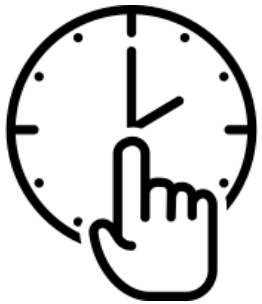
Optimization of the therapy of Primary Biliary Cholangitis

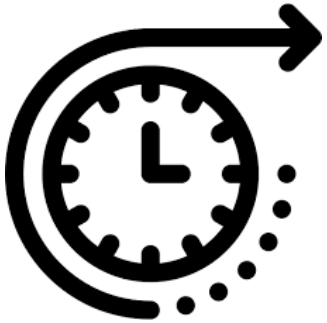
Nora Cazzagon

Dipartimento di Scienze Chirurgiche, Oncologiche e Gastroenterologiche, Università degli Studi di Padova

Agenda

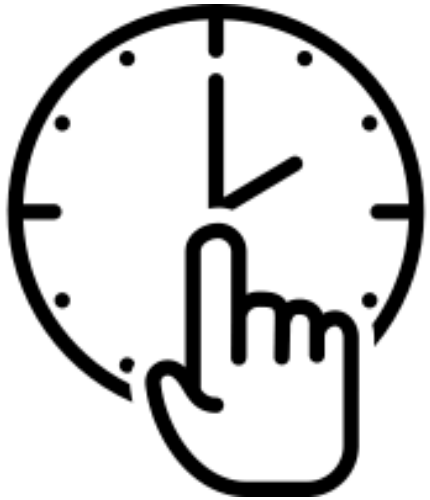


- **Ottimizzare la terapia di prima e seconda linea nella PBC**



- **Novità dagli studi di fase 3 con PPAR agonisti**
- **Studi sperimentali in corso**

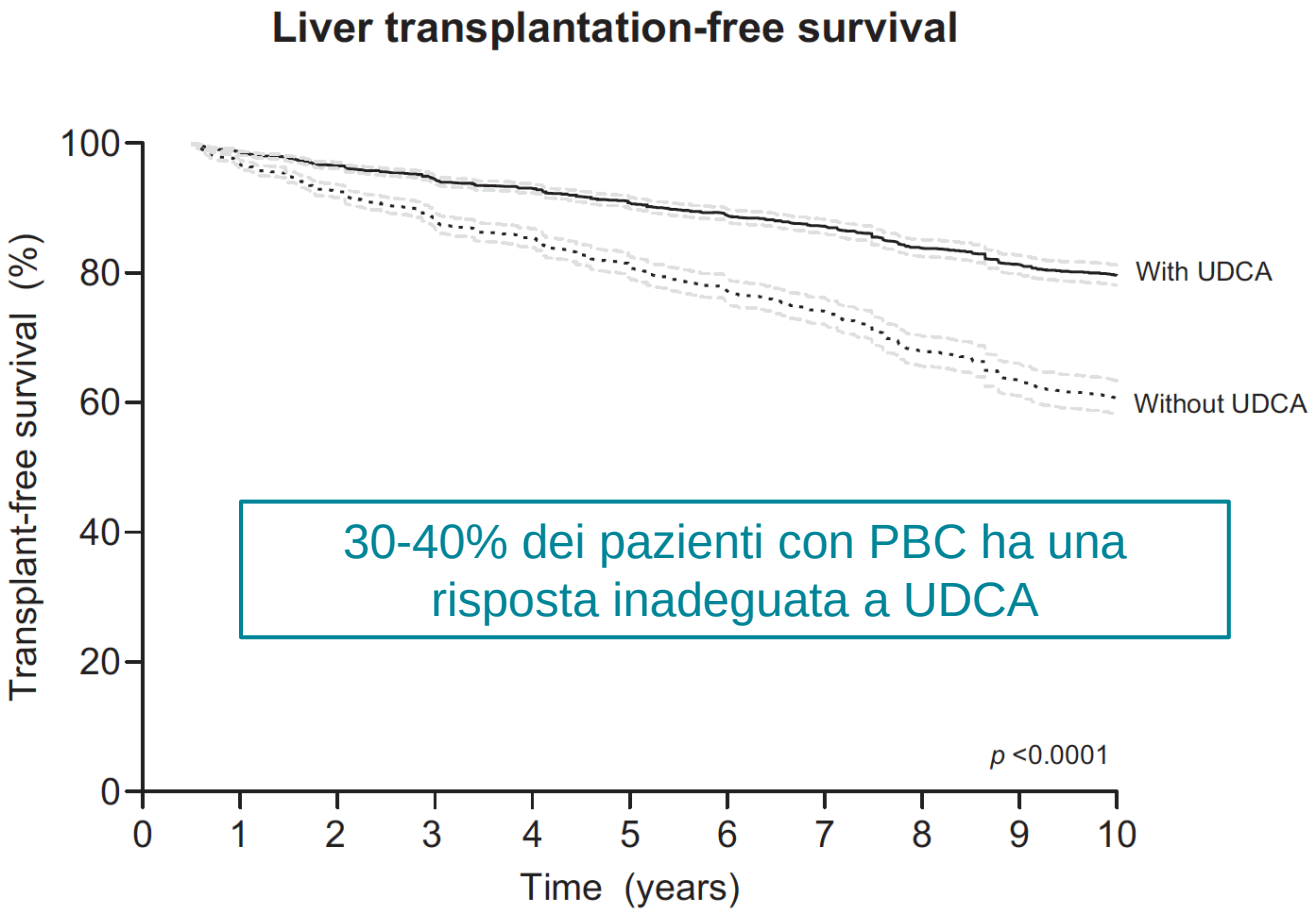
Ottimizzare la terapia di prima e seconda linea nella PBC



UDCA

UDCA : 13-15 mg/Kg/die

N. 3902 pazienti
con PBC

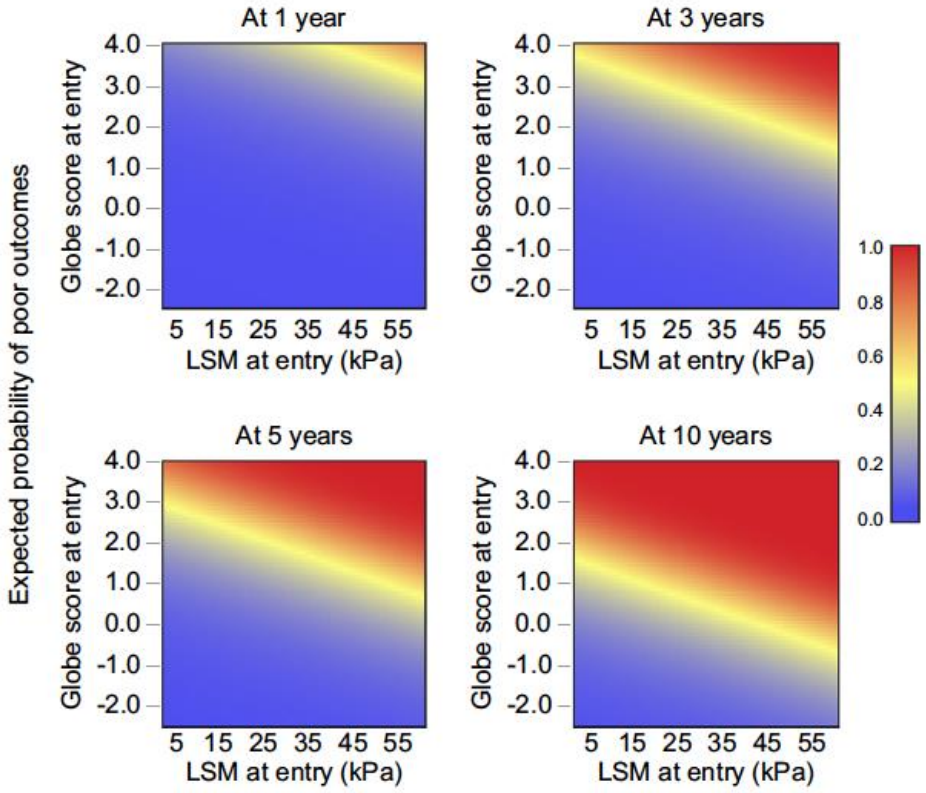


30-40% dei pazienti con PBC ha una risposta inadeguata a UDCA

Harms *et al*, J Hepatol 2019

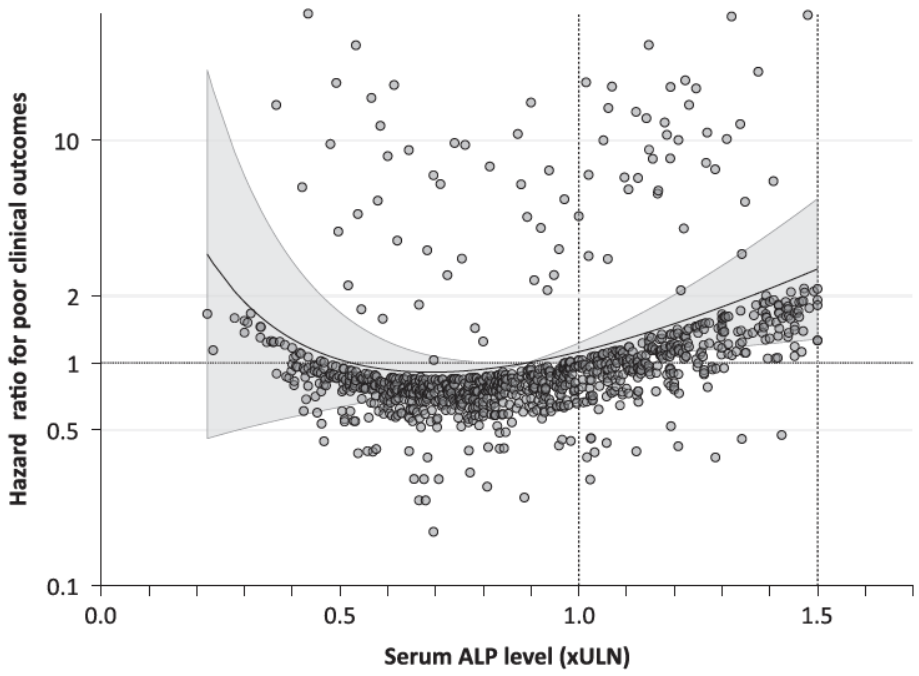
Definire la risposta incompleta a UDCA

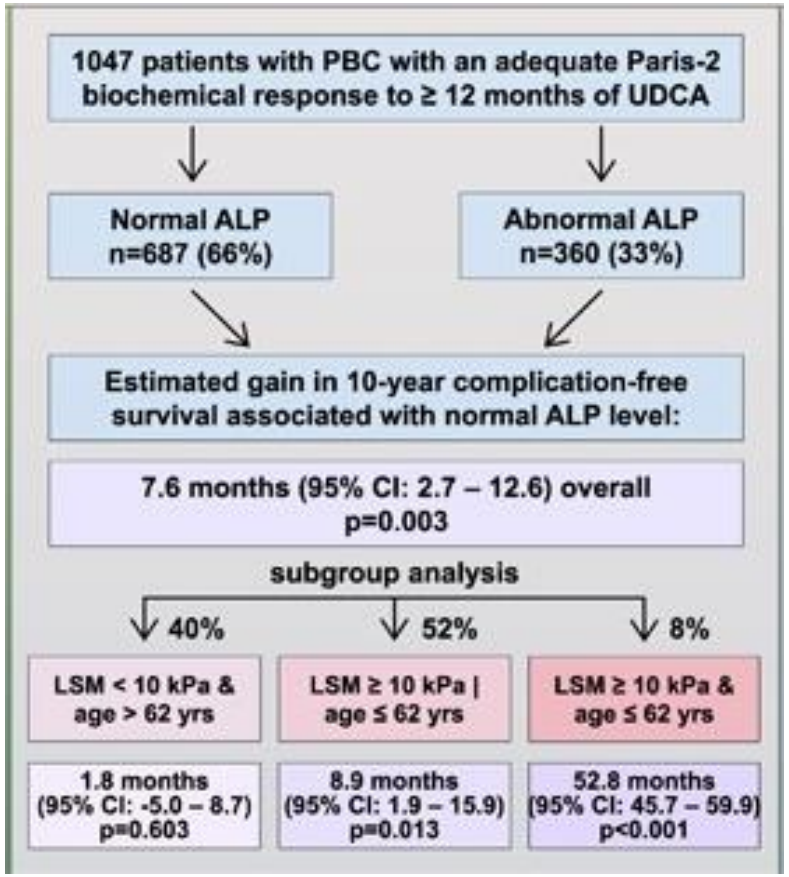
- Definizioni binarie e score continui
- Fosfatasi alcalina (ALP)
  - ALP> 1.5 x ULN nonostante UDCA
- Bilirubina
  - > 1.0 x ULN
  - < 0.6 x ULN è protettiva
- Età
  - Pazienti giovani outcome peggiore
- <u>Fibrosi valutata tramite VCTE</u>



EASL CPG PBC J Hepatol 2017; Murillo-Perez *et al,* Am J Gastroenterol 2020
Corpechot *et al,* J Hepatol 2022

Adequate vs. Deep response to UDCA





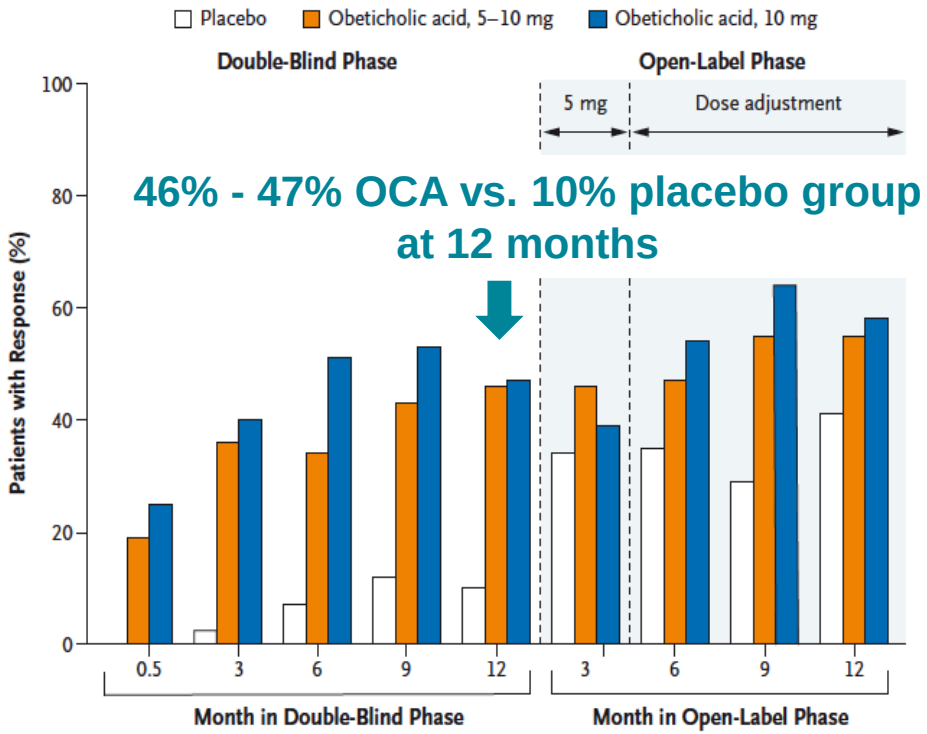
Corpechot *et al,* Hepatology 2024

Management dei pazienti con risposta inadeguata a UDCA

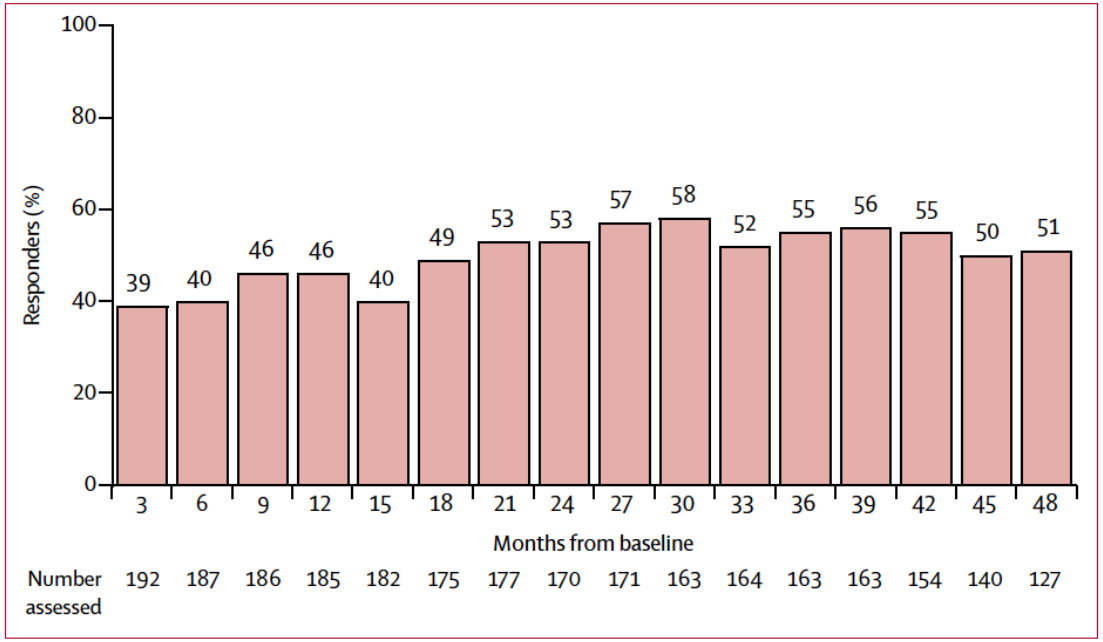
- Osservazione (pazienti anziani e/o comorbidità significative)
- Ottimizzare il dosaggio di UDCA (aumento di peso corporeo, risultati controversi 28-32 mg/Kg)
- Avvio della terapia di II° linea
  - Acido obeticolico
  - Fibrati* off label per CBP
  - OCA + Fibrati* off label per CBP
- Trial clinici

Acido obeticolico (OCA): studio POISE e OLE

Endpoint primario (POISE criteria)
ALP < 1.67 x ULN e riduzione di ALP di almeno 15% rispetto al basale e bilirubina < 1x ULN



POISE response to OCA in OLE



Nevens *et al,* NEJM 2016
Trauner *et al*, Lancet Gastroenterol Hepatol 2019

OCA negli outcome a lungo termine: studio COBALT

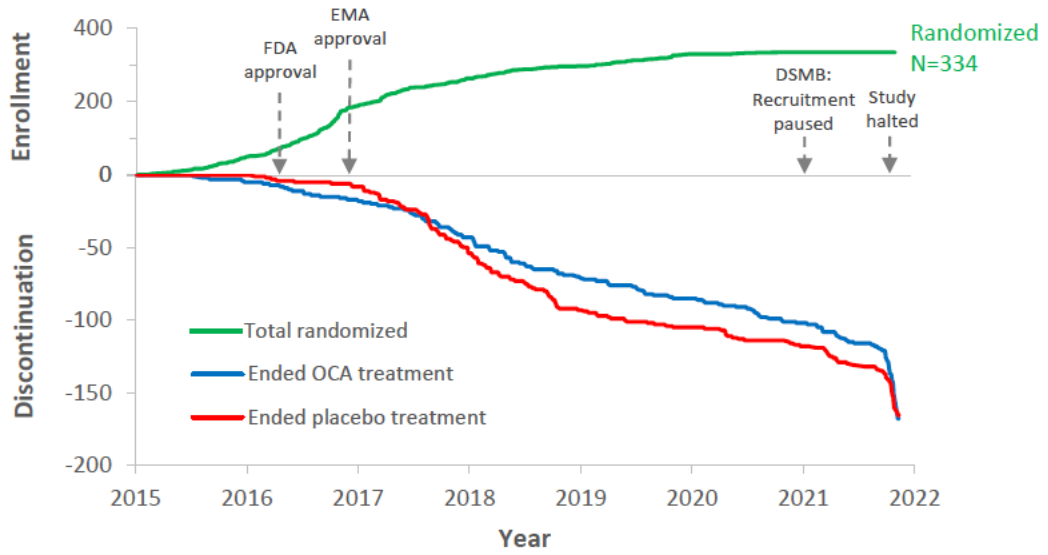
The Challenge of Confirmatory Trials in Rare Disease: Lessons Learned From the COBALT Trial in Primary Biliary Cholangitis

Kris V. Kowdley[1]; Darren Wheeler[2]; Elizabeth S. Malecha[2]; Nora Cazzagon[3]

[1]Liver Institute Northwest and Elson S. Floyd College of Medicine, Washington State University, Seattle, WA, USA; [2]Intercept Pharmaceuticals, Morristown, New Jersey, USA; [3]Department of Surgery, Oncology and Gastroenterology, University of Padova, Italy

Poster 4578-C

Figure 1. Patient recruitment and retention in the COBALT trial over time



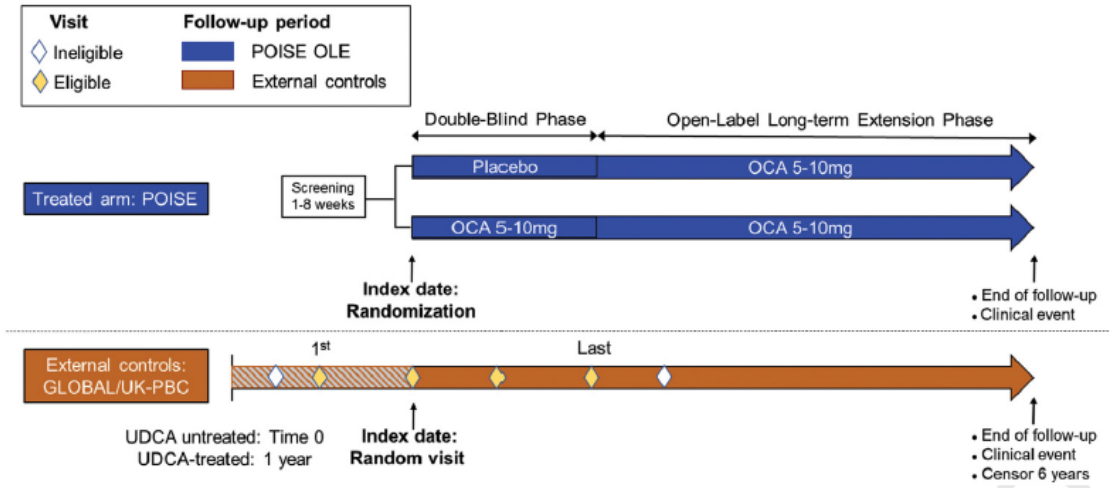
Abbreviations: DSMB, data safety monitoring board; EMA, European Medicines Agency; FDA, US Food and Drug Administration; OCA, obeticholic acid.

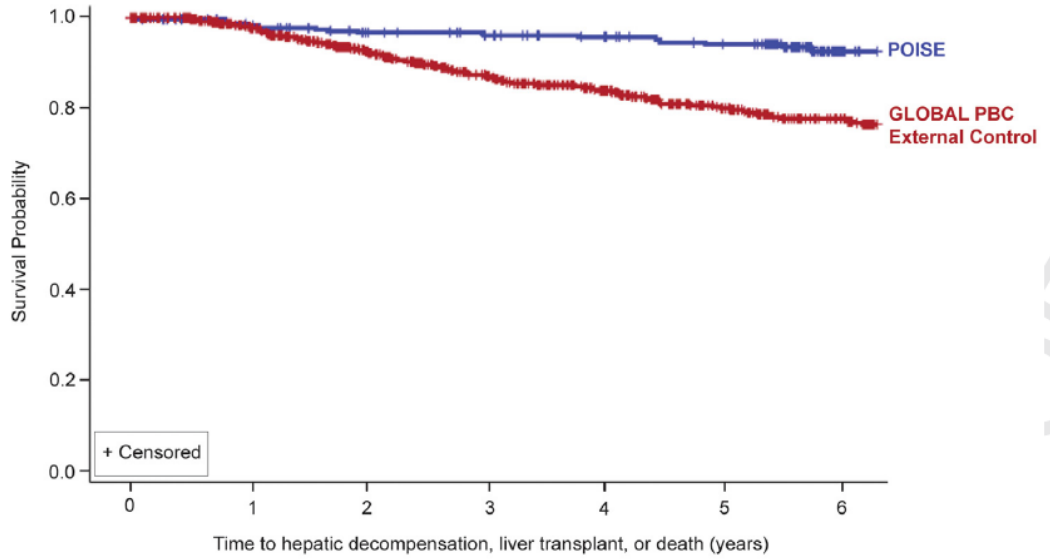
Conclusions

- In this long-term outcomes study, different trends in ALP levels between the two treatment arms led to functional unblinding and treatment crossover in the placebo group
- This compromised assessment of the primary study objective and biased the results
- Alternative study designs, including real–world-based approaches, such as external control arms and patient registry analyses, are needed to assess the efficacy/effectiveness of important therapies in rare diseases

Kowdley *et al*, AASLD 2023 Poster 4578

OCA e sopravvivenza libera da trapianto: studio COPEC





FIRST EVENT	POISE (n=16)	Global PBC (n=212)
Decompensation	12	126
Liver Transplant*	1	23
Death	3	63

Murillo Perez, Fisher *et al*, Gastroenterology 2022

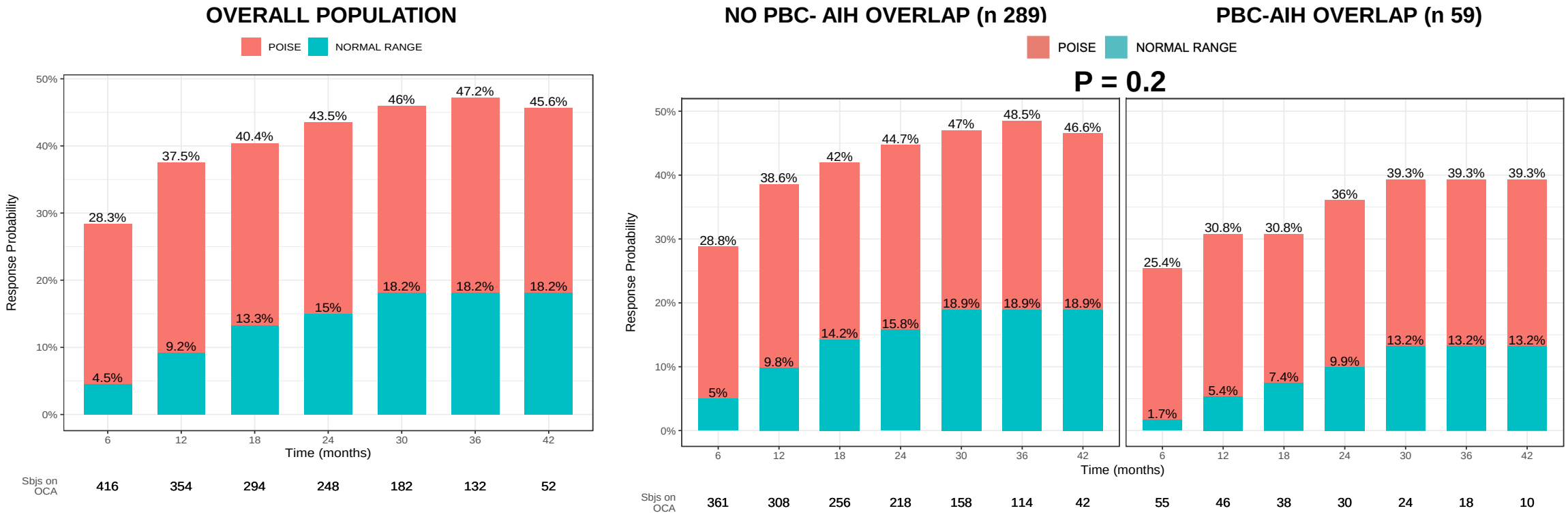
Efficacia e sicurezza di OCA nel real life

				
Number of patients	36	191	100 (cirrhotic)	78
OCA duration (months)	12	12	12	12
POISE response	18%	51.9%	32%	29.5%
OCA discontinuation	17%	17%	22%	12%
Reason for discontinuation	45.5% pruritus 19% hepatic SAE	66% pruritus 9% hepatic SAE	46% pruritus 41% hepatic SAE	71% pruritus 21% hepatic SAE

Roberts *et al.* Hepatol Commun 2020; D'Amato, De Vincentis *et al.* JHEP Reports 2021;
De Vincentis, D'Amato *et al*, Liv Int 2022; Gomez *et al.* Aliment Pharmacol Ther 2021

Efficacia di OCA su endpoint primari e secondari

Popolazione in studio: 441 pazienti con PBC

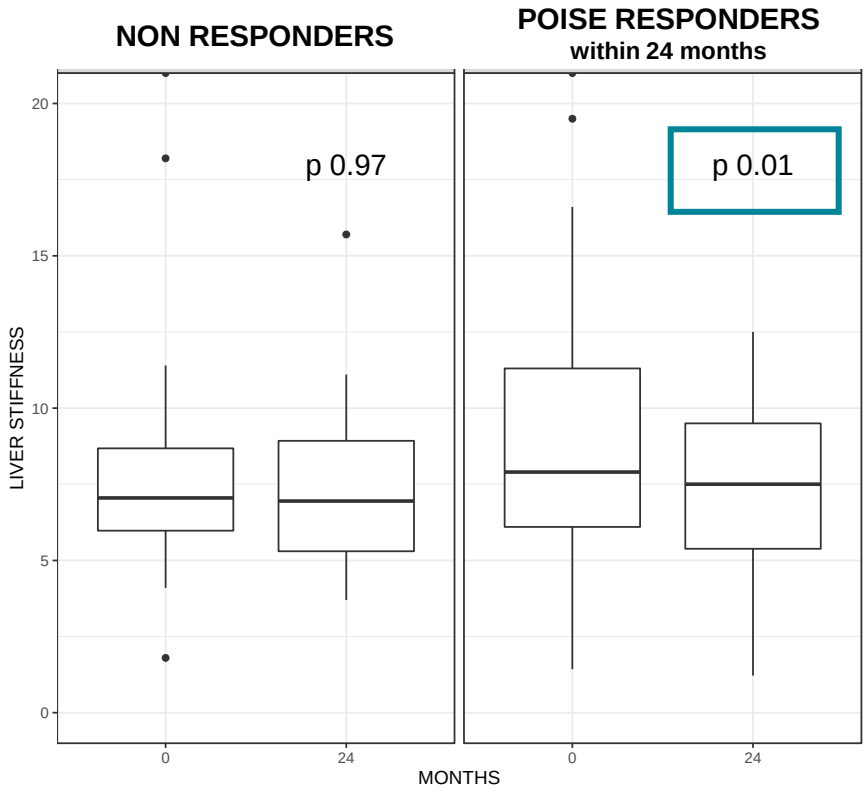


Courtesy Dr. Francesca Terracciani, UNICAMPUS Roma

Oral presentation, ILC 2023 Vienna

Stiffness epatica (VCTE) al basale e a 24 mesi dall'avvio di OCA

66 patients
- **41** responders
- **28** non-responders



Courtesy Dr. Francesca Terracciani, UNICAMPUS Roma

Oral presentation, ILC 2023 Vienna

OCA Response Score

OCA Response Score (ORS)

To estimate the probability of response of patients with Primary Biliary Cholangitis treated with Obeticholic Acid.

DERIVATION COHORT
RECAPITULATE cohort N 441

COX PROPORTIONAL REGRESSION MODELS
Reduced Model with backward selection (ORS)
ORS + ALP/ULN and bilirubin 6 months (ORS+)

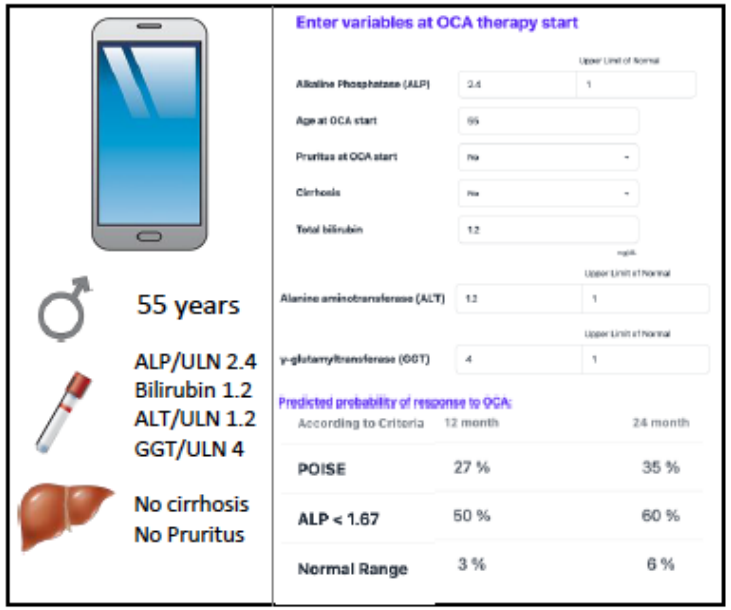
EXTERNAL VALIDATION
IBER-PBC cohort (N 244)

DISCRIMINATION (c-statistics)

	POISE		ALP/ULN<1.67		NORMAL RANGE	
	ORS	ORS+	ORS	ORS+	ORS	ORS+
DERIVATION	0.75	0.83	0.78	0.88	0.72	0.81
VALIDATION	0.70	0.80	0.72	0.84	0.71	0.78

ONLINE CALCULATOR

https://ocaresponsescore.github.io/calculator/



Clinical Gastroenterology and Hepatology

De Vincentis et al, CGH 2024 in press

Cause di discontinuazione di OCA

Reason OCA discontinuation	N 86
Pruritus	41
Hepatic Severe Adverse Events (SAE)	19
Lack of efficacy	6
Pregnancy	2
Abdominal pain	2
Amenorrea	1
Anemia	1
Complication after hip fracture	1
Covid19 pandemic	1
Demyelinating disease	1
Dizzying syndrome	1
FDA warning	1
Headache	1
Cerebrovascular event	1
Intolerance	1
Myalgia	1
Ophthalmological toxicity	1
Liver transplantation for severe pruritus	1
Skin reactions	1
Spontaneously, covid related fear	1
Swelling of hand and asthenia	1

Hepatic SAE	n(19)
Decompensation (ascites, GI bleeding, EPS)	10 (10 cirrhotics)
Worsening liver function (jaundice)	8 (7 cirrhotics)
Worsening liver enzymes	1 (non cirrhotic)

Courtesy Dr. Francesca Terracciani, UNICAMPUS Roma

Oral presentation, ILC 2023 Vienna

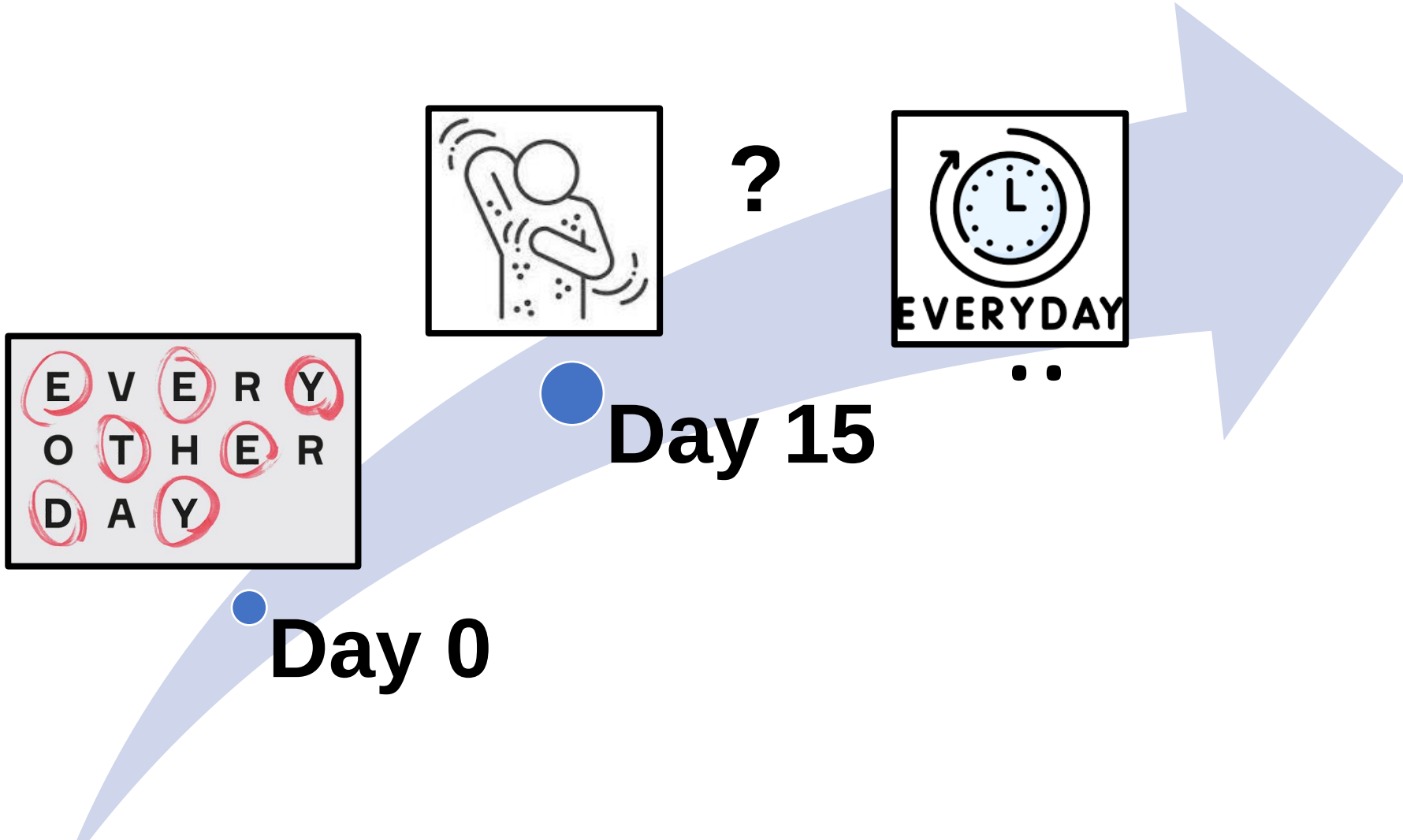
Impatto di OCA nei sintomi e QoL

Assessment of the effect of obeticholic acid on:

1. Biochemistry
2. Liver stiffness
3. Symptoms
4. Health related Quality of Life
5. Illness perception

Rollo,.. Cazzagon AISF 2023,

Padua protocol for OCA



Padua protocol for OCA

Baseline → 6 months → 12 months → 18 months → 24 months → 30 months → 36 months …

Liver function tests (LFTs)
Lipids, Blood cell count

Physical examination, clinical outcomes
General well-being
Adverse events
Symptoms and QoL: Scale 5-D, PBC-40, VAS, Fatigue Impact Scale, Euro-QoL 5D-5L

Liver stiffness by VCTE

Liver stiffness by VCTE

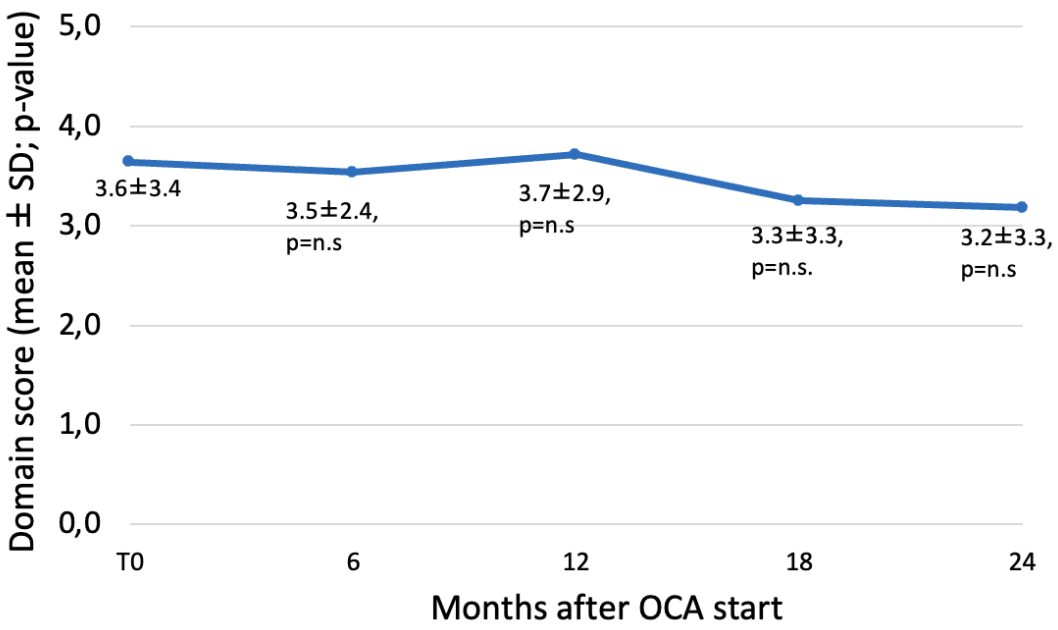
Liver stiffness by VCTE

Liver stiffness by VCTE

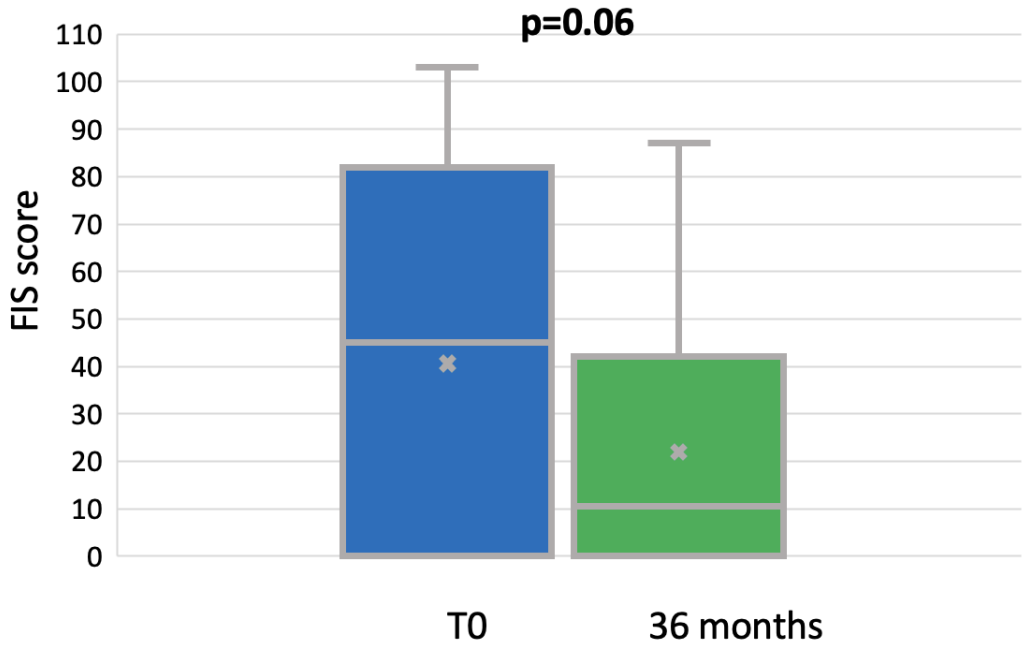
Rollo,.. Cazzagon AISF 2023,

Effetto di OCA sui sintomi della PBC

Itch domain of PBC-40



Fatique Impact Scale (FIS)

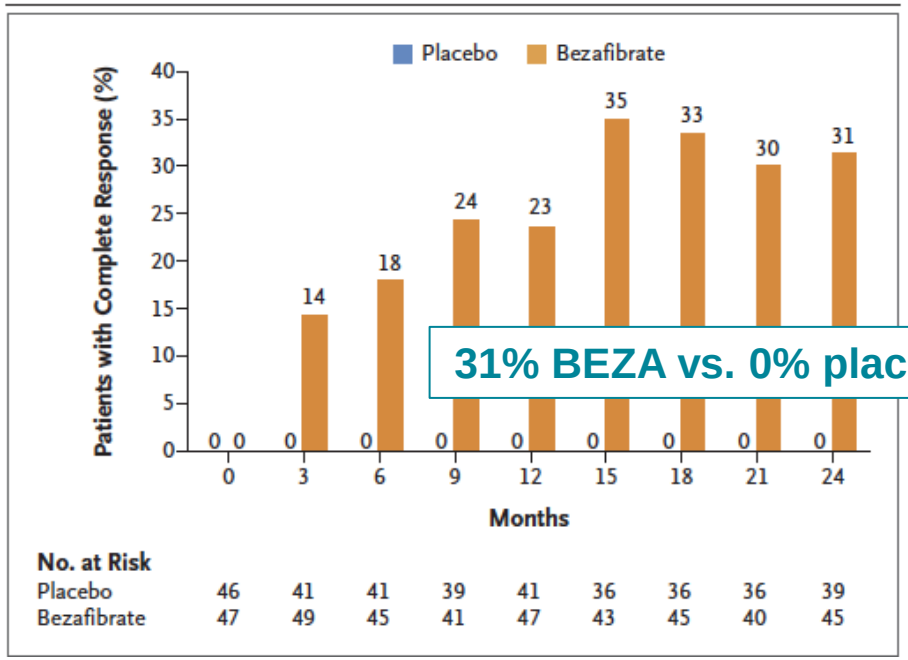


Three patients reported new onset of pruritus of mild intensity.

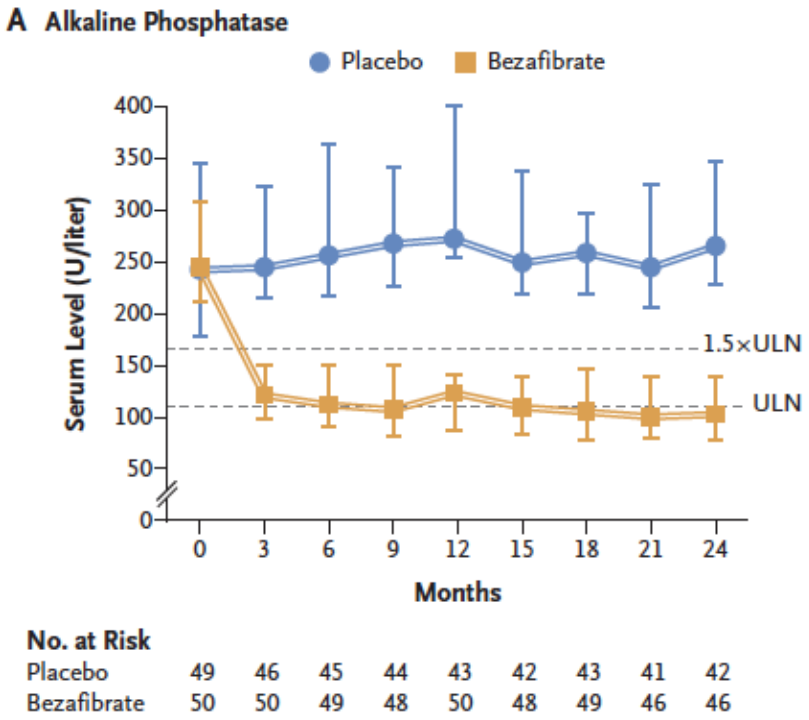
Rollo,.. Cazzagon AISF 2023,

Bezafibrato* nella PBC: studio BEZURSO

Endpoint: risposta completa (normalizzazione di ALP, bil. tot, transaminasi, albumina e PT).



31% BEZA vs. 0% placebo



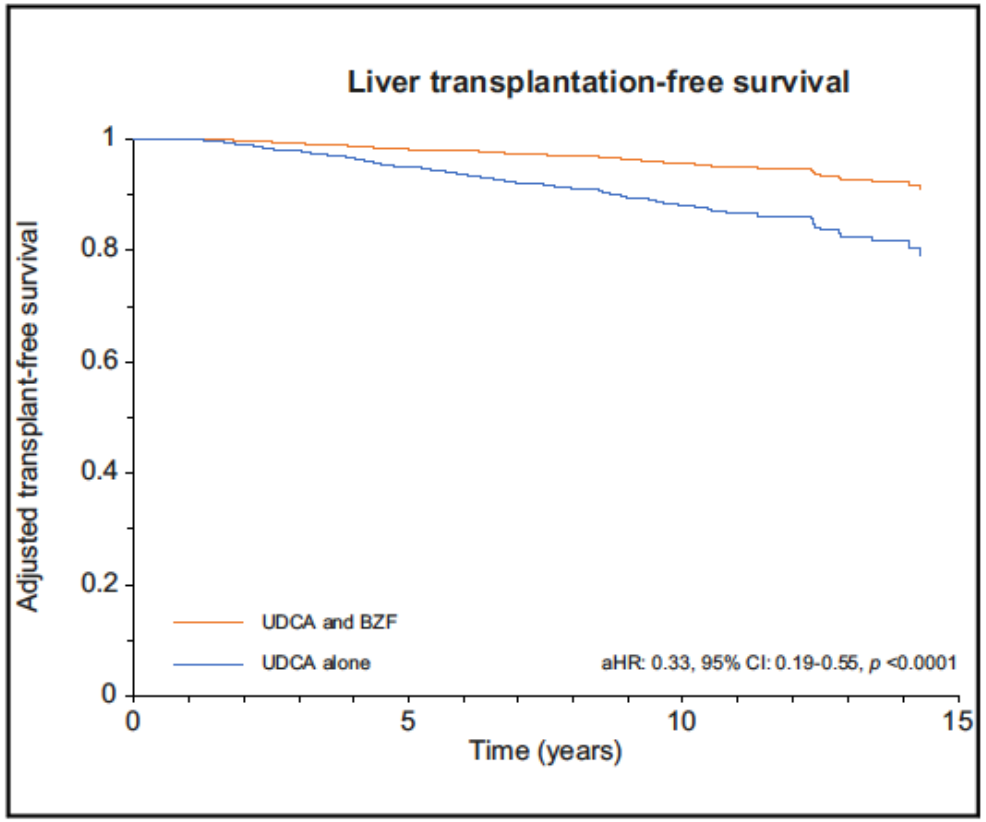
*off-label per PBC

Corpechot *et al*, NEJM 2018

Bezafibrato* e sopravvivenza libera da trapianto

Highlights

- Long-term efficacy of second-line therapies for PBC (obeticholic acid, bezafibrate) remains to be established.
- In Japan, bezafibrate has been used since 2000 as a *de facto* second-line treatment for UDCA-resistant PBC.
- In this large Japanese retrospective cohort study (n = 3,908), addition of bezafibrate to UDCA was associated with improved transplant-free survival.
- Bezafibrate is currently the only drug in PBC demonstrating efficacy in improving symptoms, biochemical markers, and prognosis.



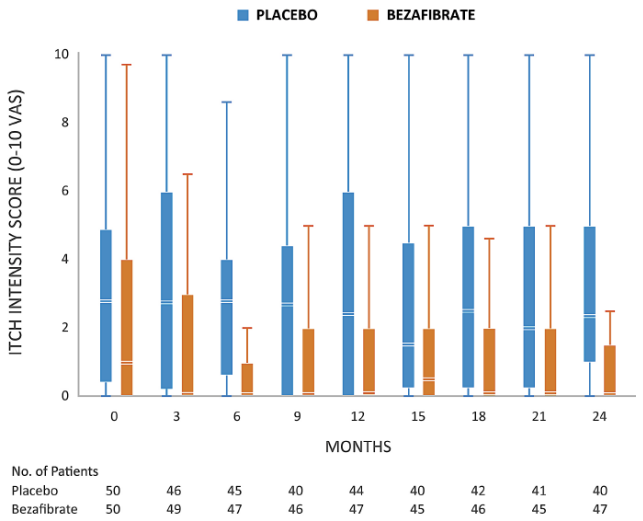
*off-label per PBC

Tanaka *et al*, J Hepatol 2021

Bezafibrato nel prurito della PBC: studi BEZURSO e FITCH

The BEZURSO trial

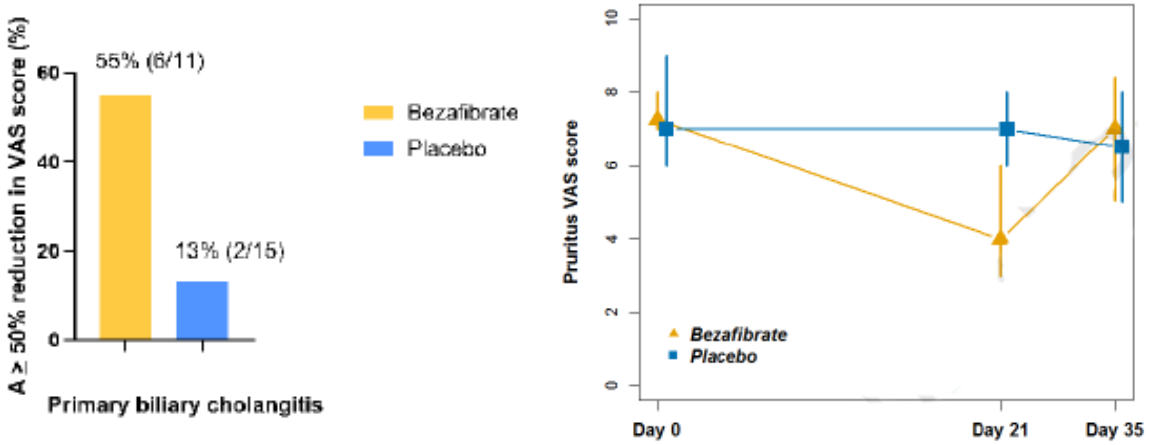
Figure S5. Itch intensity score



No. of Patients									
Placebo	50	46	45	40	44	40	42	41	40
Bezafibrate	50	49	47	46	47	45	46	45	47

Riduzione dell'intensità del prurito a 24 mesi associata a bezafibrato
-95% [-241%; 50%]

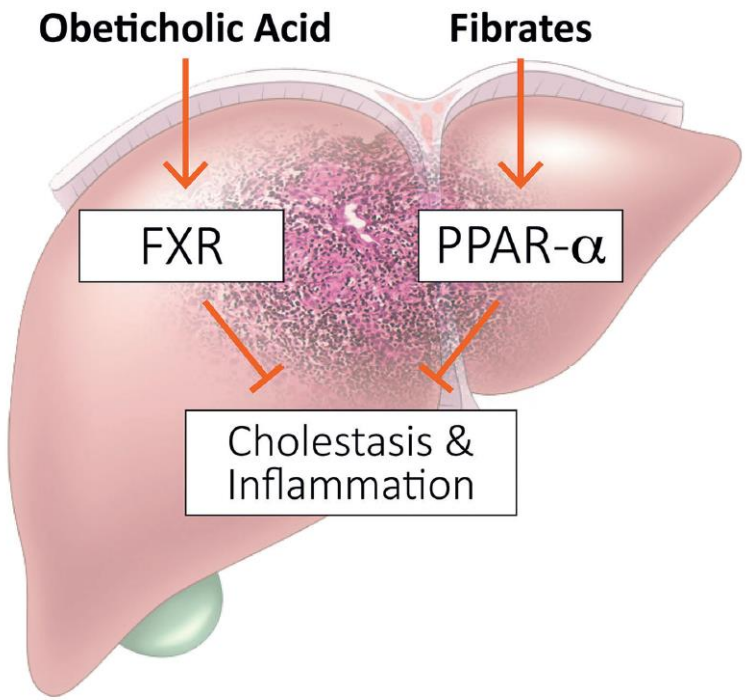
The FITCH trial

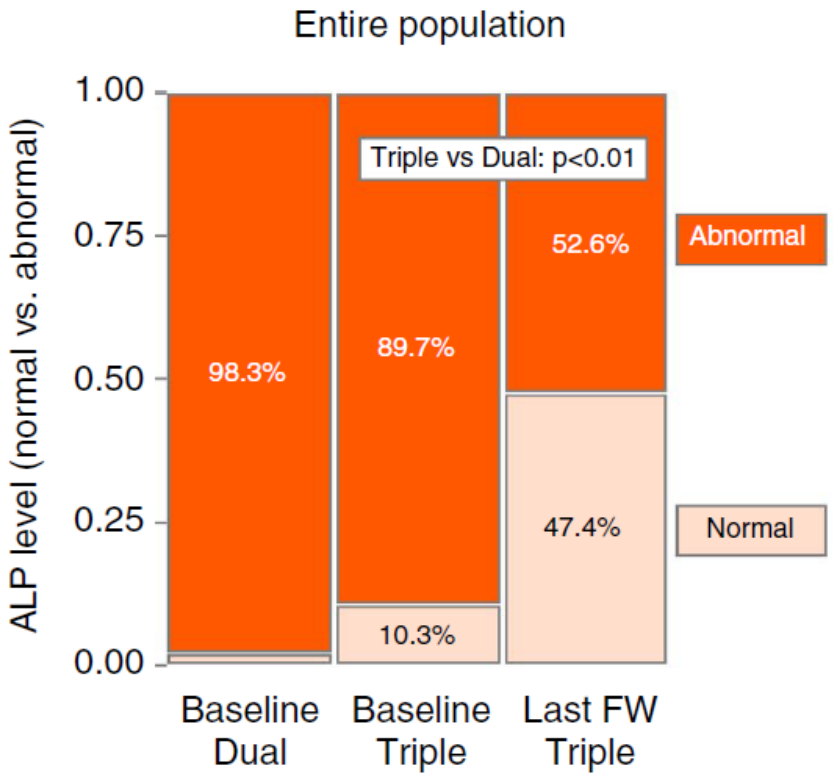


Aumento della creatinina sierica del 3% nel gruppo con BEZA *vs.* 5% nel gruppo placebo (p= n.s.).
Non dati sulla sicurezza a lungo termine.

Corpechot *et al*, NEJM 2018. De Vries *et al*, Gastroenterology 2020

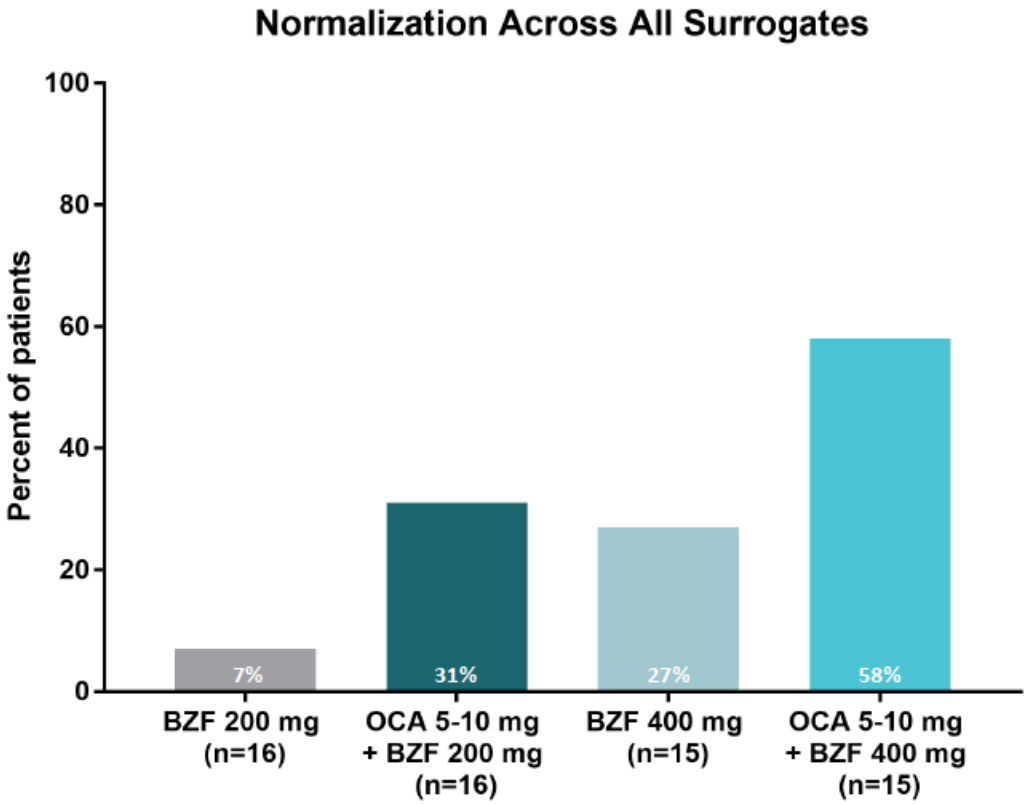
Efficacia della triplice terapia: UDCA, OCA, fibrati*





Soret *et al*, Aliment Pharmacol Ther. 2021

OCA 5-10 mg + BZF 400 mg Induced a Biochemical Remission in 58% of Subjects



Biochemical remission:
ALP, GGT, ALT, AST
All ≤ULN
AND
Total bilirubin
≤0.6x ULN

Data are shown as LS mean values ± standard error of the mean.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BZF, bezafibrate; GGT, gamma-glutamyl transferase; LS, least-squares; OCA, obeticholic acid; ULN, upper limit of normal.

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EASL CONGRESS Vienna, Austria 21–24 June 2023

Nevens *et al*, Oral Presentation, EASL 2023

Summary of Adverse Events Through Week 12

All groups have comparable adverse event rates

	BZF 200 mg (n=16) N (%)	OCA 5-10 mg + BZF 200 mg (n=16) N (%)	BZF 400 mg (n=15) N (%)	OCA 5-10 mg + BZF 400 mg (n=15) N (%)
Subjects with TEAE	**8** (50.0)	**11** (68.8)	**12** (80.0)	**9** (60.0)
Pruritus	**4** (25.0)	**4** (25.0)	**3** (20.0)	**2** (13.3)
Serious TEAEs	0	0	0	**1** (6.7)[a]
TEAE leading to discontinuation	0	0	0	**1** (6.7)[a]
TEAEs leading to death	0	0	0	0

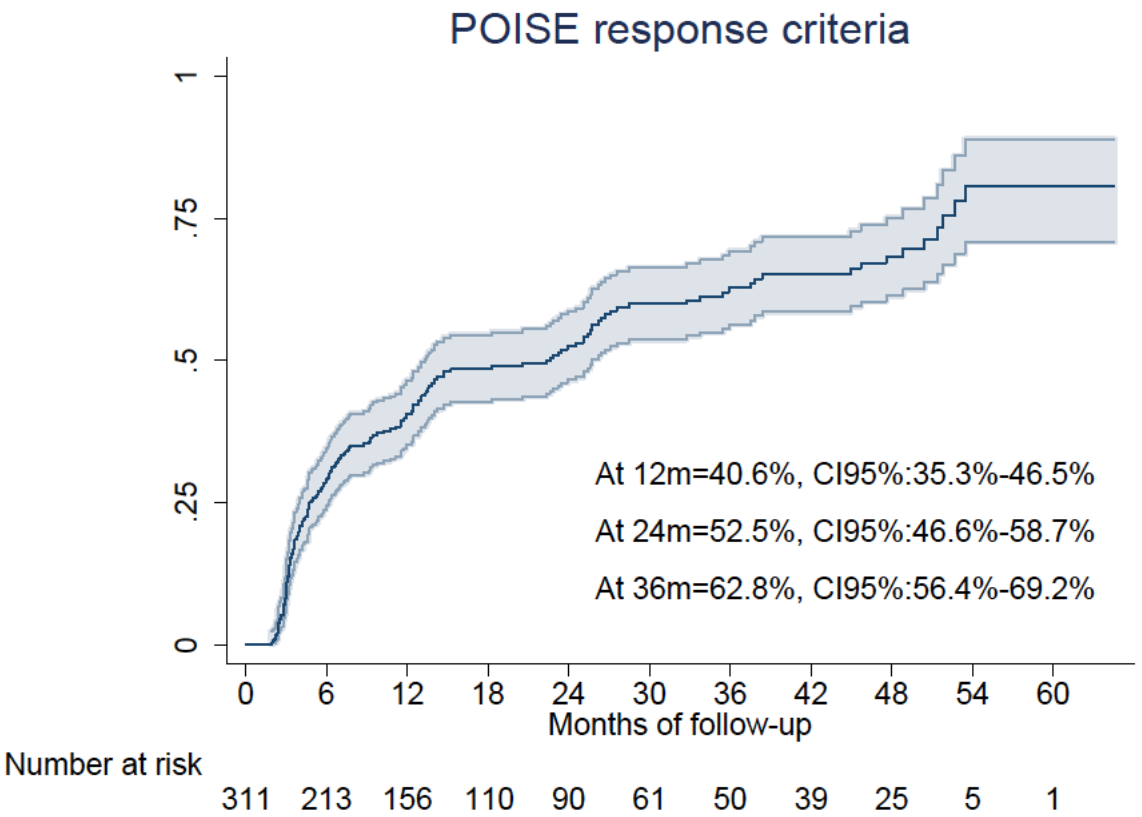
- Pruritus event rate in the combination groups of OCA 5-10 mg + BZF was 19.4%
- No difference in Gastrointestinal or Musculoskeletal adverse events between groups

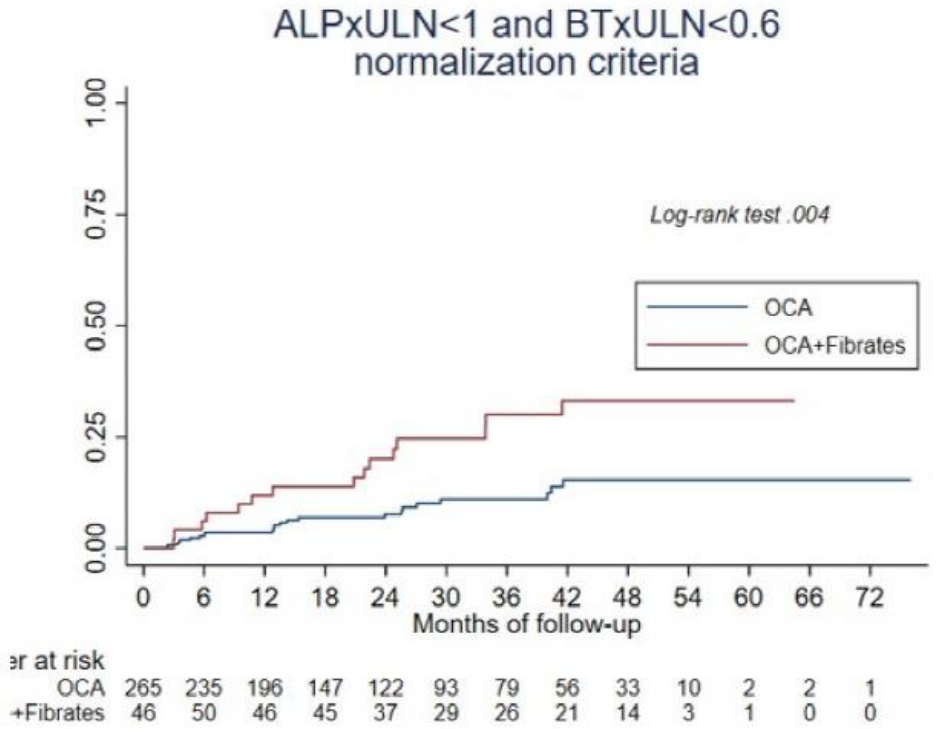
[a]1 event of pruritus led to discontinuation from the study.

Abbreviations: BZF, bezafibrate; OCA, obeticholic acid; TEAEs, treatment-emergent adverse events.

Nevens *et al*, Oral Presentation, EASL 2023

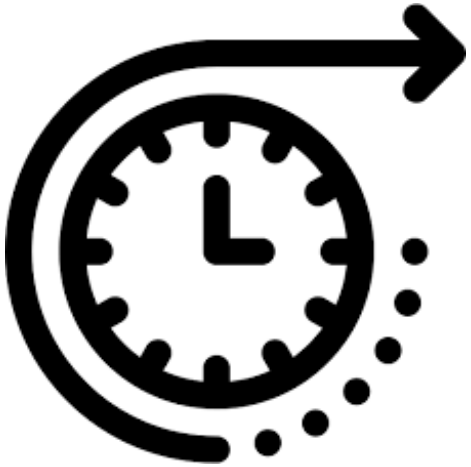
Efficacia a lungo termine di OCA +/- fibrati: la coorte IBER-PBC





Férnandez-Rodriguéz et al, Oral Presentation, AASLD 2023 November 13th

Novità dagli studi di fase 3 con PPAR agonisti



Efficacy and Safety of Seladelpar in Patients With Primary Biliary Cholangitis in the RESPONSE Trial:
A Phase 3 International, Randomized, Placebo-Controlled Study

Gideon M. Hirschfield,[1] Christopher L. Bowlus,[2] Marlyn J. Mayo,[3] Andreas E. Kremer,[4] John M. Vierling,[5] Kris V. Kowdley,[6] Cynthia Levy,[7] Susheela Carroll,[8] Ke Yang,[8] Yun-Jung Choi,[8] Daria B. Crittenden,[8] Charles A. McWherter,[8] the RESPONSE Study Investigators

1. Toronto Centre for Liver Disease, Division of Gastroenterology and Hepatology, University Health Network, Toronto General Hospital, Toronto, Canada; 2. University of California Davis School of Medicine, Sacramento, United States; 3. University of Texas Southwestern Medical School, Dallas, United States; 4. University Hospital Zürich, Zürich, Switzerland; 5. Baylor College of Medicine, Houston, United States; 6. Liver Institute Northwest, Seattle, United States; 7. University of Miami, Miami, United States; 8. CymaBay Therapeutics, Inc., Newark, United States

Sponsor: CymaBay Therapeutics, Inc.

AASLD The Liver Meeting® Nov. 10-14, 2023

Presented by Gideon Hirschfield, FRCP, PhD

Toronto Centre for Liver Disease
University of Toronto

Efficacy and safety of elafibranor in primary biliary cholangitis: Results from the ELATIVE™ double-blind, randomized, placebo-controlled phase 3 trial

ELATIVE™

Plain language version

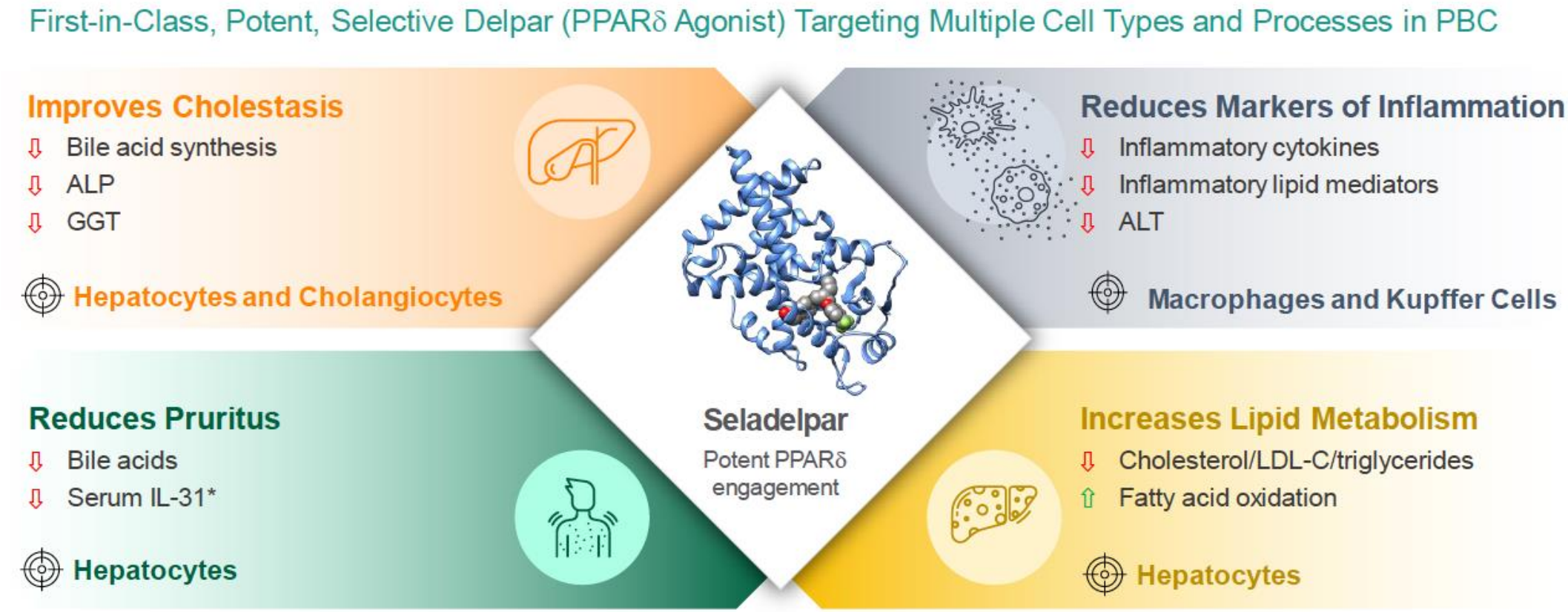
AASLD The Liver Meeting® Nov. 10-14, 2023

Christopher L. Bowlus,[1] Kris V. Kowdley,[2,3] Cynthia Levy,[4] Ulus Akarca,[5] Mario Reis Alvares-da-Silva,[6] Pietro Andreone,[7] Marco Arrese,[8] Christophe Corpechot,[9] Sven Francque,[10,11] Michael A. Heneghan,[12] Pietro Invernizzi,[13,14] David Jones,[15] Frederik C. Kruger,[16,17] Eric Lawitz,[18] Marlyn J. Mayo,[19] Mitchell L. Shiffman,[20] Mark G. Swain,[21] José Miguel Valera,[22] Victor Vargas,[23] John M. Vierling,[24] Alejandra Villamil,[25] Carol Addy,[26] Julie Dietrich,[26] Jean-Michel Germain,[27] Sarah Mazain,[28] Dragutin Rafailovic,[27] Bachirou Taddé,[27] Benjamin Miller,[29] Jianfen Shu,[29] Claudia O. Zein,[29] Jörn M. Schattenberg,[30] and the ELATIVE™ Study Group

Presented at The Liver Meeting, AASLD 2023 | Boston, MA, USA | November 10–14 2023

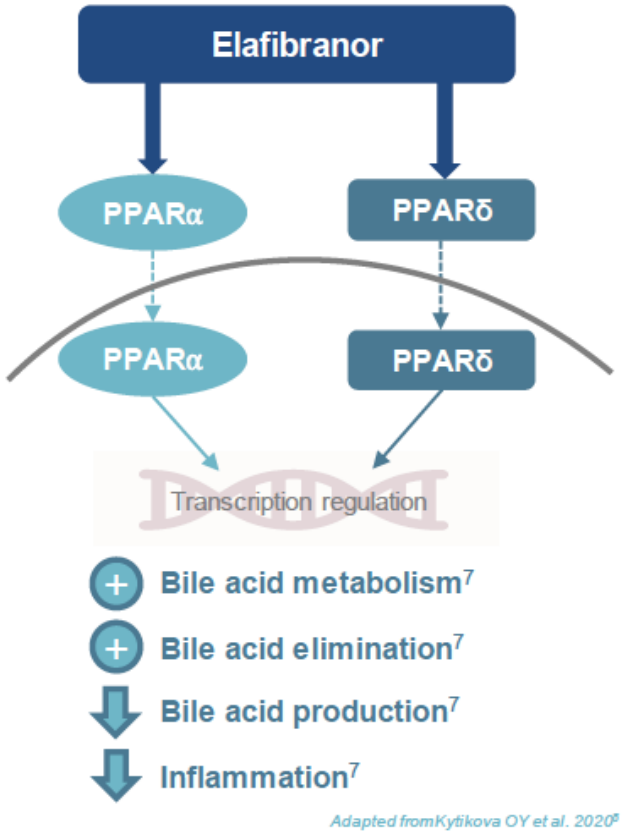
#48490

Seladelpar: agonista selettivo di PPAR*δ*



Hirschfield *et al*, AASLD 2023 Late Breaker abstract

Elafibranor: agonista PPARα e PPARδ



Modified from Bowlus C, Late breaking AASLD, November 13th 2023
Kowdley et al, NEJM 2024

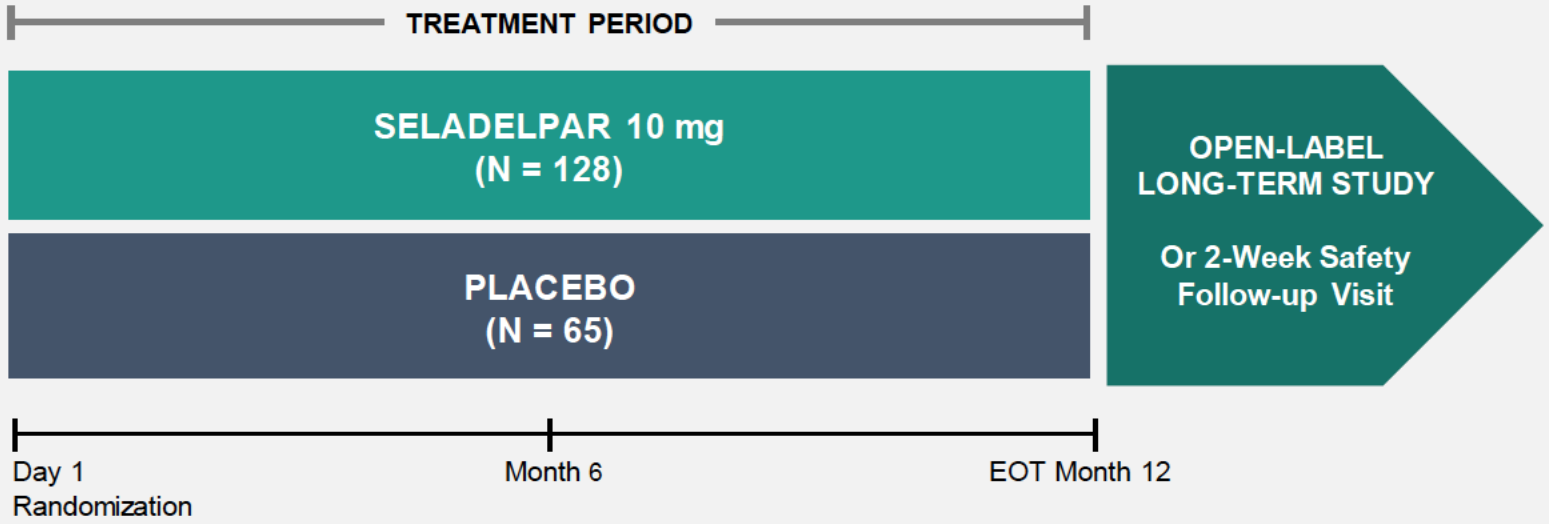
Seladelpar: disegno dello studio RESPONSE

Entry Criteria

- PBC and inadequate response or intolerance to UDCA
- ALP ≥ 1.67 × ULN
- ALT/AST ≤ 3 × ULN
- Total bilirubin ≤ 2 × ULN
- Compensated cirrhosis allowed

Stratification

- ALP < 350 U/L vs ALP ≥ 350 U/L
- Pruritus NRS < 4 vs NRS ≥ 4



PRIMARY ENDPOINT – COMPOSITE RESPONDER RATE AT MONTH 12

ALP < 1.67 × ULN; ALP decrease ≥ 15%; total bilirubin ≤ 1 × ULN

KEY SECONDARY ENDPOINTS

- ALP normalization rate (ALP ≤ 1 × ULN) at Month 12
- Change in pruritus NRS at Month 6 in patients with baseline NRS ≥ 4

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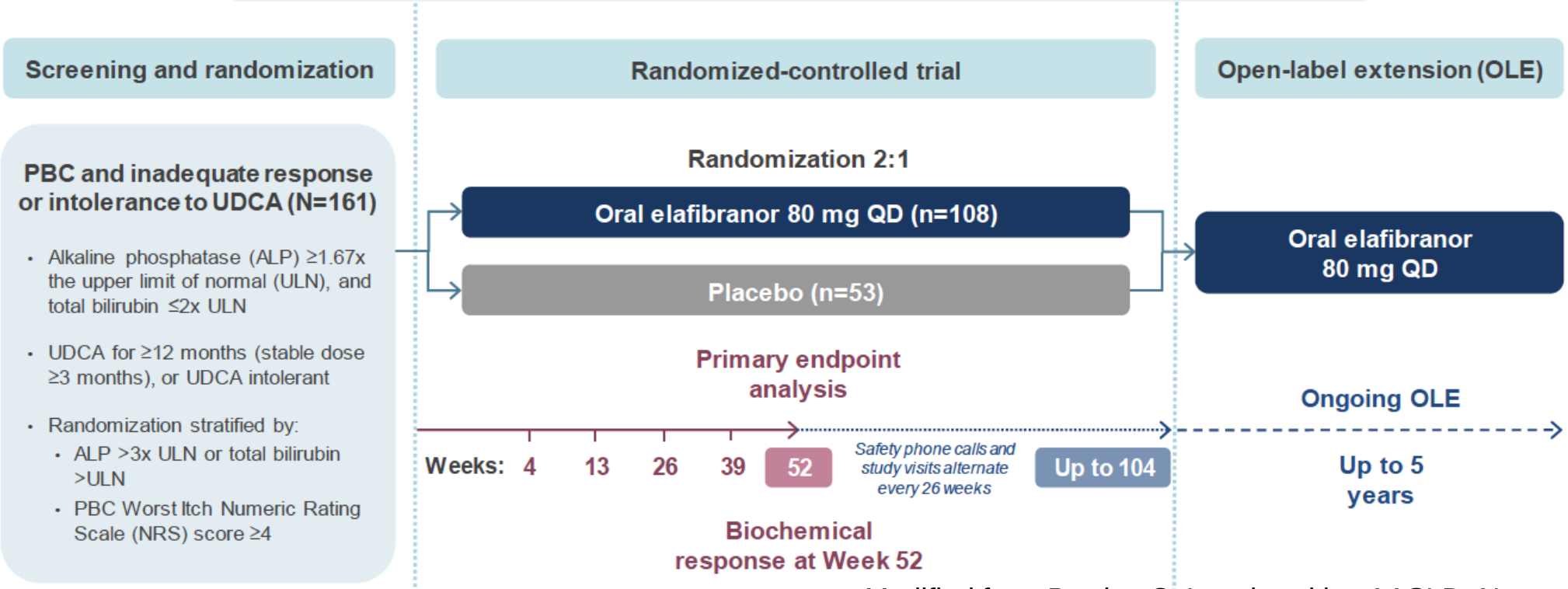
Elafibranor: disegno dello studio ELATIVE

ELATIVE™ aimed to evaluate the **efficacy and safety of elafibranor** in adult patients with PBC with an **inadequate response or intolerance to UDCA**



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Seladelpar: caratteristiche al basale nello studio RESPONSE

Mean (SD)		Placebo (N = 65)	Seladelpar 10 mg (N = 128)
Female, n (%)		60 (92.3%)	123 (96.1%)
Age, years		57.0 (9.2)	56.6 (10.0)
Duration of disease, years		8.6 (6.5)	8.2 (6.7)
On UDCA, n (%)		61 (93.8%)	120 (93.8%)
Pruritus NRS ≥ 4, n (%)		23 (35.4%)	49 (38.3%)
Cirrhosis, n (%)		9 (13.8%)	18 (14.1%)
ALP, U/L	ULN: 116 U/L	313.8 (117.7)	314.6 (123.0)
TB, mg/dL	ULN: 1.1 mg/dL	0.74 (0.3)	0.77 (0.3)
ALT, U/L	ULN: 41 U/L	48.2 (22.8)	47.4 (23.5)
AST, U/L	ULN: 34 U/L	41.7 (16.0)	39.6 (16.1)
GGT, U/L	ULN: 38 U/L	287.5 (249.6)	269.0 (240.0)

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Elafibranor: caratteristiche al basale nello studio ELATIVE

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Elafibranor Group (N=108)	Placebo Group (N=53)	Total (N=161)
Age — yr	57.5±8.4	56.4±9.3	57.1±8.7
Female sex — no. (%)	102 (94)	52 (98)	154 (96)
White race — no. (%)†	101 (94)	46 (87)	147 (91)
Time since diagnosis — yr	7.9±5.9	8.3±6.8	8.0±6.2
Alkaline phosphatase			
Mean — U/liter	321.3±121.9	323.1±198.6	321.9±150.9
>3× ULN — no. (%)‡	43 (40)	20 (38)	63 (39)
Total bilirubin — μmol/liter§	9.7±5.1	9.4±5.0	9.6±5.1
Aspartate aminotransferase — U/liter	45.0±24.2	47.2±32.8	45.7±27.2
Alanine aminotransferase — U/liter	49.3±29.4	50.3±38.7	49.6±32.6
γ-Glutamyltransferase — U/liter	213.3±186.1	220.0±220.3	215.5±197.4
Concurrent ursodeoxycholic acid — no. (%)	102 (94)	51 (96)	153 (95)
WI-NRS score¶			
Mean	3.3±2.8	3.2±2.9	3.3±2.8
Moderate-to-severe pruritus — no. (%)‖	44 (41)	22 (42)	66 (41)
Liver stiffness**			
Mean — kPa	9.9±7.8	10.7±8.9	10.1±8.2
>10.0 kPa — no./total no. (%)	31/104 (30)	17/50 (34)	48/154 (31)
Bridging fibrosis or cirrhosis — no./total no. (%)††	12/31 (39)	8/16 (50)	20/47 (43)
Liver stiffness >10 kPa or bridging fibrosis (or both) or cirrhosis — no./total no. (%)**††	35/104 (34)	19/50 (38)	54/154 (35)

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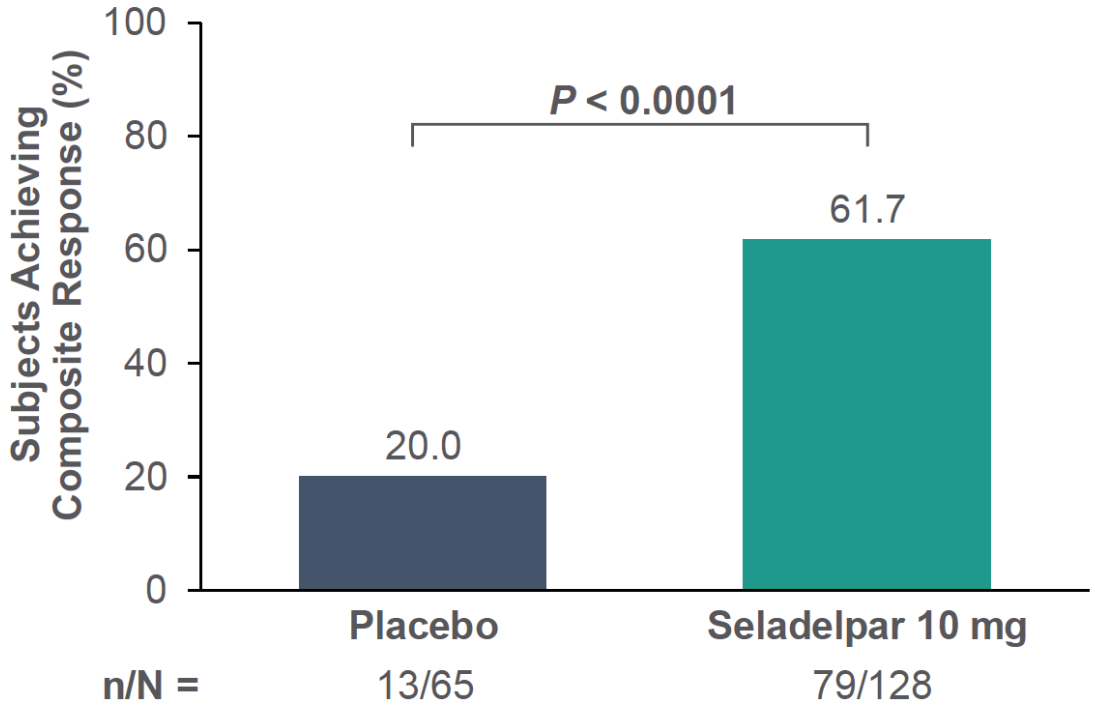
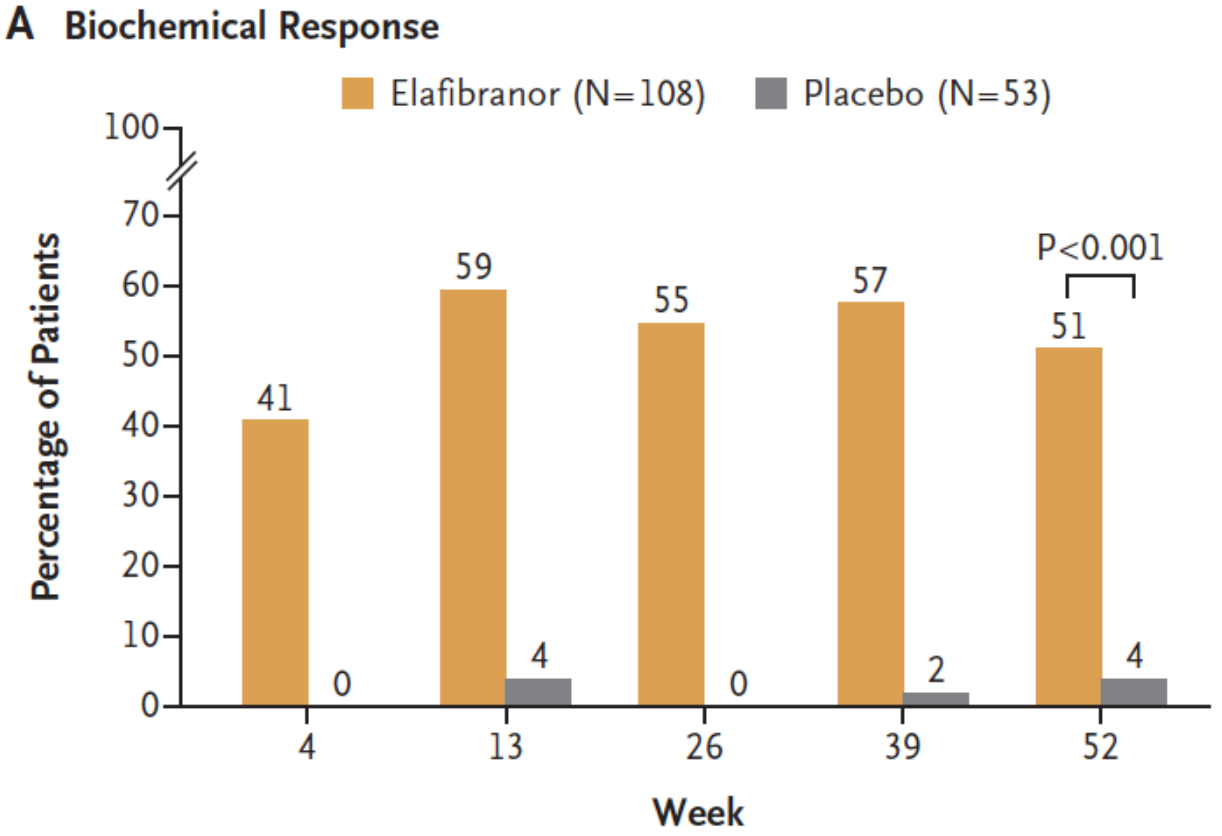
Efficacia di Seladelpar e Elafibranor: endpoint primario





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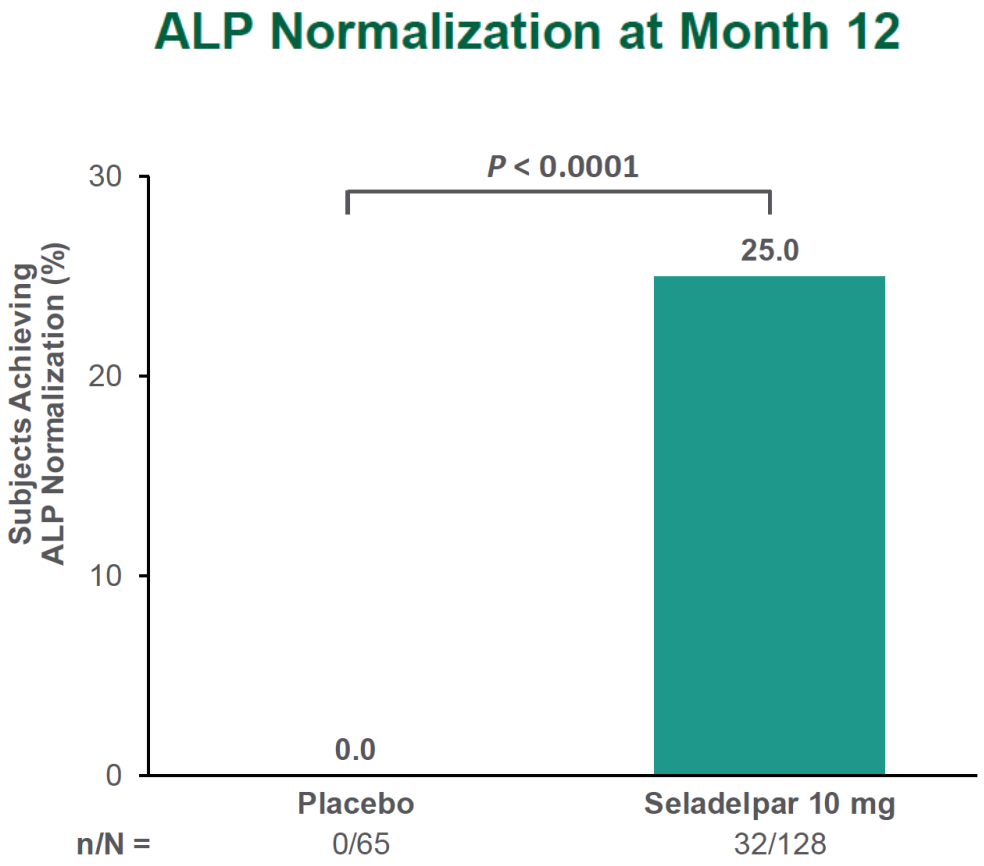
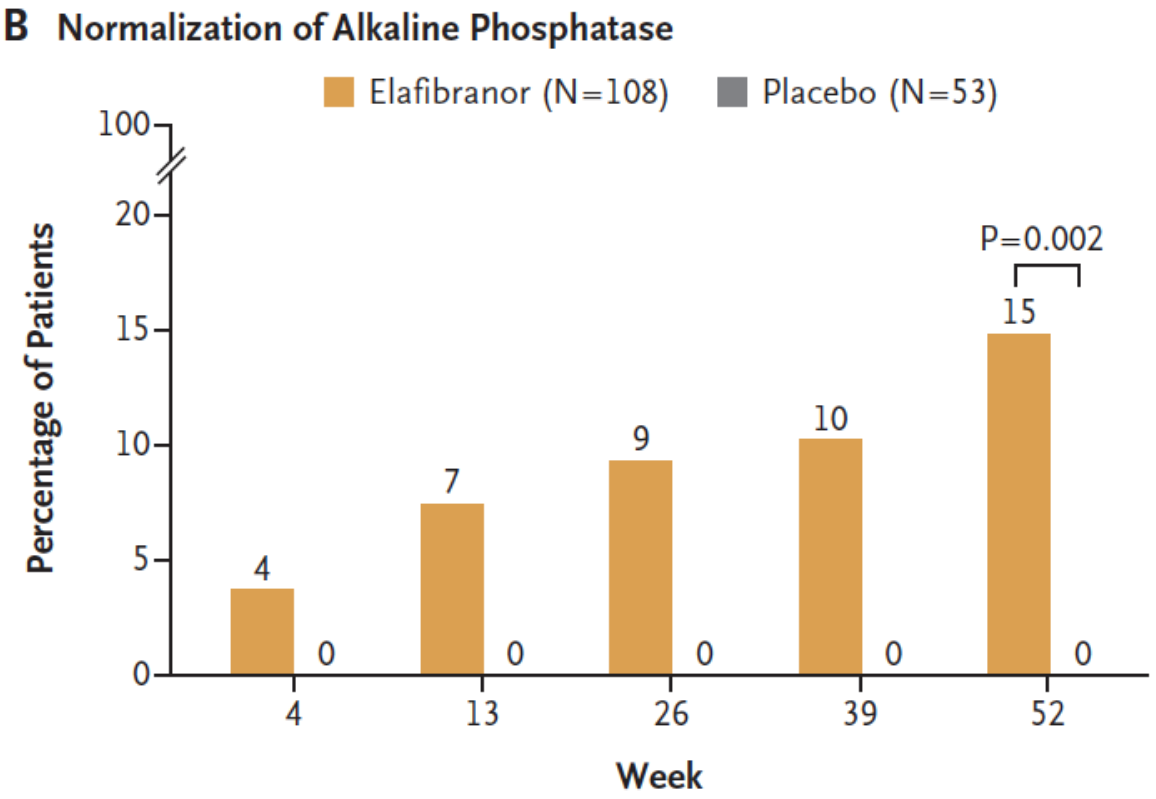
Efficacia di Seladelpar e Elafibranor: endpoint secondari



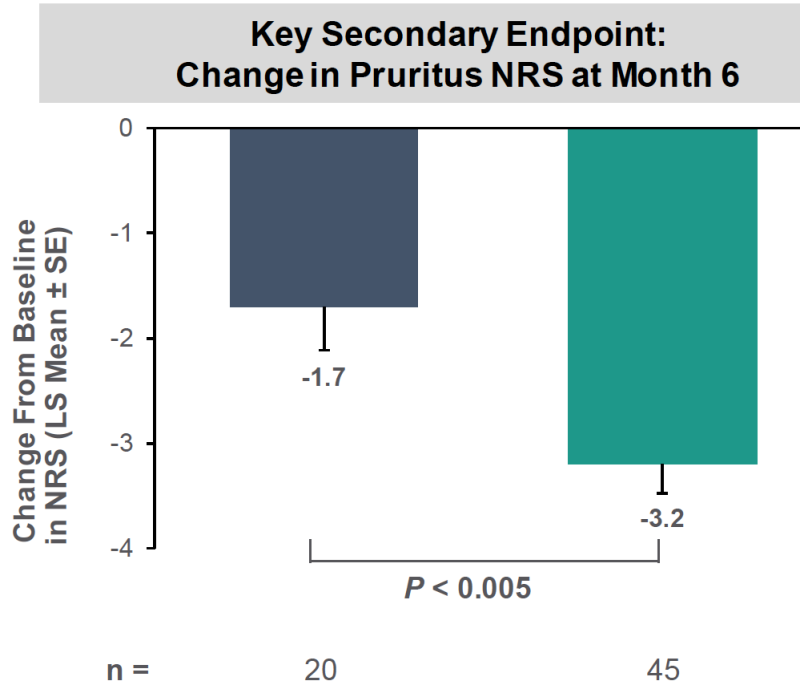


Hirschfield *et al*, NEJM 2024; Kowdley *et al*, NEJM 2024

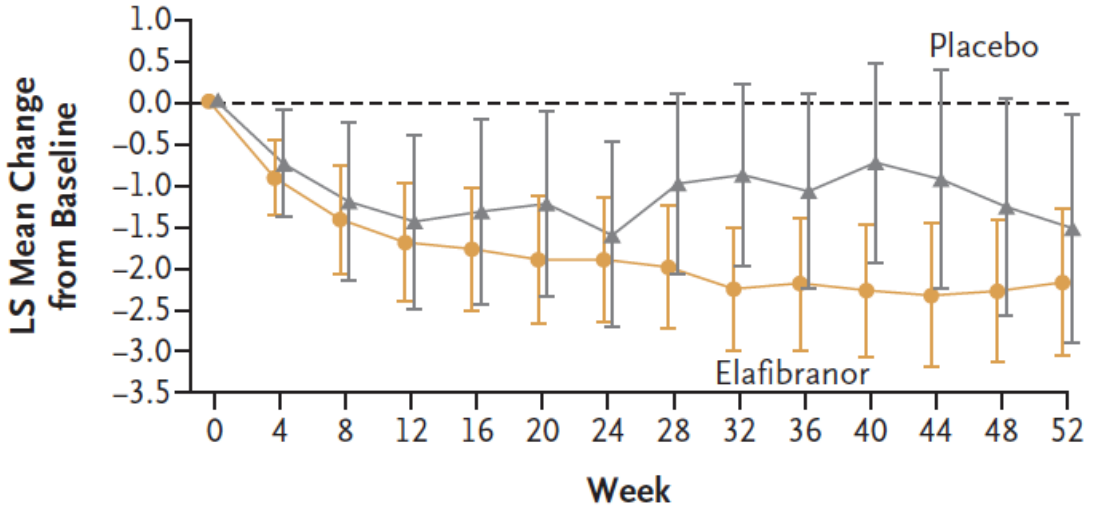
Efficacia di Seladelpar e Elafibranor: endpoint secondari

Seladelpar Significantly Improved Pruritus

Subjects With Baseline NRS ≥ 4



C Change in Score on the Worst Itch Numeric Rating Scale (WI-NRS)



No. at Risk

Placebo	22	21	19	18	18	17	16	15	15	16	15	14	13	12
Elafibranor	44	41	40	39	40	38	37	34	35	34	32	34	35	32

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Sicurezza di Seladelpar

No Meaningful Differences Between Placebo and Seladelpar

Safety Population, n (%)	Placebo (N = 65)	Seladelpar 10 mg (N = 128)
Subjects with at least 1 AE	55 (84.6)	111 (86.7)
Any treatment-related AE	8 (12.3)	22 (17.2)
Any treatment-related AE ≥ Grade 3 (CTCAE)	0	0
Any AE with outcome of death	0	0
Any SAE	4 (6.2)	9 (7.0)
Any treatment-related SAE	0	0
Any AE leading to study drug discontinuation	3 (4.6)	4 (3.1)
Liver-related AEs*	6 (9.2)	8 (6.3)
Muscle-related AEs*	5 (7.7)	8 (6.3)

96% of eligible patients completing treatment agreed to enter open-label safety study†

Hirschfield *et al*, NEJM 2024

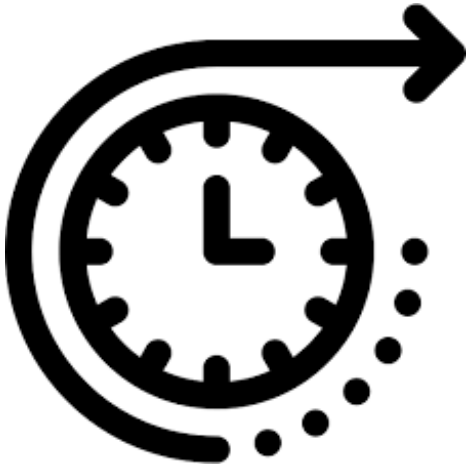
Elafibranor: dati di sicurezza

Table 3. Summary of Adverse Events and Adverse Events Occurring in More than 10% of Patients in Either Group.

Event	Elafibranor (N=108)	Placebo (N=53)
	no. of patients (%)	
Any adverse event that emerged during treatment period*	104 (96)	48 (91)
Covid-19	31 (29)	20 (38)
Pruritus	22 (20)	14 (26)
Abnormal weight gain	21 (19)	10 (19)
Abdominal pain, including upper and lower abdomen	12 (11)	3 (6)
Diarrhea	12 (11)	5 (9)
Nausea	12 (11)	3 (6)
Urinary tract infection	12 (11)	10 (19)
Vomiting	12 (11)	1 (2)
Fatigue	10 (9)	7 (13)
Headache	9 (8)	6 (11)
Back pain	4 (4)	6 (11)
Any severe adverse event†	12 (11)	6 (11)
Any adverse event attributed to the trial regimen that emerged during treatment period‡	42 (39)	21 (40)
Any serious adverse event that emerged during treatment period§	11 (10)	7 (13)
Any adverse event leading to discontinuation of the trial regimen that emerged during treatment period	11 (10)	5 (9)
Any fatal adverse event	2 (2)	0

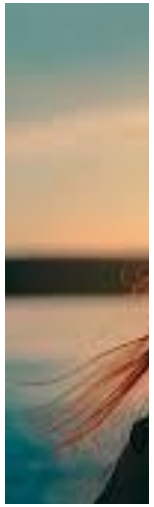
Kowdley *et al*, NEJM 2023

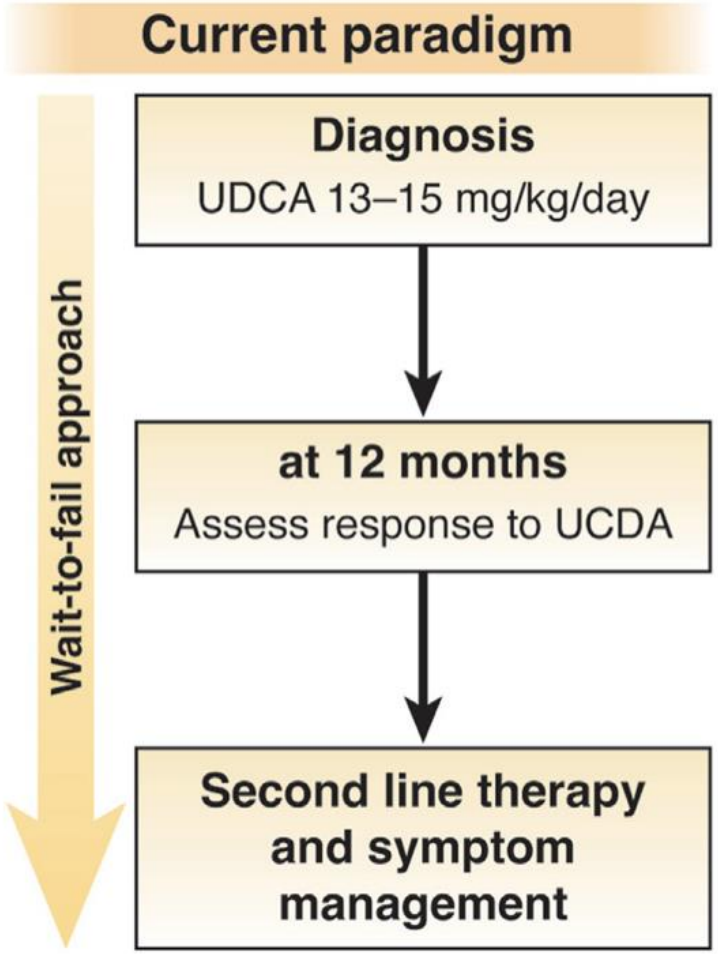
Studi sperimentali in corso



Agent	Mechanism	Clinical Trial Stage	Results
Elafibranor	PPAR α e PPAR δ agonist	Phase III/to start	Result published/long term study to follow
Seladelpar	PPAR δ agonist	Phase III/to start	Results presented/long term study to follow
Bezafibrate + OCA	FXR agonist e PPAR agonist	Phase II	Ongoing
Saroglitazar	PPAR α e PPAR δ agonist	Phase II	ongoing
Setanaxib	NOX2 and NOX4 inhibitor	**Phase III**	Ongoing
EDP-305	FXR agonist	Phase II	Completed, results not yet published
Tropifexor	FXR agonist	Phase II	Completed, result published
Cilofexor	FXR agonist	Phase II	Completed
RhuDex	T-lymphocyte co-stimulation	Pahse II	suspended
Linerixibat	**IBAT**	**Phase III**	**Ongoing**
Volixibat	IBAT	Phase II	Ongoing
Golexanolone	GABA-A receptor-modulating steroid antagonist	Phase Ib/II	To start
Mesenchymal stem cell transplantation	Immunoregulation		To start

Novel paradigms in PBC therapy





Levy et al CGH 2023