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): November 16, 2023

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

Delaware	**001-39044**	**83-4066827**
(State or other jurisdiction of incorporation)	**(Commission File Number)**	**(I.R.S. Employer Identification No.)**

100 Washington Blvd Stamford, CT	**06902**
(Address of principal executive offices)	(Zip Code)

Registrant's telephone number, including area code: **(203) 883-9490**

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	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, par value $0.0001 per share	SWTX	The Nasdaq Global Select 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 November 16, 2023, SpringWorks Therapeutics, Inc. ("SpringWorks" or the "Company") issued a press release announcing topline clinical data from its potentially registrational Phase 2b ReNeu trial of mirdametinib, an investigational MEK inhibitor, in adult and pediatric patients with NF-1-associated plexiform neurofibromas ("NF1-PN"). The press release is furnished as Exhibit 99.1 to this Current Report on Form 8-K.

The information in Item 7.01 of this Form 8-K (including Exhibit 99.1) shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), 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, or the Exchange Act, except as expressly set forth by specific reference in such a filing.

Item 8.01 Other Events.

On November 16, 2023, SpringWorks announced positive topline results from its potentially registrational Phase 2b ReNeu trial of mirdametinib, an investigational MEK inhibitor, in adult and pediatric patients with NF1-PN. The ReNeu trial enrolled 114 patients in two cohorts (pediatric and adult) across 50 sites in the United States The primary endpoint was confirmed objective response rate, defined as ≥ 20% reduction in target tumor volume as measured by MRI and assessed by Blinded Independent Central Review ("BICR"). As of the data cutoff date of September 20, 2023, 52% (29/56) of pediatric patients and 41% (24/58) of adult patients had BICR confirmed objective responses within the 24-cycle treatment period (cycle length: 28 days). An additional pediatric patient and two additional adult patients achieved confirmed objective responses after Cycle 24 in the long-term follow up phase of the trial, where patients continue to receive mirdametinib treatment. Median best percent change from baseline in target tumor volume was -42% and -41% in the pediatric cohort and adult cohort, respectively. As of the data cut-off, the median duration of treatment was 22 months in both the pediatric and adult cohorts. Median duration of response was not reached in either cohort. Pediatric and adult patients in the ReNeu trial also experienced statistically significant improvements from baseline in pain, quality of life, and physical function, as assessed across multiple patient-reported outcome tools.

Mirdametinib was generally well tolerated in the ReNeu trial, with the majority of adverse events ("AE"s) being Grade 1 or Grade 2. The most frequently reported AEs were rash, diarrhea, and vomiting in the pediatric cohort and rash, diarrhea, and nausea in the adult cohort. 25% of pediatric patients and 16% of adult patients experienced a Grade 3 or higher treatment-related AE. Additional data are expected to be presented at an upcoming medical conference in the first half of 2024 and to be submitted for publication in a peer-reviewed journal.

The U.S. Food and Drug Administration ("FDA") and the European Commission have granted Orphan Drug designation for mirdametinib for the treatment of NF1. The FDA has also granted Fast Track designation for the treatment of patients ≥ 2 years of age with NF1-PN that are progressing or causing significant morbidity. In July 2023, FDA granted mirdametinib Rare Pediatric Disease Designation for the treatment of NF1, and as such, if approved, mirdametinib will be eligible to receive a priority review voucher. SpringWorks plans to submit a New Drug Application (NDA) for mirdametinib to the FDA in the first half of 2024.

A copy of the Company's presentation materials relating to the announcement are attached as Exhibit 99.2 to this Current Report on Form 8-K and are incorporated herein by reference.

Forward Looking Statements

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, relating to our business, operations, and financial conditions, including, but not limited to, current beliefs, expectations and assumptions regarding the potential for the results of the Phase 2b ReNeu clinical trial to support an NDA submission for mirdametinib, the potential for mirdametinib to become an important new treatment for patients with NF1-PN, the potential for the Company to receive a priority review voucher following an FDA approval of mirdametinib, as well as relating to other future conditions. Words such as, but not limited to, "look forward to," "believe," "expect," "anticipate," "estimate," "intend," "plan," "would," "should" and "could," and similar expressions or words, identify forward-looking statements. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertainties. Any forward-looking statements in this Item 8.01 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 Item 8.01, including, without limitation, risks relating to: (i) the success and timing of our product development activities, including the initiation and completion of SpringWorks' clinical trials, (ii) our expectations regarding the potential clinical benefit of mirdametinib for patients with NF1-PN, (iii) the fact that topline or interim data from a clinical study may not be predictive of the final or more detailed results of such study, or the results of other ongoing or future studies, (iv) the success and timing of our collaboration partners' ongoing and planned clinical trials, (vi) the timing of our planned regulatory submissions and interactions, including our planned NDA submission for mirdametinib in the first half of 2024, and the timing and outcome of decisions made by the FDA, the European Medicines Agency (EMA) and other regulatory authorities, investigational review boards at clinical trial sites and publication review bodies; (vi) whether FDA, EMA or other regulatory authorities will require additional information or further studies, or may fail or refuse to approve or may delay approval of our product candidates, (vii) our ability to obtain and maintain regulatory approval of any of our product candidates, (viii) our plans to research, discover and develop additional product candidates, (ix) our ability to enter into collaborations for the development of new product candidates and our ability to realize the benefits expected from such collaborations, (x) our ability to maintain adequate patent protection and successfully enforce patent claims against third parties (xi) our ability to establish and maintain manufacturing capabilities, and our and our collaboration partners' abilities to manufacture our products and product candidates and scale production, and (xii) our ability to meet any specific milestones set forth herein.

For further information regarding the risks, uncertainties and other factors that may cause differences between the Company's expectations and actual results, you should review the "Risk Factors" in Item 1A of Part II of the Company's Quarterly Report on Form 10-Q for the quarter ended September 30, 2023, as well as discussions of potential risks, uncertainties and other important factors in the Company's subsequent filings. All disclosure under this Item 8.01 is as of the date of this Form 8-K, and the Company undertakes no duty to update this information unless required by law.

Item 9.01 Financial Statements and Exhibits

(d) Exhibits.

Exhibit Number	Description
99.1	Press Release issued by SpringWorks Therapeutics, Inc. on November 16, 2023.
99.2	Presentation titled "ReNeu Topline Results."
104	Cover Page Interactive Data File (embedded with the Inline XBRL document).

SIGNATURES

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.

Date: November 17, 2023

SpringWorks Therapeutics, Inc.

By: /s/ Francis I. Perier, Jr.
Francis I. Perier, Jr.
Chief Financial Officer

Exhibit 99.1

SpringWorks Therapeutics Announces Positive Topline Results from the Phase 2b ReNeu Trial of Mirdametinib in NF1-PN

– Confirmed objective response rate of 52% in pediatric patients and 41% in adult patients, as assessed by Blinded Independent Central Review –

– Mirdametinib treatment resulted in deep and durable responses and significant improvements in key secondary patient-reported outcome measures

– Mirdametinib was generally well tolerated with low rates of Grade 3+ adverse events –

– Additional data expected to be presented at medical conference and NDA submission to the U.S. FDA planned in the first half of 2024 –

– Company to host conference call today at 8:30 a.m. Eastern Time –

STAMFORD, Conn., November 16, 2023 – SpringWorks Therapeutics, Inc. (Nasdaq: SWTX), a clinical-stage biopharmaceutical company focused on developing life-changing medicines for patients with severe rare diseases and cancer, today announced positive topline results from the pivotal Phase 2b ReNeu trial evaluating mirdametinib, an investigational MEK inhibitor, in pediatric and adult patients with neurofibromatosis type 1-associated plexiform neurofibromas (NF1-PN).

The ReNeu trial enrolled 114 patients in two cohorts (pediatric and adult) across 50 sites in the U.S. The primary endpoint was confirmed objective response rate (ORR), defined as ≥ 20% reduction in target tumor volume as measured by MRI and assessed by Blinded Independent Central Review (BICR). As of the data cutoff date of September 20, 2023, 52% (29/56) of pediatric patients and 41% (24/58) of adult patients had BICR confirmed objective responses within the 24-cycle treatment period (cycle length: 28 days). An additional pediatric patient and two additional adult patients achieved confirmed objective responses after Cycle 24 in the long-term follow up phase of the trial, where patients continue to receive mirdametinib treatment. Median best percent change from baseline in target tumor volume was -42% and -41% in the pediatric and adult cohort, respectively. As of the data cut-off, the median duration of treatment was 22 months in both the pediatric and adult cohorts. Median duration of response was not reached in either cohort. Pediatric and adult patients in the ReNeu trial also experienced statistically significant improvements from baseline in pain, quality of life, and physical function, as assessed across multiple patient-reported outcome tools.

Mirdametinib was generally well tolerated in the ReNeu trial, with the majority of adverse events (AEs) being Grade 1 or Grade 2. The most frequently reported AEs were rash, diarrhea, and vomiting in the pediatric cohort and rash, diarrhea, and nausea in the adult cohort. Twenty-five percent of pediatric patients and 16% of adult patients experienced a Grade 3 or higher treatment-related AE. Additional data are expected to be presented at an upcoming medical conference in the first half of 2024 and to be submitted for publication in a peer-reviewed journal.

“Plexiform neurofibromas can grow aggressively along peripheral nerves and lead to extreme pain, disfigurement and other morbidities that have a significant impact on the lives of patients and their families,” said Saqib Islam, Chief Executive Officer of SpringWorks. “We are extremely pleased that the results of our ReNeu trial demonstrate a compelling clinical profile across measures of both safety and efficacy. Our data indicates that mirdametinib has the potential to be the best-in-class therapy for children and the first approved treatment for adults with NF1-PN and we are working with urgency to bring this differentiated medicine to patients.”

The U.S. Food and Drug Administration (FDA) and the European Commission have granted Orphan Drug designation for mirdametinib for the treatment of NF1. The FDA has also granted Fast Track designation for the treatment of patients ≥ 2 years of age with NF1-PN that are progressing or causing significant morbidity. In July 2023, FDA granted mirdametinib Rare Pediatric Disease Designation for the treatment of NF1, and as such, if approved, mirdametinib will be eligible to receive a priority review voucher. SpringWorks plans to submit a New Drug Application (NDA) for mirdametinib to the FDA in the first half of 2024.

About the ReNeu Trial

ReNeu (NCT03962543) is an ongoing, multi-center, open-label Phase 2b trial evaluating the efficacy, safety, and tolerability of mirdametinib in patients two years of age and older with an inoperable NF1-associated PN causing significant morbidity. The study enrolled 114 patients to receive mirdametinib at a dose of 2 mg/m^2 twice daily (maximum dose of 4 mg twice daily) without regard to food. Mirdametinib is administered orally in a 3-week on, 1-week off dosing schedule and has a pediatric formulation (dispersible tablet) for patients who cannot swallow a pill. The primary endpoint of the ReNeu trial is confirmed objective response rate defined as ≥ 20% reduction in target tumor volume as measured by MRI and assessed by blinded independent central review. Secondary endpoints include safety and tolerability, duration of response, and changes from baseline in patient reported outcomes.

About NF1-PN

Neurofibromatosis type 1 (NF1) is a rare genetic disorder that arises from mutations in the NF1 gene, which encodes for neurofibromin, a key suppressor of the MAPK pathway.[1,2] NF1 is the most common form of neurofibromatosis, with an estimated global birth incidence of approximately 1 in 3,000 individuals, and approximately 100,000 patients living with NF1 in the United States.[3,4] The clinical course of NF1 is heterogeneous and manifests in a variety of symptoms across numerous organ systems, including abnormal pigmentation, skeletal deformities, tumor growth and neurological complications, such as cognitive impairment.[5] Patients with NF1 have an eight to 15-year mean reduction in their life expectancy compared to the general population.[2]

NF1 patients have approximately a 30-50% lifetime risk of developing plexiform neurofibromas, or PN, which are tumors that grow in an infiltrative pattern along the peripheral nerve sheath and that can cause severe disfigurement, pain and functional impairment; in rare cases, NF1-PN may be fatal.[3,4,6] Patients with NF1 can also experience additional manifestations, including neurocognitive deficits and developmental delays.[4] NF1-PNs are most often diagnosed in the first two decades of life.[3] These tumors can be aggressive and are associated with clinically significant morbidities; typically, they grow more rapidly during childhood.[7,8]

Surgical removal of these tumors is challenging due to the infiltrative tumor growth pattern along nerves and can lead to permanent nerve damage and disfigurement.[9] MEK inhibitors have emerged as a validated class of treatment for NF1-PN.[4]

About Mirdametinib

Mirdametinib is a potent, oral, allosteric small molecule MEK inhibitor in development as a monotherapy treatment for neurofibromatosis type 1-associated plexiform neurofibromas (NF1-PN) and low-grade glioma (LGG), and as a combination therapy for the treatment of several subsets of biomarker-defined metastatic solid tumors.

Mirdametinib is designed to inhibit MEK1 and MEK2, which occupy pivotal positions in the MAPK pathway. The MAPK pathway is a key signaling network that regulates cell growth and survival and that plays a central role in multiple oncology and rare disease indications when genetically altered.

Conference Call and Webcast Information

SpringWorks will host a conference call and webcast to discuss the ReNeu topline data today, November 16, at 8:30 a.m. ET. To join the live webcast and view the corresponding slides, please click here. To access the live call by phone, please pre-register for the call here. Once registration is complete, participants will be provided with a dial-in number and conference code to access the call. A replay of the webcast will be available for a limited time following the event on the Investors and Media section of the Company's website at https://ir.springworkstx.com.

About SpringWorks Therapeutics

SpringWorks is a clinical-stage biopharmaceutical company applying a precision medicine approach to acquiring, developing and commercializing life-changing medicines for patients living with severe rare diseases and cancer. SpringWorks has a differentiated targeted oncology pipeline spanning solid tumors and hematological cancers, including two late-stage clinical trials in rare tumor types as well as several programs addressing highly prevalent, genetically defined cancers. SpringWorks' strategic approach and operational excellence in clinical development have enabled it to rapidly advance its two lead product candidates into late-stage clinical trials while simultaneously entering into multiple shared-value partnerships with innovators in industry and academia to unlock the full potential for its portfolio and create more solutions for patients with cancer. For more information, visit www.springworkstx.com and follow @SpringWorksTx on Twitter and LinkedIn.

SpringWorks Forward-Looking Statements

This press release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, relating to our business, operations, and financial conditions, including, but not limited to, current beliefs, expectations and assumptions regarding the future of our business, future plans and strategies, our development plans, our preclinical and clinical results, the potential for the results of the Phase 2b ReNeu clinical trial to support an NDA submission for mirdametinib, the potential for mirdametinib to become an important new treatment for patients with NF1-PN, our plans for seeking regulatory approval for and making mirdametinib available for NF1-PN patients, if approved, the potential for SpringWorks to receive a priority review voucher following an FDA approval of mirdametinib, as well as relating to other future conditions. Words such as, but not limited to, "look forward to," "believe," "expect," "anticipate," "estimate," "intend," "plan," "would," "should" and "could," and similar expressions or words, identify forward-looking statements. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertainties. 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 relating to: (i) the success and timing of our product development activities, including the initiation and completion of SpringWorks' clinical trials, (ii) our expectations regarding the potential clinical benefit of mirdametinib for patients with NF1-PN, (iii) the fact that topline or interim data from a clinical study may not be predictive of the final or more detailed results of such study, or the results of other ongoing or future studies, (iv) the success and timing of our collaboration partners' ongoing and planned clinical trials, (vi) the timing of our planned regulatory submissions and interactions, including our planned NDA submission for mirdametinib in the first half of 2024, and the timing and outcome of decisions made by the FDA, the European Medicines Agency (EMA) and other regulatory authorities, investigational review boards at clinical trial sites and publication review bodies; (vi) whether FDA, EMA or other regulatory authorities will require additional information or further studies, or may fail or refuse to approve or may delay approval of our product candidates, (vii) our ability to obtain and maintain regulatory approval of any of our product candidates, (viii) our plans to research, discover and develop additional product candidates, (ix) our ability to enter into collaborations for the development of new product candidates and our ability to realize the benefits expected from such collaborations, (x) our ability to maintain adequate patent protection and successfully enforce patent claims against third parties (xi) our ability to establish and maintain manufacturing capabilities, and our and our collaboration partners' abilities to manufacture our products and product candidates and scale production, and (xii) our ability to meet any specific milestones set forth herein.

Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise. Although we believe the expectations reflected in such forward-looking statements are reasonable, we can give no assurance that such expectations will prove to be correct. Accordingly, readers are cautioned not to place undue reliance on these forward-looking statements.

For further information regarding the risks, uncertainties and other factors that may cause differences between SpringWorks' expectations and actual results, you should review the "Risk Factors" in Item 1A of Part II of SpringWorks' Quarterly Report on Form 10-Q for the quarter ended September 30, 2023, as well as discussions of potential risks, uncertainties and other important factors in SpringWorks' subsequent filings.

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References

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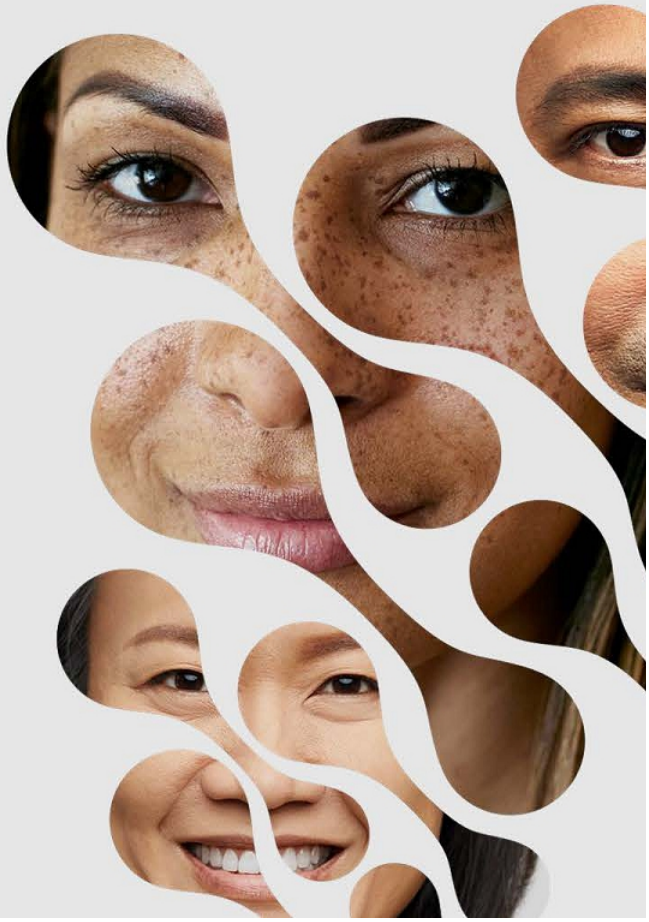
ReNeu Topline Results

Mirdametinib for NF1-PN

November 2023

SpringWorks THERAPEUTICS



Forward-Looking Statements

Note: Unless otherwise indicated, the information presented herein is as of November 16, 2023.

This presentation may contain "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, relating to our business, opera conditions, including but not limited to current beliefs, expectations and assumptions regarding the future of our business, future plans and strategies, our development plans, our p the potential for nirogacestat to become an important new treatment for adult patients with desmoid tumors, the potential for a Marketing Authorisation Application for nirogacestat, timing and results of the U.S. Food and Drug Administration (FDA)'s review of the NDA for nirogacestat, including the FDA's PDUFA target action date for the NDA, and the adequ the NDA to serve as the basis for an approval of nirogacestat for the treatment of adults with desmoid tumors, the potential for the results of the Phase 2b ReNeu clinical trial to sup mirdametinib, the potential for mirdametinib to become an important new treatment for patients with NF1-PN, our plans for seeking regulatory approval for and making mirdametinib patients, if approved, expectations regarding the timing and initial data from the Phase 2 trial evaluating nirogacestat in patients with recurrent ovarian granulosa cell tumors, our pl New Drug Application for SW-682 in 2023, our plans to report additional clinical data of nirogacestat in combination with BCMA-directed therapies and initiate additional planned Ph our expectations regarding the potential for the Phase 1b dose expansion phase of brimarafenib, expectations about whether our patents for our lead assets will adequately protect competition, as well as relating to other future conditions. Words such as, but not limited to, "look forward to," "believe," "expect," "anticipate," "estimate," "intend," "plan," "would," "s similar expressions or words, identify forward-looking statements. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertain statements in this presentation are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cau differ materially from those expressed or implied by any forward-looking statements contained in this presentation, including, without limitation, risks relating to: (i) the success and development activities, including the initiation and completion of SpringWorks' clinical trials, (ii) our expectations regarding the potential clinical benefit of mirdametinib for patients v topline or interim data from clinical studies may not be predictive of the final or more detailed results of such study or the results of other ongoing or future studies, (iv) the success collaboration partners' ongoing and planned clinical trials, (iv) the timing of our planned regulatory submissions and interactions, including the timing and outcome of decisions mad Medicines Agency (EMA) and other regulatory authorities, investigational review boards at clinical trial sites and publication review bodies, (vi) whether FDA, EMA or other regulato additional information or further studies, or may fail or refuse to approve or may delay approval of our drug candidates, including nirogacestat and mirdametinib, (vii) our ability to ob approval of any of our product candidates, (viii) our plans to research, discover and develop additional product candidates, (ix) our ability to enter into collaborations for the develop candidates and our ability to realize the benefits expected from such collaborations, (x) our ability to maintain adequate patent protection and successfully enforce patent claims ag adequacy of our cash position to fund our operations through any time period indicated herein, (xii) our ability to establish manufacturing capabilities, and our and our collaboration manufacture our product candidates and scale production, and (xiii) our ability to meet any specific milestones set forth herein.

Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, futu circumstances or otherwise. Although we believe the expectations reflected in such forward-looking statements are reasonable, we can give no assurance that such expectations w Accordingly, readers are cautioned not to place undue reliance on these forward-looking statements.

For further information regarding the risks, uncertainties and other factors that may cause differences between SpringWorks' expectations and actual results, you should review the our filings with the Securities and Exchange Commission.

Certain information contained in this presentation relates to or is based on studies, publications, surveys and other data obtained from third-party sources and our own internal esti SpringWorks believes these third-party sources to be reliable as of the date of this presentation, we have not independently verified, and make no representation as to the adequac completeness of, any information obtained from third-party sources. In addition, all of the market data included in this presentation involves a number of assumptions and limitations guarantee as to the accuracy or reliability of such assumptions. Finally, while we believe our own internal research is reliable, such research has not been verified by any independ

Today's Agenda

Sections	Presenter
Introduction	**Saqib Islam** *Chief Executive Officer*
ReNeu Phase 2b Data	**Jim Cassidy, MD, PhD** *Chief Medical Officer*
Program Highlights and Next Steps	**Badreddin Edris, PhD** *Chief Operating Officer*
Q&A	**All**

Introduction

Saqib Islam

Chief Executive Officer

Positive Topline Results From ReNeu Demonstrate Mirdametinib's Potentially Tra
Benefit for NF1-PN Patients

Kylie, NF1-PN patient

Gus, NF1-PN patient

Katie, NF1-PN patient

ReNeu

- *Topline data suggest class-leading p both children and adults with NF1-PN*
- *Robust objective response rates con Blinded Independent Central Review*
- *Differentiated depths of response wi treatment durations*
- *Manageable tolerability profile with p features designed to enhance compl*
- *Anti-tumor activity supported by imp pain and quality of life measures*

Note: NF1-PN: Neurofibromatosis type 1-associated plexiform neurofibroma.

A Substantial Unmet Need Remains for a Best-in-Class Therapy for NF1-PN Patient

Disfiguring and highly morbid growth along nerves, often causing chronic, disabling pain

Significant impact on patient and caregiver quality of life with emotional and psychological burden

Surgery is difficult due to infiltrative growth along nerves, and an inadequate long-term solution[1,2]

Challenging dosing / administration, tolerability, and label restrictions limit utility of currently approved MEK inhibitors[3]

Savanna, NF1-PN patient

Sources: (1) SpringWorks Market Research; (2) Korf, American Journal of Medical Genetics, 1999; (3) Koselugo prescribing information.

ReNeu Phase 2b Data

Jim Cassidy, MD, PhD

Chief Medical Officer

Phase 2b ReNeu Trial Summary

TRIAL DESIGN	▪ Phase 2b open-label; n = 114 patients in 2 cohorts (pediatric and adults) across 50 U.S. ▪ 2 mg/m^2 BID dosing with intermittent course (4-week cycles of 3 weeks on, 1 week off) t cycles; maximum dose of 4 mg BID ▪ Pediatric formulation (dispersible tablet) introduced in 2H 2020
PRIMARY ENDPOINT	▪ Confirmed objective response rate (≥20% reduction in tumor volume per REiNS criteria) by BICR by end of treatment phase
SECONDARY AND EXPLORATORY ENDPOINTS	▪ Safety and tolerability, duration of response, QoL and physical functioning assessments measures of pain)

Note: REiNS: Response Evaluation in Neurofibromatosis and Schwannomatosis; BICR: blinded independent central review; BID: twice daily; QoL: quality of life.

Baseline Patient Demographics and Disease Characteristics

Pediatric Participants (n=56)

Characteristic	n (%)
Patients enrolled	56
Median age at enrollment [range] - years	10.0 [2 – 17]
Sex	
Male	26 (46)
Female	30 (54)
Location of target neurofibroma	
Head and Neck	28 (50)
Lower / Upper Extremities	8 (14)
Paraspinal	4 (7)
Other	16 (29)
Type of neurofibroma-related complication	
Pain	39 (70)
Disfigurement or Major Deformity	28 (50)
Motor Dysfunction or Weakness	15 (27)
Airway Dysfunction	7 (13)
Other	12 (21)
Target PN progressing at study entry	35 (63)

Adult Participants (n=58)

Characteristic
Patients enrolled
Median age at enrollment [range] - years
Sex
Male
Female
Location of target neurofibroma
Head and Neck
Lower / Upper Extremities
Paraspinal
Other
Type of neurofibroma-related complication
Pain
Disfigurement or Major Deformity
Motor Dysfunction or Weakness
Airway Dysfunction
Other
Target PN progressing at study entry

Note: PN: plexiform neurofibroma.

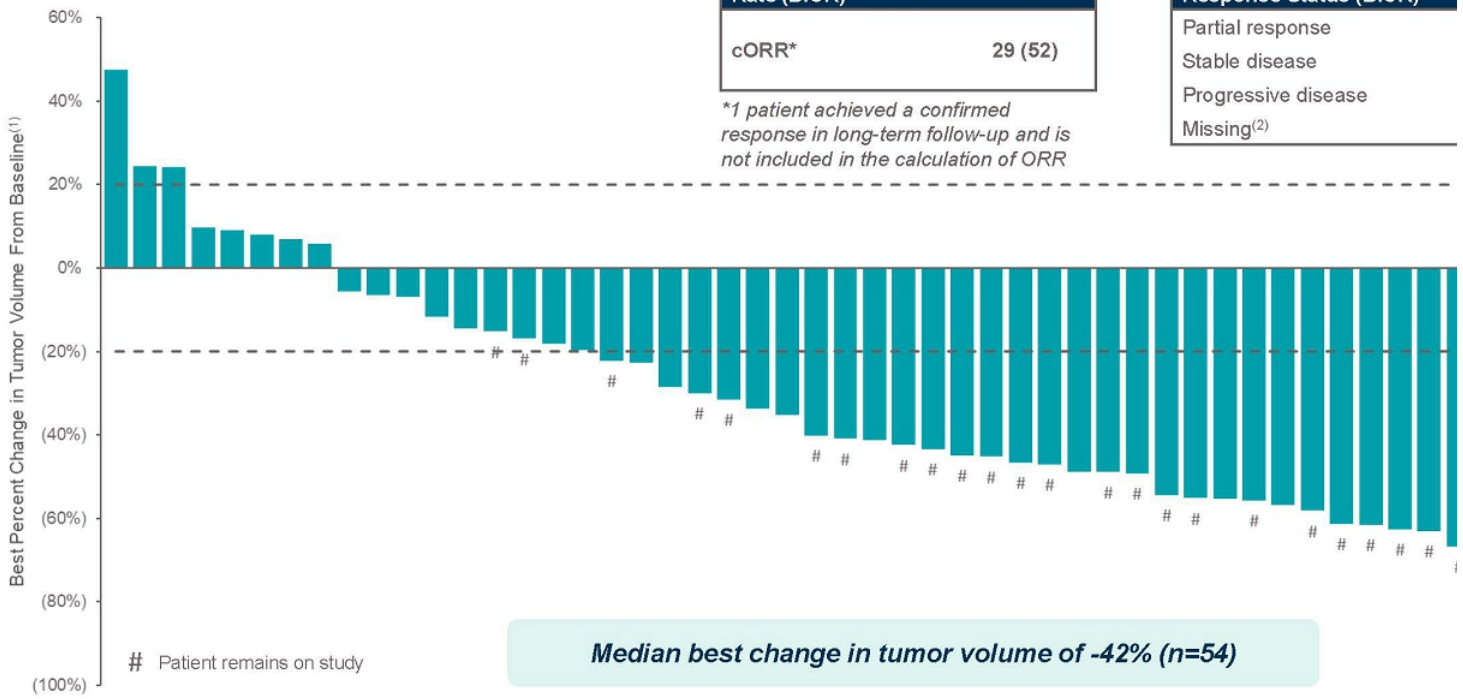
Best Tumor Response

Pediatric Cohort

Confirmed Response Rate (BICR)	n (%)
cORR*	29 (52)

**1 patient achieved a confirmed response in long-term follow-up and is not included in the calculation of ORR*

Best Overall Confirmed Response Status (BICR)
Partial response
Stable disease
Progressive disease
Missing(2)

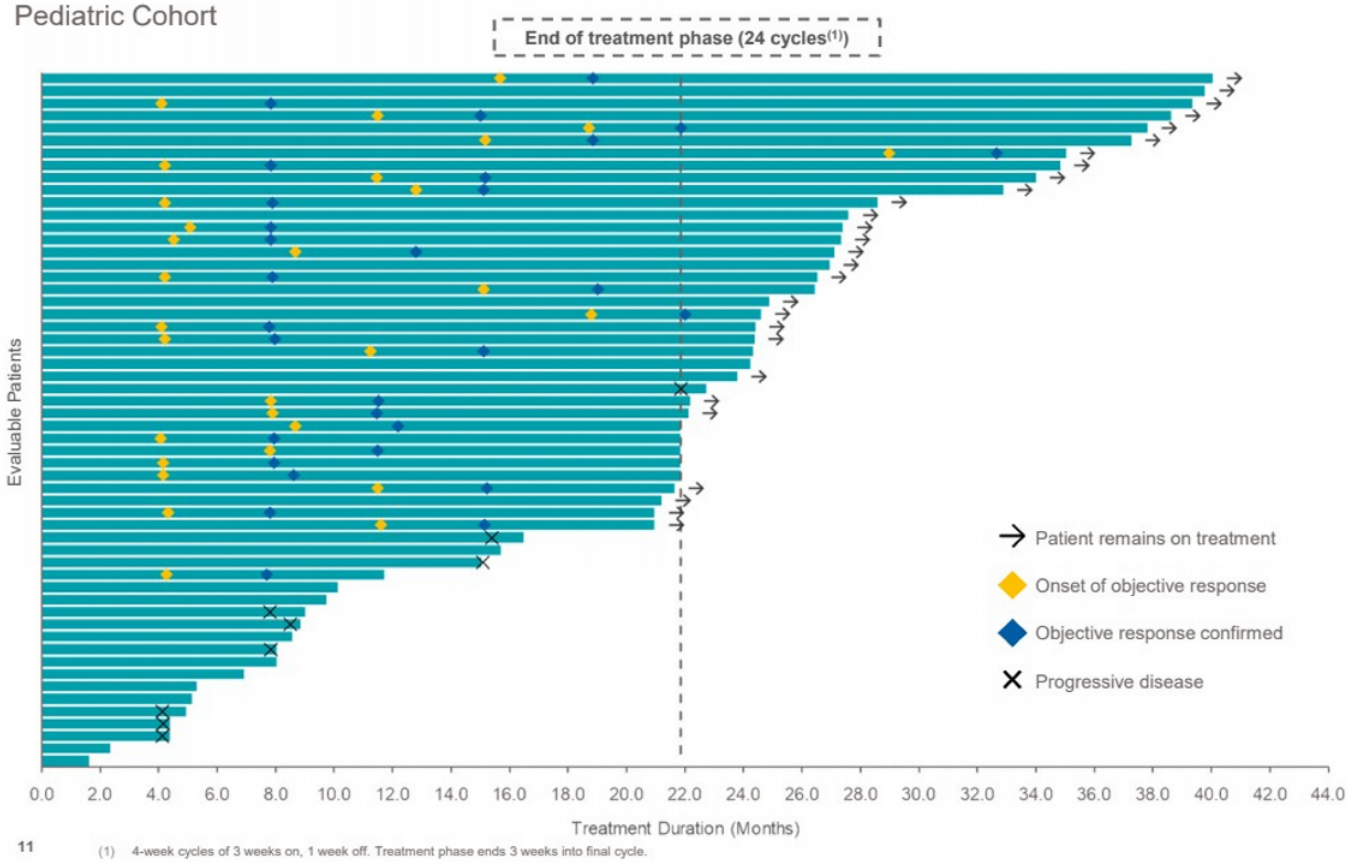


Median best change in tumor volume of -42% (n=54)

Note: BICR: blinded independent central review; cORR: confirmed objective response rate.
(1) Shows best change in tumor volume achieved at any point, including unconfirmed partial responses.
(2) Participants that discontinued study prior to any on-treatment MRI assessment.

Treatment Duration and Response

Pediatric Cohort



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(1) 4-week cycles of 3 weeks on, 1 week off. Treatment phase ends 3 weeks into final cycle.

ReN

Patient-Reported Outcomes

Pediatric Cohort

Scale	p-Value for Change from
Target Tumor Pain - Numeric Rating Scale (NRS-11)[2] (n=15)	0.003
Pain Interference Index (PII)[3]	
Self-Report (n=20)	0.004
Parent Proxy (n=18)	0.016
Pediatric Quality of Life Inventory (PedsQL)[4] – Total Score	
Self-Report (n=38)	0.096
Parent Proxy (n=43)	0.005
Pediatric Quality of Life Inventory (PedsQL)[4] – Physical Functioning	
Self-Report (n=38)	0.033
Parent Proxy (n=43)	0.037

(1) Change from baseline at Cycle 13, the pre-specified assessment for patient-reported outcome analysis per the ReNeu statistical analysis plan. Least squared means estimates using a mixed model for repeated measures (MMRM).

(2) The NRS-11 assesses target tumor pain on a scale from 0 – "no pain" to 10 – "worst pain you can imagine." NRS-11 assessments were performed for six consecutive days prior to a visit as well as on the visit day, except for the ET visit, which is done on the visit day only. The mean of these seven assessments is taken as the visit score. Baseline is defined as the most recent NRS-11 score taken on or before treatment start date.

(3) The PII assesses the degree to which pain has impacted the participants' daily activities on a scale from 0 – "not at all" to 6 – "completely." PII assessments were performed on the six consecutive days prior to a visit as well as on the visit day, except for the ET visit, which is done on the visit day only. The mean of these seven assessments is taken as the visit score. Baseline is defined as the most recent PII score taken on or before treatment start date.

(4) PedsQL assess quality of life on a Likert scale from 0 to 4. These items are then reverse scored and linearly transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, 4=0, with higher scores indicating a higher quality of life. Baseline is defined as the most recent PedsQL score taken on or before treatment start date.

Safety Summary

Pediatric Cohort

(n=56)	TEAEs ≥ 20% Subjects		TRAE
Preferred Term	**All Grades – n (%)**	**≥ Grade 3 – n (%)**	**All Grades – n (%)**
Any TEAE	**56 (100)**	**22 (39)**	**53 (95)**
Rash[1]	36 (64)	2 (4)	33 (59)
Diarrhea	31 (55)	3 (5)	21 (38)
Dermatitis acneiform	24 (43)	1 (2)	24 (43)
Vomiting	22 (39)	0 (0)	8 (14)
Headache	19 (34)	1 (2)	6 (11)
Paronychia	18 (32)	0 (0)	17 (30)
Nausea	15 (27)	0 (0)	12 (21)
Abdominal pain	15 (27)	2 (4)	8 (14)
Ejection fraction decreased	15 (27)	1 (2)	11 (20)
COVID-19	14 (25)	0 (0)	0 (0)
Upper respiratory tract infection	13 (23)	0 (0)	1 (2)
Blood creatine phosphokinase increased	12 (21)	4 (7)	11 (20)
Cough	12 (21)	0 (0)	0 (0)

(n=56)	n (%)
TEAE leading to dose interruption[2]	17 (30)
TEAE leading to dose reduction	7 (13)
TEAE leading to discontinuation	5 (9)

(1) Composite adverse event including dermatitis acneiform, rash, rash maculo-papular, rash erythematous, acne, seborrheic dermatitis, exfoliative rash, papule, rash papular, dermatitis, rash macular, rash pruritic.
(2) Dose interruptions due to treatment-related adverse events occurred in 8 patients (14%).
Note: TEAE: treatment-emergent adverse event; TRAE: treatment-related adverse event.

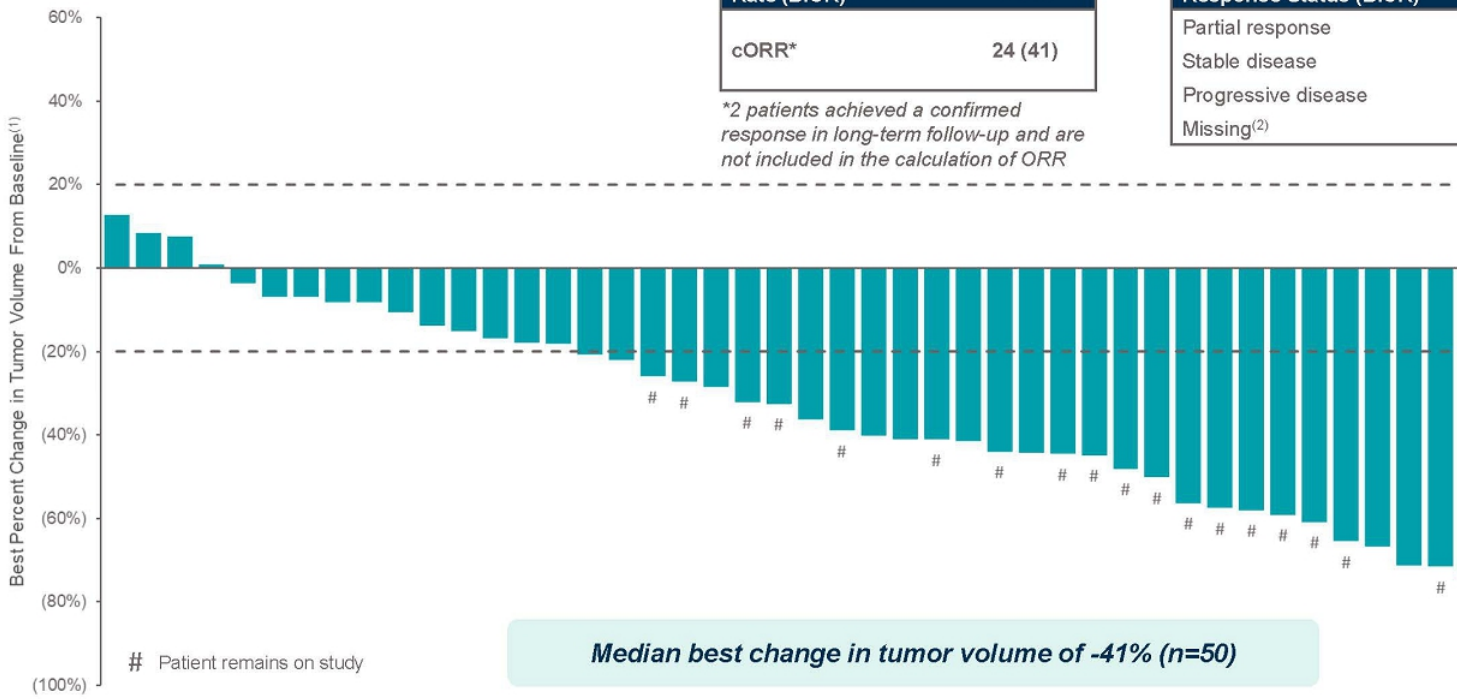
Best Tumor Response

Adult Cohort

Confirmed Response Rate (BICR)	n (%)
cORR*	24 (41)

*2 patients achieved a confirmed response in long-term follow-up and are not included in the calculation of ORR

Best Overall Confirmed Response Status (BICR)
Partial response
Stable disease
Progressive disease
Missing(2)

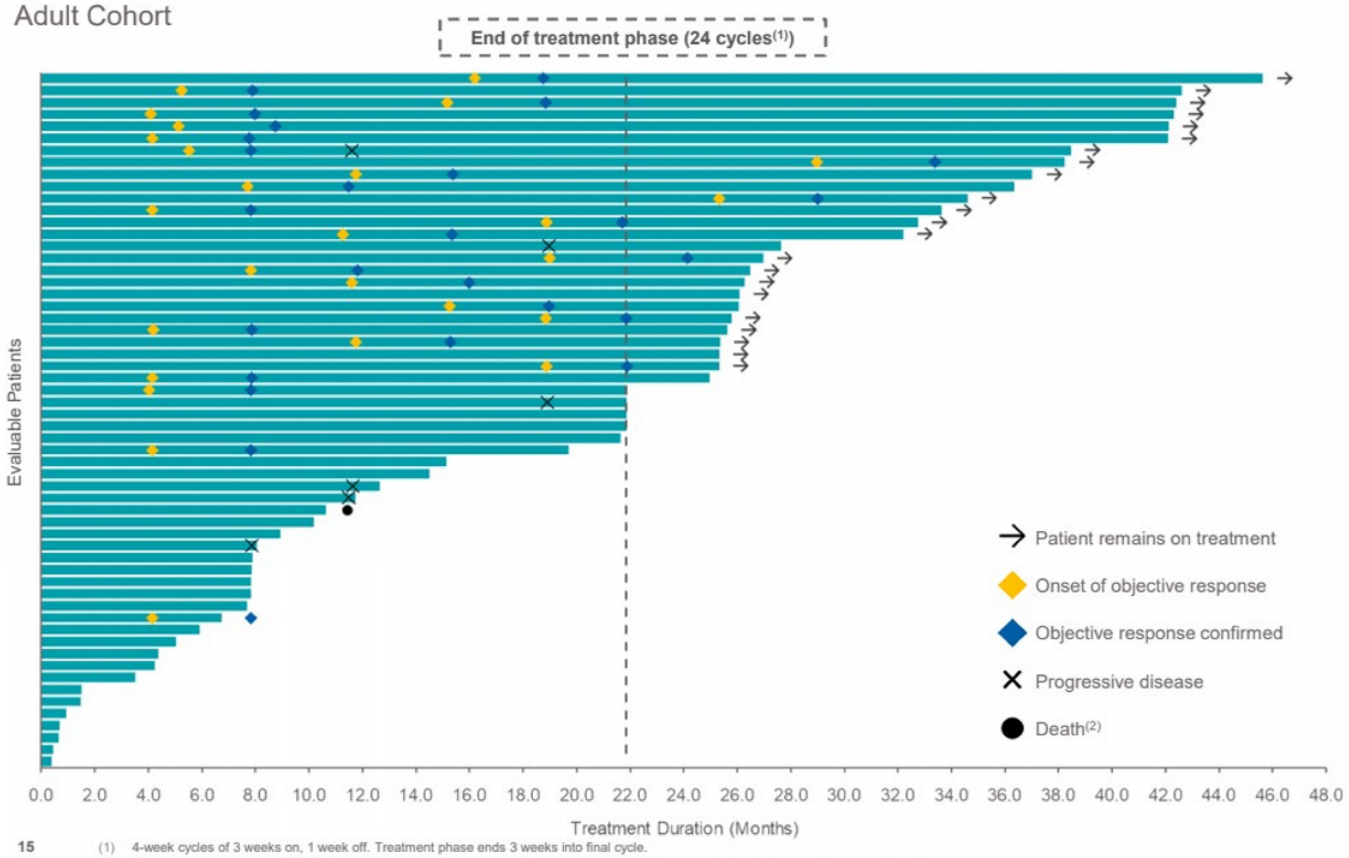


Median best change in tumor volume of -41% (n=50)

Note: BICR: blinded independent central review; cORR: confirmed objective response rate.
(1) Shows best change in tumor volume achieved at any point, including unconfirmed partial responses.
(2) Participants that discontinued study prior to any on-treatment MRI assessment.

Treatment Duration and Response

Adult Cohort



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(1) 4-week cycles of 3 weeks on, 1 week off. Treatment phase ends 3 weeks into final cycle.
(2) One patient death due to COVID-19 occurred within 30 days of discontinuing study treatment and was deemed not related to mirdametinib.

ReN

Patient-Reported Outcomes

Adult Cohort

Scale	p-Value for Change from
Target Tumor Pain Numeric Rating Scale (NRS-11)[2] (n=21)	<0.001
Pain Interference Index (PII)[3] (n=22)	<0.001
Pediatric Quality of Life Inventory (PedsQL)[4] – Total Score (n=34)	0.009
Pediatric Quality of Life Inventory (PedsQL)[4] – Physical Functioning (n=34)	0.009

(1) Change from baseline at Cycle 13, the pre-specified assessment for patient-reported outcome analysis per the ReNeu statistical analysis plan. Least squared means estimates using a mixed model for repeated measures (MMRM).

(2) The NRS-11 assesses target tumor pain on a scale from 0 – "no pain" to 10 – "worst pain you can imagine." NRS-11 assessments were performed for six consecutive days prior to a visit as well as on the visit day, except for the ET visit, which is done on the visit day only. The mean of these seven assessments is taken as the visit score. Baseline is defined as the most recent NRS-11 score taken on or before treatment start date.

(3) The PII assesses the degree to which pain has impacted the participants' daily activities on a scale from 0 – "not at all" to 6 – "completely." PII assessments were performed on the six consecutive days prior to a visit as well as on the visit day, except for the ET visit, which is done on the visit day only. The mean of these seven assessments is taken as the visit score. Baseline is defined as the most recent PII score taken on or before treatment start date.

(4) PedsQL assess quality of life on a Likert scale from 0 to 4. These items are then reverse scored and linearly transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, 4=0, with higher scores indicating a higher quality of life. Baseline is defined as the most recent PedsQL score taken on or before treatment start date.

Safety Summary

Adult Cohort

(n=58)	TEAEs ≥ 20% Subjects		TRAE
Preferred Term	**All Grades – n (%)**	**≥ Grade 3 – n (%)**	**All Grades – n (%)**
Any TEAE	**58 (100)**	**21 (36)**	**57 (98)**
Rash[1]	54 (93)	6 (10)	54 (93)
Dermatitis acneiform	45 (78)	5 (9)	45 (78)
Diarrhea	34 (59)	0 (0)	28 (48)
Nausea	30 (52)	0 (0)	21 (36)
Vomiting	22 (38)	0 (0)	16 (28)
Fatigue	17 (29)	1 (2)	12 (21)
COVID-19	13 (22)	3 (5)	0 (0)
SARS-COV-2 test positive	12 (21)	2 (3)	0 (0)

(n=58)	n (%)
TEAE leading to dose interruption[2]	18 (31)
TEAE leading to dose reduction	10 (17)
TEAE leading to discontinuation	13 (22)

(1) Composite adverse event including dermatitis acneiform, rash, rash maculo-papular, rash erythematous, acne, seborrheic dermatitis, exfoliative rash, papule, rash papular, dermatitis, rash macular, rash pruritic.
(2) Dose interruptions due to treatment-related adverse events occurred in 5 patients (9%).
Note: TEAE: treatment-emergent adverse event; TRAE: treatment-related adverse event.

Program Highlights and Next Steps

Badreddin Edris, PhD

Chief Operating Officer

Mirdametinib Has the Potential to Address the Substantial Unmet Needs That Rema Meaningful Population of NF1-PN Patients With Its Differentiated Profile

~100,000

Individuals with an NF1 diagnosis in the U.S.(1)

~40,000

Patients living with NF1-PN in the U.S.(2,3)

- Potential therapeutic option for broader age spectrum, encom pediatric and adult patients
- Robust antitumor activity: BICR ORR of 52% for pediatric pati for adult patients with evidence of deep and durable response
- Statistical significance demonstrated across several importan patient-reported outcome measures related to quality of life a
- Manageable safety profile with low rates of Grade 3+ toxicities cohorts supports opportunity for long-term dosing potential i
- Differentiated product formulation designed for ease of admin
- Convenient therapy designed to enhance compliance with no requirement, optimized dosing, and limited drug-drug interact

Sources: (1) Lammert et al., Arch Dermat, 2005. U.S. Census Data; (2) Fisher et al., Neuro-Oncology, 2022. (3) SpringWorks market research.

Regulatory Status and Next Steps

Regulatory Designations:

- Orphan Drug Designation for NF1 granted by FDA and European Commission and Fast Track Designation for NF1-P
- Rare Pediatric Disease Designation granted by FDA in July 2023

Upcoming Submissions:

- Plan to request Pre-NDA meeting with FDA to be held in 1Q24 and NDA submission expected in 1H24

Upcoming Data:

- Expect to present detailed study results from pediatric and adult cohorts of ReNeu trial at medical conference in 1H2
- Plan to submit manuscript for peer-reviewed journal publication in 2024

Positive Results From ReNeu Advance Our Goal of Two Potential Approvals by 202

Nirogacestat

DeFi

- If approved, would be the first FDA-approved therapy for desmoid tumors (PDUFA date: November 27, 2023)
- Phase 3 DeFi trial achieved statistically significant and clinically meaningful results on primary and all key secondary endpoints[1]
- Opportunity to transform the standard of care for desmoid tumor patients

Mirdametinib

ReNeu

- Topline ReNeu data demonstrated potential for robust antitumor activity and clinical benefit, safety and tolerability, and convenience
- Differentiated option for pediatric patients and potential to be first approved in adults
- Opportunity to deliver a best-in-class therapy for adult and pediatric NF1-PN patients by 2025, if approved

(1) Gounder et al., *NEJM*, 2023.
Note: PDUFA: Prescription Drug User Fee Act; NF1-PN: Neurofibromatosis type 1-associated plexiform neurofibroma.

Thank Y

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Q&A

Saqib Islam
Chief Executive Officer

Jim Cassidy, MD, PhD
Chief Medical Officer

Badreddin Ed
Chief Operatin