset multisystemic inflammatory disease (NOMID)/chronic infantile neurological cutaneous articular syndrome (CINCA)
  - Familial Mediterranean Fever (FMF)
  - Hyper-IgD syndrome
  - TRAPS (TNF receptor-associated periodic syndrome)
- Canakinumab, rilonacept and anakinra (anti-IL-1β therapies) proven to be highly efficacious but are injectable, expensive and have differing durations of action

Overview of CTS-2090 Development Plan



Highlights of Conatus Approach

- Like inflammasome intervention, caspase 1 inhibition is a small molecule strategy to block the formation of IL-1β
- Additional benefits include IL-18 inhibition, gasdermin D inhibition, and a decrease in inflammation driven cell death (pyroptosis) vs. IL-1β blocking agents
- Multiple routes of administration possible (oral, inhaled, topical, ophthalmology, etc.)
- Conatus has developed a portfolio of novel, potent, orally bioavailable, highly selective inhibitors of caspase 1
  - Demonstrated functional activity and selectivity in cellular and animal models
- Lead compound CTS-2090 selected to advance toward clinical development
  - IND-enabling studies in progress, projecting initial clinical trial 1H20

Expanded Pipeline Addressing Underserved Chronic Disease Markets

Program (Indication)	Preclinical	Phase 1	Phase 2	Milestone
***Emricasan** **ENCORE-PH** **(NASH Cirrhosis)**	263 patients at 75 sites in the US and EU		Liver Function, Clinical Endpoint	Phase 2b extension data expected mid-19
***Emricasan** **ENCORE-LF** **(NASH Cirrhosis)**	~210 patients at ~90 sites in the US		Clinical Endpoint	Phase 2b top-line data expected mid-19
CTS-2090 **Caspase-1 Inhibitor** **(Inflammasome Diseases)**				Initial clinical trial expected to begin 1H20

Two Phase 2b NASH cirrhosis clinical trials with lead partnered program and one independent preclinical program provide multiple paths forward

*Emricasan is partnered with Novartis

Financial Snapshot

Cash, cash equivalents & marketable securities as of 12/31/18	**$40.7 million**
Debt	**–***
Shares outstanding as of 12/31/18	**33.2 million**
Projected cash, cash equivalents & marketable securities year-end 2019	**$10 – 15 million**

*Novartis note converted to CNAT stock at 20% pricing premium in December 2018

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