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Tumor volume and T2 hyperintensity changes from DeFi: a phase 3, randomized, controlled trial of nirogacestat in patients with desmoid tumors

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Background: Use of magnetic resonance imaging (MRI) to assess changes in tumor volume or T2 signal intensity represents a novel imaging technique that could have prognostic or predictive value in patients with desmoid tumors (DT). For example, hyperintense areas on T2-weighted images are associated with active fibroblastic proliferation and have been reported to be associated with DT disease progression, whereas iso- or hypo-intense areas can be associated with inactive disease. In the global, phase 3, randomized, controlled, DeFi study, the novel gamma secretase inhibitor nirogacestat (n=70) demonstrated statistically significant and clinically meaningful improvement compared with placebo (n=72) in the primary endpoint of progression-free survival (hazard ratio, 0.29; 95% CI, 0.15, 0.55; $P<0.001$) and in all key secondary efficacy endpoints of objective response rate per blinded independent central review (41% vs 8%; $P<0.001$); pain, disease-specific symptom burden, physical functioning, role functioning, and overall quality of life ($P<0.01$ for all). Complete responses were achieved in 7% of patients with nirogacestat and 0% with placebo.

Methods: Here, we present an exploratory analysis of MRI tumor volume and T2 signal intensity changes in DeFi (NCT03785964). Eligible adults had histologically confirmed DT that had progressed ≥20% per RECIST v1.1 within 12 months of screening. Patients were randomized 1:1 to receive nirogacestat 150 mg or placebo twice daily taken orally in continuously in 28-day cycles. MRI or computed tomographic scans were obtained at screening, cycle 4, and every 3 cycles thereafter. As exploratory DeFi endpoints, volumetric MRI (no contrast required) and T2 hyperintensity of each patient's largest target tumor were evaluated at screening and every 6 cycles during the double-blind phase. CT or MRI scans (investigator's choice) were acquired to assess tumor changes; consequently, volumetric MRI was not evaluable in all patients. MRI T2 signal intensity is represented as the ratio of hyperintensity in total tumor volume to muscle background. All scans for tumor volume and T2 hyperintensity were assessed by blinded independent central review.

Results: At baseline, median tumor volume of the largest target tumor was 152.0 mL (interquartile range [IQR], 55.8 to 508.0 mL) for nirogacestat and 162.4 mL (IQR, 47.0 to 576.7 mL) for placebo. Treatment with nirogacestat led to significant reduction from baseline in MRI-

assessed tumor volume and T2 hyperintensity ratio of the largest target tumor versus placebo (Table). Descriptive analyses suggest deeper and more sustained decreases over time were observed with nirogacestat than with placebo in the largest target tumor's volume and T2 hyperintensity signal ratio.

Conclusions: The phase 3 DeFi study is the largest dataset to date to prospectively evaluate and report volumetric MRI and T2 hyperintensity results in desmoid tumors. In exploratory DeFi endpoints, significant reduction in MRI-assessed tumor volume and T2 hyperintensity of the largest target tumor was observed with nirogacestat compared with placebo. These exploratory, imaging-based results from DeFi are consistent with the significant improvement in progression-free survival and objective response achieved with nirogacestat compared with placebo in adult patients with desmoid tumors. Further exploration of the relationships among changes in longest tumor diameter (per RECIST version 1.1), tumor volume, T2 hyperintensity, and patient-reported outcomes from DeFi are ongoing.

Table. MRI Tumor Volume and T2 Hyperintensity of the Largest Tumor

Best % change from baseline at any time post-treatment	**Median**	**Interquartile range (Q1, Q3)**	***P* value**
Tumor volume			
Nirogacestat (n=61)	–58.9%	–84.7%, –8.9%	*P*<0.001
Placebo (n=61)	13.8%	–26.1%, 58.6%	
T2 hyperintensity ratio			
Nirogacestat (n=53)	–55.1%	–73.5%, –20.4%	*P*<0.001
Placebo (n=60)	–21.4%	–42.9%, 3.4%	

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Identification of clinical trials: The DeFi study is registered at clinicaltrials.gov as NCT03785964.

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