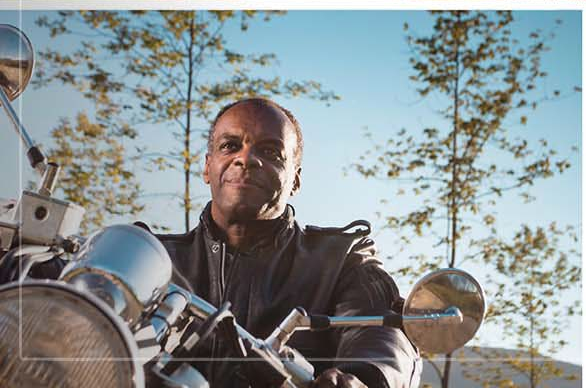
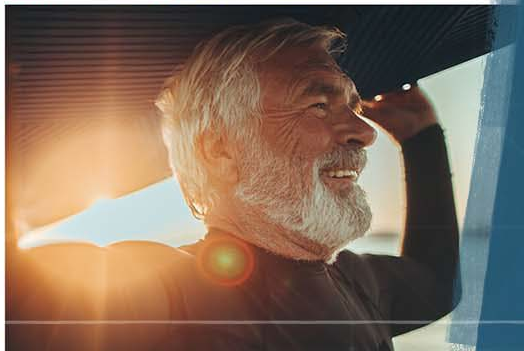




VERTEX

THE SCIENCE *of* POSSIBILITY

FIRST QUARTER 2022 FINANCIAL RESULTS

MAY 5, 2022

AGENDA

Introduction

Michael Partridge, Senior Vice President, Investor Relations

CEO Perspective and Pipeline Update

Reshma Kewalramani, M.D., Chief Executive Officer and President

Commercial Update

Stuart Arbuckle, Executive Vice President and Chief Operating Officer

Financial Results

Charlie Wagner, Executive Vice President and Chief Financial Officer

SAFE HARBOR STATEMENT & NON-GAAP FINANCIAL MEASURES

This presentation contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, the information provided regarding future financial performance and operations, the section captioned "Full-Year 2022 Financial Guidance", and statements regarding (i) the expectations, development plans, anticipated timelines for and potential benefits of the company's products and product candidates, including study designs, clinical site initiations, patient enrollment, data availability, anticipated regulatory filings, approvals, and timing thereof, (ii) expectations for continued growth in the number of CF patients treated with our products, including reaching all CF patients who can benefit from our marketed products, expansion of treatment options for the patients who do not benefit from CFTR modulators and anticipated size of patient populations, (iii) our plans to treat additional CF patients with mRNA, including plans for a CFTR mRNA IND filing in 2022, (iv) expectations for our next-in-class, once-daily triple regimen for CF patients, including our Phase 3 program expectations, enrollment plans and related economics, (v) our plans regarding Phase 2/3 study of VX-147 in AMKD, and our beliefs regarding anticipated results of the study and the possibility for accelerated approval in the U.S., (vi) expectations for the CTX001 program, including the potential of CTX001 to be a curative approach for patients with TDT and SCD, expectations for program approval and launch, and potential commercial opportunity, (vi) expectations regarding the potential benefits of our pain program and products, and plans for the advancement of VX-548 into pivotal development in acute pain in the second half of 2022 (vii) expectations for uptake of and expanded access to the company's products, including additional reimbursement agreements, label expansions and approvals in new markets, (viii) the potential benefits and safety of VX-880, our plans and expectations regarding our Phase 1/2 program for VX-880, and our plans to continue to progress the Phase 1/2 program for VX-880, (ix) beliefs about delivering treatments and potential cures for more patients in multiple new disease areas, including potential commercial opportunities in the disease areas in which we focus, and (x) our plans to continue to invest in internal and external innovation. While Vertex believes the forward-looking statements contained in this presentation are accurate, these forward-looking statements represent the company's beliefs only as of the date of this presentation and there are a number of risks and uncertainties that could cause actual events or results to differ materially from those expressed or implied by such forward-looking statements. Those risks and uncertainties include, among other things, that the company's expectations regarding its future financial and operating performance may be incorrect (including because one or more of the company's assumptions underlying its expectations may not be realized), that the company may not be able to submit anticipated regulatory filings on expected timelines, or at all, that external factors may have different or more significant impacts on the company's business or operations than the company currently expects, that data from preclinical testing or clinical trials, especially if based on a limited number of patients, may not be indicative of final results, that actual patient populations able to participate in our trials or eligible for our products may be smaller than we anticipated, that data from the company's development programs may not be available on expected timelines, or at all, and may not support registration or further development of its potential medicines due to safety, efficacy or other reasons, and other risks listed under "Risk Factors" in Vertex's annual report and subsequent quarterly reports filed with the Securities and Exchange Commission (SEC) and available through the company's website at www.vrtx.com and on the SEC's website at www.sec.gov. You should not place undue reliance on these statements or the scientific data presented. Vertex disclaims any obligation to update the information contained in this presentation as new information becomes available.

In this presentation, Vertex's financial results and financial guidance are provided in accordance with accounting principles generally accepted in the United States (GAAP) and using certain non-GAAP financial measures. In particular, non-GAAP financial results and guidance exclude from Vertex's pre-tax income (i) stock-based compensation expense, (ii) gains or losses related to the fair value of the company's strategic investments, (iii) increases or decreases in the fair value of contingent consideration, (iv) acquisition-related costs and (v) other adjustments. The company's non-GAAP financial results also exclude from its provision for income taxes the estimated tax impact related to its non-GAAP adjustments to pre-tax income described above and certain discrete items. These results should not be viewed as a substitute for the company's GAAP results and are provided as a complement to results provided in accordance with GAAP. Management believes these non-GAAP financial measures help indicate underlying trends in the company's business, are important in comparing current results with prior period results and provide additional information regarding the company's financial position that the company believes is helpful to an understanding of its ongoing business. Management also uses these non-GAAP financial measures to establish budgets and operational goals that are communicated internally and externally, to manage the company's business and to evaluate its performance. The company's calculation of non-GAAP financial measures likely differs from the calculations used by other companies. The company provides guidance regarding combined R&D and SG&A expenses and effective tax rate on a non-GAAP basis. The guidance regarding combined GAAP and non-GAAP R&D and SG&A expenses does not include estimates associated with any potential future business development transactions, including collaborations, asset acquisitions and/or licensing of third-party intellectual property rights. The company does not provide guidance regarding its GAAP effective tax rate because it is unable to forecast with reasonable certainty the impact of excess tax benefits related to stock-based compensation and the possibility of certain discrete items, which could be material. Non-GAAP financial measures are presented compared to corresponding GAAP measures in the appendix hereto. A reconciliation of the GAAP financial results to non-GAAP financial results is included in the company's Q1 2022 press release dated May 5, 2022.

A New Inflection Point for Vertex

Strengthening long-term leadership in CF

- Treating more patients with our CF medicines
- TRIKAFTA real-world data continue to raise the bar
- Advancing next-gen CFTR modulators
- Plan to file IND for CFTR mRNA therapy in 2H22; clinical trials to begin thereafter

Unique and differentiated R+D strategy continues to deliver

- Recent Phase 2 read outs establish PoC across multiple disease areas and modalities
- Clinical stage pipeline now spans 6 disease areas including CF
- Next wave of therapies in IND-enabling studies

Strong financial profile

- 1Q22 product revenues: $2.1B
  - 22% year-over-year growth
  - Non-GAAP operating margin 56%
- Reiterating product revenue guidance of $8.4B to $8.6B
- Cash & investments (March 31, 2022): $8.2B

Notes: An explanation of non-GAAP financial measures and reconciliation of GAAP operating income to non-GAAP operating income is included in the company's Q1 2022 press release dated May 5, 2022.

PROGRESS ACROSS THE CLINICAL STAGE PIPELINE OVER THE LAST 6-12 MONTHS

Recent Highlights
Completed enrollment and dosed >75 patients in pivotal studies of CTX001
Phase 3 studies initiated for VX-121/tezacaftor/VX-561 with **more than 180 sites open and enrolling**
Achieved positive proof of concept in VX-147 Phase 2 study in APOL-1 mediated FSGS
Achieved positive proof of concept for VX-548 in two types of acute pain
Achieved positive proof of concept for VX-880 in type 1 diabetes

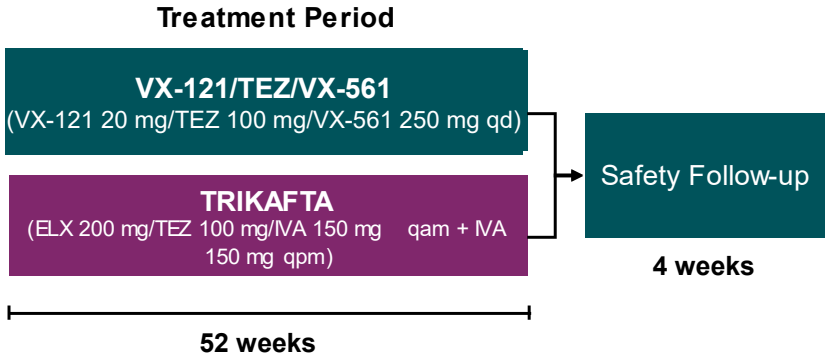
NEXT WAVE OF INNOVATION ADVANCING RAPIDLY

Recent Highlights		Key Milestones Ahead
IND-enabling studies completed for CFTR mRNA program	→	On track to **file IND** in 2H 22 and **begin clinical development thereafter**
Continued **advancement of IND-enabling studies** for cells + device program in type 1 diabetes	→	On track to **file IND** in 2H 22 and **begin clinical development thereafter**
IND-enabling studies initiated for next-generation small molecules for AATD	→	On track to **file IND** in 2H 22 **and begin clinical development thereafter**
IND-enabling studies initiated for gene editing program for DMD	→	Plan to **file IND in 2023** and **begin clinical development thereafter**
Advancement of **follow-on and next-generation molecules** across the pipeline	→	Progression to **IND-enabling studies and First-in-Human clinical trials throughout 2022**

VX-121/TEZACAFTOR/VX-561 TRIPLE REGIMEN MAY FURTHER ENHANCE PATIENT BENEFIT IN CYSTIC FIBROSIS

Two Phase 3 global, randomized, double-blind, active-controlled trials underway (N=950 total):

SKYLINE SKYLINE

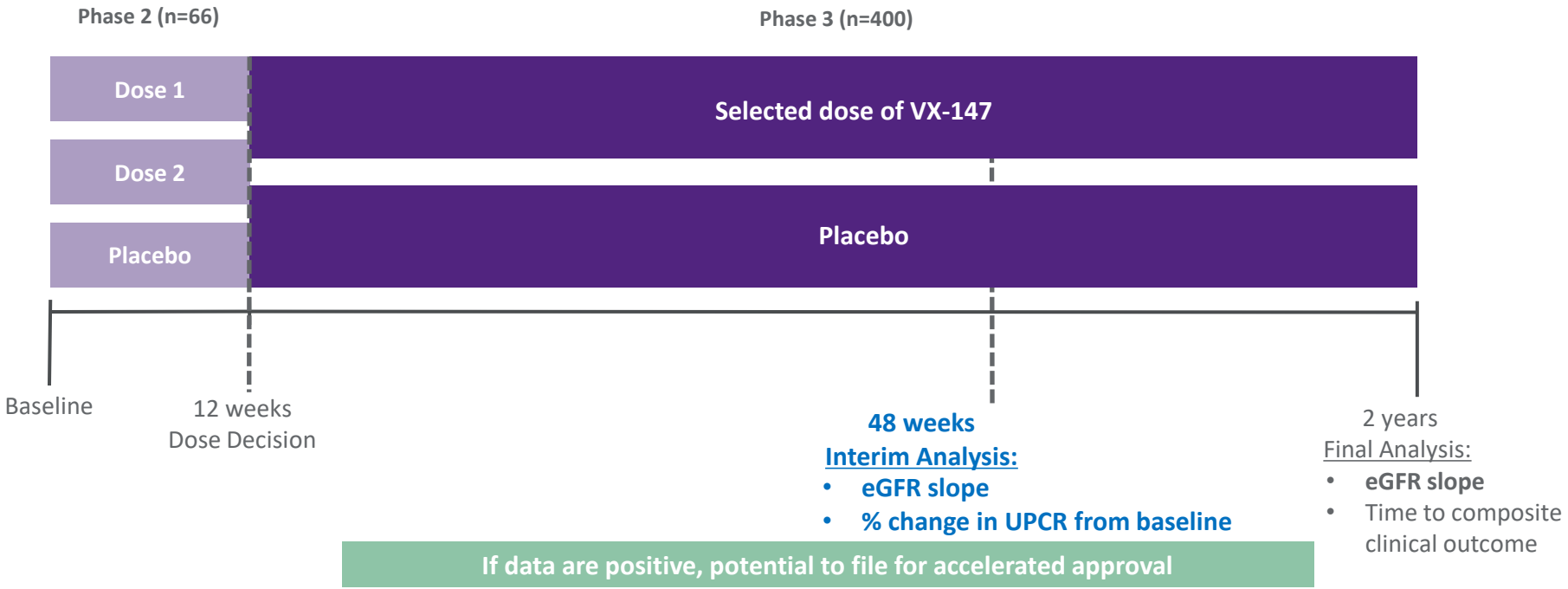


Next-in-Class, Once-Daily, Oral Triple Regimen

- More than 180 clinical sites across both studies open and enrolling
- Plan to complete pivotal program enrollment by late 2022/early 2023
- Preclinical and Phase 2 clinical data for next-in-class triple demonstrate potential for superior efficacy over TRIKAFTA
- Once-daily regimen
- Enhanced economics

VX-147 PIVOTAL PROGRAM UNDERWAY FOR PATIENTS WITH APOL1-MEDIATED KIDNEY DISEASE (AMKD)

Program targets broad AMKD label; interim analysis at 48 weeks may provide path to accelerated U.S. approval



VX-548: STATISTICALLY SIGNIFICANT AND CLINICALLY MEANINGFUL PAIN RELIEF COMPARED TO PLACEBO IN TWO PHASE 2 ACUTE PAIN STUDIES

Decrease in pain with VX-548 was rapid, sustained and consistent across both studies

	548-101 Bunionectomy N = 274					548-102 Abdominoplasty N = 303				
	Placebo N = 59	**VX-548** 50 mg q12h N = 60	**VX-548** 30 mg q12h N = 62	**VX-548** 10 mg q12h N = 33	**HB/APAP** 5 mg/325 mg q6h N = 60	**Placebo** N = 77	**VX-548** 50 mg q12h N = 76	**VX-548** 30 mg q12h N = 74	**HB/APAP** 5 mg/325 mg q6h N = 76
Mean SPID48	101.0	**137.8**	86.9	112.9	115.6	72.7	**110.5**	95.1	85.2
Mean SPID48 difference from placebo	--	**36.8**	-14.1	11.9	14.7	--	**37.8**	22.4	12.5
P-value vs. placebo	--	**0.0251**	0.3859	0.5379	0.3706	--	**0.0097**	0.1266	0.3914

SPID48 = time-weighted sum of the pain intensity difference (SPID) from time of first dose up to 48 hours. All VX-548 patients received a loading dose equivalent to 2x their q12h dose.
HB/APAP = hydrocodone bitartrate /acetaminophen reference arm. All p-values are based on comparison to placebo.

VX-880 TYPE 1 DIABETES PROGRAM UPDATE

- VX-880 Phase 1/2 study has been placed on clinical hold in the U.S. by the FDA
- We are working collaboratively with the Agency to understand and address their questions
- Across the program, VX-880 has been well tolerated, with no SAEs related to VX-880; majority of AEs mild to moderate

Patient 1 (Part A)

- Received half dose
- Insulin independent at Day 270 with HbA1c of 5.2%

Patient 2 (Part A)

- Received half dose
- Restoration of glucose-responsive insulin production, improvement in glycemic control, reduction in exogenous insulin requirements at Day 150

Patient 3 (Part B)

- Received full target dose
- Reached Day 29 milestone with encouraging early efficacy; detailed efficacy assessment to be performed at day 90 visit

Additional Type 1 Diabetes Portfolio Progress

- IND filing for cells + device program on track for 2H 2022
- Hypoimmune cells program advancing through preclinical development

CONTINUED UPTAKE OF OUR CFTR MODULATORS AROUND THE WORLD

UNITED STATES

- Ongoing strong demand, high persistence and compliance rates with TRIKAFTA in the U.S.
- Continued uptake of TRIKAFTA in U.S. for children ages 6-11 following approval in June 2021

EUROPE and OTHER MARKETS

- KAFTRIO/TRIKAFTA now available and reimbursed in more than 25 countries, now including Australia
- Approval for KAFTRIO/TRIKAFTA in Europe, the UK and Canada in children ages 6-11, with at least one *F508del* mutation

CONTINUED GROWTH AHEAD IN CF

83,000 patients with CF in U.S., Europe, Australia and Canada

Rapid uptake for our CF medicines in currently eligible patients

Growth Opportunities

1. **>25,000 patients** that are addressable with triple combination are still untreated
   - Continued uptake
   - New reimbursements
   - Label expansion to younger ages
2. **NEW:** potential to treat approximately **5,000** additional patients with mRNA; IND planned for 2H 2022

COMMERCIALIZATION SPOTLIGHT: CTX 001 AND VX 548

CTX001

- Initial multibillion-dollar opportunity is ~32,000 patients with severe sickle cell disease and beta-thalassemia
- Launch preparation activities progressing rapidly – key leadership positions and teams in place
- Centers of Excellence and referral networks identified for launch
- Payer engagement underway

VX-548

- Significant unmet need for new non-opioid medicines with improved risk/benefit profile, no addictive potential
- More than 1.5 billion treatment days annually for acute pain in the U.S.
- Large specialty market fits Vertex model
- Pivotal study initiation planned for 2H22

Q1 2022 FINANCIAL HIGHLIGHTS

($ in millions except where noted or per share data and percentages)	Q1 21	FY 21	Q1 22
Total CF product revenues	$1.72B	$7.57B	**$2.10B**
TRIKAFTA/KAFTRIO	$1.19B	$5.70B	**$1.76B**
SYMDEKO/SYMKEVI	125	420	**65**
ORKAMBI	219	772	**132**
KALYDECO	186	684	**139**
Combined non-GAAP R&D and SG&A expenses	531	3.44B	**687**
Non-GAAP operating income	1.00B	3.23B	**1.17B**
Non-GAAP operating margin %	58%	43%	**56%**
Non-GAAP net income	781	2.51B	**907**
Non-GAAP net income per share – diluted	$2.98	$9.67	**$3.52**
Cash, cash equivalents & marketable securities (period-end)	$6.9B	$7.5B	**$8.2B**

Notes: Starting in the first quarter of 2022, Vertex no longer excludes research and development charges resulting from upfront or contingent milestone payments in connection with collaborations, asset acquisitions and/or licensing of third-party intellectual property rights from its Non-GAAP financial measures. Non-GAAP financial measures for the first quarter of 2021 and FY 2021 have been recast to reflect this change. An explanation of non-GAAP financial measures and reconciliation of combined non-GAAP R&D and SG&A expenses, non-GAAP operating income and non-GAAP net income to corresponding GAAP measures are included in the company's Q1 2022 press release dated May 5, 2022. Non-GAAP financial measures are presented compared to corresponding GAAP measures in the appendix of this presentation. Totals above may not add due to rounding.

FULL YEAR 2022 FINANCIAL GUIDANCE

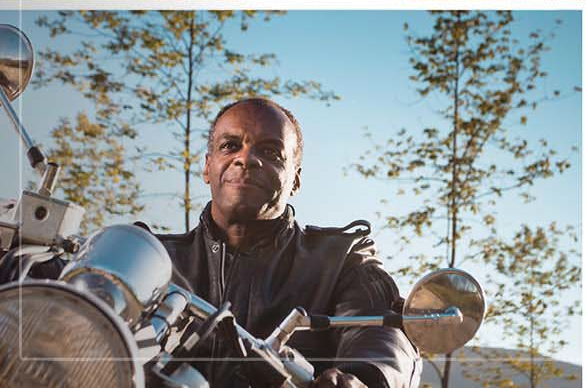
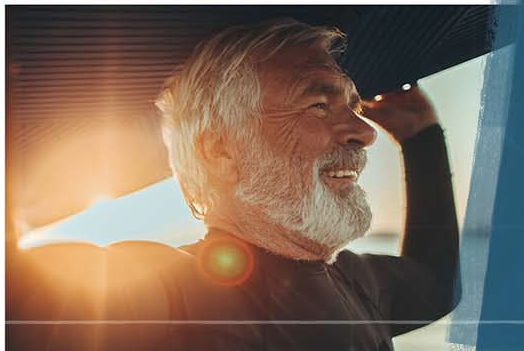
	FY 2022 Guidance	FY 2022 Commentary
Total CF Product Revenues	**$8.4 - $8.6B**	Guidance provided in January 2022 is reiterated; anticipate continued CF revenue growth in 2022 based on treatment of new patients
Combined GAAP R&D and SG&A Expenses	**$3.3 - $3.45B**	Unchanged from guidance provided in January 2022
Combined Non-GAAP R&D and SG&A Expenses	**$2.82 - $2.92B**	Guidance revised from $2.70-$2.75B provided in January 2022, reflecting the inclusion of milestone payments related to existing collaborations that are expected to occur in 2022.
Non-GAAP Effective Tax Rate	**21% - 22%**	Unchanged from guidance provided in January 2022

RECENT ADVANCES POSITION VERTEX FOR MULTIPLE CLINICAL MILESTONES AHEAD

Recent Highlights	Key Milestones Ahead
Filed sNDA for ORKAMBI in patients with CF 12 to <24 months of age	**Regulatory approval expected** in 2H22
Completed enrollment in Phase 3 study of TRIKAFTA in patients with CF 2 to 5 years of age	Plan to **file sNDA** by the end of 2022
Dosed >75 patients in pivotal studies of CTX001	Plan to **file for regulatory approval** in 2022; **updated clinical data presentation** at medical meetings in 2022
More than 180 sites open and enrolling in VX-121/tezacaftor/VX-561 Phase 3 studies	**Enrollment completion** expected late 2022 or early 2023
Reached **agreement with FDA on VX-147 pivotal program design:** single adaptive study in broad AMKD population	Ramp **enrollment in pivotal program**
Achieved proof of concept for VX-548 in two types of acute pain	Advance **into pivotal development** in 2H22
Established **proof of concept** for VX-880 in type 1 diabetes; 1st patient in Part B has been dosed	**Work with FDA** to address their questions and resume the study in the U.S





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MAY 5, 2022

APPENDIX

GAAP TO NON-GAAP FINANCIAL INFORMATION

($ in millions except as noted, per share data and percentages)	Q1 21	FY 21	Q1 22
Combined R&D and SG&A			
GAAP	648	**3.89B**	818
Non-GAAP	531	**3.44B**	687
Operating income			
GAAP	888	**2.78B**	1.04B
Non-GAAP	1.00B	**3.23B**	1.17B
Operating Margin %:			
GAAP	51%	**37%**	50%
Non-GAAP	58%	**43%**	56%
Net income			
GAAP	653	**2.34B**	762
Non-GAAP	781	**2.51B**	907
Net income per share - diluted			
GAAP	$2.49	**$9.01**	$2.96
Non-GAAP	$2.98	**$9.67**	$3.52

Note: Starting in the first quarter of 2022, Vertex no longer excludes research and development charges resulting from upfront or contingent milestone payments in connection with collaborations, asset acquisitions and/or licensing of third-party intellectual property rights from its Non-GAAP financial measures. Non-GAAP financial measures for the first quarter of 2021 and FY 2021 have been recast to reflect this change. An explanation of non-GAAP financial measures and reconciliations of combined non-GAAP R&D and SG&A expenses, non-GAAP operating income and non-GAAP net income to corresponding GAAP measures are included in the company's Q1 2022 press release dated May 5, 2022.