APPENDIX 6

LICAVIR Study Synopsis and Table Shells

LICAVIR Study Synopsis and Tables

Background

Data from different studies on the risk of de novo hepatocellular carcinoma (HCC) in direct acting antiviral (DAA) treated patients are conflicting and inconsistent. While a potential mechanism may be immune modulation resulting from the rapid decrease of the hepatitis C virus (HCV) viral load,[1] several studies from large cohorts found no evidence of an increased risk of de novo HCC in DAA-treated patients.[2-5]

Given the contemporaneous impact of liver inflammation and fibrosis, cirrhosis, duration of HCV infection, baseline patient demographics including patient age, HCV genotype, and prior treatment response associated with the development of HCC, the evaluation of the causal role of DAAs in the development of incident HCC in HCV infected patients is challenging.

The LICAVIR study was initiated by the ANRS (Agence Française de Recherches Sur Le VIH/Sida et Les Hépatites Virales)/INSERM (Institut National de la Santé et de la Recherche Médicale) and aims to study predisposing factors, clinical, biological, radiological and histological characteristics of HCC at the time of diagnosis from the data obtained from both CIRVIR and HEPATHER cohorts; HCC therapeutic procedures, prognosis and predictive factors of survival will also be analyzed.

AbbVie has engaged with the ANRS-INSERM group to obtain the results of the LICAVIR study and to present them to the Pharmacovigilance Risk Assessment Committee (PRAC) as the response to the following PRAC request: "The MAH should present the complete results of specific analyses from the HEPATHER and CIRVIR cohorts regarding the pattern of presentation of HCC cases (number, size, aggressiveness) in DAA treated and in untreated patients according to the indications presented in the PRAC Assessment Report and include them in the next PSURs."

Study Objective

To characterize the de novo HCC cases that occurred with and without DAA treatment

Study Methodology

A retrospective data collection from a cohort of patients with chronic HCV infection, who developed HCC up to the end of 2019.

A descriptive analysis of patients treated with any DAA who develop HCC after DAA initiation and patients who develop HCC without DAA treatment. No direct comparisons of treatment groups will be performed. Summary statistics were provided as mean (SD) for continuous variables, for all individuals with non-missing values, and N (%) for categorical variables.

Patient characteristics were assessed over the period from data start through 1 day prior to HCC diagnosis. For characteristics with multiple measurements or assessments (i.e., labs, fibrosis stage, etc.), the value closest but prior to HCC diagnosis was selected.

Table 1. Characteristics of Treatments

	Frequency	Achieved SVR_{12}, N (%)				Achieved SVR_{24}, N (%)				Months Since Last Treatment, Mean (SD)[a]
	N, %	Yes	No	Other[b]	Missing	Yes	No	Other[b]	Missing	
DAA	191									22 (17)
DAA only	103 (54)	85 (83)	8 (8)	1 (1)	9 (8)	70 (67)	8 (8)	1 (1)	24 (24)	20 (16)
DAA + IFN	0 (0)	-	-	-	-	-	-	-	-	-
DAA + ribavirin	78 (41)	68 (87)	6 (8)	0 (0)	4 (5)	59 (76)	7 (9)	0 (0)	12 (15)	26 (17)
DAA + IFN + ribavirin	10 (5)	8 (80)	0 (0)	0 (0)	2 (20)	8 (80)	0 (0)	0 (0)	2 (20)	23 (22)
No DAA treatment	206									46 (43)
IFN	9 (4)	0 (0)	5 (56)	1 (11)	3 (33)	1 (11)	0 (0)	1 (11)	7 (78)	31 (48)
Ribavirin	10 (5)	1 (10)	6 (60)	2 (20)	1 (10)	0 (0)	0 (0)	2 (20)	8 (80)	51 (41)
IFN + Ribavirin	16 (8)	1 (6)	5 (31)	2 (13)	8 (50)	1 (6)	0 (0)	2 (13)	13 (81)	62 (45)
Other	7 (3)	1 (14)	0 (0)	5 (72)	1 (14)	1 (14)	0 (0)	5 (72)	1 (14)	23 (16)
No treatment	114 (56)	-	-	-	-	-	-	-	-	-
DAA after HCC[c]	50 (24)	38 (76)	3 (6)	0 (0)	9 (18)	33 (66)	3 (6)	0 (0)	14 (28)	-

DAA = Direct acting antiviral; HCC = Hepatocellular Carcinoma; IFN = Interferon; SVR = Sustained viral response

a. Computed as the time (in months) between start of treatment and the date of HCC diagnosis.

b. Ongoing treatment or missing information about end of treatment.

c. For untreated patients (at the time of HCC diagnosis) who started DAA after HCC.

Table 2. Frequency of Direct Acting Antiviral therapy in the Study Population

Treatment	N (%)
DAA	191
Daclatasvir/Sofosbuvir	62 (32.46)
Daclatasvir/Sofosbuvir/Ribavirine	33 (17.28)
Simeprevir/Sofosbuvir	21 (10.99)
Sofosbuvir/Ledipasvir/Ribavirine	20 (10.47)
Sofosbuvir/Ledipasvir	14 (7.33)
Sofosbuvir/Ribavirine	13 (6.81)
Simeprevir/Sofosbuvir/Ribavirine	7 (3.66)
Interferon/Sofosbuvir/Ribavirine	6 (3.14)
Glecaprevir/Pibrentasvir/Sofosbuvir	2 (1.05)
Interferon/Simeprevir/Sofosbuvir/Ribavirine	2 (1.05)
Asunaprevir/Daclatasvir	1 (0.52)
Asunaprevir/Daclatasvir/Ribavirine	1 (0.52)
Daclatasvir/Interferon/Sofosbuvir/Ribavirine	1 (0.52)
Daclatasvir/Sofosbuvir/Telaprevir/Ribavirine	1 (0.52)
Dasabuvir/Ombitasvir/Paritaprevir/Ritonavir	1 (0.52)
Dasabuvir/Ombitasvir/Paritaprevir/Ritonavir/Ribavirine	1 (0.52)
Interferon/Sofosbuvir/Sofosbuvir/Ledipasvir/Ribavirine	1 (0.52)
Ombitasvir/Paritaprevir/Ritonavir/Ribavirine	1 (0.52)
Other/Sofosbuvir/Ledipasvir	1 (0.52)
Simeprevir/Sofosbuvir/Ledipasvir/Ribavirine	1 (0.52)
Sofosbuvir/Velpatasvir	1 (0.52)

Note: These groups are not mutually exclusive and may include combination of therapy and/or multiple rounds of therapy.

Table 3. Patient Characteristics at Time of Hepatocellular Carcinoma Diagnosis, With and Without Prior Direct Acting Antiviral Treatment, in the LICAVIR Study Population

Baseline Characteristics	All Patients (N = 397)	DAA Treated (N = 191)	DAA Untreated (N = 206)
Cohort, N (%)			
Hepather	302 (76)	178 (93)	124 (60)
Cirvir	39 (10)	1 (1)	38 (19)
Hepather and Cirvir	56 (14)	12 (6)	44 (21)
Gender, N (%)			
Male	305 (77)	152 (80)	153 (74)
Female	92 (23)	39 (20)	53 (26)
Age, mean (SD) years	62 (10)	62 (9)	62 (10)
Country of origin, N (%)			
France	254 (64)	131 (69)	123 (60)
North Africa	38 (10)	18 (9)	20 (10)
Sub-Saharan Africa	24 (6)	10 (5)	14 (7)
Europe	68 (17)	27 (14)	41 (20)
Asia	10 (3)	5 (3)	5 (2)
North America	1 (0)	0 (0)	1 (0)
Missing	2 (0)	0 (0)	2 (1)
BMI, mean (SD) kg/m^2	26 (4)	26 (4)	26 (4)
Missing	7	1	6
Diabetes, N (%)			
YES	92 (23)	46 (24)	46 (22)
NO	289 (73)	135 (71)	154 (75)
Missing	16 (4)	10 (5)	6 (3)
Dyslipidemia, N (%)			
YES	30 (8)	12 (6)	18 (9)
NO	349 (88)	167 (88)	182 (88)
Missing	18 (4)	12 (6)	6 (3)
Past history of cardiovascular events, N (%)			
YES	35 (9)	13 (7)	22 (11)
NO	362 (91)	178 (93)	184 (89)

Baseline Characteristics	All Patients (N = 397)	DAA Treated (N = 191)	DAA Untreated (N = 206)
Arterial Hypertension, N (%)			
YES	2 (0)	2 (1)	0 (0)
NO	385 (97)	185 (97)	200 (97)
Missing	10 (3)	4 (2)	6 (3)
HIV co-infection, N (%)			
YES	1 (0)	0 (0)	1 (0)
NO	396 (100)	191 (100)	205 (100)
Missing	0 (0)	0 (0)	0 (0)
HBV co-infection, N (%)			
YES	6 (2)	2 (1)	4 (2)
NO	391 (98)	189 (99)	202 (98)
Past excessive alcohol intake[a], N (%)			
YES	82 (21)	46 (24)	36 (17)
NO	301 (76)	143 (75)	158 (77)
Missing	14 (3)	2 (1)	12 (6)
Ongoing alcohol consumption, N (%)			
YES	140 (35)	68 (36)	72 (35)
NO	243 (61)	121 (63)	122 (59)
Missing	14 (4)	2 (1)	12 (6)
Injection drug use, N (%)			
Past	7 (2)	1 (1)	6 (3)
Ongoing	1 (0)	0 (0)	1 (0)
Never	99 (25)	57 (30)	42 (21)
Missing	290 (73)	133 (69)	157 (76)
Smoking, N (%)			
Past	131 (33)	63 (33)	68 (33)
Ongoing	148 (37)	74 (39)	74 (36)
Never	117 (30)	53 (27)	64 (31)
Missing	1 (0)	1 (1)	0 (0)
Past history of extrahepatic cancer, N (%)			
YES	38 (10)	18 (9)	20 (10)
NO	359 (90)	173 (91)	186 (90)

Baseline Characteristics	All Patients (N = 397)	DAA Treated (N = 191)	DAA Untreated (N = 206)
Signs of Portal hypertension, N (%)			
YES	56 (14)	30 (16)	26 (13)
NO	268 (68)	125 (65)	143 (69)
Missing	73 (18)	36 (19)	37 (18)
Gastroesophageal varices[b], N (%)			
YES	45 (11)	27 (14)	18 (9)
NO	320 (81)	146 (77)	174 (84)
Missing	32 (8)	18 (9)	14 (7)
Thrombocytopenia, N (%)			
YES	5 (1)	4 (2)	1 (0)
NO	332 (84)	180 (94)	152 (74)
Missing	60 (15)	7 (4)	53 (26)
LSE by TE ≥ 20-25 kPa			
YES	113 (28)	66 (35)	47 (23)
NO	282 (71)	124 (64)	158 (77)
Missing	2 (1)	1 (1)	1 (0)
Imaging showing collateral circulation, N (%)			
YES	27 (7)	11 (6)	16 (8)
NO	368 (93)	179 (93)	189 (92)
Missing	2 (0)	1 (1)	1 (0)
Fibrosis stage, N (%)			
F0	0 (0)	0 (0)	0 (0)
F1	3 (1)	2 (1)	1 (0)
F2	7 (2)	2 (1)	5 (3)
F3	42 (11)	15 (8)	27 (13)
F4	173 (43)	76 (40)	97 (47)
Missing	172 (43)	96 (50)	76 (37)

Baseline Characteristics	All Patients (N = 397)	DAA Treated (N = 191)	DAA Untreated (N = 206)
In F4/cirrhotic patients, Child-Pugh-Turcotte Classification, N (%)	173 (43)	76 (40)	97 (47)
Child-Pugh A	107 (62)	49 (64)	58 (60)
Child-Pugh B	18 (10)	7 (9)	11 (11)
Child-Pugh C	6 (4)	5 (7)	1 (1)
Missing	42 (24)	15 (20)	27 (28)
MELD score (mean, SD)	30 (10)	31 (10)	29 (10)
Missing for MELD	21 (5)	3 (2)	18 (9)
History of prior hepatic decompensation[c], N (%)			
YES	103 (26)	60 (31)	43 (21)
NO	294 (74)	131 (69)	163 (79)
Laboratory testing			
HCV genotype, N (%)			
Genotype 1	229 (58)	113 (59)	116 (56)
Genotype 2	17 (4)	8 (4)	9 (4)
Genotype 3	74 (19)	47 (25)	27 (13)
Genotype 4	30 (7)	18 (9)	12 (6)
Genotype 5	7 (2)	4 (2)	3 (2)
Genotype 6	1 (0)	1 (1)	0 (0)
Missing	39 (10)	0 (0)	39 (19)
Serum albumin g/dL, mean (SD)	4 (1)	4 (1)	4 (1)
Missing	82 (21)	32 (17)	50 (24)
Platelet count $10^3/mm^3$, mean (SD)	144 (77)	144 (83)	143 (71)
Missing	43 (11)	9 (5)	34 (17)
Prothrombin time %, mean (SD)	81 (16)	80 (17)	82 (16)
Missing	49 (12)	19 (10)	30 (15)
INR (no units), mean (SD)	1 (0.3)	1 (0.3)	1 (0.2)
Missing	101 (25)	33 (17)	68 (33)
Total bilirubin µmol/L, mean (SD)	376 (550)	390 (691)	349 (362)
Missing	46 (12)	16 (8)	30 (15)
Alpha-fetoprotein ng/mL, mean (SD)	43 (172)	17 (56)	68 (227)
Missing	80 (20)	39 (20)	41 (20)

Baseline Characteristics	All Patients (N = 397)	DAA Treated (N = 191)	DAA Untreated (N = 206)
AST U/L, mean (SD)	76 (109)	66 (122)	85 (94)
Missing	35 (9)	15 (8)	20 (10)
ALT U/L, mean (SD)	59 (80)	49 (91)	69 (67)
Missing	31 (8)	12 (6)	19 (9)
HBsAg, N (%)			
YES	22 (6)	2 (1)	20 (10)
NO	1 (0)	0 (0)	1 (0)
Missing	374 (94)	189 (99)	185 (90)

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; BMI = Body mass index; DDA = Direct-acting antiviral; HBV = Hepatitis B virus; HBsAG = Hepatitis B surface antigen; HCV = Hepatitis C virus; HIV = Human immunodeficiency virus; INR = International normalized ratio; LSE = liver stiffness evaluation; MELD = Model end stage liver disease; TE = transient elastography

a. Constructed as abstinent with a past consumption of more than 2 glasses per day for females and more than 3 glasses per day for males.

b. Constructed as gastric varices or esophageal varices or both.

c. Defined as the development of ascites, variceal haemorrhage, encephalopathy, jaundice, or combination of these.

Table 4. Characteristics of the Hepatocellular Carcinoma Cases

Characteristics	All Patients	DAA Treated	DAA Untreated
Number of patients with HCC	397	191	206
Child-Pugh classification	173 (43)	76 (40)	97 (47)
A	107 (62)	49 (64)	58 (60)
B	18 (10)	7 (9)	11 (11)
C	6 (4)	5 (7)	1 (1)
Missing	42 (24)	15 (20)	27 (28)
Diagnostic method used, %			
CT	114 (29)	56 (29)	58 (28)
MRI	179 (45)	88 (46)	91 (44)
contrast-enhanced ultrasound	57 (14)	22 (12)	35 (17)
biopsy	13 (3)	7 (4)	6 (3)
other	34 (9)	18 (9)	16 (8)
Number of nodules, %			
1	236 (59)	116 (61)	120 (58)
2 – 3 nodules	92 (23)	45 (24)	47 (23)
> 3 nodules	46 (12)	18 (9)	28 (14)
missing	23 (6)	12 (6)	11 (5)
Diameter of largest nodule, mm, n (%)			
≤ 20	161 (41)	84 (44)	77 (37)
21 – 30	88 (22)	43 (23)	45 (22)
31 – 50	64 (16)	24 (13)	40 (20)
> 50	30 (8)	15 (7)	15 (7)
missing	54 (15)	25 (13)	29 (14)
Portal invasion, n (%)			
Yes	60 (15)	30 (16)	30 (15)
No	310 (78)	146 (76)	164 (80)
missing	27 (7)	15 (8)	12 (5)
Milan criteria			
Within Milan criteria, n (%)	55 (14)	34 (18)	21 (10)
1 nodule ≤ 50 mm	42 (76)	28 (82)	14 (67)
2 or 3 nodules ≤ 30 mm	13 (24)	6 (18)	7 (33)

Characteristics	All Patients	DAA Treated	DAA Untreated
Outside Milan criteria, n (%)	311 (78)	134 (70)	177 (86)
Missing	31 (8)	23 (12)	8 (4)
Days between last imaging examination and HCC diagnosis, mean (SD)	397 (526)	351 (355)	424 (610)
Missing	78 (20)	32 (17)	46 (22)
Number of screening exams before HCC diagnosis, mean (SD)	1 (1)	1 (1)	1 (1)
Missing	1 (0)	0 (0)	1 (0)
Extrahepatic spread, n (%)			
YES	25 (6)	16 (8)	9 (4)
NO	349 (88)	162 (85)	187 (91)
Missing	23 (6)	13 (7)	10 (5)
Intervention for HCC treatment	308 (78)	163 (85)	145 (70)
Curative treatment, N (%)	196 (64)	103 (63)	93 (64)
Transplantation	34 (17)	22 (21)	12 (13)
Resection	60 (31)	30 (29)	30 (32)
Ablation	11 (6)	9 (9)	2 (2)
Percutaneous	51 (26)	26 (25)	25 (27)
Radiotherapy	30 (15)	15 (15)	15 (16)
Percutaneous + Resection	2 (1)	0 (0)	2 (2)
Percutaneous + Radiotherapy	8 (4)	1 (1)	7 (8)
Palliative treatment, N (%)	110 (36)	59 (36)	51 (35)
TACE	40 (36)	22 (37)	18 (35)
Systemic therapy, 1st line	53 (48)	26 (44)	27 (53)
Systemic therapy, 2nd line	1 (1)	1 (2)	0 (0)
Radio embolisation	15 (14)	10 (17)	5 (10)
Radio embolisation + TACE	1 (1)	0 (0)	1 (2)
Curative & Palliative treatment, N (%)	2 (0)	1 (1)	1 (1)
Percutaneous + TACE	2 (100)	1 (100)	1 (100)
Missing	89 (22)	28 (15)	61 (30)

Characteristics	All Patients	DAA Treated	DAA Untreated
AFP levels at HCC diagnosis µg/L, mean (SD)[a]	78 (184)	58 (150)	98 (218)
Missing	313 (79)	175 (92)	138 (67)
Imaging examinations performed during follow-up in HCC, N (%)	237 (60)	110 (58)	127 (62)
Survival in months, mean (SD)			
Overall[b]	18 (10)	16 (11)	20 (15)
Missing	0 (0)	0 (0)	0 (0)
Progression-free (in months)[c]	10 (13)	11 (11)	9 (16)
Missing	177 (45)	88 (46)	89 (43)
Days until progression Mean (SD)[d]	374 (309)	405 (339)	344 (279)
Death, N (%)			
YES	92 (23)	42 (22)	50 (24)
NO	305 (77)	149 (78)	156 (76)
Hepatic decompensation, N (%)			
YES	58 (15)	39 (20)	19 (9)
NO	339 (85)	152 (80)	187 (91)

AFP = Alpha fetoprotein; CT = Computed tomography; DAA = Direct-acting antiviral; HCC = Hepatocellular Carcinoma; MRI = Magnetic resonance imaging; TACE = Transarterial chemoembolization

a. Status or value within 6 months before the date of HCC diagnosis.

b. Computed as time between HCC diagnosis and death or the last follow-up visit.

c. Computed as time between start of HCC treatment and progression of disease (response of treatment equal progression) or death or last follow-up visit.

d. Computed as time in days between start of treatment and disease progression

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