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): June 28, 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 June 28, 2021, Kymera Therapeutics, Inc. (the "Company") issued a press release, a copy of which is furnished herewith as Exhibit 99.1. In addition, on June 28, 2021, the Company intends to host a conference call to discuss the Company's ongoing Phase 1 trial of KT-474. A form of the slide presentation that will be used at these meetings 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 June 28, 2021, the Company announced the U.S. Food and Drug Administration ("FDA"), lifted the partial clinical hold on the Company's ongoing Phase 1 trial of KT-474 following review of interim results from the single ascending dose ("SAD") portion of the Phase 1 trial. It also announced interim results from the healthy volunteer SAD portion of the Phase 1 trial, including safety, pharmacokinetic, and pharmacodynamic data from the first four study cohorts. Interim data showed dose and time-dependent IRAK4 degradation, as measured in peripheral blood mononuclear cells (PBMC) using mass spectrometry. Following a single KT-474 oral dose, IRAK4 reduction was observed as early as eight hours post-dose, reached maximal reduction at 48 to 72 hours, and was sustained for at least six days with subsequent recovery towards pre-treatment baseline across all dose groups. In the fourth cohort, following a single 300 mg dose of KT-474, median IRAK4 reduction from baseline at 48 hours was 90% compared to a 16% increase in the placebo group ($p<0.0001$), with maximum IRAK4 reduction of 94%, demonstrating proof-of-mechanism for KT-474 (see table below).

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

	Placebo (n=8)	Cohort 1 (n=6)	Cohort 2 (n=6)	Cohort 3 (n=6)	Cohort 4 (n=6)
KT-474 dose	—	25 mg	75 mg	150 mg	300 mg
Median IRAK4 Change		-41%	-71%	-78%	-90%
	+16%	(p=0.0057)	(p<0.0001)	(p<0.0001)	(p<0.0001)

No treatment-related adverse events have been observed to date.

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 March 31, 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 June 28, 2021, furnished herewith.
99.2	Kymera Therapeutics, Inc. Corporate Presentation, dated June 28, 2021, furnished herewith.

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: June 28, 2021

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

KYMERA

Kymera Therapeutics Announces Positive Interim Results from Single Ascending Dose Phase 1 Trial of KT-474 Demonstrating Degrader Proof-of-Mechanism

KT-474 has achieved and exceeded Phase 1 target degradation of 85% within the SAD portion of the Phase 1 trial dosed to date, with 90% median degradation at the 300 mg dose

After single dose administration, degradation was maintained for at least six days at all dose levels, with no treatment-related adverse events observed to date

Data represent the first proof-of-mechanism for targeted protein degradation in a randomized, placebo-controlled healthy volunteer study

FDA has lifted partial clinical hold on Multiple Ascending Dose portion of Phase 1 trial and Kymera plans to initiate repeat dosing in July 2021

Kymera to host conference call today at 8 a.m. ET

Watertown, Mass. (June 28, 2021) – Kymera Therapeutics, Inc. (NASDAQ: KYMR), a clinical-stage biopharmaceutical company advancing targeted protein degradation to deliver novel small molecule protein degrader medicines, today announced positive interim results from the Single Ascending Dose (SAD) portion of the Phase 1 clinical trial of KT-474, demonstrating the first degrader proof-of-mechanism in targeted protein degradation in a randomized, placebo-controlled healthy volunteer study. KT-474 has achieved and exceeded the Phase 1 target degradation of 85% within the SAD portion of the Phase 1 trial dosed to date, with profound IRAK4 degradation after a single oral dose that lasted for at least six days at all dose levels. The partial clinical hold on the Multiple Ascending Dose (MAD) portion of the Phase 1 trial of KT-474 has been lifted following review by the U.S. Food and Drug Administration (FDA) of interim safety, pharmacokinetic and pharmacodynamic data from the first three cohorts of the SAD healthy volunteer portion of the Phase 1 study.

In the SAD portion of the trial, healthy volunteer subjects are randomized 6:2 to either a single oral dose of KT-474 or placebo. Interim data (n=32), which also include results from the fourth cohort of the trial, showed dose and time-dependent IRAK4 degradation following single oral KT-474 dose administration (KT-474 dose levels of 25, 75, 150 and 300 mg). IRAK4 levels were measured in peripheral blood mononuclear cells (PBMC) using mass spectrometry. Following a single KT-474 oral dose, IRAK4 reduction was observed as early as eight hours post-dose, reached maximal reduction at 48 to 72 hours, and was sustained for at least six days with subsequent recovery towards pre-treatment baseline across all dose groups. In the fourth cohort, following a single 300 mg dose of KT-474, median IRAK4 reduction from baseline at 48 hours was 90% compared to a 16% increase in the placebo group ($p<0.0001$), with maximum IRAK4 reduction of 94%, demonstrating proof-of-mechanism for KT-474 (see table below). KT-474, to date, has demonstrated oral bioavailability, predictable and dose-dependent plasma exposures, and a half-life supportive of oral daily dosing. No treatment-related adverse events have been observed to date.

“This study marks the first time a heterobifunctional small molecule degrader has been studied in humans in a placebo-controlled study,” said Nello Mainolfi, PhD, Co-Founder, President and CEO, Kymera Therapeutics. “We have shown that KT-474 can lead to rapid, marked and sustained IRAK4 reduction after a single dose. The ability to reach and sustain biologically relevant levels of target degradation after just a single dose not only validates Kymera’s platform, but importantly, further de-risks the development of KT-474 as a potentially best-in-class anti-inflammatory oral agent.”

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

	Placebo (n=8)	Cohort 1 (n=6)	Cohort 2 (n=6)	Cohort 3 (n=6)	Cohort 4 (n=6)
KT-474 dose	**—**	**25 mg**	**75 mg**	**150 mg**	**300 mg**
Median IRAK4 Change	**+16%**	**-41%** (p=0.0057)	**-71%** (p<0.0001)	**-78%** (p<0.0001)	**-90%** (p<0.0001)

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 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.

“We are encouraged by the safety, pharmacokinetic and pharmacodynamic profile observed to date with single oral doses of KT-474 and look forward to initiating the MAD portion of the trial while continuing to dose escalate in the SAD portion. The IRAK4 reduction in PBMC observed after single doses of KT-474 shows robust translation of the pharmacodynamic effect from preclinical studies to humans. We are excited to have reached and exceeded our target degradation of 85% after just a single dose, and with 14 days of dosing in the MAD portion we anticipate reaching our target degradation with even lower daily doses of KT-474,” said Jared Gollob, MD, Chief Medical Officer at Kymera Therapeutics.

Kymera plans to continue dose escalation in the SAD portion of the Phase 1 trial and also assess for any food effect. In parallel, starting next month, Kymera plans to initiate 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 in the MAD portion of the trial. Kymera expects to present updated results from the healthy volunteer SAD and MAD portions of the trial in Q4’21, including IRAK4 degradation in both skin and PBMC and effects on inflammatory biomarkers. The dose level in the MAD healthy volunteer portion which demonstrates maximal IRAK4 degradation in PBMC and skin 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.

Conference Call Information

Kymera will host a conference call and webcast today, Monday, June 28, at 8:00 a.m. ET to discuss the KT-474 program updates. To access the conference call via phone, please dial 833-740-0921 (U.S.) or +1 409-937-8885 (International) and using the conference ID 7376053. 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 dosing of healthy volunteers in the Single Ascending Dose portion of a 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 immuno-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 its: plans to present updated results from the healthy volunteer SAD and MAD portions of the KT-474 trial; its views on KT-474 as validating its platform and approach to drug development; strategy, business plans and objectives for the IRAK4 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 Kymera Therapeutics has operations or does business, as well as on the timing and anticipated results of its 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 topline or interim results of current clinical studies may not be predictive of future results in connection with current or future clinical trials; Kymera Therapeutics' ability to successfully demonstrate the safety and efficacy of its drug candidates; the timing and outcome of planned interactions with regulatory authorities, including for the advancement in development of KT-474; 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 Report on Form 10-Q for the period ended March 31, 2021, filed on May 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:
Paul Cox
VP, Investor Relations and Communications
pcox@kymeratx.com
917-754-0207

Media Contact:
Lissette L. Steele
Verge Scientific Communications for Kymera Therapeutics
lsteele@vergescientific.com
202-930-4762

Exhibit 99.2

INVENTING NEW MEDICINES
WITH TARGETED PROTEIN DEGRADATION

KT-474 Phase 1 Clinical Trial Update

June 28, 2021

Forward-Looking Statements

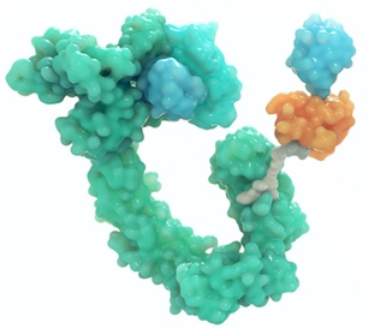
This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 (PSLRA) and other federal securities laws. These statements include information about our current and future prospects and our operations and financial results, which are based 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.

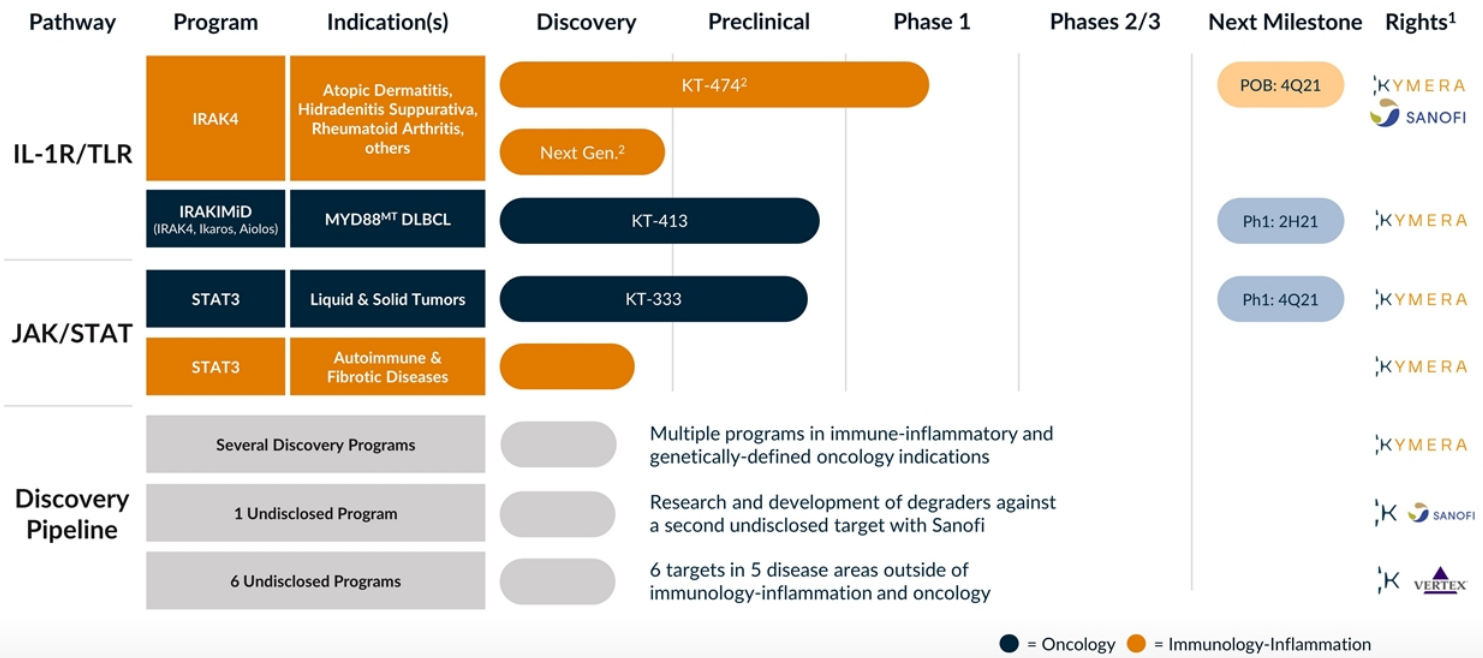
Kymera: A Leading TPD Company

KYMERA



VISION	Fully integrated, **disease agnostic** protein degrader medicine company
KEY PARTNERSHIPS	SANOFI VERTEX gsk
INITIAL FOCUS	**Immune inflammation (I/I)** and **oncology**
FIRST-IN-CLASS	**First** to show **placebo-controlled** degrader **proof-of-mechanism**
CLINICAL PIPELINE	**2** additional **INDs** and clinical initiations expected by end of **2021**
PROOF-OF-BIOLOGY	To be established in humans in **2021**
WELL-POSITIONED	**$435M** cash balance at **Q1 2021**

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.

Near-Term Milestones Provide Significant Opportunity

Program	Compound	Indication(s)	Expected Upcoming Milestones
IRAK4	KT-474	AD, HS, RA, others	✓ Initiated SAD portion of Phase 1 trial in healthy volunteers (Feb 2021) ✓ Established degrader proof-of-mechanism in healthy volunteer SAD portion of Phase 1 trial (June 2021) • Initiate enrollment in MAD portion of Phase 1 trial (July 2021) • Present data from atopic dermatitis cohort in non-interventional study (2H21) • Establish Phase 1 proof-of-biology in healthy volunteers (4Q21) and in patient cohort (1H22)
IRAKIMiD (IRAK4, Ikaros, Aiolos)	KT-413	$MYD88^{MT}$ DLBCL	✓ Presentation of preclinical data updates at AACR, ICML meetings (2Q21) • Submit IND to initiate Phase 1 clinical trial in r/r B cell lymphomas (2H21) • Present additional KT-413 preclinical data and potential expansion strategies (2H21) • Establish Phase 1 proof-of-biology in patients (2022) • Establish Phase 1 initial clinical proof-of-concept in patients (2022)
STAT3	KT-333	Liquid & Solid Tumors	✓ Nominated development candidate for liquid & solid tumor indications (1Q21) • Present additional preclinical data in liquid & solid tumor indications (2H21) • Submit IND to initiate Phase 1 clinical trial in liquid and solid tumors (4Q21) • Establish Phase 1 proof-of-biology in patients (2022) • Establish Phase 1 initial clinical proof-of-concept in patients (2022)
Discovery Programs & Platform			• Continue pipeline expansion by advancing early-stage discovery programs toward IND-enabling studies • Further expand Pegasus platform to generate novel degrader product candidates • Leverage Whole-Body Atlas to unlock new opportunities across broad therapeutic applications

● = Oncology ● = Immunology-Inflammation


IRAK4 Degrader KT-474
KYMERA

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

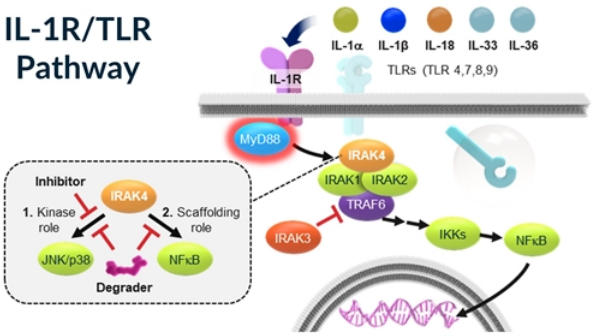
Unmet Medical Need

Validated Biology

Undrugged Node

Precision Medicine Approach

IL-1R/TLR Pathway



Clinical Pathway Validation

IL1-Rα/IL-1β : Rheumatologic Diseases
IL-1α: Atopic Dermatitis
IL-1β: CANTOS Data, Atherosclerosis, Lung Cancer
IL-18: Macrophage Activation Syndrome
IL-36: Generalized Pustular Psoriasis
IRAK4 SMI: Rheumatoid Arthritis

- IRAK4 is a key component of the myddosome protein complex involved in innate immunity that mediates signals through IL-1R and TLRs
- Several commercial and clinical stage drugs have validated this pathway in multiple diseases
- Degrading IRAK4, and fully blocking IL-1R/TLR signaling, is expected to be superior to antibody-based therapies that block only single cytokines, with convenience of a daily oral therapy
- IRAK4 degradation can block pathway fully vs kinase inhibitors that partially block signaling
- Human genetics de-risk safety: adults that lack IRAK4 are healthy

KT-474 Opportunity

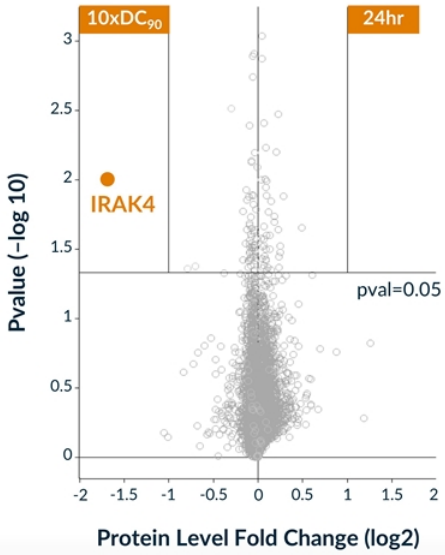
Immune-inflammatory disorders collectively impacting millions of patients in the U.S.

	Total Prevalence (U.S.)	
Atopic Dermatitis (AD)	>16.0M [1]	• Chronic, pruritic **inflammatory skin disease** • Large unmet need for safe and effective oral agents for patients with AD
Rheumatoid Arthritis (RA)	>1.3M [2]	• Chronic, systemic **autoimmune disease** that can cause irreversible joint damage • Multiple therapies targeting the **IL-1R/TLR pathway** are approved
Hidradenitis Suppurativa (HS)	>325K [3]	• Chronic and debilitating inflammatory skin disease • **~25%** of patients with moderate-to-severe disease[4] • Adalimumab is approved, which provides some benefit to **~50% of patients** with moderate-to-severe disease[5]
Additional Opportunities	→	• Immune-inflammatory diseases impacted by **IL-1R/TLR pathway**

1. Chiesa Fuxench et al. J Invest Dermatol. 2019 Mar;139(3):583-590.
2. Hunter et al. Rheumatol Int . 2017 Sep;37(9):1551-1557.
3. Garg et al. JAMA Dermatol. 2017;153(8):760-764.
4. Calao et al. PLoS One. 2018; 13(7): e0200683.
5. Kyriakou et al. Dermatol Reports. 2018 Oct 1; 10(2): 7859.

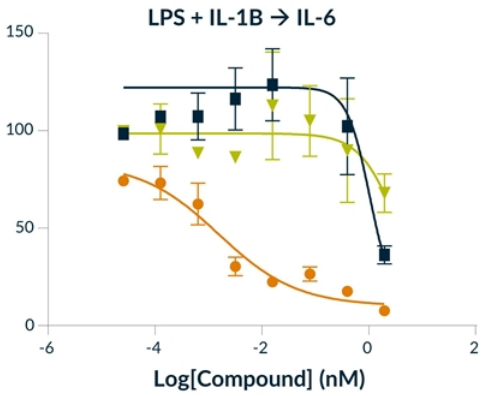
KT-474: Potent and Specific IRAK4 Degradation Superior to Kinase Inhibition

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-1B than clinically active IRAK4 SM kinase inhibitor PF-06550833

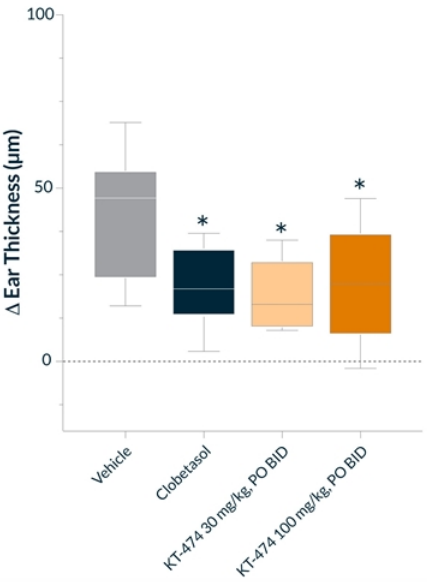
Superiority over SM kinase Inhibitor

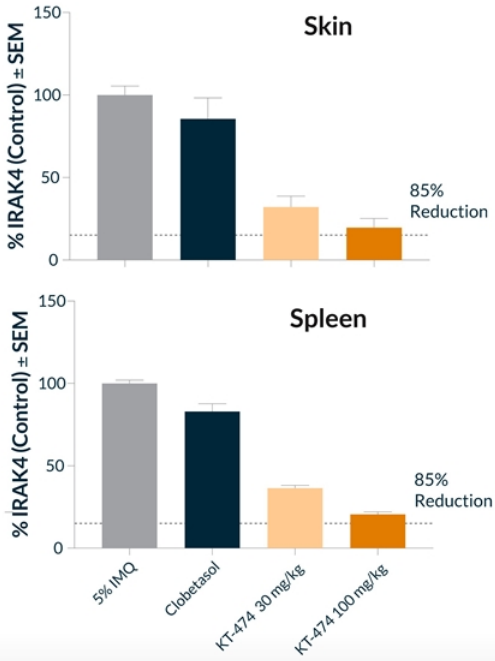


Legend	Compound	IL-6 IC_{50} (nM)
	IRAK4 Degrader	0.8
	Negative control	450
	IRAK4 SMI *(PF-06550833)*	N/A

85% IRAK4 Degradation Sufficient for Maximal *In Vivo* Efficacy in Preclinical Models

- Ability to inhibit topical skin thickening induced by imiquimod was measured in a mouse model of psoriasis
- Orally dosed KT-474 inhibited thickening, a reflection of local and systemic inflammation, comparable to a topic corticosteroid after 2 or 4 days of dosing
- Full efficacy at doses achieving at 65-80% IRAK4 reduction in skin and spleen. In other models KT-474 has demonstrated full efficacy with 85% degradation

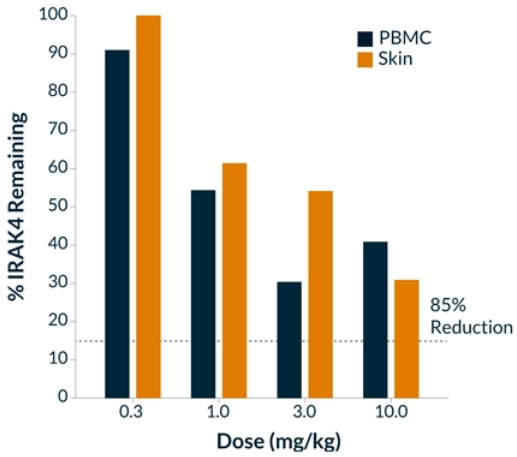




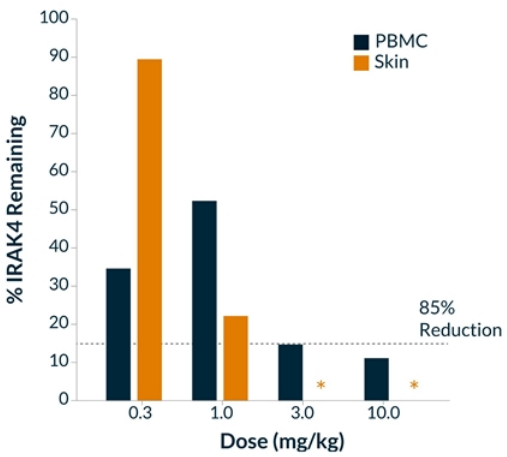
KT-474 in Dog: Multi-dosing Required to Achieve Target Degradation

- Orally-administered KT-474 achieves >85% knockdown of IRAK4 at Day 7 with repeat dosing in MAD study
- Multiple doses (MAD) lead to optimal degradation profile vs SAD upon reaching steady-state
- Consistency of IRAK4 knockdown observed across peripheral blood mononuclear cells (PBMC) and skin tissue

Dog Single Ascending Dose (SAD)
IRAK4 Knockdown at Day 1



Dog Multiple Ascending Dose (MAD)
IRAK4 Knockdown at Day 7



* = Below Limit of Quantitation


KT-474 Interim Phase 1 SAD Results
KYMERA

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 SAD Portion — Healthy Volunteers

- **7** cohorts (up to 56 adult healthy subjects)
- **8** per cohort (6:2 randomization)
- **Single** dosing (starting dose 25 mg)

2 MAD Portion — Healthy Volunteers

- **5** cohorts (up to 60 adult healthy subjects)
- **12** per cohort (9:3 randomization)
- **14x** daily doses (starting dose 25 mg)

3 MAD Portion — Patient Cohort

- **1** cohort (up to 20 AD and HS patients)
- Open-label
- **14x** daily doses

Endpoints

Primary

- Safety & tolerability

Secondary/ Exploratory

SAD & MAD

- Pharmacokinetic measures (half-life, bioavailability)
- IRAK4 knockdown in PBMC

Exploratory

MAD only

- IRAK4 knockdown in skin biopsies
- Proinflammatory cytokine and chemokine levels in skin biopsies
- C-reactive protein and cytokine levels in plasma
- *Ex vivo* response of whole blood to TLR agonists and IL-1β

KT-474 Phase 1 Trial Goals

Establishing proof-of-mechanism and proof-of-biology

De-risking Milestones

1 SAD Portion
Healthy Volunteers

Oral Bioavailability and Proof-of-Mechanism

- Efficacious plasma exposures that are safe and well-tolerated
- Proof-of-mechanism with IRAK4 knockdown following single KT-474 dose
- Predictable PK/PD supporting oral daily dosing regimen

2 MAD Portion
Healthy Volunteers

Optimal IRAK4 Reduction and Proof-of-Biology

- ≥85% IRAK4 knockdown in skin and blood with daily dosing x 14 days that is safe and well-tolerated
- Proof-of-biology with systemic anti-inflammatory effect: reduction in plasma hsCRP and inhibition of whole blood *ex vivo* response to TLR agonists and IL-1β
- Establishment of maximum effective dose

3 MAD Portion
Patient Cohort

Establish Proof-of-Biology in Patients

- ≥85% IRAK4 degradation in diseased skin and blood
- Anti-inflammatory effect in diseased skin and reduction of plasma cytokines and hsCRP
- Confirmation of dose for subsequent Phase 2 studies

KT-474 Interim Phase 1 Healthy Volunteer SAD Overview

Interim Results (Cohorts 1-4)

- **32** subjects randomized
- **24** subjects administered KT-474
- **8** subjects administered placebo

Dosing

- Single dose administration of oral KT-474 tablet
- Dose levels (mg):
  25
  75
  150
  300

Pharmacokinetic (PK) Features

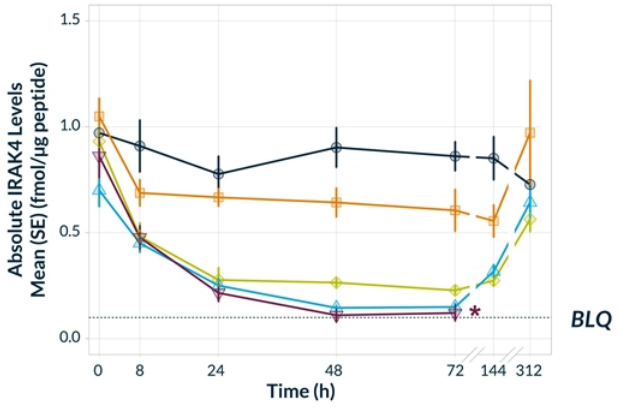
- PK profile consistent with oral daily dosing
- Predictable, dose-dependent plasma exposures after single oral dose of KT-474
- Half-life:
  25-32 hours

Safety & Tolerability

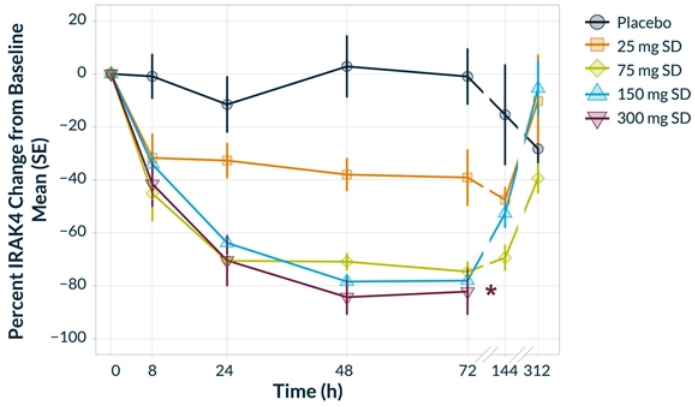
- No treatment-related adverse events
- No Serious Adverse Events

KT-474 Achieved Profound IRAK4 Degradation after Single Oral Dose that Lasted for at Least 6 Days

Absolute IRAK4 Levels



Mean % Reduction of IRAK4

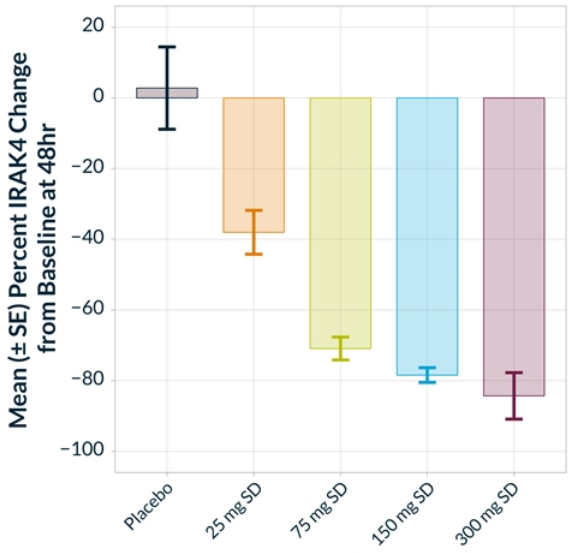


BLQ = Below Limit of Quantitation

* SAD4 144/312 h PD timepoints pending

- Measured by mass spectrometry in circulating PBMC
- IRAK4 levels nadired at 48-72 hours
- IRAK4 reduction lasted for at least 144h (6 days post-dose) in all dose groups

IRAK4 Degradation >85% Achieved Following Single KT-474 Dose



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

	Placebo (n=8)	Cohort 1 (n=6)	Cohort 2 (n=6)	Cohort 3 (n=6)	Cohort 4 (n=6)
KT-474 dose	-	25 mg	75 mg	150 mg	300 mg
Mean IRAK4 Change	+3%	-38%	-71%	-78%	-84%
Median IRAK4 Change	+16%	-41%	-71%	-78%	-90%
*p value**		*0.0057*	*<0.0001*	*<0.0001*	*<0.0001*

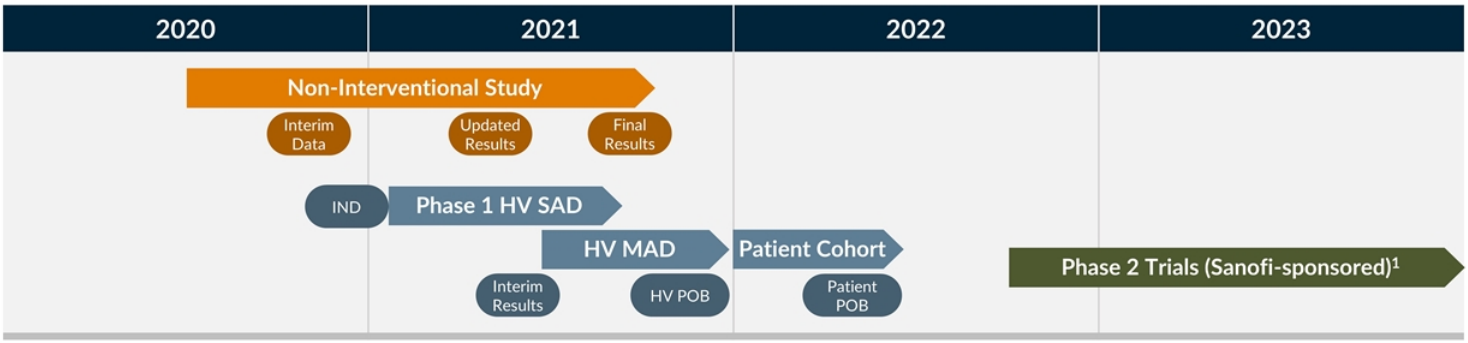
** p-values relative to placebo*

Interim Results from Phase 1 Healthy Volunteer SAD

Summary and Next Steps

- **KT-474 interim Phase 1 results demonstrate degrader proof-of-mechanism, first time for TPD in a placebo-controlled study**
  - Median IRAK4 reduction of 90% ($p<0.0001$ vs placebo) and maximum reduction of 94% at 48 hours following single dose of 300 mg, with sustained degradation that lasted for at least 6 days at all dose levels
  - Based on potency, PK and PD profiles with deep and sustained multiday degradation, expect to achieve biologically relevant (85%) level of degradation with repeat dosing at lower doses; selected MAD starting dose of 25 mg
  - Demonstrated predictable, dose-dependent and biologically active plasma exposures, and half-life that supports oral daily dosing
  - No treatment-related adverse events or serious adverse events observed to date
  - Demonstrating Phase 1 target degradation of >85% de-risks KT-474 ability to reach clinically relevant biological effects in future development as a potential best-in-class anti-inflammatory oral drug
- **FDA lifted partial clinical hold following review of interim healthy volunteer SAD results**
  - Dose escalation in SAD portion of Phase 1 to continue, including assessment of food-effect
  - In July, plan to initiate MAD portion of Phase 1 in healthy volunteers assessing daily dosing of KT-474 for 14 days
- **Expect to present updated results from healthy volunteer SAD/MAD portions in Q4'21**
  - Data to include IRAK4 degradation in skin and PBMC and effects on inflammatory biomarkers after repeat dosing
  - Optimal dose from MAD healthy volunteer portion to be evaluated in an open label cohort of patients with atopic dermatitis and hidradenitis suppurativa

KT-474 Development Plan



Non-Interventional

- 40 patients (HS n=30; AD n=10)
- Biomarker endpoints in blood and skin: IRAK4, cytokines, acute phase reactants
- Data updates:
  - Interim: **Oct 2020**
  - Updated HS: **May 2021**
  - Final AD: **2H21**

Phase 1

- SAD dosing initiated **1Q21**
- SAD/MAD studies: healthy volunteers (HV) and AD/HS patients
- Endpoints: primary - **Safety**; secondary - **Proof-of-Biology**
- Data updates:
  - Interim SAD proof-of-mechanism: **June 2021**
  - HV proof-of-biology: **4Q21**
  - Patient proof-of-biology: **1H22**

Phase 2

- Randomized, placebo-controlled trials in patients in potential indications such as AD, HS, RA, others

1. Estimated clinical development timeline.

THANK YOU

investors@kymeratx.com

media@kymeratx.com

inquiries@kymeratx.com