SELECTION BASED ON SAF ACTIVITY SCORE, NOT NASH CRN NAFLD ACTIVITY SCORE, LEADS TO SELECTION OF A PATIENT COHORT WITH MORE SEVERE NASH WITH MORE ADVANCED FIBROSIS: EXPERIENCE FROM THE NATIVE PHASE 2b STUDY OF THE PANPPAR AGONIST LANIFIBRANOR

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Background: Biopsy remains the gold standard for assessment of NAFLD severity and treatment efficacy. Semi-quantitative scoring of steatosis, ballooning, lobular inflammation and fibrosis are the most discriminative characteristics. NAFLD Activity Score (NAS) by NASH CRN is most frequently used to describe steatohepatitis severity but combines steatosis and activity. SAF scoring separately reports steatosis and activity, gives equal weight to ballooning and lobular inflammation and defines ballooning based on cell size, thereby potentially more accurately and reproducibly scoring activity. Lanifibranor is a panPPAR agonist tested in Phase 2b (NATIVE, NCT03008070) for non-cirrhotic NASH with highly significant results on resolution of NASH without worsening of fibrosis, regression of fibrosis of ≥1 point without worsening of fibrosis, and on the combination of resolution of NASH and fibrosis regression. Main inclusion criterion was a SAF activity score (A) ≥3 (with a SAF A reduction of ≥2 as primary efficacy endpoint). We here report the histological characteristics of the patients screened for NATIVE based on this innovative inclusion criterion.

Methods: Liver biopsies of patients screened for NATIVE were centrally scored by a single experienced pathologist. Biopsy could be performed up to 6 months before screening on the condition of metabolic stability or was obtained during screening.

Results: Out of 868 patients screened, 554 had biopsies of sufficient quality for reading. Results are summarised in the table. 284 corresponded to the SAF inclusion criteria A≥3 and F<4, all of whom had NASH and NAS≥4; 94 had NASH with NAS≥4 but SAF A<3. In the 284 patients with A≥3, the % of NAS>5 was high (75%) with a mean NAS of 5.9 ± 1.0 compared to those with A<3, in whom there was no patient with NAS >5 and mean NAS was 4.5 ± 0.5. Mean fibrosis score was 2.1±0.8 vs. 1.1±0.8, with 78% F2-F3 vs. only 29% in A≥3 vs. A<3 respectively. Mean steatosis score was comparable, although no patients with A<3 had steatosis score 1, compared to 30 (11%) in A≥3. When compared to the pooled population of 378 with NAS≥4, the % of patients with NAS>5 was 25% higher in the A≥3 population with a higher mean NAS and mean fibrosis score.

Conclusion: By using SAF A≥3 as inclusion criterion rather than NAS≥4, NATIVE selected a higher percentage of patients with severely active steatohepatitis associated with advanced fibrosis (although no *a priori* minimum fibrosis criterion was set). These results support the concept of deleting steatosis from a score of NASH activity in order to select the more severe patients for pharmacological treatment.

		NAS ≥ 4		
		A ≥ 3 N=284	A<3 N=94	Total N=378
NAS categories	4	25 (9%)	44 (47%)	69 (18%)
	5	48 (17%)	50 (53%)	98 (26%)
	6	148 (52%)	0 (0%)	148 (39%)
	7	47 (17%)	0 (0%)	47 (12%)
	8	16 (6%)	0 (0%)	16 (4%)
NAS	Mean ± SD	5.9 ± 1.0	4.5 ± 0.5	5.6 ± 1.1
Steatosis grade	Mean ± SD	2.6 ± 0.7	2.5 ± 0.5	2.6 ± 0.6
Fibrosis stage	0	6 (2%)	19 (20%)	25 (7%)
	1	56 (20%)	47 (50%)	103 (27%)
	2	123 (43%)	23 (24%)	146 (39%)
	3	99 (35%)	5 (5%)	104 (28%)
Fibrosis score	Mean ± SD	2.1 ± 0.8	1.1 ± 0.8	1.9 ± 0.9