UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): October 27, 2021

KYMERA THERAPEUTICS, INC.
(Exact name of registrant as specified in its charter)

Delaware	**001-39460**	**81-2992166**
(State or other jurisdiction of incorporation)	**(Commission File Number)**	**(I.R.S. Employer Identification No.)**

Kymera Therapeutics, Inc.
200 Arsenal Yards Blvd., Suite 230
Watertown, Massachusetts 02472
(Address of principal executive offices, including zip code)

(857) 285-5300
(Registrant's telephone number, including area code)

Not Applicable
(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trade Symbol(s)	Name of each exchange on which registered
Common Stock, $0.0001 par value per share	**KYMR**	**The Nasdaq Global Market**

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure.

On October 27, 2021, Kymera Therapeutics, Inc. (the "Company") issued a press release, a copy of which is furnished herewith as Exhibit 99.1. In addition, on October 27, 2021, the Company presented at the 4th Annual Targeted Protein Degradation Summit and intends to host a conference call to discuss the results of the Single Ascending Dose (SAD) portion of the Company's ongoing Phase 1 trial of KT-474. A form of the slide presentation is being furnished as Exhibit 99.2 to this Current Report on Form 8-K. The Company undertakes no obligation to update, supplement or amend the materials attached hereto as Exhibit 99.2.

The information in this Item 7.01, including Exhibit 99.1 and Exhibit 99.2 attached hereto, shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, except as expressly set forth by specific reference in such filing.

Item 8.01 Other Events

On October 27, 2021, the Company announced results from the SAD portion of its ongoing Phase 1 trial of KT-474, including the seven KT-474 single dose cohorts, comprising 57 healthy volunteer subjects randomized 6:2 to either a single oral dose of KT-474 or placebo. The data demonstrated robust, dose-dependent IRAK4 reduction, maintained for up to 6 days, in peripheral blood mononuclear cells (PBMC) measured by mass spectrometry, resulting in mean IRAK4 reduction from baseline of 93-96% achieved at 48 hours post-dose at the top three dose levels, achieving strong proof-of-mechanism (see Table 1). Flow cytometry demonstrated that the effect of KT-474 on IRAK4 levels was similar in lymphocytes and monocytes.

Table 1: Percent IRAK4 Change from Baseline in PBMC at 48 Hours Post-Dose using Mass Spectrometry

	Placebo (n=13)	Cohort 1 (n=6)	Cohort 2 (n=6)	Cohort 3 (n=6)	Cohort 4 (n=6)	Cohort 5 (n=7)	Cohort 6 (n=5)	Cohort 7 (n=6)
KT-474 dose	—	25 mg	75 mg	150 mg	300 mg	600 mg	1000 mg	1600 mg
Mean IRAK4 Change	-1%	-26% (p=0.1)	-73% (p<0.0001)	-81% (p<0.0001)	-84% (p<0.0001)	-96% (p<0.0001)	-93% (p<0.0001)	-95% (p<0.0001)

The Company also announced that proof-of-biology was also established, with inhibition of *ex vivo* R848- or LPS-mediated induction of multiple pro-inflammatory cytokines in whole blood at doses and exposures associated with mean IRAK4 reduction in PBMC of ³85% at 24-48 hours post-dose. In Cohort 7, where mean IRAK4 reduction at 24 and 48 hours was 89% and 95%, respectively, mean maximum cytokine inhibition as great as 97% was observed (see Table 2). KT-474 demonstrated oral bioavailability, a half-life supportive of daily dosing, and dose-dependent plasma exposures that plateaued after 1000 mg. KT-474 was observed to be well-tolerated; mild to moderate, self-limited headache and nausea were the most common possible or probable treatment-related adverse events, and there were no serious adverse events.

Table 2: Mean Maximum Percent Change from Baseline at 24-48 Hours in *Ex Vivo* Proinflammatory Cytokine Induction by R848 and LPS in Whole Blood at Cohort 7

Proinflammatory Cytokine	IFNg	IL1ß	IL6	IL8	IL10	IL12	IL17	TNFα
R848 (TLR 7/8 agonist)	-97%[2]	-92%[1]	-88%[1]	-54%	-89%[1]	-93%[1]	-79%[1]	-88%[2]
LPS (TLR 4 agonist)	-42%	-68%[1]	-62%[1]	-81%[1]	-83%[1]	-35%[2]	-43%[2]	-42%[2]

1 = p value < 0.01; 2 = p value < 0.05, for comparison to placebo

The disclosure under this Item 8.01 contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, express or implied statements regarding the Company's views on KT-474 as validating its platform and approach to drug development; strategy, business plans and objectives for its IRAK4 degrader program; and plans and timelines for the clinical development of its product candidates, including the therapeutic potential and clinical benefits thereof. The words "may," "will," "could," "would," "should," "expect," "plan," "anticipate," "intend," "believe," "estimate," "predict," "project," "potential," "continue," "target" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

Any forward-looking statements in this press release are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this press release, including, without limitation, those risks and uncertainties related: the Company's ability to execute on its strategy; the therapeutic potential and safety of KT-474; the timing and completion of the Company's Phase 1 study of KT-474 and final audit and quality controlled verification of initial data and related analyses; positive results from initial data analyses not necessarily being predictive of final results; the Company's planned regulatory submissions and developments; and other risks identified in the Company's SEC filings, including those risks discussed under the heading "Risk Factors" in the Company's Quarterly Report on Form 10-Q for the quarter ended June 30, 2021, as well as other risks detailed in the Company's subsequent filings with the SEC. We caution you not to place undue reliance on any forward-looking statements, which speak only as of the date they are made. The Company disclaims any obligation to publicly update or revise any such statements to reflect any change in expectations or in events, conditions or circumstances on which any such statements may be based, or that may affect the likelihood that actual results will differ from those set forth in the forward-looking statements. Any forward-looking statement included in this Item 8.01 speaks only as of the date on which it was made. The Company undertakes no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events or otherwise, except as required by law.

Item 9.01. Exhibits

(d) Exhibits

Exhibit No.	Description
99.1	Press release issued by Kymera Therapeutics, Inc. on October 27, 2021, furnished herewith.
99.2	Kymera Therapeutics, Inc. Corporate Presentation, dated October 27, 2021, furnished herewith.
104	Cover Page Interactive Data

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Kymera Therapeutics, Inc.

Date: October 27, 2021

By: /s/ Nello Mainolfi
Nello Mainolfi, Ph.D.
Founder, President and Chief Executive Officer

Kymera Therapeutics Presents Positive Data Demonstrating Robust IRAK4 Degradation and First Proof-of-Biology with Inhibition of Cytokine Induction from the Single Ascending Dose Portion of KT-474 Phase 1 Trial in Healthy Volunteers

Mean IRAK4 degradation of up to 96% in PBMC and up to 97% inhibition of ex vivo induction of multiple proinflammatory cytokines observed, suggesting potential for broad anti-inflammatory effect

KT-474 was well-tolerated at all dose levels

Kymera to present results at 4th Annual Targeted Protein Degradation Summit today at 8:30 a.m. ET

Kymera to host conference call today at 10:30 a.m. ET

Watertown, Mass. (Oct. 27, 2021) – Kymera Therapeutics, Inc. (NASDAQ: KYMR), a clinical-stage biopharmaceutical company advancing targeted protein degradation (TPD) to deliver novel small molecule protein degrader medicines, today presented new safety, pharmacokinetic (PK) and pharmacodynamic (PD) data, including cytokines, from the Single Ascending Dose (SAD) portion of the KT-474 Phase 1 randomized, placebo-controlled healthy volunteer trial, at the 4th Annual Targeted Protein Degradation Summit.

The presentation included data from the seven KT-474 single dose cohorts, comprising 57 healthy volunteer subjects randomized 6:2 to either a single oral dose of KT-474 or placebo. The data demonstrated robust, dose-dependent IRAK4 reduction, maintained for up to 6 days, in peripheral blood mononuclear cells (PBMC) measured by mass spectrometry, resulting in mean IRAK4 reduction from baseline of 93-96% achieved at 48 hours post-dose at the top three dose levels, achieving strong proof-of-mechanism (see Table 1). Flow cytometry demonstrated that the effect of KT-474 on IRAK4 levels was similar in lymphocytes and monocytes.

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KT-474 dose	**—**	**25 mg**	**75 mg**	**150 mg**	**300 mg**	**600 mg**	**1000 mg**	**1600 mg**
Mean IRAK4 Change	**-1%**	**-26%** (p=0.1)	**-73%** (p<0.0001)	**-81%** (p<0.0001)	**-84%** (p<0.0001)	**-96%** (p<0.0001)	**-93%** (p<0.0001)	**-95%** (p<0.0001)

For the first time, proof-of-biology was also established, with inhibition of *ex vivo* R848- or LPS-mediated induction of multiple pro-inflammatory cytokines in whole blood at doses and exposures associated with mean IRAK4 reduction in PBMC of ³85% at 24-48 hours post-dose. In Cohort 7, where mean IRAK4 reduction at 24 and 48 hours was 89% and 95%, respectively, mean maximum cytokine inhibition as great as 97% was observed (see Table 2). KT-474 demonstrated oral bioavailability, a half-life supportive of daily dosing, and dose-dependent plasma exposures that plateaued after 1000 mg. KT-474 was observed to be well-tolerated; mild to moderate, self-limited headache and nausea were the most common possible or probable treatment-related adverse events, and there were no serious adverse events.

Table 2: Mean Maximum Percent Change from Baseline at 24-48 Hours in *Ex Vivo* Proinflammatory Cytokine Induction by R848 and LPS in Whole Blood at Cohort 7.

Proinflammatory Cytokine	IFNg	IL1b	IL6	IL8	IL10	IL12	IL17	TNFα
R848 (TLR 7/8 agonist)	-97%[2]	-92%[1]	-88%[1]	-54%	-89%[1]	-93%[1]	-79%[1]	-88%[2]
LPS (TLR 4 agonist)	-42%	-68%[1]	-62%[1]	-81%[1]	-83%[1]	-35%[2]	-43%[2]	-42%[2]

[1] = p value < 0.01; [2] = p value < 0.05, for comparison to placebo

"We are pleased to have completed dose escalation in the SAD portion of our Phase 1 trial and are encouraged by our ability to achieve plasma exposures following single doses of KT-474 that maximize IRAK4 degradation and are well-tolerated, with up to 96% mean reduction of IRAK4 in PBMC," said Jared Gollob, MD, Chief Medical Officer at Kymera Therapeutics. "Importantly, we have now shown that IRAK4 knockdown of [3] 85% *in vivo* in circulating PBMC leads to profound TLR/IL-1R pathway inhibition, as demonstrated by up to 97% suppression of *ex vivo* response of whole blood to TLR agonists. Daily dosing with KT-474 is currently being evaluated in the multiple ascending dose (MAD) portion of the trial; based on the PK properties of KT-474 and the observed PK-PD relationship, we anticipate achieving similar levels of IRAK4 degradation and cytokine inhibition with substantially lower daily doses."

"The proof-of-mechanism and proof-of-biology that have been achieved with just single doses of KT-474 attest to the potency of this drug and validates the strategy of targeting IRAK4 with a degrader to maximize blockade of TLR/IL-1R signaling," said Nello Mainolfi, PhD, Co-Founder, President and CEO, Kymera Therapeutics. "The potent, broad effect of IRAK4 knockdown observed on multiple different proinflammatory cytokines implicated in a variety of autoimmune inflammatory diseases highlights the potential for KT-474 to be a best-in-class oral anti-inflammatory drug, especially in a shifting external landscape for safe, broadly active small molecule anti-inflammatory agents."

KT-474 is a highly active and selective, orally bioavailable IRAK4 degrader being developed for the treatment of toll-like receptor (TLR)/interleukin-1 receptor (IL-1R)-driven immune-inflammatory diseases, such as atopic dermatitis, hidradenitis suppurativa, rheumatoid arthritis and potentially other indications. The Phase 1 clinical trial is a randomized, double-blind, placebo-controlled study (a first in targeted protein degradation) to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of KT-474 in up to 116 healthy volunteers, and in a subsequent cohort of up to 20 patients with atopic dermatitis and hidradenitis suppurativa.

In July 2021, Kymera initiated dosing of healthy volunteers in the Multiple Ascending Dose (MAD) portion of the Phase 1 trial of KT-474. The multiple ascending dose portion of the trial is designed to evaluate repeat daily dosing of KT-474 for 14 days, beginning with the 25 mg dose, in healthy volunteers randomized 9:3 to KT-474 or placebo. Kymera plans to present data from the MAD portion of the healthy volunteer study before year end.

The dose level in the MAD healthy volunteer portion which demonstrates maximal IRAK4 degradation and has been well tolerated, will then be selected for evaluation in an open-label cohort of patients with atopic dermatitis and hidradenitis suppurativa (up to 20 patients). Additional information on this clinical trial can be found on www.clinicaltrials.gov.

Upcoming Kymera Presentation Details at 4th Annual Targeted Protein Degradation Summit:

- Keynote Presentation: Safety, PK and PD from Single Ascending Dose Portion of KT-474 Phase 1 Trial in Healthy Volunteers
    - Presenter: Jared Gollob, MD, Chief Medical Officer, Kymera Therapeutics
    - Time: 8:30 a.m. ET on Wednesday, Oct. 27, 2021
- Industry Leaders Panel Discussion: 2021 in Review
    - Panel participation by Jared Gollob, MD, Chief Medical Officer, Kymera Therapeutics
    - Time: 9:30 a.m. ET on Wednesday, Oct. 27, 2021
- Presentation: Impact of Understanding PKPD for Development of a STAT3 Targeted Protein Degrader
    - Presenter: Chris De Savi, PhD, Vice President, Head of Drug Discovery, Kymera Therapeutics
    - Time: 4:15 p.m. ET on Wednesday, Oct. 27, 2021
- Presentation: Considerations for E3 Ligase Pairing and Screening of Immune-Inflammation Targets
    - Presenter: Veronica Campbell, Associate Director, Immunology, Kymera Therapeutics
    - Time: 2:30 p.m. ET on Thursday, Oct. 28, 2021

Previous Kymera Presentations at the 4th Annual Targeted Protein Degradation Summit:

- Workshop: De-risking Clinical Development of a Novel Protein Degrader
    - Presenter: Alice McDonald, Director, Translational Medicine, Kymera Therapeutics
    - Conducted on: Tuesday, Oct. 26, 2021

For more information and to register for the 4th Annual Targeted Protein Degradation Summit, please visit: www.proteindegradation.com. Copies of the presentations will be available for download at: www.kymeratx.com/scientific-resources/.

Kymera Webcast and Conference Call Details:

Kymera will host a conference call and webcast at 10:30 a.m. ET, Wednesday, October 27. To access the conference call via phone, please dial 833-740-0921 (U.S.) or +1 409-937-8885 (International) and use the conference ID 3796327. A live webcast of the event will be available under “Events and Presentations” in the Investors section of the Company’s website at www.kymeratx.com. A replay of the webcast will be archived and available for one month following the event.

About IRAK4 and KT-474

IRAK4 is a key protein involved in inflammation mediated by the activation of toll-like receptors (TLRs) and IL-1 receptors (IL-1Rs). Aberrant activation of these pathways is the underlying cause of multiple immune-inflammatory conditions. KT-474, a potential first-in-class, orally bioavailable IRAK4 degrader, is being developed for the treatment of TLR/IL-1R-driven immune-inflammatory diseases with high unmet medical need, such as atopic dermatitis, hidradenitis suppurativa, rheumatoid arthritis, and potentially others. KT-474 is designed to block TLR/IL-1R-mediated inflammation more broadly compared to monoclonal antibodies targeting single cytokines, and to enable pathway inhibition that is superior to IRAK4 kinase inhibitors by abolishing both the kinase and scaffolding functions of IRAK4. In February 2021, Kymera initiated the first-in-human Phase 1 Single and Multiple Ascending Dose trial designed to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of orally administered KT-474 in adult healthy volunteers and patients with atopic dermatitis and hidradenitis suppurativa.

Kymera is collaborating with Sanofi on the development of degrader candidates targeting IRAK4, including KT-474 (SAR444656), outside of the oncology and 3mmune-oncology fields.

About Pegasus™

Pegasus™ is Kymera Therapeutics' proprietary protein degradation platform, created by its team of experienced drug hunters to improve the effectiveness of targeted protein degradation and generate a pipeline of novel therapeutics for previously undruggable diseases. The platform consists of informatics-driven target identification, novel E3 ligases, proprietary ternary complex predictive modeling capabilities, and degradation tools.

About Kymera Therapeutics

Kymera Therapeutics (Nasdaq: KYMR) is a clinical-stage biopharmaceutical company founded with the mission to discover, develop, and commercialize transformative therapies while leading the evolution of targeted protein degradation, a transformative new approach to address previously intractable disease targets. Kymera's Pegasus™ platform enables the discovery of novel small molecule degraders designed to harness the body's natural protein recycling machinery to degrade disease-causing proteins, with a focus on undrugged nodes in validated pathways currently inaccessible with conventional therapeutics. Kymera's initial programs are IRAK4, IRAKIMiD, and STAT3, each of which addresses high impact targets within the IL-1R/TLR or JAK/STAT pathways, providing the opportunity to treat a broad range of immune-inflammatory diseases, hematologic malignancies, and solid tumors. Kymera's goal is to be a fully integrated biopharmaceutical company at the forefront of this new class of protein degrader medicines, with a pipeline of novel degrader medicines targeting disease-causing proteins that were previously intractable.

Founded in 2016, Kymera is headquartered in Watertown, Mass. Kymera has been named a "Fierce 15" biotechnology company by FierceBiotech and has been recognized by the Boston Business Journal as one of Boston's "Best Places to Work." For more information about our people, science, and pipeline, please visit www.kymeratx.com or follow us on Twitter or LinkedIn.

Cautionary Note Regarding Forward-Looking Statements

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, implied and express statements regarding Kymera Therapeutics': plans to present results from the MAD portion of the KT-474 trial; views on KT-474 as validating its platform and approach to drug development;: strategy, business plans and objectives for the KT-474 degrader program; and plans and timelines for the clinical development of Kymera Therapeutics' product candidates, including the therapeutic potential and clinical benefits thereof. The words "may," "might," "will," "could," "would," "should," "expect," "plan," "anticipate," "intend," "believe," "expect," "estimate," "seek," "predict," "future," "project," "potential," "continue," "target" and similar words or expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Any forward-looking statements in this press release are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this press release, including, without limitation, risks associated with: the impact of COVID-19 on countries or regions in which we have operations or do business, as well as on the timing and anticipated results of our current preclinical studies and future clinical trials, strategy and future operations; the delay of any current preclinical studies or future clinical trials or the development of Kymera Therapeutics' drug candidates; the risk that the results of current clinical trials and preclinical studies may not be predictive of future results in connection with future clinical trials; Kymera Therapeutics' ability to successfully demonstrate the safety and efficacy of its drug candidates; the timing and outcome of the Company's planned interactions with regulatory authorities; and obtaining, maintaining and protecting its intellectual property. These and other risks and uncertainties are described in greater detail in the section entitled "Risk Factors" in the Quarterly Reporton Form 10-Q for the period ended June 30, 2021, filed on August 6, 2021, as well as discussions of potential risks, uncertainties, and other important factors in Kymera Therapeutics' subsequent filings with the Securities and Exchange Commission. In addition, any forward-looking statements represent Kymera Therapeutics' views only as of today and should not be relied upon as representing its views as of any subsequent date. Kymera Therapeutics explicitly disclaims any obligation to update any forward-looking statements. No representations or warranties (expressed or implied) are made about the accuracy of any such forward-looking statements.

Investor Contact:

Bruce Jacobs
Chief Financial Officer
investors@kymeratx.com
857-285-5300

Chris Brinzey
Managing Director, Westwicke
chris.brinzey@westwicke.com
339-970-2843

Media Contact:

Tyler Gagnon
Director, Corporate Communications
tgagnon@kymeratx.com
508-904-9446

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Exhibit 99.2

Safety, PK and PD from Single Ascending Dose Portion of KT-474 Phase 1 Trial in Healthy Volunteers

Jared Gollob, M.D. - Chief Medical Officer

4th Annual TPD Summit, Keynote Plenary Session

October 27, 2021

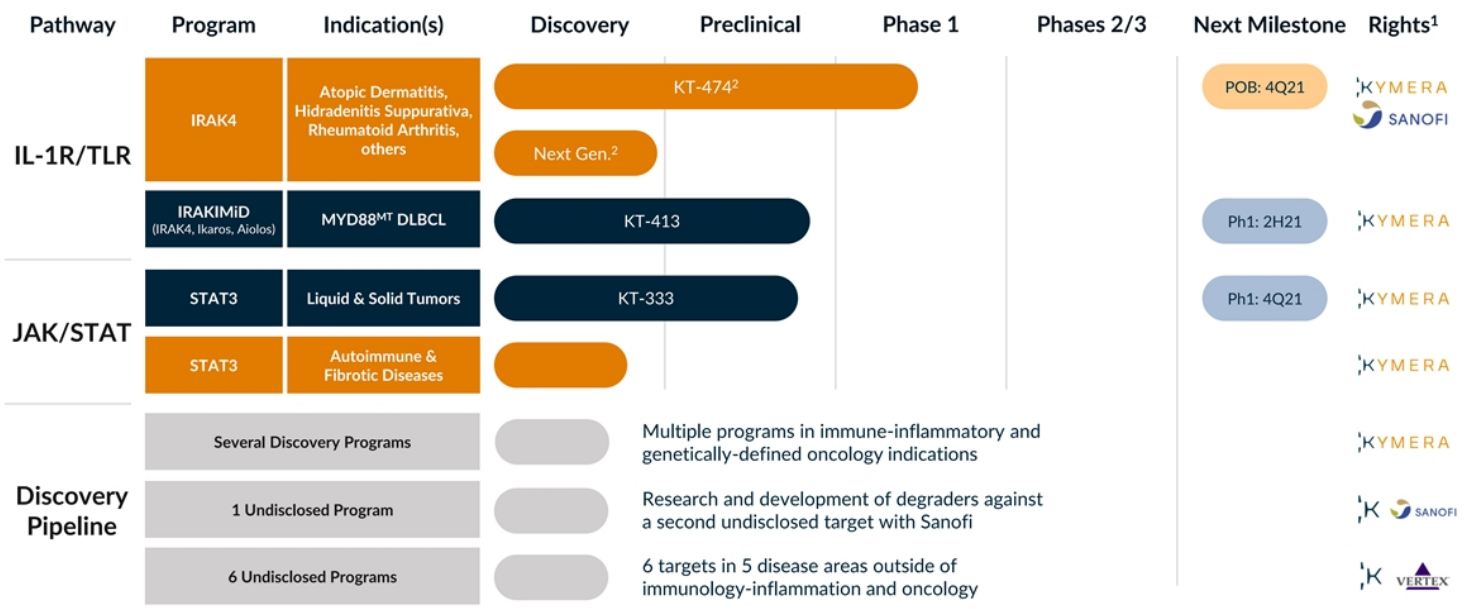
Forward-Looking Statements

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 (PSLRA) and other federal securities laws. These statements include information about our current and future prospects and our operations and financial results, which are based on currently available information. All statements other than statements of historical facts contained in this presentation, including express or implied statements regarding our strategy, future financial condition, future operations, projected costs, prospects, plans, objectives of management and expected market growth, are forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as "aim," "anticipate," "assume," "believe," "contemplate," "continue," "could," "design," "due," "estimate," "expect," "goal," "intend," "may," "objective," "plan," "predict," "positioned," "potential," "seek," "should," "target," "will," "would" and other similar expressions that are predictions of or indicate future events and future trends, or the negative of these terms or other comparable terminology. These forward-looking statements include statements about the initiation, timing, progress and results of our future clinical trials and current and future preclinical studies of our product candidates and of our research and development programs; our plans to develop and commercialize our current product candidates and any future product candidates and the implementation of our business model and strategic plans for our business, current product candidates and any future product candidates. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. You should not rely upon forward-looking statements as predictions of future events.

Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We undertake no obligation to update or revise any forward-looking statements, whether as a result of new information, the occurrence of certain events or otherwise. As a result of these risks and others, including those set forth in our most recent and future filings with the Securities and Exchange Commission, actual results could vary significantly from those anticipated in this presentation, and our financial condition and results of operations could be materially adversely affected. This presentation contains trademarks, trade names and service marks of other companies, which are the property of their respective owners.

Certain information contained in this presentation and statements made orally during this presentation relate to or is based on studies, publications, surveys and other data obtained from third-party sources and the Company's own internal estimates and research. While the Company believes these third-party studies, publications, surveys and other data to be reliable as of the date of the presentation, it has not independently verified, and makes no representation as to the adequacy, fairness, accuracy or completeness of, any information obtained from third-party sources. In addition, no independent sources has evaluated the reasonableness or accuracy of the Company's internal estimates or research and no reliance should be made on any information or statements made in this presentation relating to or based on such internal estimates and research.

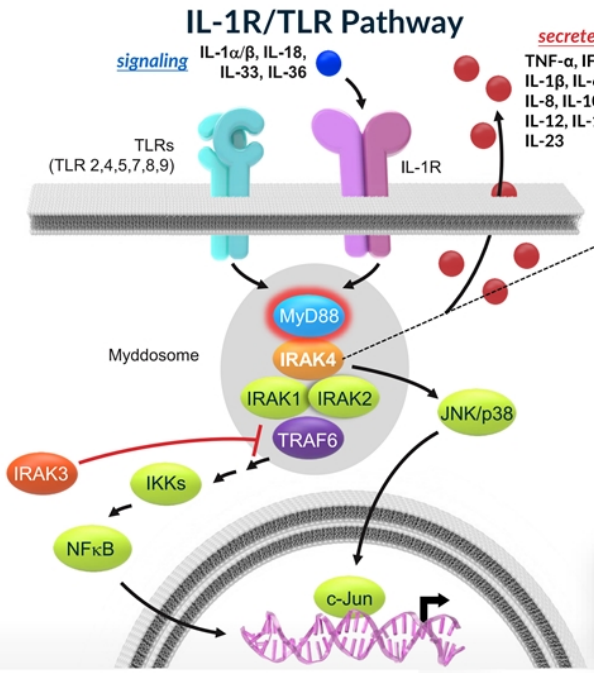
Kymera's Pipeline of Novel Protein Degraders



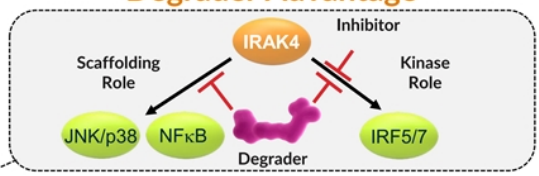
1. Option to participate equally in the development and commercialization of Sanofi-partnered programs in the US.
2. Sanofi collaboration to develop IRAK4 degrader candidates, including KT-474 (SAR444656), outside of oncology and immuno-oncology fields.

● = Oncology ● = Immunology-Inflammation

IRAK4 Targeting: Degrader Advantage, Clinical Validation, and Human Genetics De-risking



Degrader Advantage



Clinical Pathway Validation

IL-1α/IL-1β : Rheumatoid Arthritis, CAPS, Hidradenitis Suppurativa
IL-1α: Atopic Dermatitis
IL-1β: Gout; CANTOS Outcomes Data in Atherosclerosis and Lung Cancer
IL-18: Macrophage Activation Syndrome
IL-36: Generalized Pustular Psoriasis, Atopic Dermatitis
IRAK4 SMI: Rheumatoid Arthritis

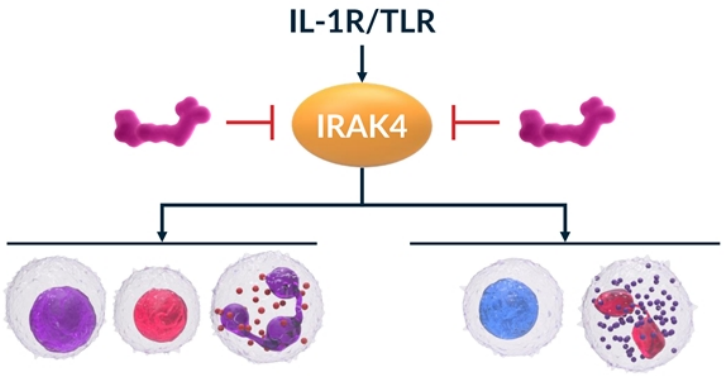
Human Genetics

Humans with **IRAK4 Null Mutation are healthy**

IRAK4 degrader has potential to achieve a **broad, well-tolerated anti-inflammatory effect,** providing multiple development opportunities in autoimmune inflammatory diseases

Development Opportunities for IRAK4 Degrader in Inflammation

Potential for Broad Activity Across Th1-Th17 and Th2 Diseases



Th1-Th17/Neutrophils

- **Hidradenitis Suppurativa**
- **Rheumatoid Arthritis**
- Systemic Lupus Erythematosus
- Inflammatory Bowel Disease
- Gout
- Psoriasis
- Behcet's Disease

Th2/Eosinophils

- **Atopic Dermatitis**
- Asthma
- COPD
- CRSwNP

Limitations of Current Therapies

Anti-Cytokine/Cytokine Receptor Antibodies

- Target only 1-2 cytokines
- Require injection

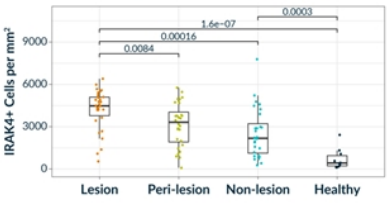
Small Molecule Inhibitors

- Limited pathway blockade (IRAK4 SMI)
- Safety issues (JAK family)

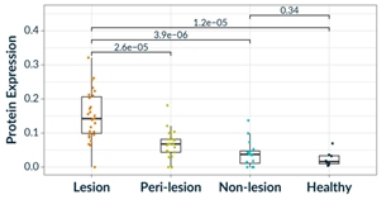
IRAK4 Protein Expression in Autoimmune Diseases: Upregulation in Skin of HS Patients Compared to Healthy Subjects

IRAK4 protein levels overexpressed in HS patient skin lesions

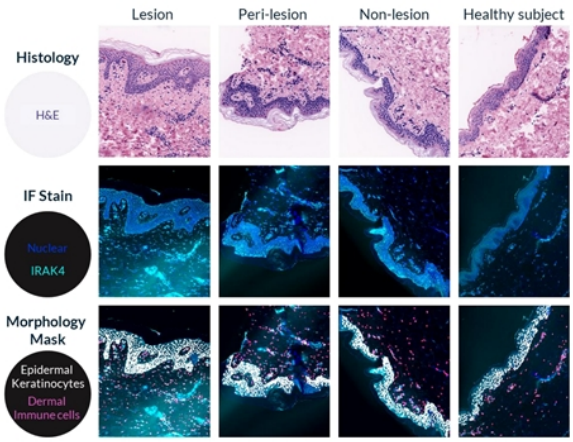
Immunofluorescence (IF)



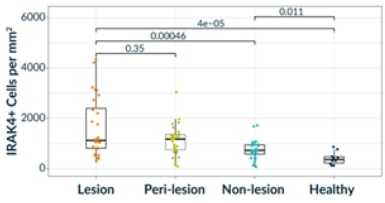
Mass Spectrometry (MS)



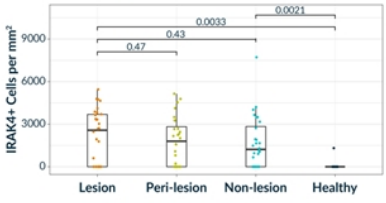
IRAK4 expression is upregulated in dermis and epidermis of HS patients relative to healthy subject skin



Dermal Immune Cells

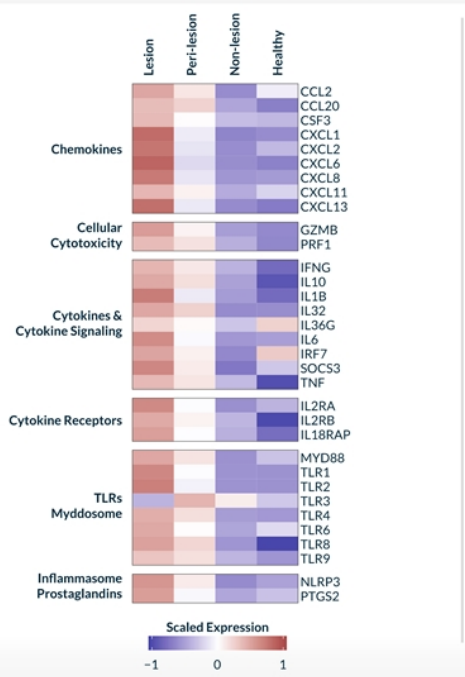


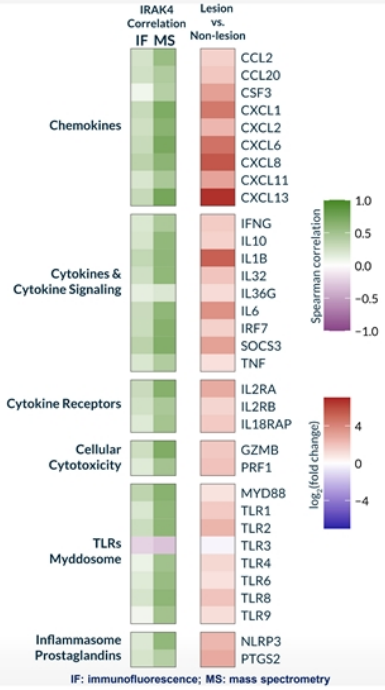
Epidermal Keratinocytes



Alavi et al., Society for Investigative Dermatology Annual Meeting, 2021

Multiple Proinflammatory Transcripts Are Upregulated and Correlate with IRAK4 Protein Levels in HS Skin Lesions





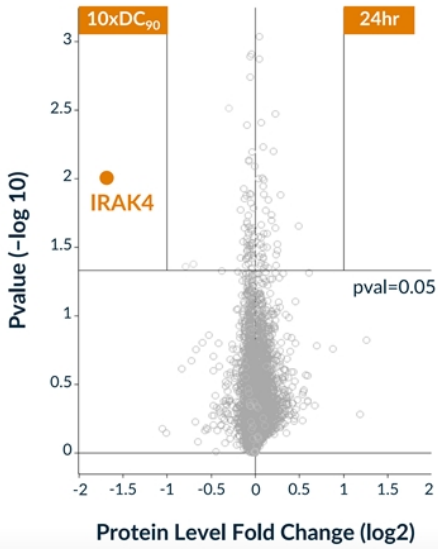
IF: immunofluorescence; MS: mass spectrometry

- Upregulation of TLRs, IL-1β/IL-36, MYD88, and multiple additional drivers of inflammation that all correlate with IRAK4 protein expression
- Highlights potential of IRAK4 targeting to treat diseases like HS characterized by marked pleiotropic inflammation

Alavi et al., Society for Investigative Dermatology Annual Meeting, 2021

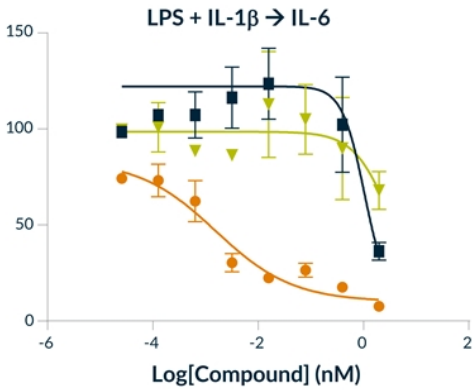
KT-474: Potent and Specific IRAK4 Degradation with Impact on Cytokines Superior to Kinase Inhibition

Degradation and Selectivity



- KT-474 DC_{50} = 2.1 nM in human immune cells
- KT-474 only degraded IRAK4 in human immune cells at concentration 10-fold above the DC_{90}
- KT-474 better able to inhibit IL-6 under both LPS and LPS + IL-1β than clinically active IRAK4 SM kinase inhibitor PF-06550833

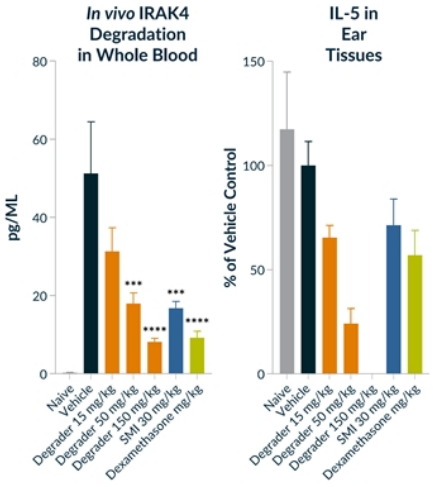
Superiority over SM kinase Inhibitor



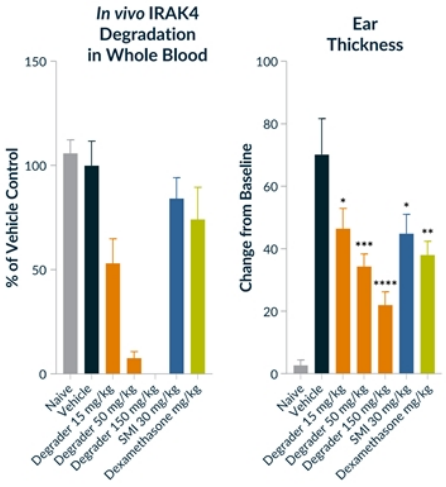
Legend	Compound	IL-6 IC_{50} (nM)
	IRAK4 Degrader	0.8
	Negative control	450
	IRAK4 SMI *(PF-06550833)*	N/A

KT-474 is Superior to IRAK4 Small Molecule Inhibitor (SMI) Across Multiple Preclinical Immune-inflammatory *In Vivo* Models

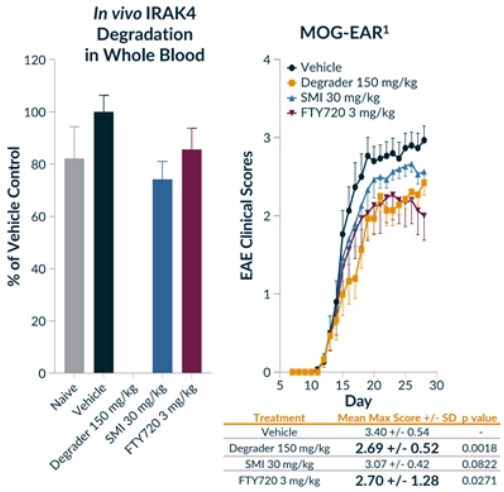
rmIL-33 Intradermal Challenge Model



rhIL-36αβγ Intradermal Challenge Model



Th17-mediated Multiple Sclerosis Model

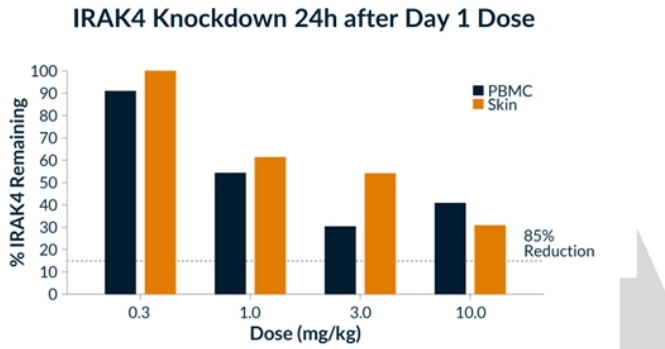


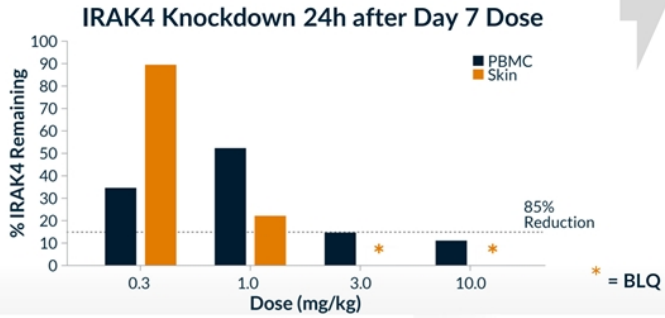
Treatment	Mean Max Score +/- SD	p value
Vehicle	3.40 +/- 0.54	-
Degrader 150 mg/kg	**2.69 +/- 0.52**	0.0018
SMI 30 mg/kg	3.07 +/- 0.42	0.0822
FTY720 3 mg/kg	**2.70 +/- 1.28**	0.0271

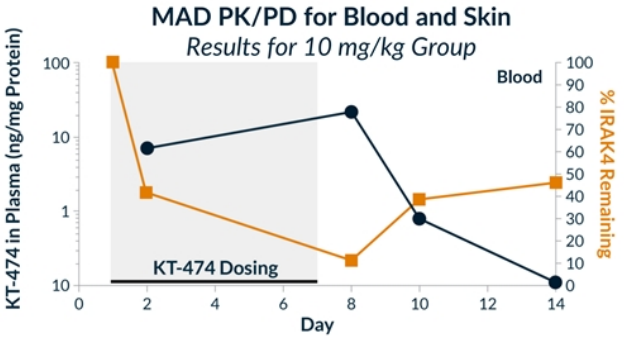
IRAK4 knockdown of ≥85% in whole blood achieved anti-inflammatory effect comparable to potent corticosteroids or approved standard of care drugs in these models as well as in models of TLR4 (MSU-Gout) or TLR7/8 (Imiquimod-Psoriasis) activation that was superior to IRAK4 small molecule inhibitor

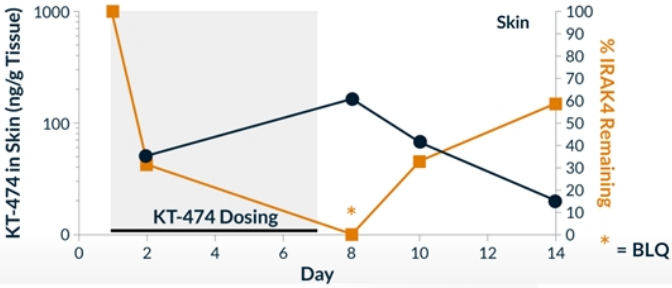
1. Myelin Oligodendrocyte Glycoprotein-induced Experimental Autoimmune Encephalomyelitis (MOG-EAR) Model

KT-474 Multi-dosing (Daily x 7 Days) Maximizes IRAK4 Degradation at Lower Doses in Dogs



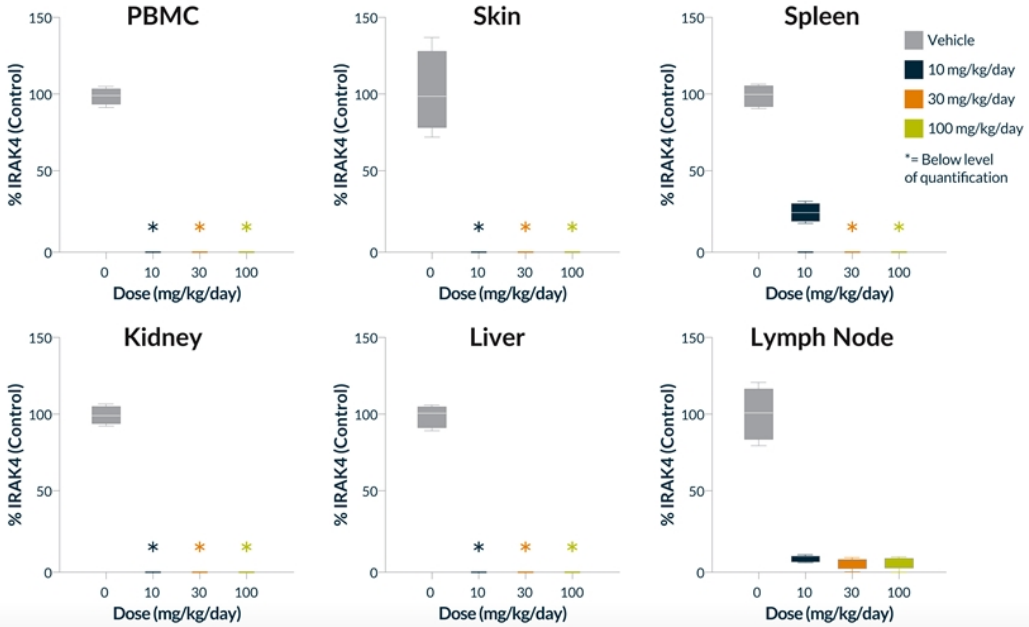






KT-474: Near Complete Systemic IRAK4 Degradation is Well Tolerated in Preclinical Non-rodent Model

- Orally-administered KT-474 evaluated in a 14-day non-GLP tox and PKPD study in rodent and non-rodents (shown).
- Almost complete knockdown demonstrated across multiple tissues at multiple doses
- Compound well-tolerated at all doses up to 600 mg/kg for rodents and 100 mg/kg for non-rodents



KT-474 Phase 1 Trial Design

Double-blind, Placebo-controlled, Single Ascending Dose (SAD) and Multiple Ascending Dose (MAD) trial

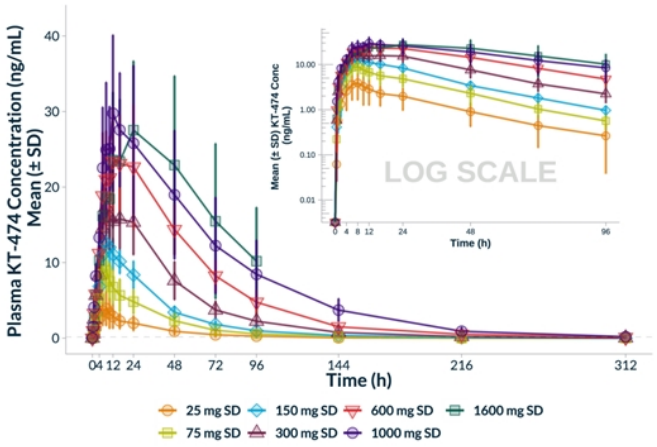
Three-part Phase 1 Design

1	2	3
SAD Portion	**MAD Portion**	**MAD Portion**
Healthy Volunteers	Healthy Volunteers	Patient Cohort
• **7** cohorts (up to 56 adult healthy subjects)	• **5** cohorts (up to 60 adult healthy subjects)	• **1** cohort (up to 20 AD and HS patients)
• **8** per cohort (6:2 randomization)	• **12** per cohort (9:3 randomization)	• Open-label
• **Single** dosing (starting dose 25 mg)	• **14x** daily doses (starting dose 25 mg)	• **14x** daily doses

Endpoints

Primary	• Safety & tolerability
Secondary/ Exploratory SAD & MAD	• Pharmacokinetic measures (half-life, bioavailability) • IRAK4 knockdown in PBMC
Exploratory SAD & MAD	• *Ex vivo* response of whole blood to TLR agonists (SAD & MAD) and IL-1β (MAD only)
Exploratory MAD Only	• IRAK4 knockdown in skin biopsies • Proinflammatory cytokine and chemokine levels in skin biopsies (Patients only) • Plasma C-reactive protein (HV and Patients) and cytokine levels (Patients only)

SAD Study: Favorable PK after Single Oral Dosing

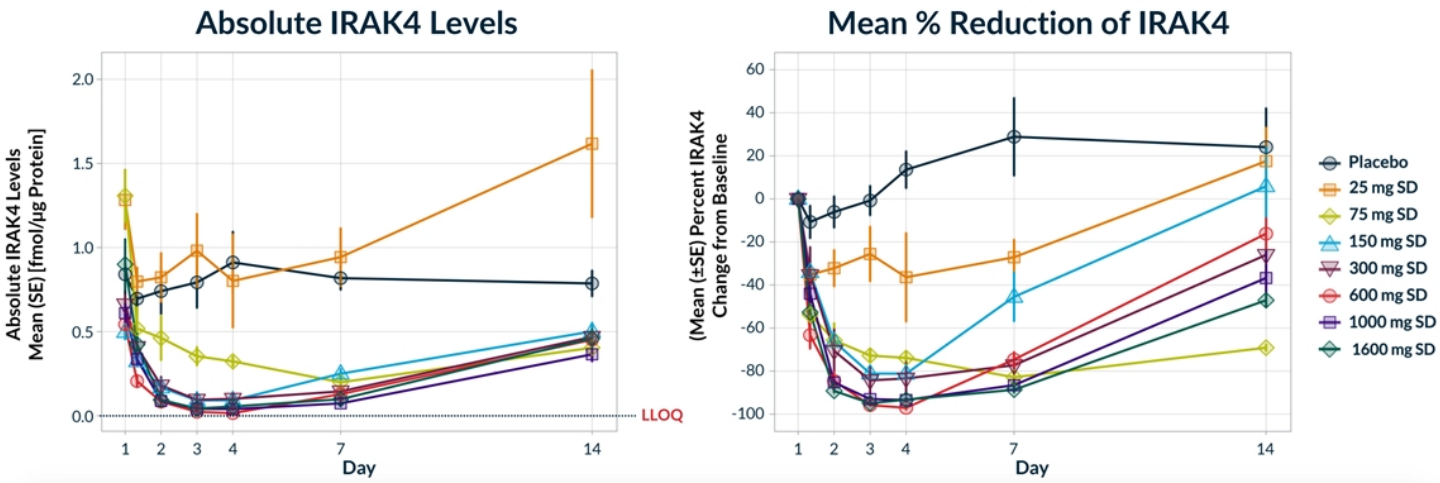


SAD #	Dose	Cmax (ng/mL)	t_{max} (h)	AUC (ng.h/mL)	$t_{1/2}$ (h)
1	25 mg	3.49 (61.2)	8.0 (6.0-8.0)	112 (65.4)	25.2 (27.0)
2	75 mg	9.08 (36.6)	7.0 (6.0-8.0)	288 (36.7)	28.7 (10.1)
3	150 mg	12.7 (25.7)	9.0 (8.0 - 10.0)	483 (21.9)	31.6 (22.1)
4	300 mg	17.4 (29.6)	8.0 (8.0 – 24.0)	869 (31.4)	36.4 (13.1)
5	600 mg	24.2 (27.5)	12.0 (6.00 – 24.0)	1530 (18.6)	40.9 (18.2)
6	1000 mg	27.8 (34.4)	20.0 (6.0 – 24.0)	1890 (60.8)	38.8 (7.0)
7	1600 mg	27.3 (36.2)	24.0 (12.0 – 48.0)	1920 (43.0)	36.4 (46.9)

Geometric Mean (%CV) reported for all parameters, except t_{max} where median (range) are presented

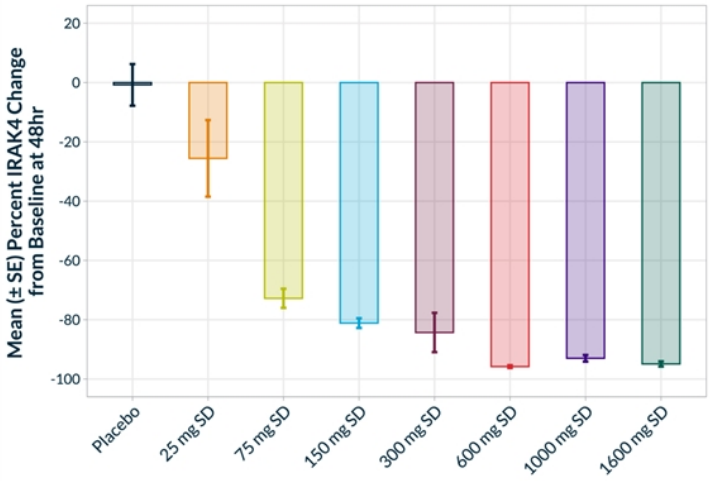
- Consistent PK after single dosing: Cmax achieved between 7-24 hours, half-life = 25-40 hours
- Dose dependent exposure increases, plateauing after the 1000 mg dose
- Low to moderate inter-subject variability in exposure

KT-474 Achieved Deep and Dose-Dependent IRAK4 Degradation after Single Oral Doses that Lasted for at Least 6 Days



- Detected by Mass Spectrometry in circulating PBMC
- IRAK4 levels nadired at 48-72 hours (Day 3-4)
- IRAK4 reduction lasted for at least 6 days post-dose in all dose groups
- SAD 5 through 7 approached or exceeded Lower Limit of Quantitation (LLOQ)

KT-474 Achieved >95% IRAK4 Degradation After Single Dose



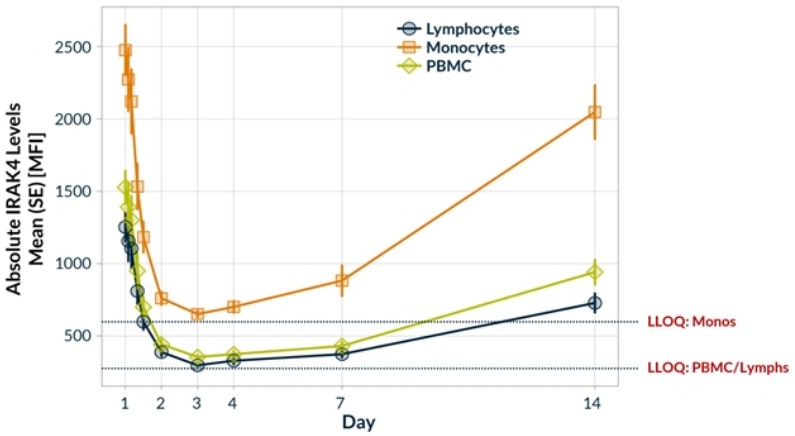
Percent IRAK4 Reduction in PBMC at 48 Hours Post-Dose using Mass Spectrometry

	N	Mean IRAK4 Change	Median IRAK4 Change	*p value*
Placebo	13	-1%	-2%	--
25 mg	6	-26%	-39%	*0.1*
75 mg	6	-73%	-75%	*<0.0001*
150 mg	6	-81%	-82%	*<0.0001*
300 mg	6	-84%	-89%	*<0.0001*
600 mg	7	-96%	-96%	*<0.0001*
1000 mg	5	-93%	-94%	*<0.0001*
1600 mg	6	-95%	-95%	*<0.0001*

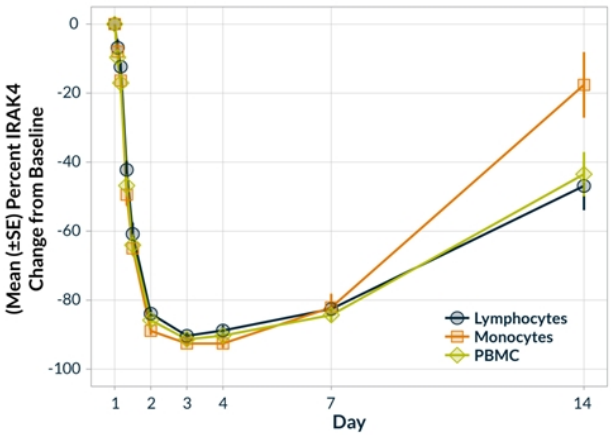
* p-values relative to placebo

Robust IRAK4 Degradation Observed in Lymphocytes and Monocytes: Flow Cytometry Results at SAD 7

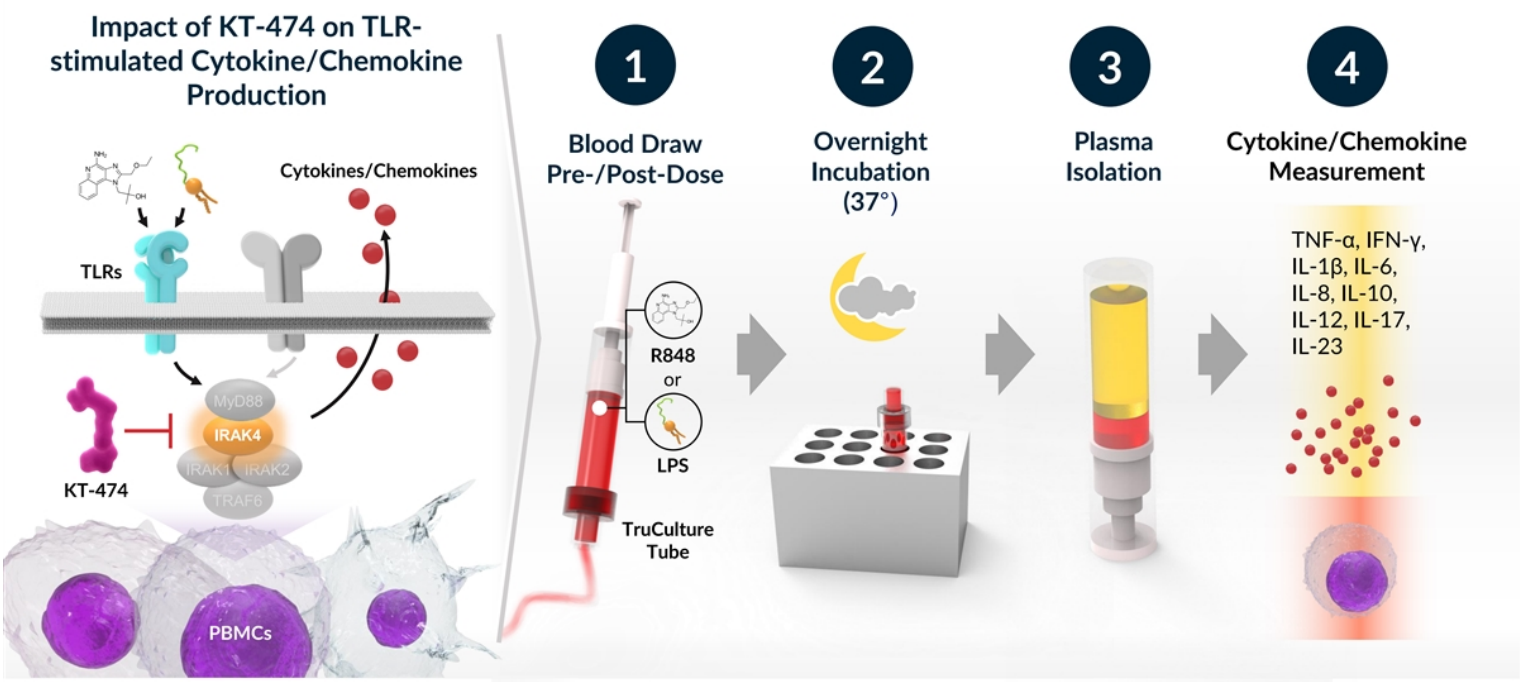
Absolute IRAK4 Levels



Mean % Reduction of IRAK4

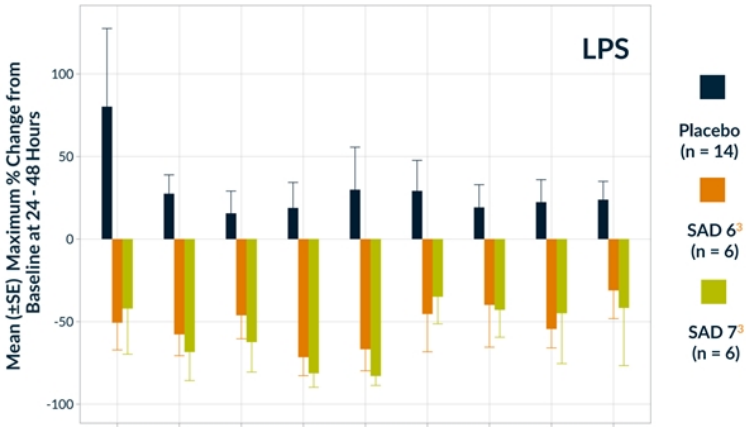


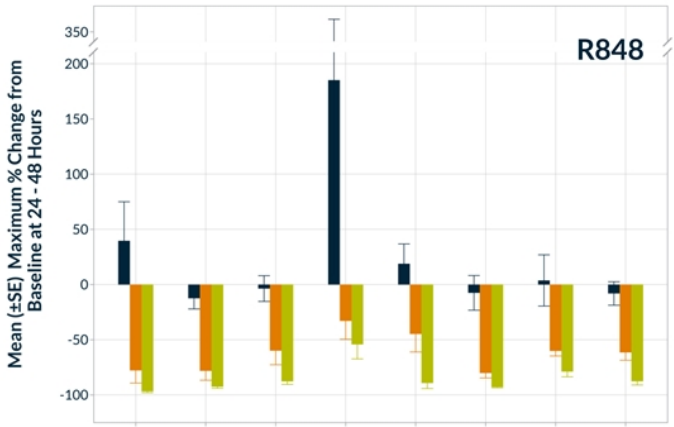
Ex Vivo Cytokine Stimulation: Methodology in KT-474 Phase 1 Trial



Up to 97% Maximum *Ex Vivo* Cytokine Inhibition 24-48h Post-Dose

Effect Against LPS (TLR4)- or R848 (TLR7/8)-Stimulated Cytokine Induction in Whole Blood





	IFNγ	IL1β	IL6	IL8	IL10	IL12	IL17	IL23	TNFα
Pbo	80%	27%	16%	19%	30%	29%	19%	22%	24%
SAD 6 85-93% Degr*	-51%	-58%[1]	-46%[2]	-72%[1]	-67%[2]	-45%[2]	-40%[2]	-54%[2]	-31%
SAD 7 89-95% Degr*	-42%	-68%[1]	-62%[1]	-81%[1]	-83%[1]	-35%[2]	-43%[2]	-45%[2]	-42%[2]

	IFNγ	IL1β	IL6	IL8	IL10	IL12	IL17	TNFα
Pbo	40%	-12%	-4%	185%	19%	-7%	4%	-8%
SAD 6	-78%	-78%[1]	-60%[1]	-33%	-45%	-80%[1]	-60%[1]	-61%
SAD 7	-97%[2]	-92%[1]	-88%[1]	-54%	-89%[1]	-93%[1]	-79%[1]	-88%[2]

[1] = p value < 0.01; [2] = p value < 0.05

**Mean IRAK4 degradation in PBMC at 24-48h*

[3]Ex vivo cytokine assay was performed at 48h nadir (maximal degradation) only in cohorts 6-7

Blinded SAD Safety Summary

- **No SAEs**
- **Treatment-related AEs observed only in SAD 5 and SAD 6; all were self-limiting and resolved**
  - No treatment-related AEs in SAD 7
- **No significant ECG changes**

Possibly or Probably Treatment-Related AEs* (>1 Subject)

AE Term	#AEs (subjects)	Severity	Cohort
Headache	4 (3)	Moderate (x2)	SAD 5, SAD 6
		Mild (x2)	SAD 5
Nausea	2 (2)	Mild (x2)	SAD 6

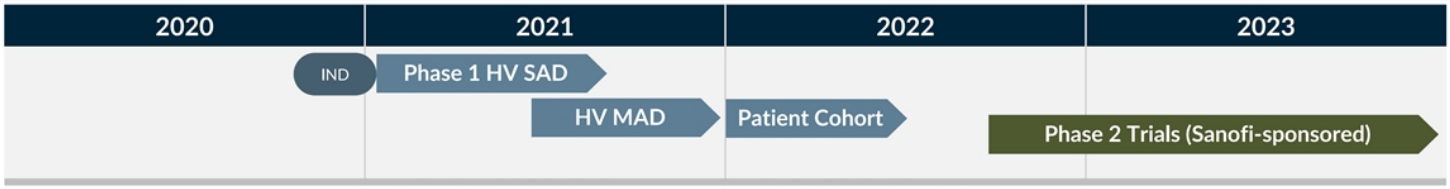
** per investigator assessment*

SAD Summary

- SAD dose escalation completed
- Single doses resulting in sustained pharmacodynamic effect were well-tolerated, with mild-moderate self-limiting headache and GI symptoms the most common treatment-related AEs seen at doses ≥ 600 mg
- **Robust, dose-dependent IRAK4 reduction in PBMC maintained for at least 6 days, with mean 93-96% KD (approaching or exceeding lower limit of quantification)** at 48 hours plateauing after 600 mg; expectation during multi-dosing is to reach these levels at much lower dose
- **Proof-of-biology established** with demonstration of broad and potent *ex vivo* cytokine inhibition in whole blood
  - Up to **79-97% inhibition of R848 or LPS induction of 8 different pro-inflammatory cytokines**, including: IFN-γ (97%), IL-12 (93%), IL-1β (92%), IL-10 (89%), IL-6 (88%), TNF-α (88%), IL-8 (81%) and IL-17 (79%)
  - Maximum cytokine effects seen with KT-474 exposures corresponding to **≥*85%* degradation in PBMC**

KT-474 SAD Phase 1 results demonstrate degrader proof-of-mechanism and proof-of-biology, first time for TPD in a placebo-controlled study

KT-474 Phase 1 Trial: Next Steps



Data readouts:
- *Oct 2021:* HV SAD POM/POB
- *Before end of 2021:* HV MAD POM/POB
- *Mid 2022:* Patients POM/POB

- Healthy volunteer MAD enrollment ongoing
  - Anticipate maximizing **IRAK4 knockdown and impact on downstream biomarkers at substantially lower doses** with daily dosing based on PK and PD and as shown in preclinical models
  - Plan to present safety, PK, and PD data before year end
  - PD includes: IRAK4 levels in blood and skin, *ex vivo* cytokine stimulation, plasma hsCRP
  - On track to complete by year-end
- Cohort of AD and HS patients (up to 20) to start enrolling in Q1'22
  - Data readout planned for mid-year