

Clinical assessment of disease severity in patients with Fabry disease treated with pegunigalsidase alfa: An integrated analysis

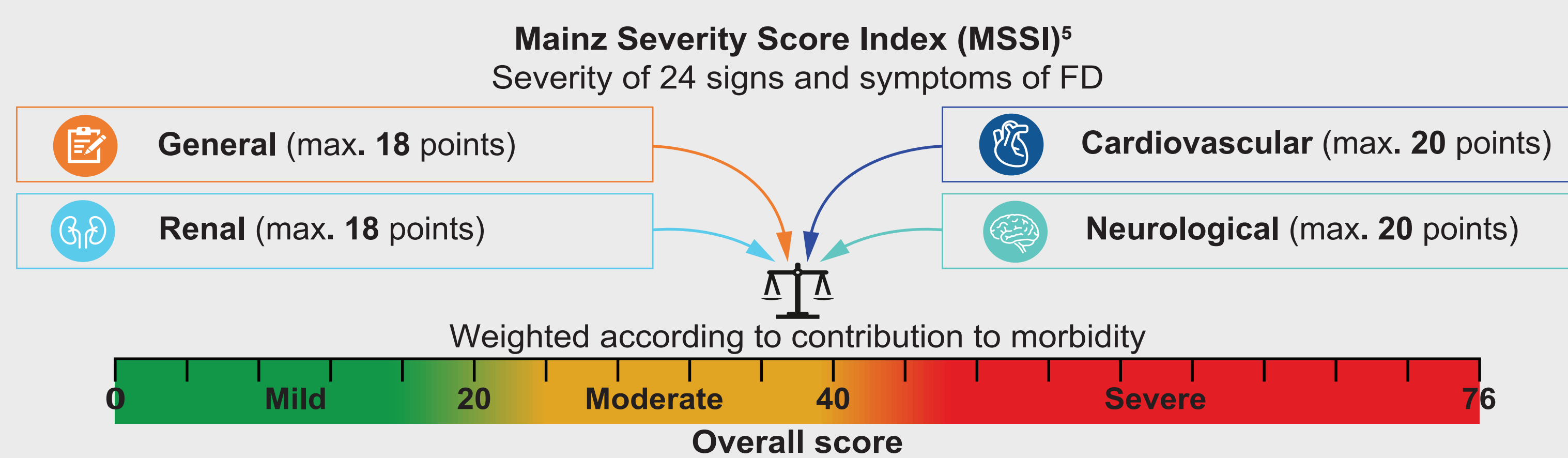
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Introduction

- Pegunigalsidase alfa is an approved enzyme replacement therapy (ERT) for adults with Fabry disease (FD), with demonstrated biomarker and clinical benefits across a clinical trial program of over 140 patients¹⁻⁴
 - In treatment-naïve patients, pegunigalsidase alfa led to a 68% reduction in renal peritubular capillary Gb3 inclusions, decreased plasma lyso-Gb3 levels, and helped maintain stable eGFR²
 - Among patients who switched from prior ERT to pegunigalsidase alfa, most had a positive change in their annualized median eGFR slope; additionally, plasma lyso-Gb3 concentrations were either reduced (prior agalsidase alfa) or stable (prior agalsidase beta)^{3,4}
- While kidney function is a typical primary efficacy endpoint in FD trials, the Mainz Severity Score Index (MSSI) provides physician-assessed data evaluating the overall severity of the disease, encompassing factors beyond renal function⁵



Objective

- To evaluate the clinical disease course in response to treatment with pegunigalsidase alfa, we analyzed change in MSSI over 24 months using pooled clinical trial data from ERT-naïve and prior ERT (switch) patients

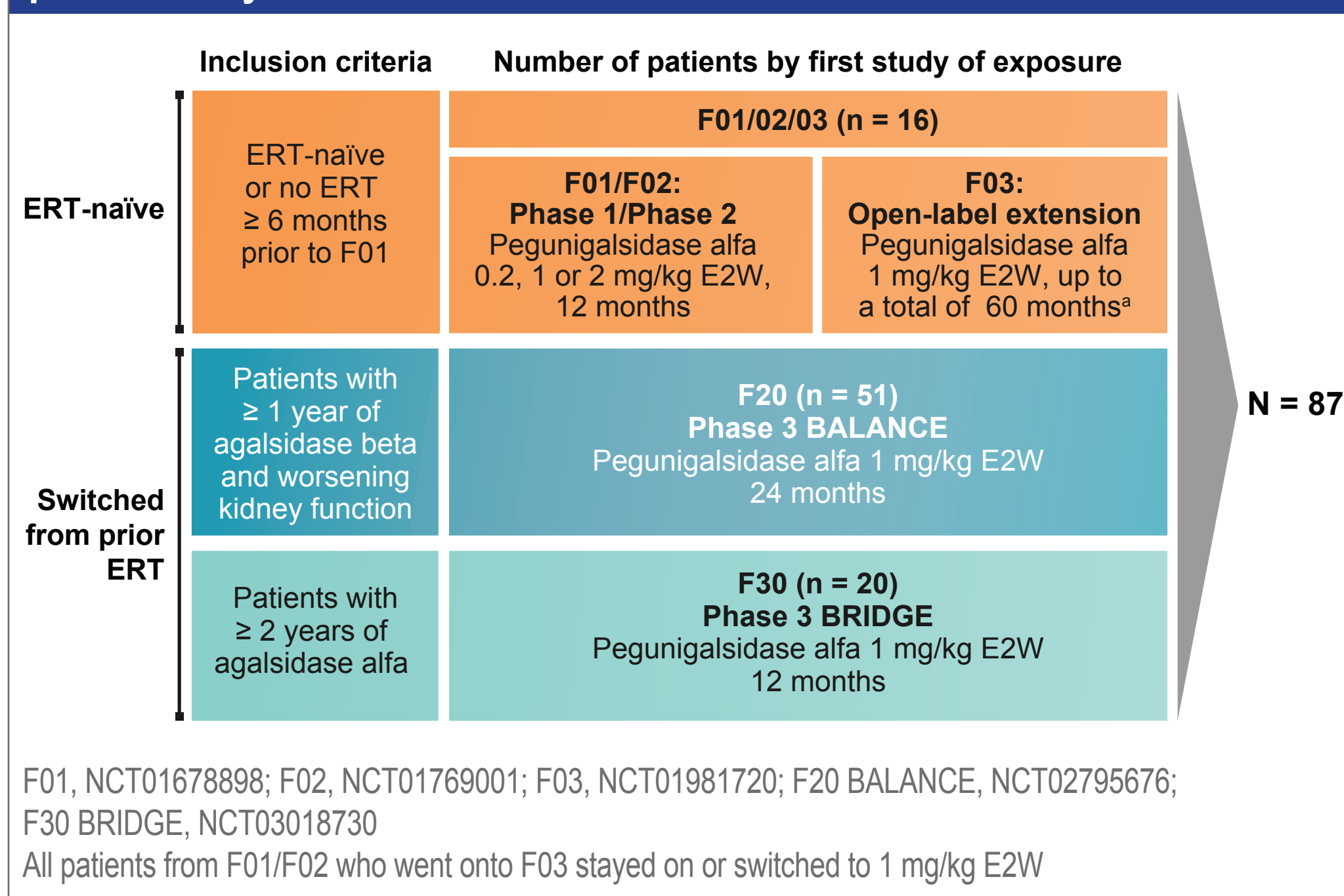
Key Takeaways

- Patients who switched from another prior ERT to pegunigalsidase alfa had stable mild/moderate MSSI scores, which were maintained for 12 months, and then trended toward improvement between 12 and 24 months
- ERT-naïve patients experienced a reduction in disease severity upon treatment with pegunigalsidase alfa in clinical trials
- In this study, most patients had stable MSSI scores and 11% (9/80) had an improvement in an MSSI category 12 months after initiating pegunigalsidase alfa treatment

Methods

- MSSI data from patients treated with pegunigalsidase alfa from three clinical trials and one extension study were assessed and stratified by prior ERT status (Figure 1)^{1-4,6}
- Data were collected at baseline and then every 6 months for up to 24 months
- Because higher MSSI scores indicate more severe disease, a negative change indicates reduced disease severity
- The change in MSSI score by clinical domain (cardiovascular, neurological, renal, and general) was also assessed

Figure 1. Overview of pegunigalsidase alfa clinical trials included in this pooled analysis



Results

- 87 patients were included in this analysis

ERT-naïve n = 16	ERT-switch n = 71
9 male	41 male
3 ADA+	25 ADA+

- At baseline, most patients had either mild (< 20) or moderate (≥ 20 – ≤ 40) overall MSSI scores (44.8% [n = 39] and 50.6% [n = 44], respectively)
- The proportions of patients with mild or moderate MSSI scores were similar at baseline by prior ERT status (Figure 2)
 - Only 4 patients (4.6%) had a severe MSSI score (> 40) at baseline; all 4 were ERT-switch (prior agalsidase alfa [n = 1]; prior agalsidase beta [n = 3])
 - Among those with a severe MSSI score, the most common abnormalities at baseline for the general, cardiovascular, neurological, and renal domains were cornea verticillata (4/4, 100%; 1 point); ECG abnormalities (4/4, 100%; 2 points); fatigue and reduced activity level (4/4, 100%; 1 point each); and tubular dysfunction/low GFR or creatinine clearance (3/4, 75%; 8 points), respectively
- The proportion of patients with mild disease at month 12 of pegunigalsidase alfa treatment vs baseline increased among ERT-naïve patients, whereas it remained stable among ERT-switch patients (Figure 3)

Figure 2. Disease severity in ERT-naïve and ERT-switch patients at baseline

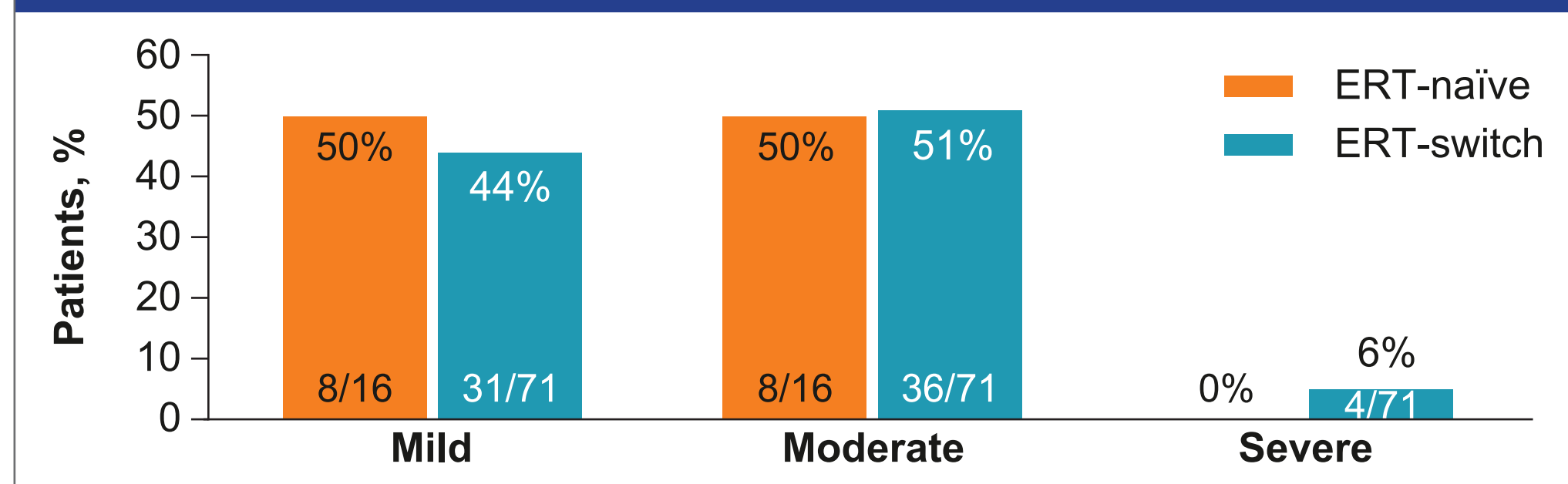
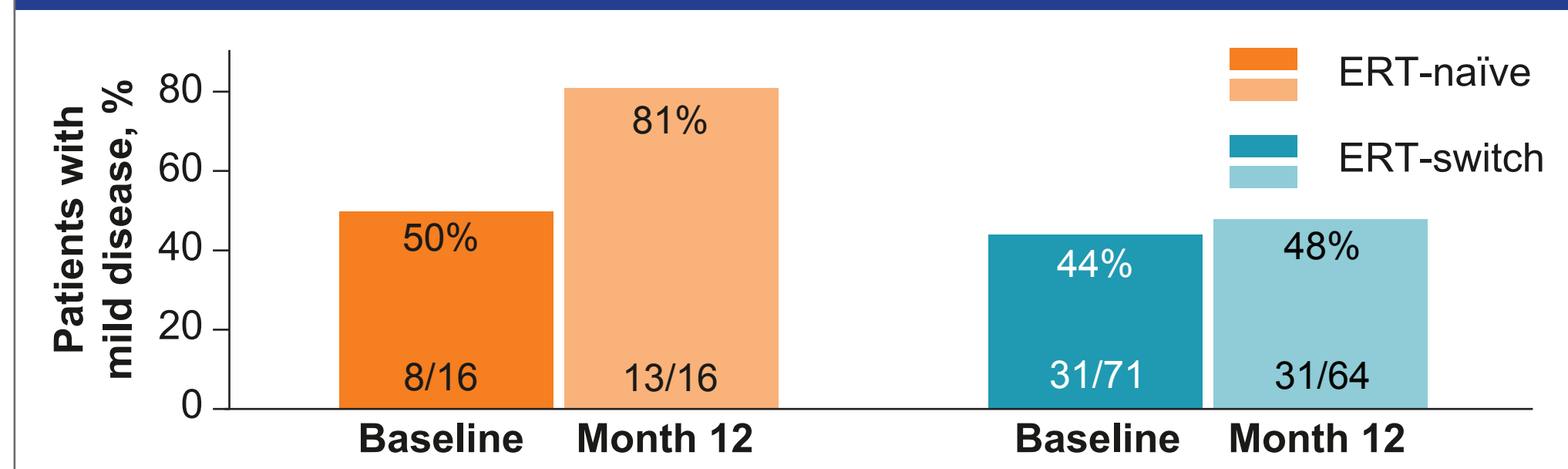
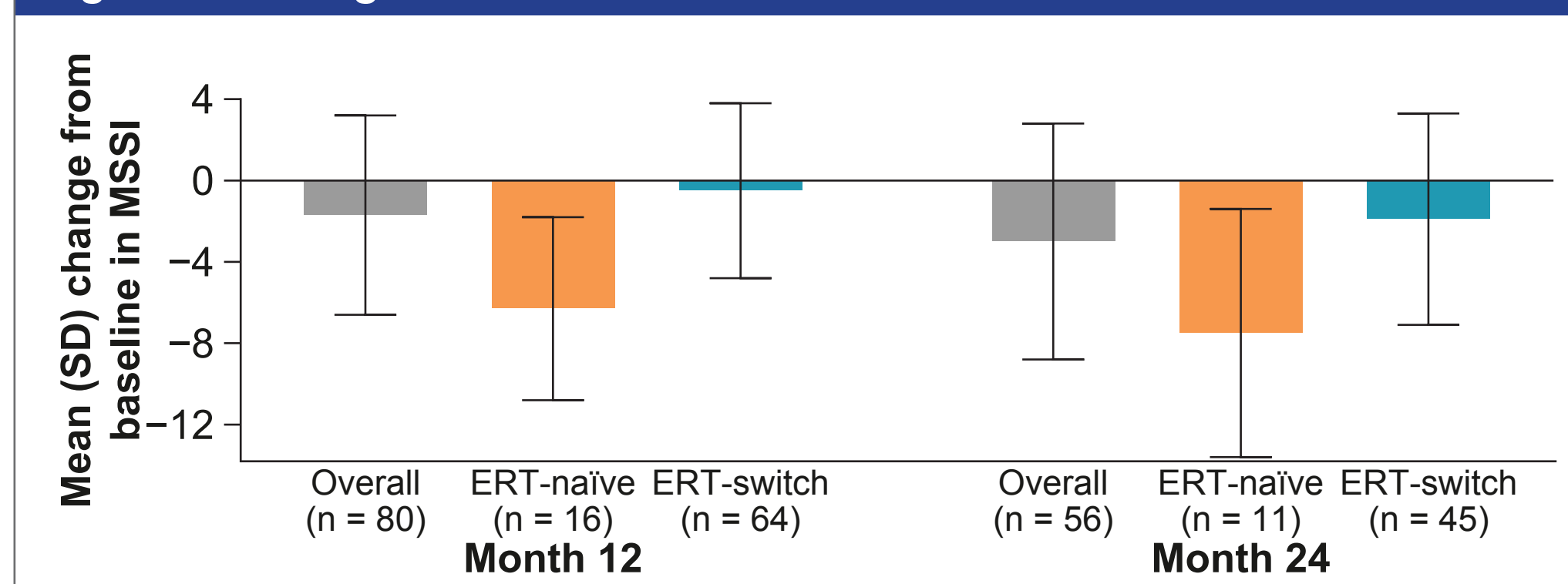


Figure 3. ERT-naïve and ERT-switch patients with mild disease at baseline and at month 12 of pegunigalsidase alfa treatment



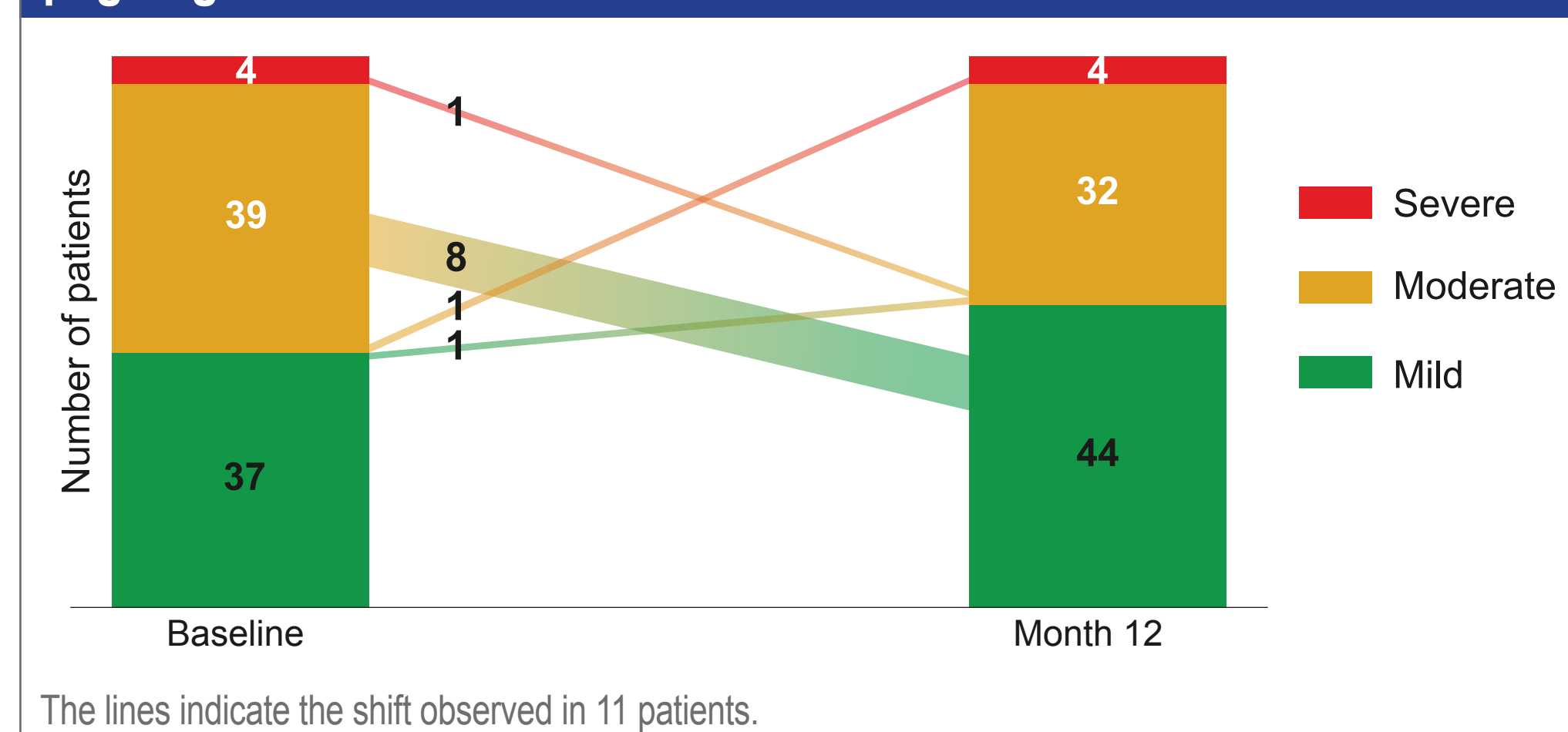
- Overall mean (SD) MSSI score change from baseline (CFB) to month 12 was -1.7 (4.9), showing a trend for reduced severity, with improvement in ERT-naïve patients (-6.3 [4.5]) and stability in ERT-switch patients (overall: -0.5 [4.3]; agalsidase beta to pegunigalsidase alfa: -0.3 [4.4]; agalsidase alfa to pegunigalsidase alfa: -1.0 [4.2]) (Figure 4)
- Among 56 patients with 24-month data, there was improvement in both ERT-naïve and ERT-switch patients, with mean MSSI (SD) score CFBs of -7.5 (6.1) and -1.9 (5.2), respectively (all ERT-switch patients had previously received agalsidase beta)

Figure 4. Change from baseline in MSSI score



- At month 12, MSSI severity category stayed the same in 69 patients and changed in 11 patients: 9/80 (11%) improved and 2/80 (2.5%) worsened (Figure 5)

Figure 5. Changes in MSSI disease severity category at month 12 of pegunigalsidase alfa treatment^a

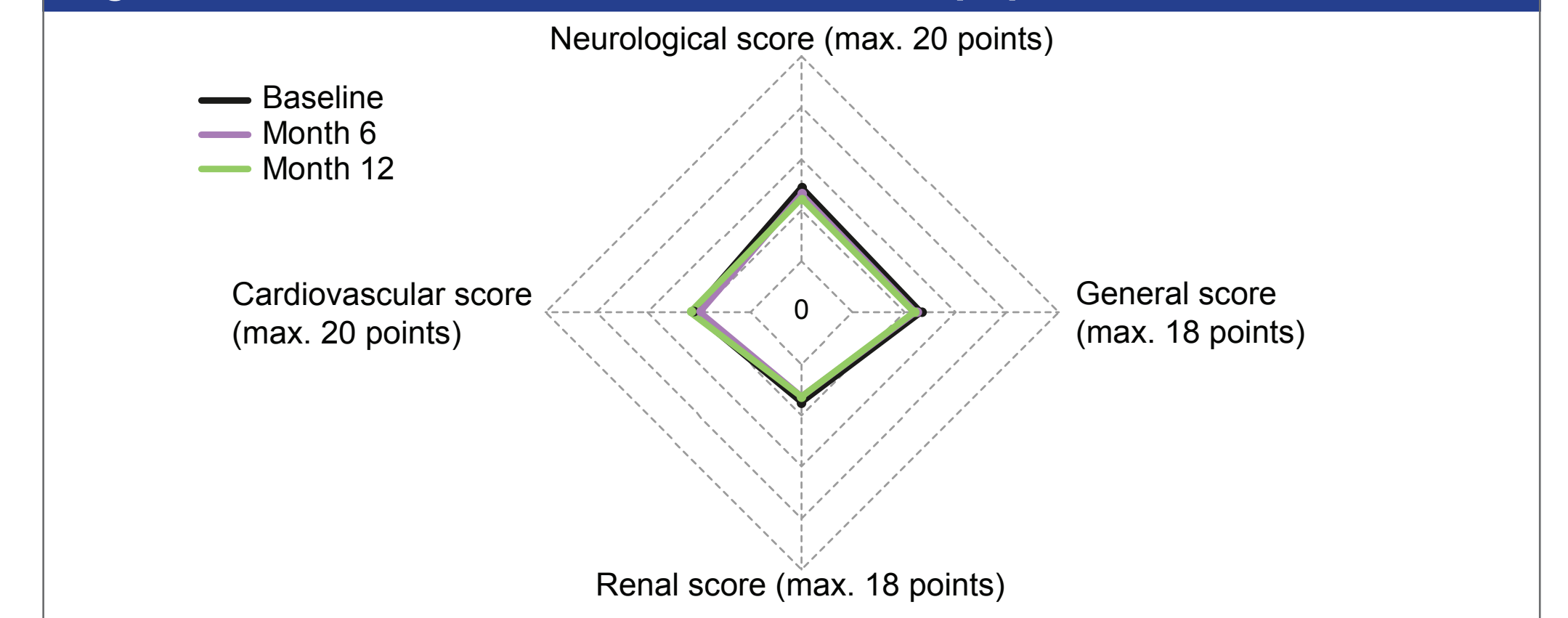


- Both patients with worsened MSSI were males with classic FD and were ADA+ at baseline
 - In both patients, MSSI general and renal domains remained unchanged, and cardiovascular and neurological domains worsened

MSSI domains

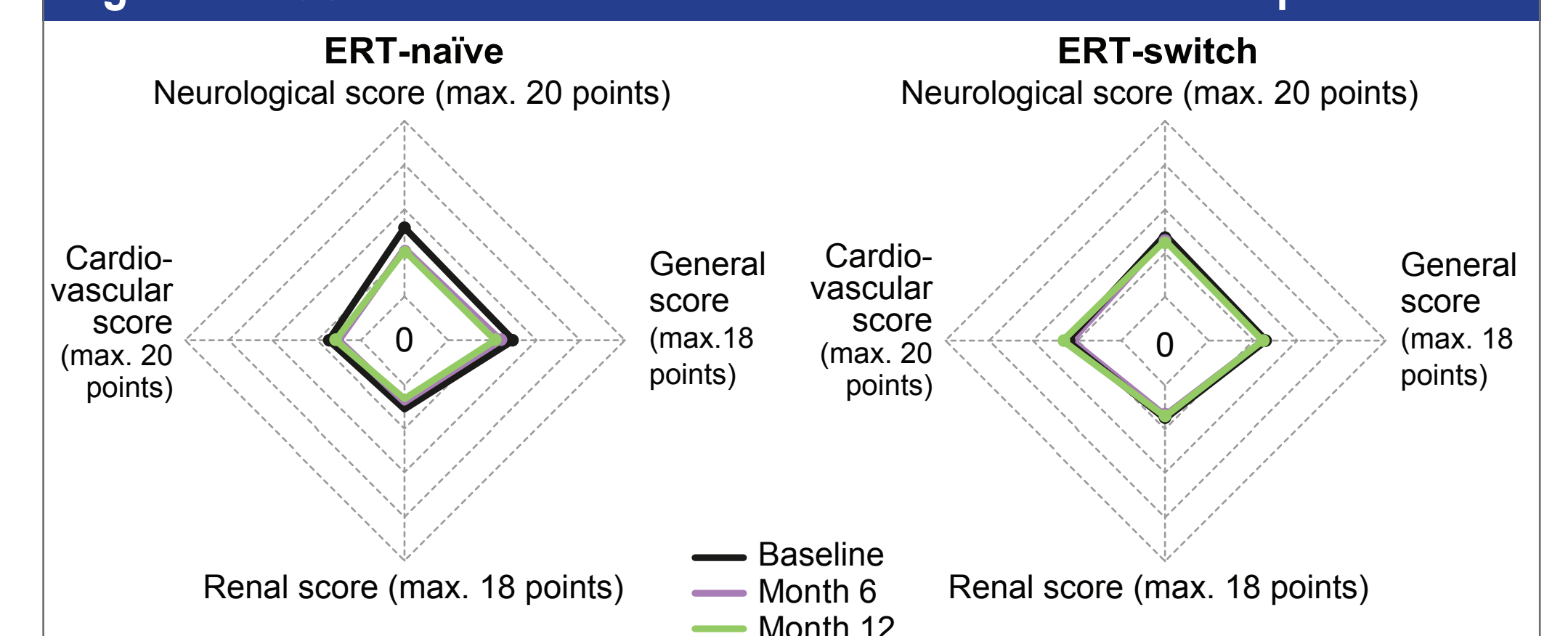
- MSSI domains showed improvement from baseline as early as month 6 of pegunigalsidase alfa treatment. The overall integrated population remained relatively stable through month 12 (Figure 6)

Figure 6. MSSI domain scores in the overall population



- When examined by prior ERT exposure, the ERT-switch cohort remained stable while ERT-naïve patients showed improvements in MSSI scores at month 6 and month 12 across all four domains (Figure 7)
 - Among ERT-naïve patients, larger improvements were seen in both the general and neurological domains, with mean (SD) CFBs at 12 months of -1.9 (2.2) and -2.6 (2.5), respectively, compared with mean CFBs of -0.8 (1.5) for the cardiovascular domain and -1.0 (1.8) for the renal domain

Figure 7. MSSI domain scores in ERT-naïve and ERT-switch patients



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Abbreviations: ADA, anti-drug antibody; CFB, change from baseline; eGFR, estimated glomerular filtration rate; E2W, every 2 weeks; ERT, enzyme replacement therapy; Gb3, globotriaosylceramide; GFR, glomerular filtration rate; FD, Fabry disease; lyso-Gb3, globotriaosylsphingosine; MSSI, Mainz Severity Score Index; SD, standard deviation.