

# Study 079 – An Open-Label, Single-Arm Phase 2 Trial Evaluating Pamrevlumab, a Monoclonal Antibody to Connective Tissue Growth Factor (CTGF) in Non-Ambulatory Subjects with Duchenne Muscular Dystrophy (NCT02606136)

## PRELIMINARY CLINICAL RESULTS

**Parent  
Project  
Muscular  
Dystrophy**

JOIN THE FIGHT.  
END DUCHENNE.

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# Agenda



- **Pamrevlumab Mechanism of Action**
- **Overall Summary of Study FG-3019-079 in Non-Ambulatory Subjects with Duchenne Muscular Dystrophy**
- **Preliminary Clinical Results: Positive data that shows improvement over previously published studies in terms of progression of DMD, as measured by**
  - Pulmonary Function Tests
  - Cardiac Function and cardiac MRI
  - Upper Arm Muscle function and muscle fibrosis by MRI
- **Conclusion**



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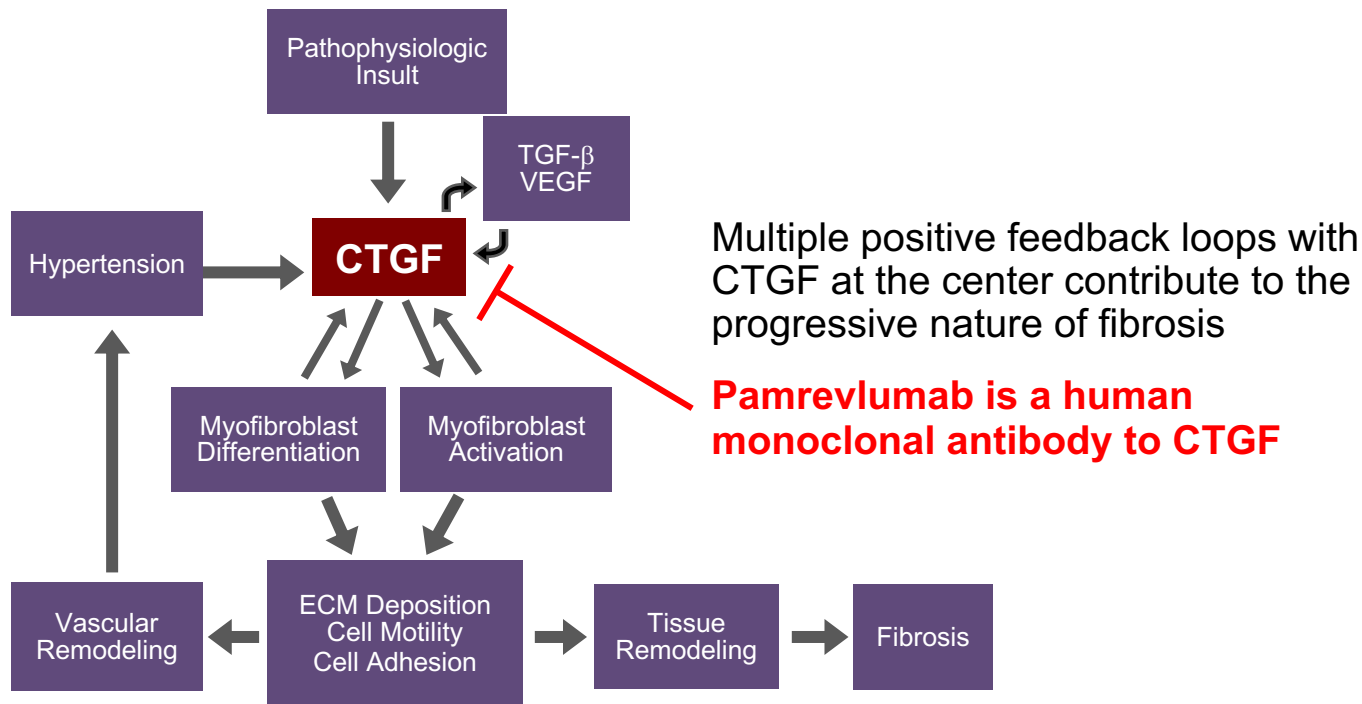
# Pamrevlumab

- Pamrevlumab (FG-3019), is a fully human monoclonal antibody (mAb) against CTGF, currently under development in non-ambulatory DMD patients, idiopathic pulmonary fibrosis (IPF), and locally advanced pancreatic cancer (LAPC).
- Pamrevlumab treatment has been shown to positively affect the course of several of these diseases in Phase 1 and Phase 2 clinical studies.



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# Connective Tissue Growth Factor (CTGF) a Central Mediator of Tissue Remodeling and Fibrosis



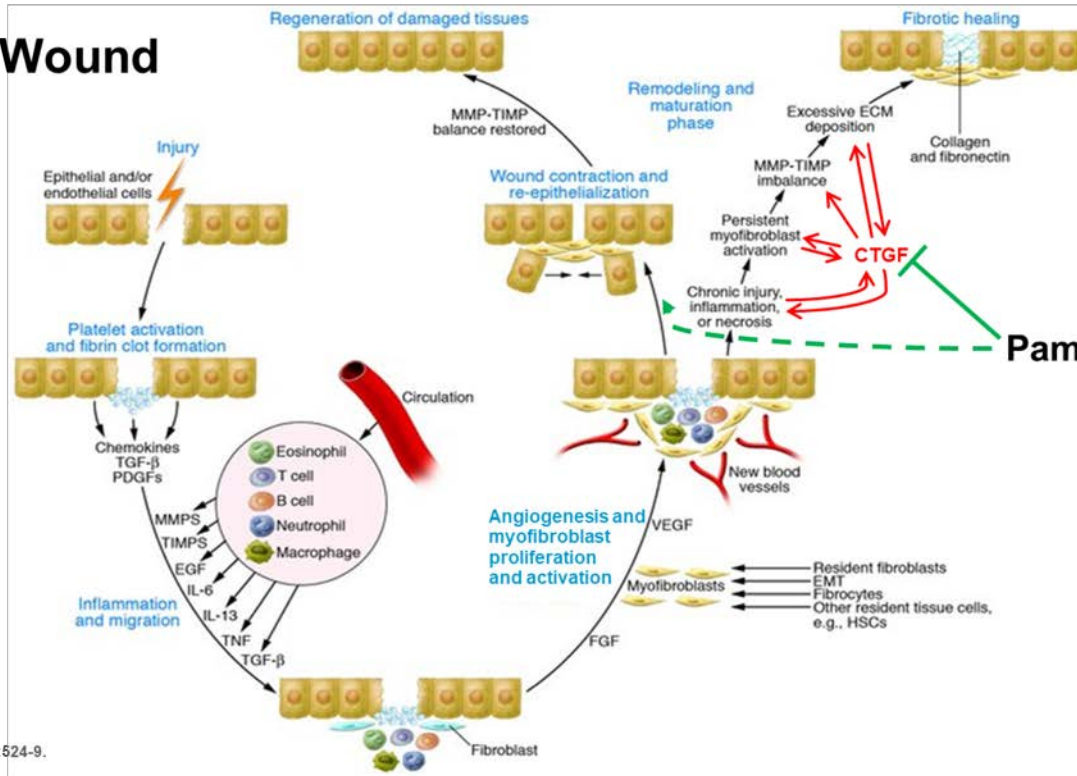
Adapted from Lipson et al. (2012) Fibrogenesis & Tissue Repair 5:S24



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# Current Understanding of Pamrevlumab Mechanism of Action

## Normal Wound Healing



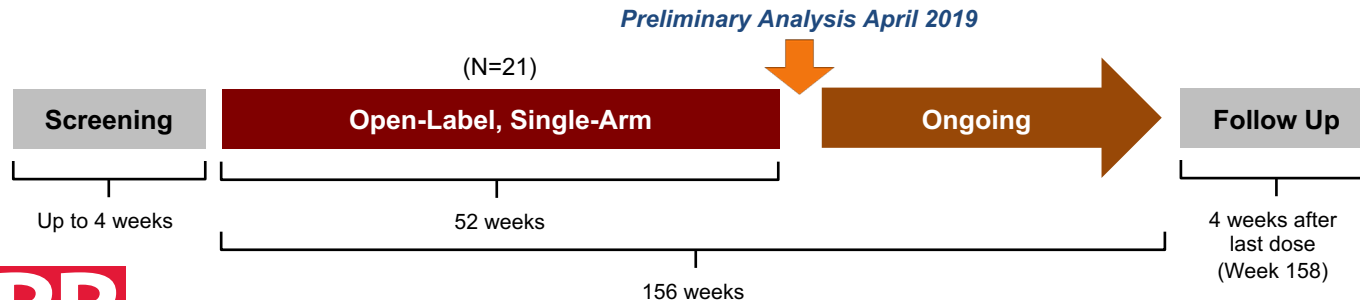
J Clin Invest. 2007; 117:524-9.



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# Study -079 Design

- This is an open-label, single-arm Phase 2 study in non-ambulatory subjects with Duchenne muscular dystrophy. Each subject will receive pamrevlumab (35 mg/kg every 2 weeks) for up to 156 weeks.
- Safety was assessed regularly by laboratory results and physical examination, and efficacy was evaluated by pulmonary function tests, upper arm muscle function tests, in addition to cardiac and muscle MRI.
- A total of 21 subjects were enrolled in the study.
- A preliminary analysis was conducted after all subjects completed 52 weeks of treatment.



# Demographics and Baseline Characteristics

- All subjects were male, non-ambulatory, with the majority being white (20 Caucasians and 1 Asian), and received 35 mg/kg IV infusions of pamrevlumab every 2 weeks.
- Median age at DMD diagnosis was 5.5 years (0.6, 12.2), with a median duration of being non-ambulatory prior to study enrollment of 3.4 years (1, 11.5).
- The median age of subjects was 15.8 years (12.4, 25.6).
- The most common reported medical history was femur fracture (33.3%), restrictive lung disease (29%), headache/migraine (29%), scoliosis (24%), tenotomy (19%), asthenia (19%), sleep apnea (19%) and cardiomyopathy (14.5%).
- The majority of subjects had dystrophin gene deletion (57%), while the rest of subjects had duplication and point mutation.
- All subjects are on corticosteroids (deflazacort 43% and prednisone 57%). Corticosteroids started approximately 9.4 years (median) before enrollment (1.1, 16.6).



# **SAFETY SUMMARY**



## Safety Results - TEAEs

- Pamrevlumab appears to be well tolerated in pediatric subjects with non-ambulatory DMD. Most treatment-emergent adverse events (TEAEs) were mild to moderate in severity per the Common Terminology Criteria for Adverse Events (CTCAE).
- There were no TEAEs that led to pamrevlumab or study discontinuation.

<b>Adverse Event Preferred Term</b>	<b>All Subjects (N=21) n (%)</b>
<b>Subjects with Any TEAEs Incidence <math>\geq</math>25%</b>	20 ( 95.2)
<b>Headache</b>	14 ( 66.7)
<b>Vomiting</b>	9 ( 42.9)
<b>Nasopharyngitis</b>	9 ( 42.9)
<b>Cough</b>	7 ( 33.3)
<b>Back Pain</b>	6 ( 28.6)



# Safety Results - SAEs

<b>Preferred Term</b>	<b>All Subjects (N=21) n (%)</b>
<b>Subjects with Any Serious TEAEs</b>	6 (28.6)
<b>Food Poisoning</b>	1 (4.8)
<b>Adverse Drug Reaction</b>	1 (4.8)
<b>Pneumonia</b>	1 (4.8)
<b>Concussion</b>	1 (4.8)
<b>Femur Fracture</b>	1 (4.8)
<b>Skull Fracture</b>	1 (4.8)
<b>Metabolic Acidosis</b>	1 (4.8)
<b>Hydronephrosis</b>	1 (4.8)
<b>Nephrolithiasis</b>	1 (4.8)
<b>Hypotension</b>	1 (4.8)

\* One subject died after the withdrawal of consent, and approximately 5 weeks after the last dose of pamrevlumab. The cause of death was neither related to study drug nor study procedure and likely due to the natural history of the disease progression per the investigator.



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**EFFICACY SUMMARY**  
**PULMONARY FUNCTION**

# Pulmonary Function

- Pulmonary dysfunction in DMD is progressive and restrictive in nature and is one of the most common causes of morbidity and mortality in non-ambulatory patients.
- In Study 079, pulmonary function was evaluated using spirometry assessments at baseline and Q12 weeks thereafter. In the preliminary analysis, PFTs were assessed by the change from baseline at one-year in ppFVC, ppFEV1, and ppPEFR.
- Pamrevlumab achieved positive results, with the data showing less disease progression — i.e., better preservation of lung function — compared to published data from previous studies on natural disease progression (e.g., Ricotti<sup>9</sup>, et al. 2019 and Meier<sup>11</sup>, et al. 2016.)



# RESULTS – Pulmonary Function (ppFVC)

## Percent Predicted Forced Vital Capacity (ppFVC):

- Forced vital capacity assessed by spirometry is the best global assessment of all respiratory muscles, because it requires a full inspiration (reflecting function of inspiratory muscles) and a full expiration (reflecting function of expiratory muscles)<sup>7</sup>.
- The results of the study published by Ricotti in 2019, show that non-steroid and steroid users aged 10 to 18 years had similar decline in ppFVC of 5.0% to 6.0% per year<sup>7,8,9</sup>.
- Baseline ppFVC:
  - In Study 079, the mean ppFVC at baseline was 54.15% and the median was 54.2% (29.1, 70.7).
  - In Ricotti's publication, study patients had a mean baseline of ppFVC of 62.1%.
- At one year, better maintenance of lung function was observed in Study 079, with less decline in ppFVC than observed in previously published data (Ricotti<sup>9</sup>, et al. 2019, –5.47%).



# RESULTS – Pulmonary Function (ppFEV1)

## Percent Predicted Forced Expiratory Volume at 1 Second (ppFEV1)

- With the exception of obstructive pulmonary disease, FEV1 very closely follows FVC with the advantage of requiring a less prolonged effort (1 second)<sup>7</sup>. Data from the placebo group in the DELOS study<sup>10</sup> has shown that yearly rates of ppFEV1 decline were -10.2% [SEM 2.0]<sup>11</sup>.
- Baseline ppFEV1
  - In Study 079, the mean baseline was 53.4% and the median was 55.2% (29.2, 73.3).
  - In Delos Study placebo arm, the mean baseline was 54.3%.
- At one year, pamrevlumab showed improved maintenance or less decline in ppFEV1 than seen in previously published study results (Meier<sup>11</sup>, et al. 2016, -8.7%.)



# RESULTS – Pulmonary Function - (ppPEFR)

## Percent Predicted Peak Expiratory Flow Rate (ppPEFR)

- The 1-year change for ppPEFR was  $-5.8\% \pm 0.6\%/year$  (mean  $\pm$  SE) based on prospective data in DMD patients (68% of patients were being treated with steroids, 42% were non-ambulatory), collected in the Neuromuscular Clinic at CHOP from 2005–2010<sup>8</sup>. In a more recent publication, the 1-year change in ppPEFR was  $-4.8\%$ . (Ricotti, et al. 2019<sup>9</sup>- N=29).
- Baseline mean percent predicted PEFr:
  - In Study 079, the mean at baseline was 54.66% and the median was 52.4% (37.9, 82.7).
  - In Ricotti’s publication, the mean baseline was 65.56%.
- At one year, treatment with pamrevlumab appeared to result in a slowing in the decline in ppPEFR, compared to what was observed in (Ricotti, et al. 2019<sup>9</sup>)





**EFFICACY SUMMARY**  
**CARDIAC FUNCTION**



# CARDIAC FUNCTION

## Cardiac Function

- Patients with DMD have progressive cardiac muscle dysfunction, which is considered to be one of the leading causes of mortality.
- Cardiac magnetic resonance imaging (cMRI) was used at baseline and Week 52 to assess the left ventricular ejection fraction percentage (LVEF%) and cardiac fibrosis in Study 079.
- Encouraging data in Study 079 suggest actual improvement in specific measurements of cardiac function may be achieved by treatment with pamrevlumab, compared to the decline in this measurement seen in earlier published results. (McDonald<sup>14</sup>, et al. 2018.)



# RESULTS – Left Ventricular Ejection Fraction (LVEF):

## Left Ventricular Ejection Fraction (LVEF)

- Based on data tracking the natural disease history, a decrease in LVEF -0.82% per year of age has been observed (McDonald et al. 2018<sup>14</sup> - N=305).
- Study 079 Baseline LVEF:
  - For All Subjects (ITT), the mean LVEF percentage at baseline (N=19) was 56.74% and the median was 59.06% (41.03, 73.81)
  - Subgroup with Baseline (N=13), LVEF of  $\geq 50\%$  the mean was 65.15% and the median was 60.55%
- Week 52 change in LVEF% from baseline results in Study 079:
  - For ITT, the estimated mean change was an increase in LVEF% of 0.29% from baseline
  - In sub-group analysis of subjects with LVEF% of  $\geq 50\%$ , the mean change was an increase in LVEF of 1.79% from baseline
- These positive results showing a net increase in mean LVEF% from baseline. Treatment with pamrevlumab present a potential improvement in cardiac function



## RESULTS – Cardiac Fibrosis by MLGE

### Cardiac Fibrosis Score Assessed by Mass of Late Gadolinium Enhancement (MLGE)

- Mass of Late Gadolinium Enhancement (MLGE) is a strong marker for the progression of left ventricular systolic dysfunction in DMD patients. Additionally, myocardial fibrosis burden correlates strongly with LVEF<sup>15</sup>.
- In Study 079, the mean MLGE (scar mass) at baseline (N=18) was 24.064 g and the median was 20.60 g (0.44, 76.09).

At Week 52, a correlation between improvement in LVEF% and reduction in cardiac fibrosis was demonstrated, consistent with what was observed by Tandon<sup>15</sup>, et al. 2015. The results showed stabilization and possible improvement in the myocardial fibrosis burden.





**EFFICACY SUMMARY**  
**MUSCLE FUNCTION**

# MUSCLE FUNCTION

## Upper Arm Function

- Preserving upper limb strength is very important in non-ambulatory DMD patients, because it provides functional independence.
- In Study 079, biceps brachii MRI was assessed at baseline and at Week 52. Additionally, functional assessments including the performance of upper limb (PUL-total score), and the grip strength assessed by hand held myometry (HHM).
- Pamrevlumab showed positive results preserving the upper limbs functions with either improvement or delay the decline, i.e., a reduction of progression in loss of the upper arm strength.



# RESULTS – Performance of the Upper Limb

## Performance of the Upper Limb (PUL)

- PUL assessment was specifically developed for patients with DMD to assess the function of the upper limb in young ambulant males to older and weaker non-ambulant adults.
- Baseline mean PUL score:
  - In Study 079, the mean score at baseline (N=21) was 24.4 and the median was 22 (13, 41).
  - In Ricotti study the mean score at baseline was 50.4.
- The one-year change from baseline in the performance of upper limb (total score):
  - In Study 079 the mean change from baseline was -1.53
  - Natural disease history from published results the annual mean change was -4.13.(Ricotti<sup>9</sup>, et al. 2019.)
- These results show a potential preservation of muscle function and/or delay in loss of function



# RESULTS – Upper Arm Muscle Fibrosis and Fat by MRI

## Upper Arm (biceps brachii) MRI Fat and Fibrosis (T2 Mapping)

- In recent years, several longitudinal studies have reported the potential value of MRI as a biomarker to assess disease progression and treatment effect in DMD.
- T2-mapping can help determine the level of inflammation, edema and fat infiltration present in the affected muscle<sup>16</sup>.
- In Study 079, a strong correlation between change from baseline to Week 52 in biceps brachii T2-mapping and change in PUL score was observed.
- This result demonstrated stabilization and even possible improvement in the muscle fibrosis burden.



# RESULTS – Upper Arm Function Grip by HHM

## HHM - Grip Strength

- Hand held myometry has shown very good reliability and feasibility in non-ambulatory DMD patients<sup>18</sup>.
- Baseline Grip Score
  - In Study 079, at baseline (N=21), the mean grip strength score was 45.86 newton (median 37.00) for the dominant hand and 41.97 (median 37.00) for the non-dominant hand.
  - In the Ricotti study, the mean grip strength at baseline was 63.75
- Study -079 results showed a positive increase in grip-strength score in both dominant and non-dominant hands at one year of treatment with pamrevlumab, while earlier results from previous published study showed a decline at one year, e.g., a grip-strength score (newton) of the dominant and non-dominant hands over time of -3.00 and -2.17 newton respectively. (Seferian<sup>19</sup> et al. 2015.)





# Cautions

- Small number of patients (N=21)
- Single-arm, open-label study
- All comparisons are with historical published data, therefore, they should be interpreted with caution as there are, among other things, differences in subject numbers, baseline characteristics, inclusion/exclusion criteria, treatment protocols, and analysis methods.
- While these positive results are clinically meaningful and encouraging, ultimately, evaluation and interpretation of this data is a matter for review with regulatory agencies.



# Conclusions

- Preliminary clinical results from Study 079, showed that one year of pamrevlumab treatment in non-ambulatory DMD subjects was well tolerated. The most common TEAEs occurred in  $\geq 25\%$  of subjects in descending order were: headache, nasopharyngitis, vomiting and cough. Most of the patients, who experienced TEAEs had pre-existing risk factors.
- Pulmonary function results assessed by ppFVC, ppPEFR, and ppFEV1 showed less decline as expected by disease progression, compared to Ricotti<sup>9</sup> and Meier<sup>11</sup> et al. papers.
- Cardiac function results assessed by MRI showed an improvement in the mean of LVEF%, compared to expected mean decline in the McDonald<sup>14</sup> paper.
- A correlation between improvement in LVEF% and reduction in cardiac fibrosis at Week 52 was observed, consistent with what was observed in Tandon<sup>15</sup>, et al. 2015
- Performance of upper arm showed less decline in PUL (total score), compared to Ricotti<sup>9</sup> et al. paper.
- A strong correlation between change from baseline to Week 52 in biceps brachii T2-mapping assessed by MRI and change in PUL total score at Week 48 was observed.
- Performance of the hands assessed by HHM, showed an improvement in grip score compared to the Ricotti<sup>9</sup> and Seferian<sup>18</sup> papers.
- Overall pamrevlumab was well tolerated and showed good promising results in term of slowing down the disease progression across all study parameters of the disease in comparison to published papers.



**THANK YOU**

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**Questions?**