

Francque S¹, Bedossa P^{2,4}, Abdelmalek M.³, Huot Marchand P⁹, Ratziu V⁸, Anstee Q.^{5,6}, Bugianesi E⁷, Balabenska R¹⁰, Mateva L¹¹, Lanthier N¹², Alkhouiri N¹³, Moreno C¹⁴, Schattenberg J¹⁵, Stepanova-Petrova D¹⁶, Vonghia L¹, Rouzier R¹⁷, Guillaume M¹⁸, Baudin M⁹, Richard M-P⁹, Abitbol J-L⁹, Broqua P⁹, Junien J-L⁹

1 Department of Gastroenterology and Hepatology, Antwerp University Hospital, Edegem, Belgium & Laboratory of Experimental Medicine and Paediatrics, Faculty of Medicine and Health Sciences, University of Antwerp, Wilrijk, Belgium. 2 Liverpat, Paris, France. 3 Division of Gastroenterology and Hepatology, Duke University, 40 Duke Medicine Circle, Durham, USA. 4 Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle Upon Tyne, UK. 5 Newcastle NIHR Biomedical Research Centre, Newcastle upon Tyne, UK. 6 Newcastle upon Tyne Hospitals NHS Foundation Trust, UK. 7 Division of Gastroenterology and Hepatology Department of Medical Sciences University of Torino A.O. Torino, Italy. 8 AP-HP Hôpital Pitié-Salpêtrière, Paris, France. 9 INVENTIVA, Daix, France. 10 Acibadem City Clinic Tokuda Hospital EAD, Sofia, Bulgaria. 11 UMHAT Sv. Ivan Rilski EAD, Sofia, Bulgaria. 12 Gastroenterology and Hepatology Unit, Brussels, Belgium. 13 The Texas Liver Institute, San Antonio, USA. 14 Cliniques d'Hépatologie et de Transplantation hépatique médicale, Brussels, Belgium. 15 Johannes Gutenberg-Universität, Mainz, Germany. 16 DCC Alexandrovska, EOOD, Sofia, Bulgaria. 17 CAP Research, Quatre Bornes, Mauritius. 18 CHU Purpan, Toulouse, France

1-INTRODUCTION

Biopsy remains the gold standard for assessment of NAFLD severity and treatment efficacy. Semiquantitative 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 both resolution of NASH and regression of fibrosis. 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.



SAF and NAS scoring

- ▶ The severity of hepatocellular ballooning and inflammation, namely disease activity, is a strong predictor for the presence of hepatic fibrosis and the risk for fibrosis progression
- ▶ NATIVE primary endpoint is a reduction of 2 points of the SAF activity score which exclude steatosis and focus on inflammation and ballooning
- ▶ Other key endpoints assess disease progression using both biopsy scoring measurements: SAF and NAS

SAF		NAS	
Steatosis-Activity-Fibrosis		NAFLD Activity Score	
0 - 3	Steatosis	0 - 3	
0 - 2	Inflammation	0 - 3	} NASH resolution
0 - 2	Ballooning	0 - 2	
0 - 4	Fibrosis	0 - 4	
} 2 points reduction of SAF activity score		} 2 points reduction of NAS score	
} Fibrosis improvement			

2-MATERIAL/METHODS

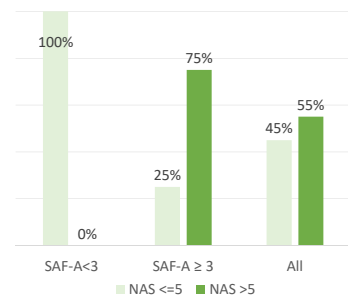
Liver biopsies of patients screened for NATIVE were centrally scored by a single experienced pathologist. Biopsy could be performed up to 6 months before screening on the condition of metabolic stability or was obtained during screening.

Out of 868 patients screened, 554 had biopsies of sufficient quality for reading. 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; 247 patients were randomized in the NATIVE phase 2b study.

3-RESULTS

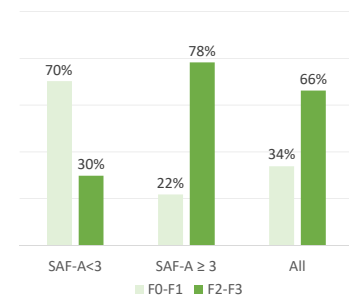
NAS score by SAF-A categories

NAS score	SAF-A<3 N=94	SAF-A ≥ 3 N=284	All N=378
Mean \pm SD	4.5 \pm 0.5	5.9 \pm 1.0	5.6 \pm 1.1



Fibrosis score by SAF-A categories

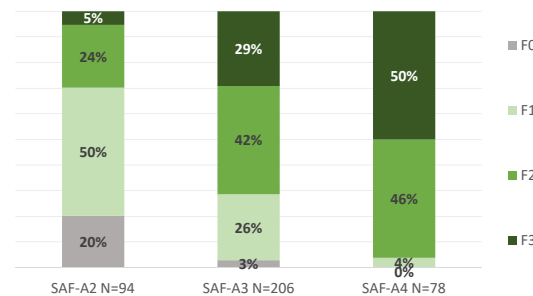
Fibrosis score	SAF-A<3 N=94	SAF-A ≥ 3 N=284	All N=378
Mean \pm SD	1.1 \pm 0.8	2.1 \pm 0.8	1.9 \pm 0.9



Comparing the subgroup SAF-A ≥ 3 with the overall population with NAS ≥ 4 (N=378), the percentage of patients with NAS ≥ 5 was 20% higher

Comparing the subgroup SAF-A ≥ 3 with the overall population with NAS ≥ 4 (N=378), the percentage of patients with F2-F3 was 12% higher

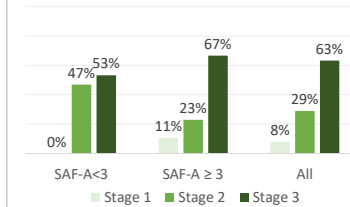
Correlation between screening SAF-Activity and Fibrosis scores



In the NATIVE Trial, there was a clear correlation between screening fibrosis severity and screening SAF-Activity score: the higher SAF-A, the higher SAF-F

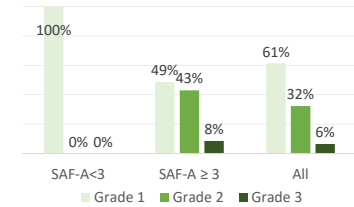
Steatosis score by SAF-A categories

Steatosis score	SAF-A<3 N=94	SAF-A ≥ 3 N=284	All N=378
Mean \pm SD	2.5 \pm 0.5	2.6 \pm 0.7	2.6 \pm 0.6



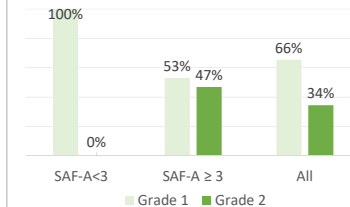
CRN-Inflammation score by SAF-A categories

CRN-I score	SAF-A<3 N=94	SAF-A ≥ 3 N=284	All N=378
Mean \pm SD	1.0 \pm 0.0	1.6 \pm 0.6	1.4 \pm 0.6



CRN-Ballooning score by SAF-A categories

CRN-B score	SAF-A<3 N=94	SAF-A ≥ 3 N=284	All N=378
Mean \pm SD	1.0 \pm 0.0	1.8 \pm 0.4	1.6 \pm 0.5



▶ Comparing the subgroup SAF-A ≥ 3 with the overall population with NAS ≥ 4 , mean steatosis score was comparable

▶ CRN-Inflammation score tended to be higher in the subgroup SAF-A ≥ 3 compared with the overall population with NAS ≥ 4

▶ Ballooning score tended to be higher in the subgroup SAF-A ≥ 3 compared with the overall population with NAS ≥ 4

4-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.

Contact information

Pr. Francque, Sven
Sven.Francque@uza.be