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, 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 nirogacestat to become an important new treatment for adult patients with desmoid tumors, the potential for a Marketing Authorisation Application for nirogacestat, expectations regarding the 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 adequacy of the data contained in 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 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, expectations regarding the timing and initial data from the Phase 2 trial evaluating nirogacestat in patients with recurrent ovarian granulosa cell tumors, our plans to file an Investigational 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 Phase 1 collaborator studies, 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 SpringWorks against 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,” “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 presentation 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 presentation, 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 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 and timing of our collaboration partners’ ongoing and planned clinical trials, (iv) the timing of our planned regulatory submissions and interactions, including 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 drug candidates, including nirogacestat and mirdametinib, (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) the 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 partners’ abilities to 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, 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” section(s) of 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 estimates and research. While 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 adequacy, fairness, accuracy or 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, and there can be no 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 independent source.

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

SpringWorks® THERAPEUTICS

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

Kylie, NF1-PN patient

Gus, NF1-PN patient

Katie, NF1-PN patient

ReNeu

- ***Topline data suggest class-leading potential for both children and adults with NF1-PN***
- ***Robust objective response rates confirmed by Blinded Independent Central Review***
- ***Differentiated depths of response with extended treatment durations***
- ***Manageable tolerability profile with product features designed to enhance compliance***
- ***Anti-tumor activity supported by improvements in pain and quality of life measures***

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

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

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

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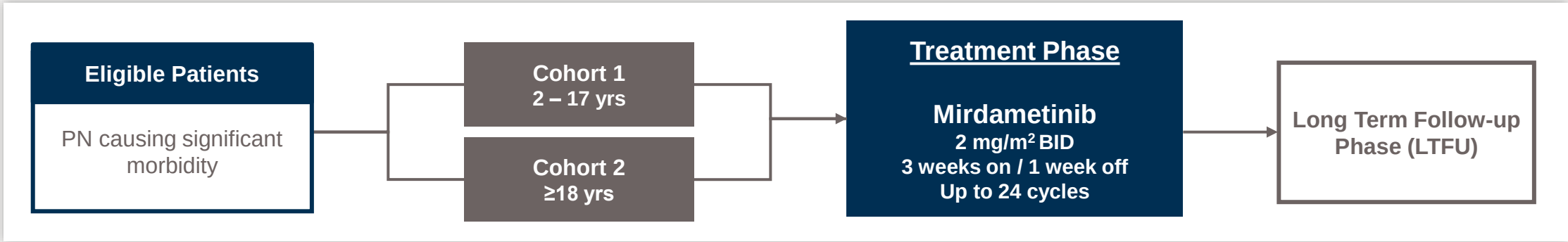
Phase 2b ReNeu Trial Summary

TRIAL DESIGN	▪ Phase 2b open-label; n = 114 patients in 2 cohorts (pediatric and adults) across 50 U.S. sites ▪ 2 mg/m^2 BID dosing with intermittent course (4-week cycles of 3 weeks on, 1 week off) for up to 24 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) determined by BICR by end of treatment phase
SECONDARY AND EXPLORATORY ENDPOINTS	▪ Safety and tolerability, duration of response, QoL and physical functioning assessments (including 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	n (%)
Patients enrolled	58
Median age at enrollment [range] - years	34.5 [18 – 69]
Sex	
Male	21 (36)
Female	37 (64)
Location of target neurofibroma	
Head and Neck	28 (48)
Lower / Upper Extremities	17 (29)
Paraspinal	5 (9)
Other	8 (14)
Type of neurofibroma-related complication	
Pain	52 (90)
Disfigurement or Major Deformity	30 (52)
Motor Dysfunction or Weakness	23 (40)
Airway Dysfunction	3 (5)
Other	10 (17)
Target PN progressing at study entry	31 (53)

Data presented is topline data as of September 20, 2023 data cutoff.
Note: PN: plexiform neurofibroma.

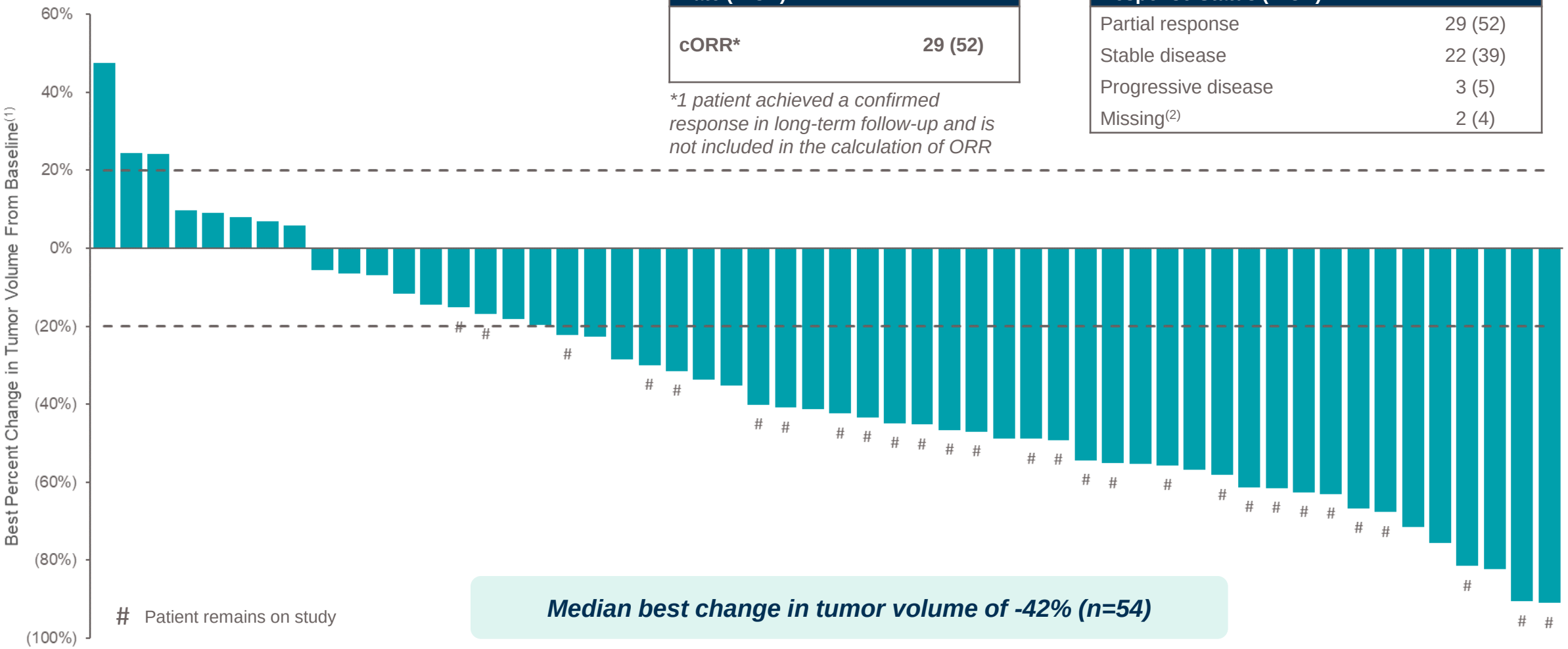
Best Tumor Response

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)	n (%)
Partial response	29 (52)
Stable disease	22 (39)
Progressive disease	3 (5)
Missing[2]	2 (4)

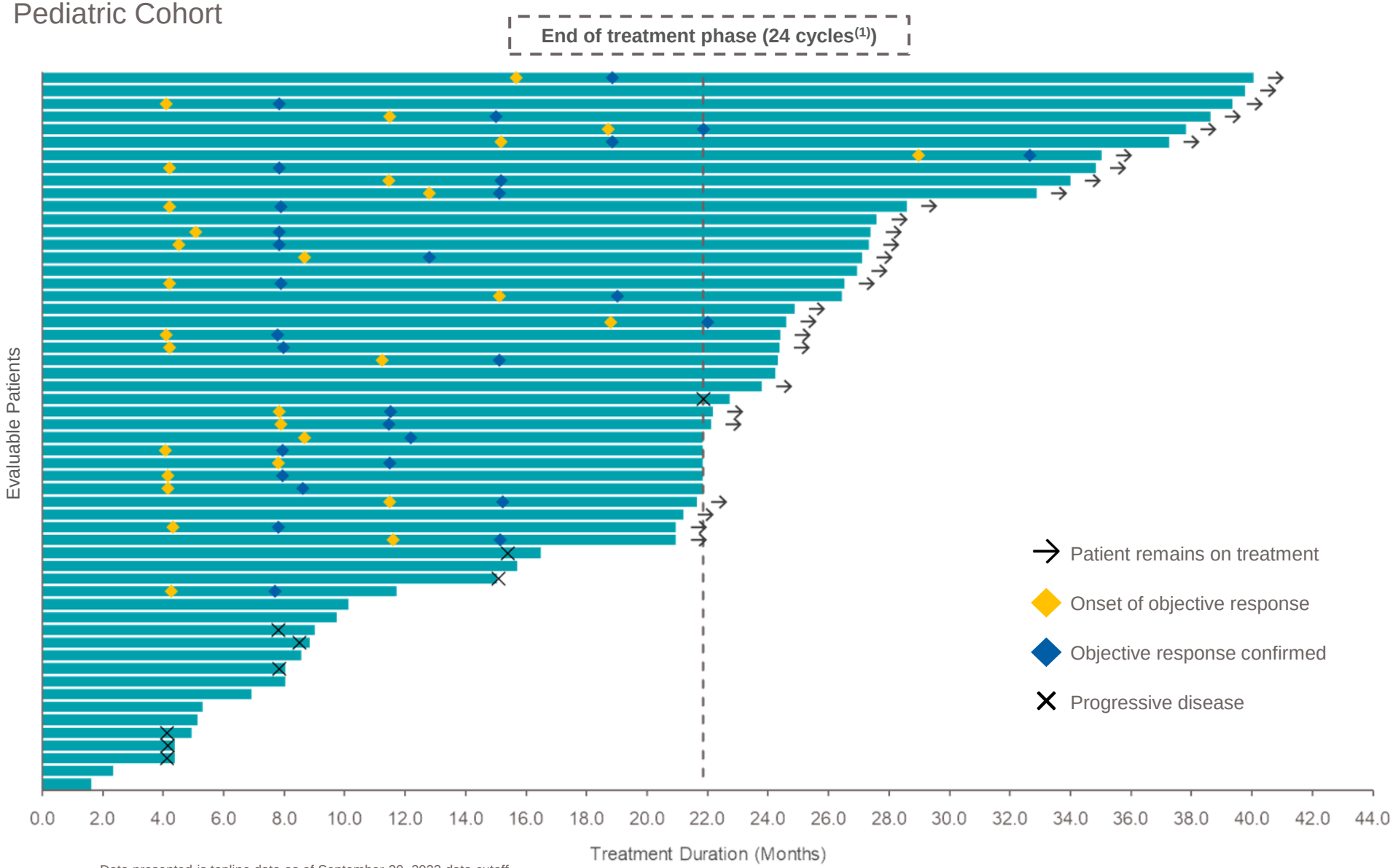


Median best change in tumor volume of -42% (n=54)

Data presented is topline data as of September 20, 2023 data cutoff.
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



- Median duration of treatment was 22.0 months
- Median time to first response was 7.9 months
  - 45% of patients had their onset of confirmed response by Cycle 5 assessment (4.2 months)
- Median duration of response was not reached
- 28 patients remained on treatment as of data cutoff
- 85% of patients that completed the treatment phase chose to continue receiving treatment in the long-term follow-up portion of the study

Data presented is topline data as of September 20, 2023 data cutoff.

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

Patient-Reported Outcomes

Pediatric Cohort

Scale	p-Value for Change from Baseline[1]
Target Tumor Pain – Numeric Rating Scale (NRS-11)[2] (n=17)	0.003
Pain Interference Index (PII)[3]	
Self-Report (n=22)	0.017
Parent Proxy (n=20)	0.025
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

Data presented is topline data as of September 20, 2023 data cutoff (updated).

(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.

ReNeu SpringWorks THERAPEUTICS

Safety Summary

Pediatric Cohort

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

Data presented is topline data as of September 20, 2023 data cutoff.

(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.

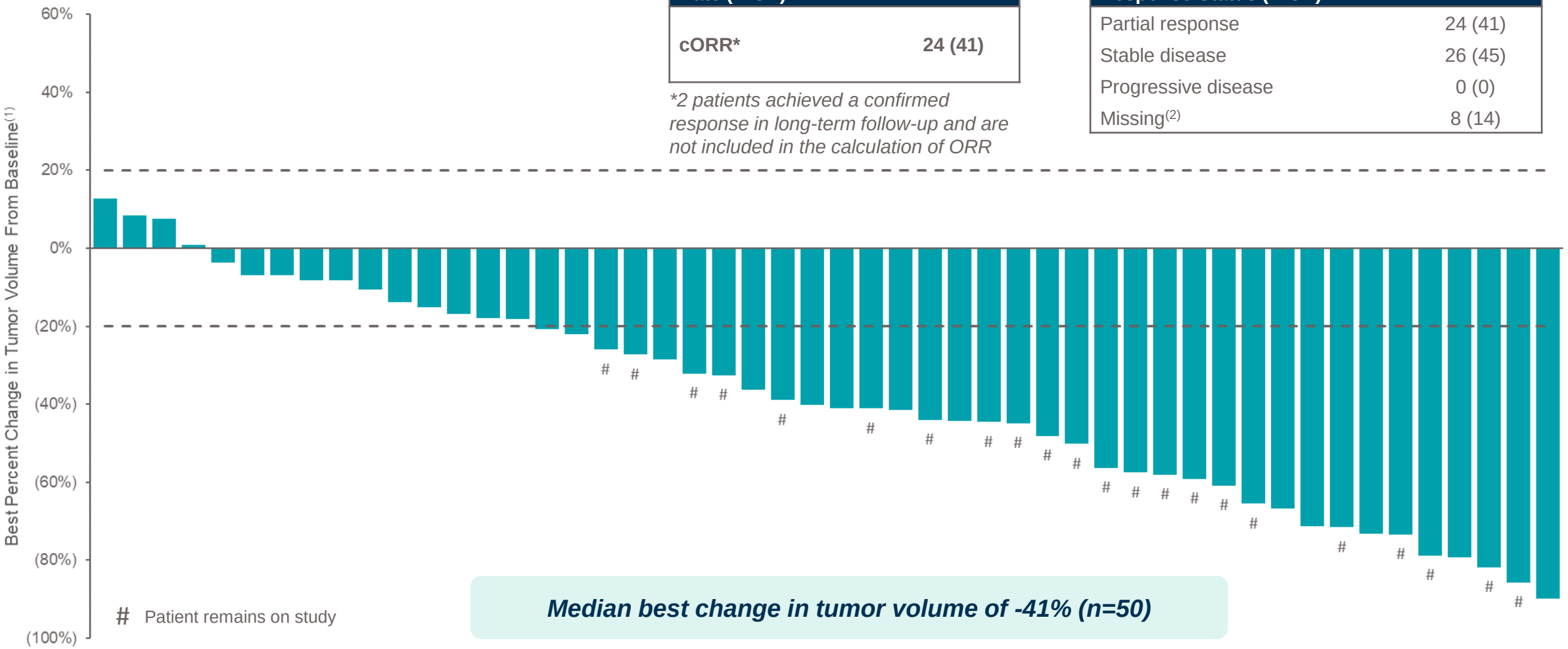
Best Tumor Response

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)	n (%)
Partial response	24 (41)
Stable disease	26 (45)
Progressive disease	0 (0)
Missing[2]	8 (14)

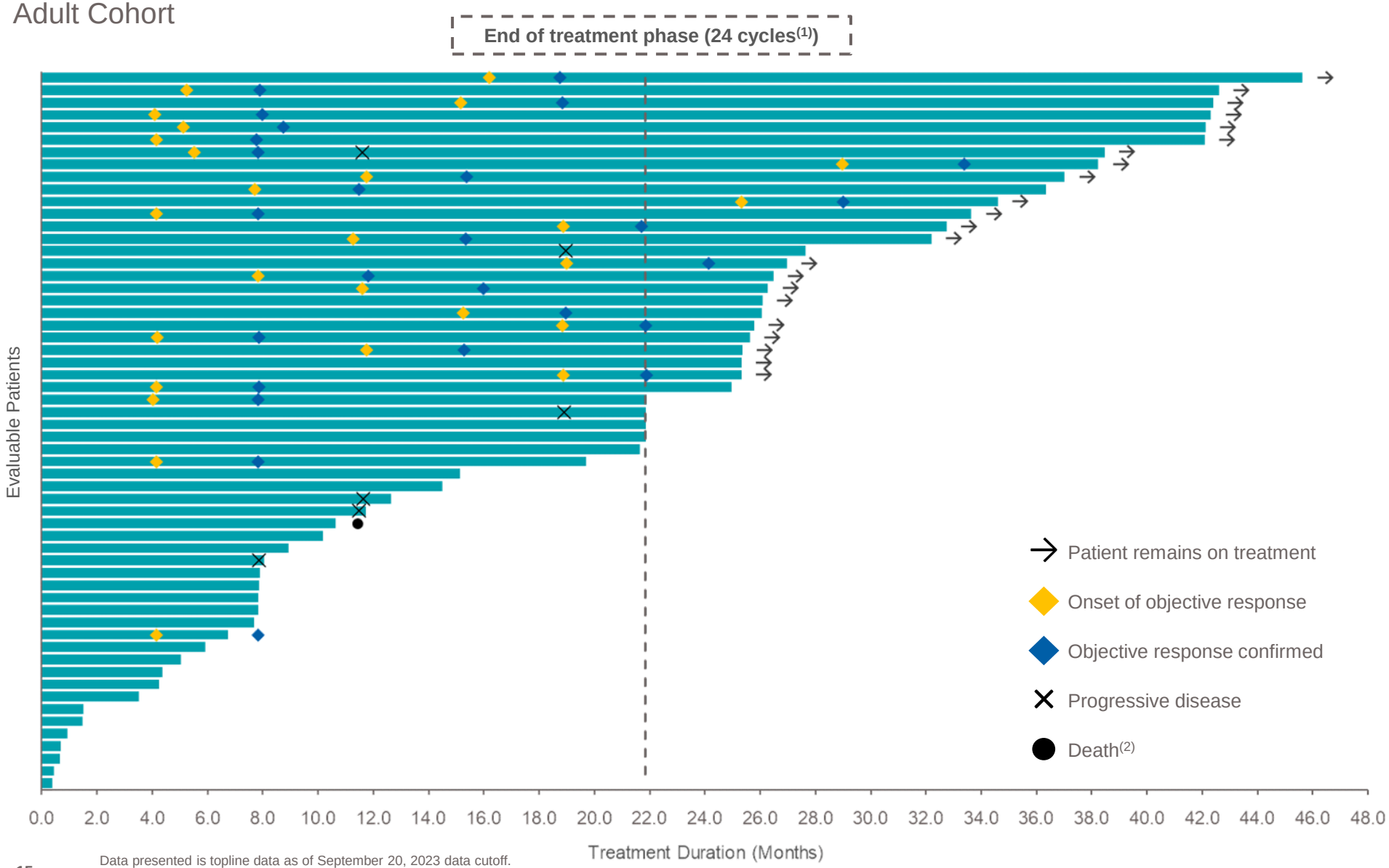


Median best change in tumor volume of -41% (n=50)

Data presented is topline data as of September 20, 2023 data cutoff.
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



- Median duration of treatment was 21.8 months
- Median time to first response was 7.8 months
  - 46% of patients had their onset of confirmed response by Cycle 5 assessment (4.2 months)
- Median duration of response was not reached
- 22 patients remained on treatment as of data cutoff
- 84% of patients that completed the treatment phase chose to continue receiving treatment in the long-term follow-up portion of the study

Data presented is topline data as of September 20, 2023 data cutoff.

(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.

Patient-Reported Outcomes

Adult Cohort

Scale	p-Value for Change from Baseline[1]
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)	0.018
Pediatric Quality of Life Inventory (PedsQL)[4] – Physical Functioning (n=34)	0.012

Data presented is topline data as of September 20, 2023 data cutoff (updated).

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

Data presented is topline data as of September 20, 2023 data cutoff.

(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

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Mirdametinib Has the Potential to Address the Substantial Unmet Needs That Remain for 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, encompassing both pediatric and adult patients**
- **Robust antitumor activity: BICR ORR of 52% for pediatric patients and 41% for adult patients with evidence of deep and durable responses**
- **Statistical significance demonstrated across several important patient-reported outcome measures related to quality of life and pain**
- **Manageable safety profile with low rates of Grade 3+ toxicities in both cohorts supports opportunity for long-term dosing potential in real world**
- **Differentiated product formulation designed for ease of administration**
- **Convenient therapy designed to enhance compliance with no fasting requirement, optimized dosing, and limited drug-drug interactions**

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-PN granted by FDA
- 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 1H24
- Plan to submit manuscript for peer-reviewed journal publication in 2024

Positive Results From ReNeu Advance Our Goal of Two Potential Approvals by 2025

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 You

SpringWorks THERAPEUTICS

Q&A

Saqib Islam

Chief Executive Officer

Jim Cassidy, MD, PhD

Chief Medical Officer

Badreddin Edris, PhD

Chief Operating Officer