

# CIBLES THÉRAPEUTIQUES DE LA CHOLESTASE ET PPARS

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Christophe Corpechot

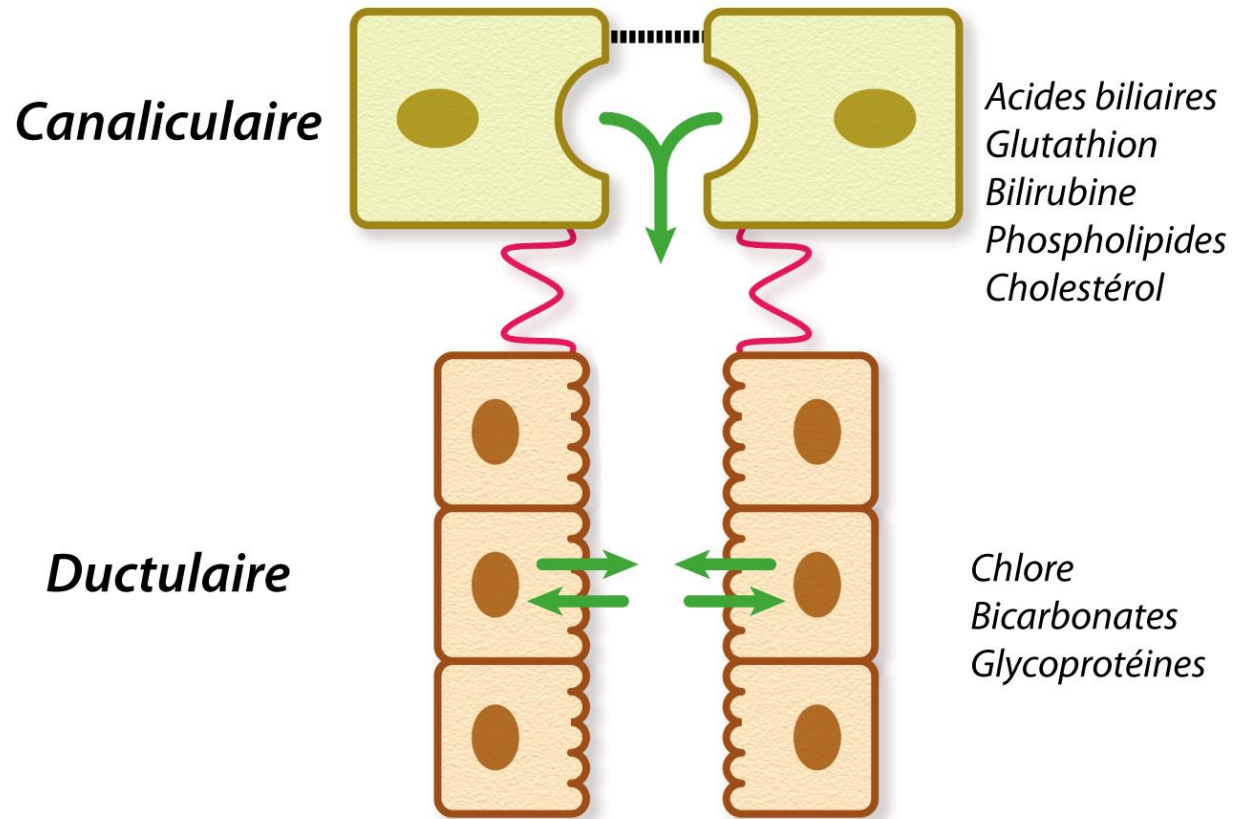
Centre de référence des maladies inflammatoires des voies biliaires et des  
hépatites auto-immunes (MIVB-H)

Hôpital Saint-Antoine, Paris

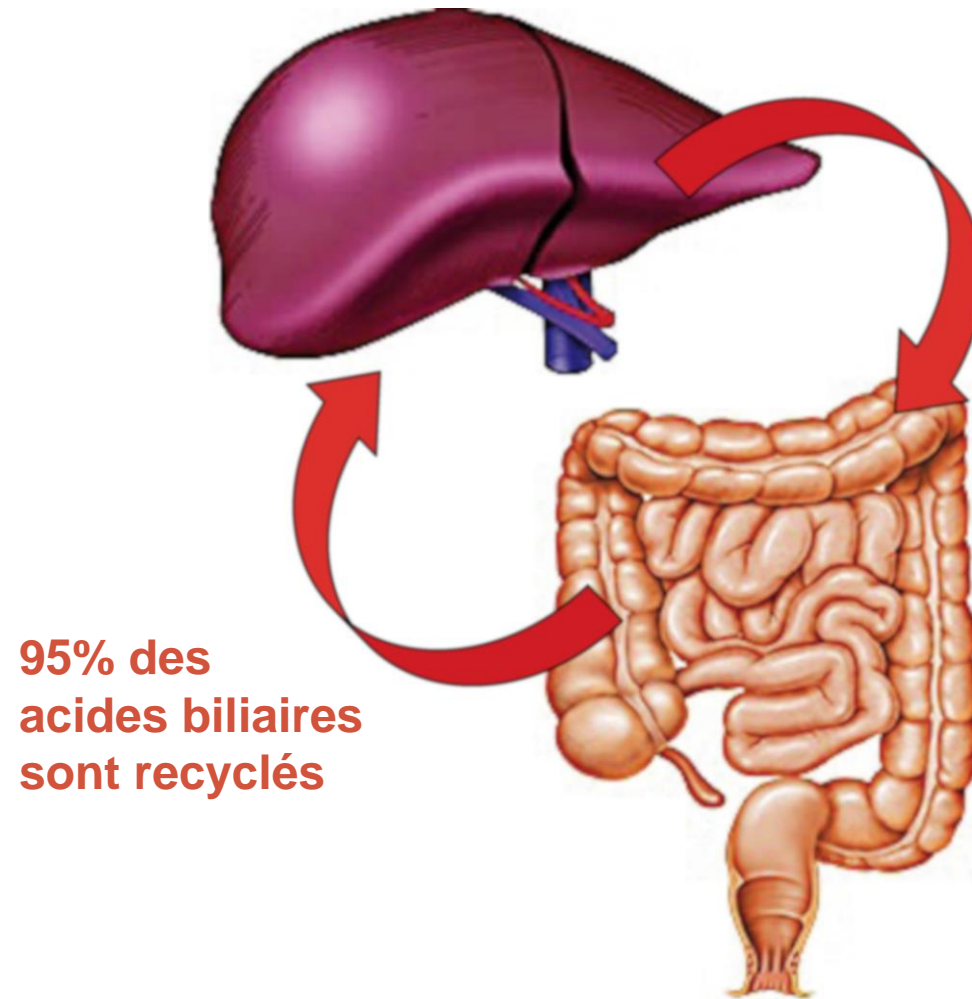
# LIENS D'INTÉRÊT

- ARROW
- INTERCEPT
- GSK

# SÉCRÉTION BILIAIRE

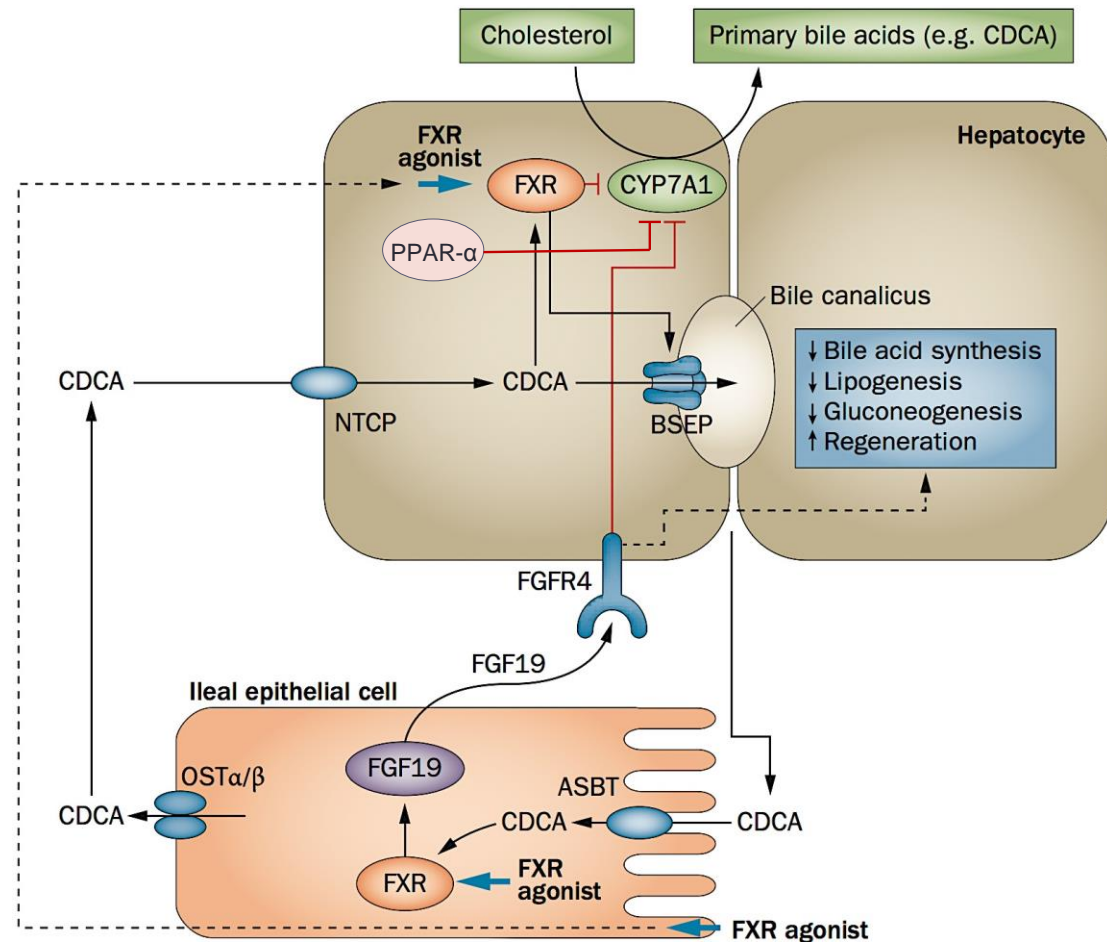


# CYCLE ENTÉRO-HÉPATIQUE

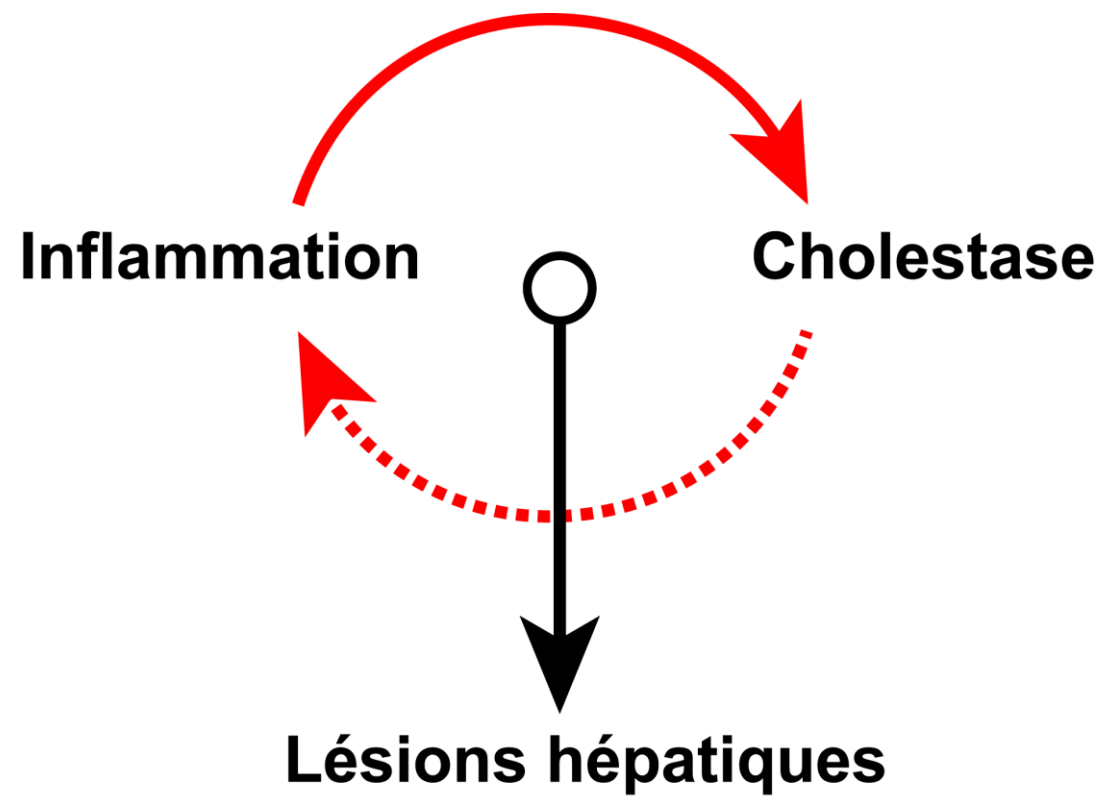


**95% des  
acides biliaires  
sont recyclés**

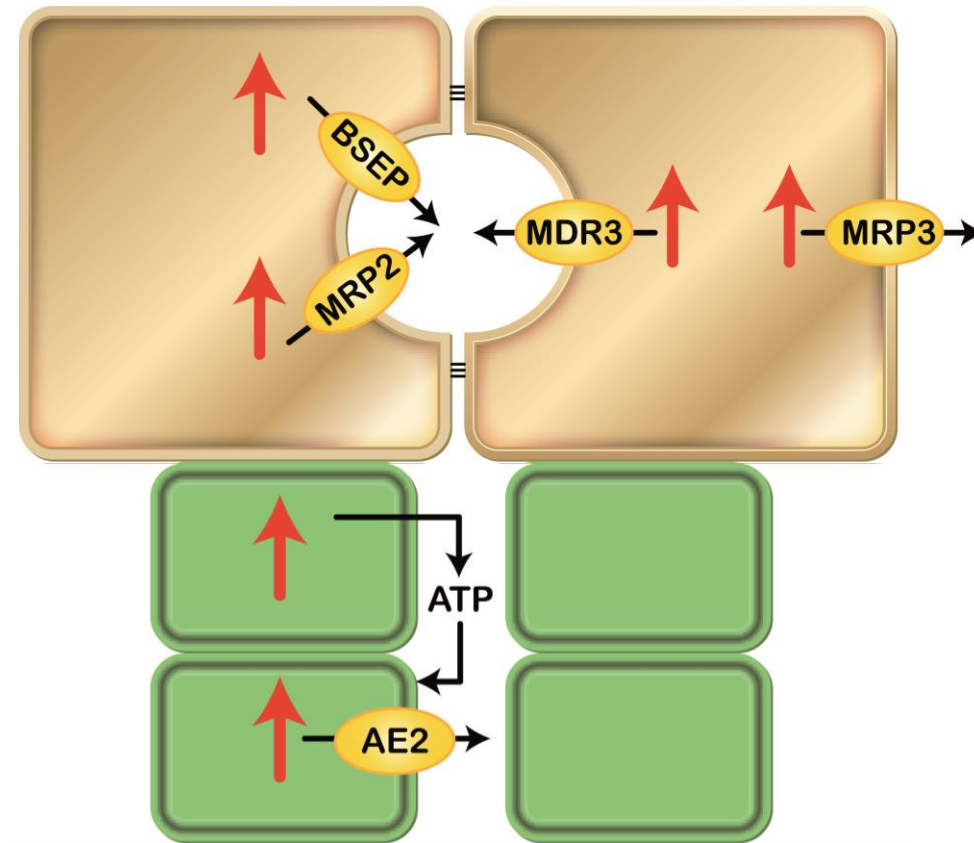
# HOMÉOSTASIE DES ACIDES BILAIRES



# INFLAMMATION ET CHOLESTASE



# ACIDE URSODÉSOXYCHOLIQUE



# NOUVELLES CIBLES THÉRAPEUTIQUES

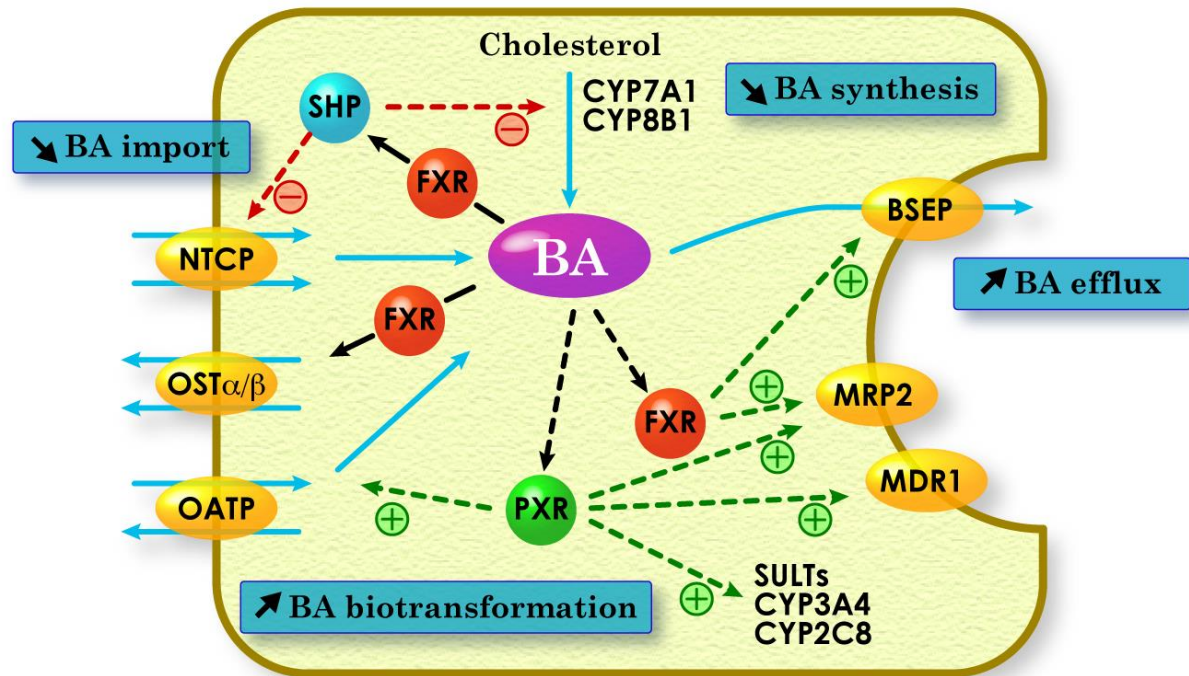
	HÉPATOCYTES	CHOLANGIOCYTES	ENTÉROCYTES
CIBLES	<ul style="list-style-type: none"> <li>- FXR</li> <li>- PPAR-<math>\alpha</math></li> <li>- FGFR4</li> <li>- GR</li> <li>- PXR</li> </ul>	<ul style="list-style-type: none"> <li>- TGR5</li> <li>- PPAR-<math>\delta</math></li> <li>- AE2</li> <li>- ASBT</li> </ul>	<ul style="list-style-type: none"> <li>- FXR</li> <li>- ASBT</li> <li>- OST-<math>\alpha</math>-<math>\beta</math></li> </ul>
EFFECTEURS	<ul style="list-style-type: none"> <li>- Agonistes FXR</li> <li>- Fibrates</li> <li>- Analogues FGF19</li> <li>- Budésonide</li> <li>- Rifampicine</li> </ul>	<ul style="list-style-type: none"> <li>- Agonistes TGR5</li> <li>- Fibrates</li> <li>- Agonistes PPAR-<math>\delta</math></li> <li>- Budésonide</li> <li>- NorAUDC</li> <li>- Inhibiteurs ASBT</li> </ul>	<ul style="list-style-type: none"> <li>- Agonistes FXR</li> <li>- Inhibiteurs ASBT</li> <li>- Inhibiteurs OST-<math>\alpha</math>-<math>\beta</math></li> </ul>
ACTIONS	<ul style="list-style-type: none"> <li>- ↓ Synthèse AB</li> <li>- ↓ Captation AB</li> <li>- ↑ Sécrétion AB</li> <li>- ↓ Inflammation</li> </ul>	<ul style="list-style-type: none"> <li>- ↑ Flux biliaire</li> <li>- ↑ Sécrétion HCO<sub>3</sub><sup>-</sup></li> <li>- ↓ Inflammation</li> </ul>	<ul style="list-style-type: none"> <li>- ↑ Élimination AB</li> <li>- ↓ Pool AB</li> </ul>



# NOUVELLES CIBLES THÉRAPEUTIQUES

	HÉPATOCYTES	CHOLANGIOCYTES	ENTÉROCYTES
CIBLES	<ul style="list-style-type: none"> <li>- <b>FXR</b></li> <li>- <b>PPAR-<math>\alpha</math></b></li> <li>- FGFR4</li> <li>- GR</li> <li>- PXR</li> </ul>	<ul style="list-style-type: none"> <li>- TGR5</li> <li>- <b>PPAR-<math>\delta</math></b></li> <li>- AE2</li> <li>- ASBT</li> </ul>	<ul style="list-style-type: none"> <li>- <b>FXR</b></li> <li>- ASBT</li> <li>- OST-<math>\alpha</math>-<math>\beta</math></li> </ul>
EFFECTEURS	<ul style="list-style-type: none"> <li>- <b>Agonistes FXR</b></li> <li>- <b>Fibrates</b></li> <li>- Analogues FGF19</li> <li>- Budésoude</li> <li>- Rifampicine</li> </ul>	<ul style="list-style-type: none"> <li>- Agonistes TGR5</li> <li>- <b>Fibrates</b></li> <li>- <b>Agonistes PPAR-<math>\delta</math></b></li> <li>- Budésoude</li> <li>- NorAUDC</li> <li>- Inhibiteurs ASBT</li> </ul>	<ul style="list-style-type: none"> <li>- <b>Agonistes FXR</b></li> <li>- Inhibiteurs ASBT</li> <li>- Inhibiteurs OST-<math>\alpha</math>-<math>\beta</math></li> </ul>
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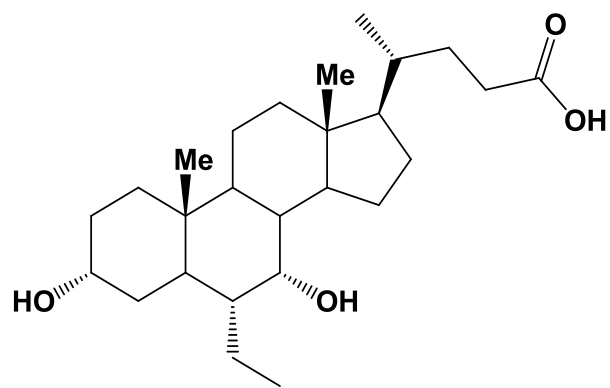
# FARNESOID X RECEPTOR (FXR)



- ↓ Synthèse des AB
- ↑ Sécrétion des AB
- ↓ Inflammation
- ↑ Régénération hépatique
- ↓ Lipogenèse
- ↓ Néoglucogénèse

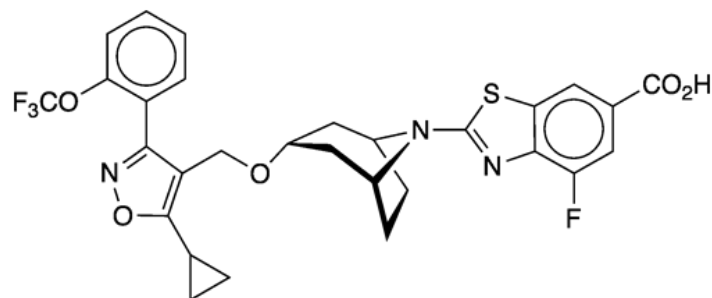
# AGONISTES FXR

ACIDE OBÉTICHIQUE



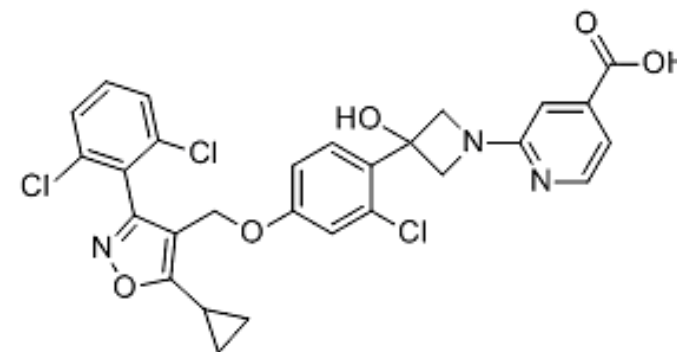
Intercept

TROPIFEXOR



Novartis

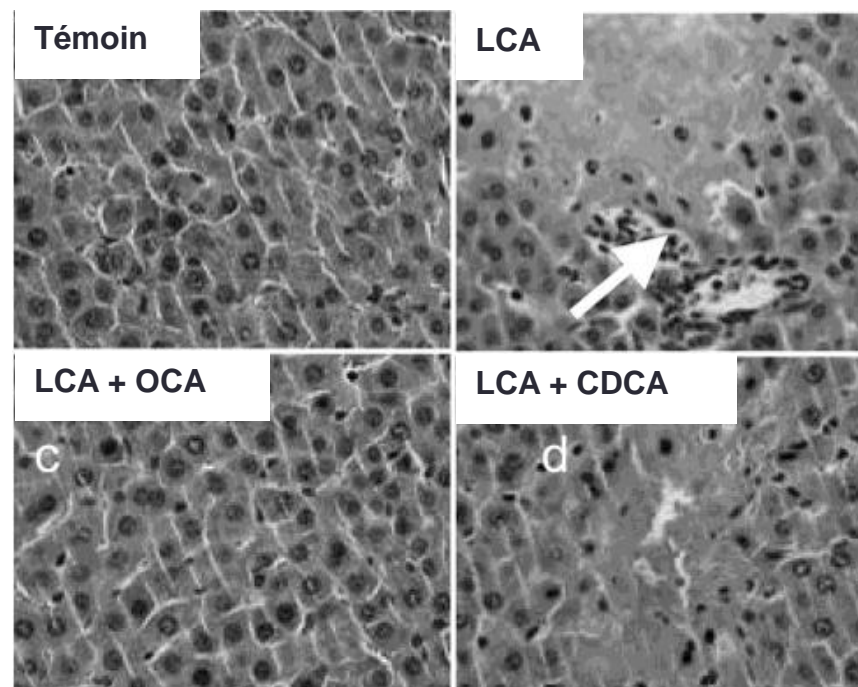
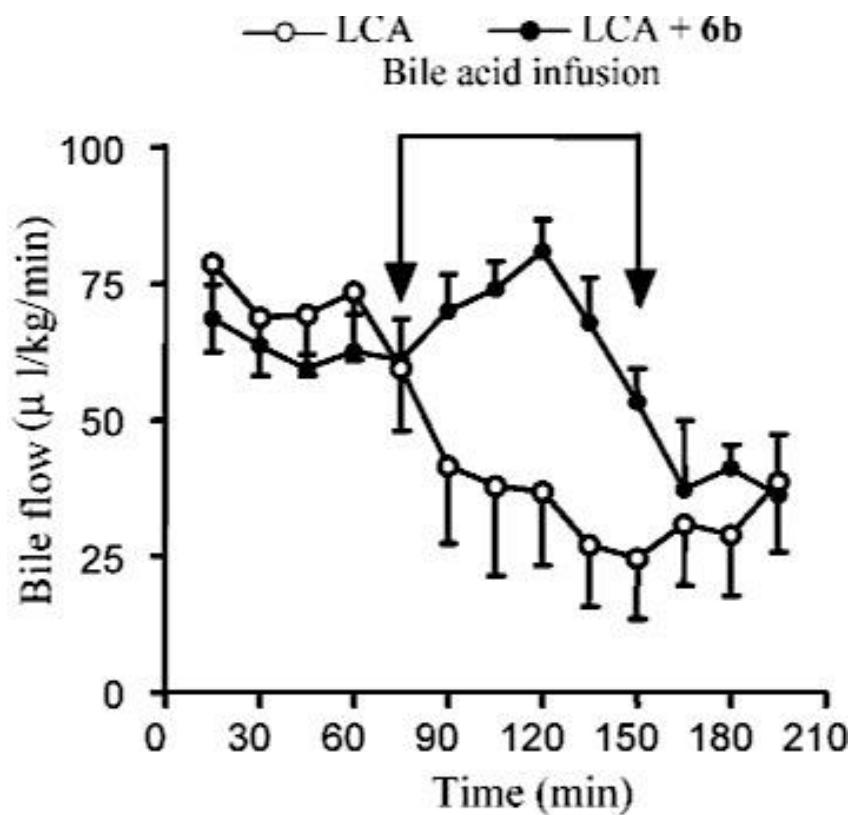
CILOFEXOR



Gilead

# ACIDE OBÉTICHIQUE: DONNÉES PRÉCLINIQUES

Cholestase induite par perfusion d'acide lithocholique chez le rat



# ACIDE OBÉTICHOLOLIQUE dans la CBP

*The NEW ENGLAND JOURNAL of MEDICINE*

ORIGINAL ARTICLE

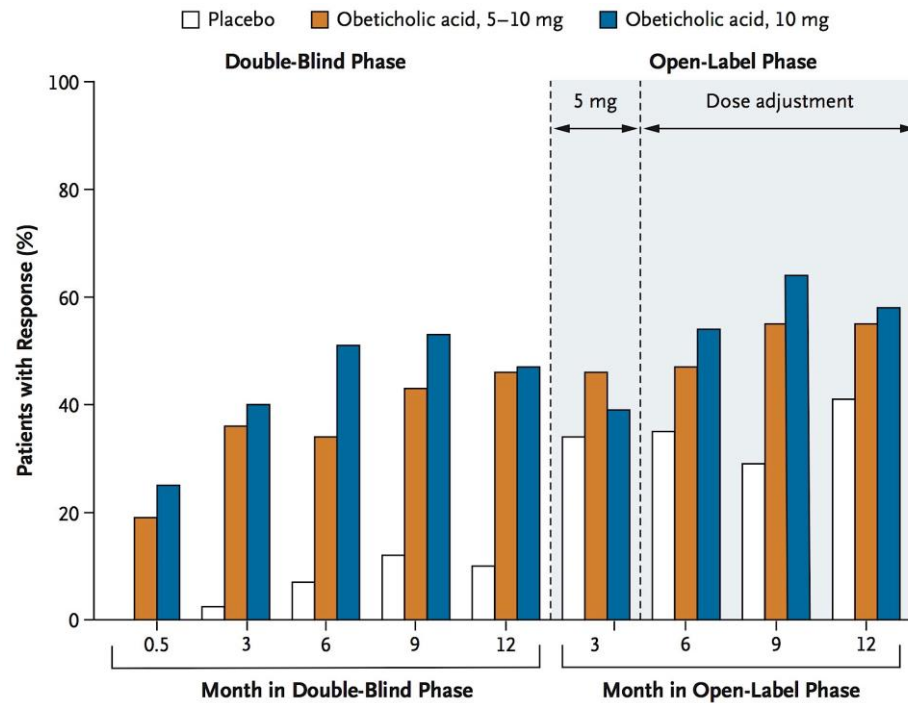
## A Placebo-Controlled Trial of Obeticholic Acid in Primary Biliary Cholangitis

F. Nevens, P. Andreone, G. Mazzella, S.I. Strasser, C. Bowlus, P. Invernizzi, J.P.H. Drenth, P.J. Pockros, J. Regula, U. Beuers, M. Trauner, D.E. Jones, A. Floreani, S. Hohenester, V. Luketic, M. Shiffman, K.J. van Erpecum, V. Vargas, C. Vincent, G.M. Hirschfield, H. Shah, B. Hansen, K.D. Lindor, H.-U. Marschall, K.V. Kowdley, R. Hooshmand-Rad, T. Marmon, S. Sheeron, R. Pencek, L. MacConell, M. Pruzanski, and D. Shapiro, for the POISE Study Group\*

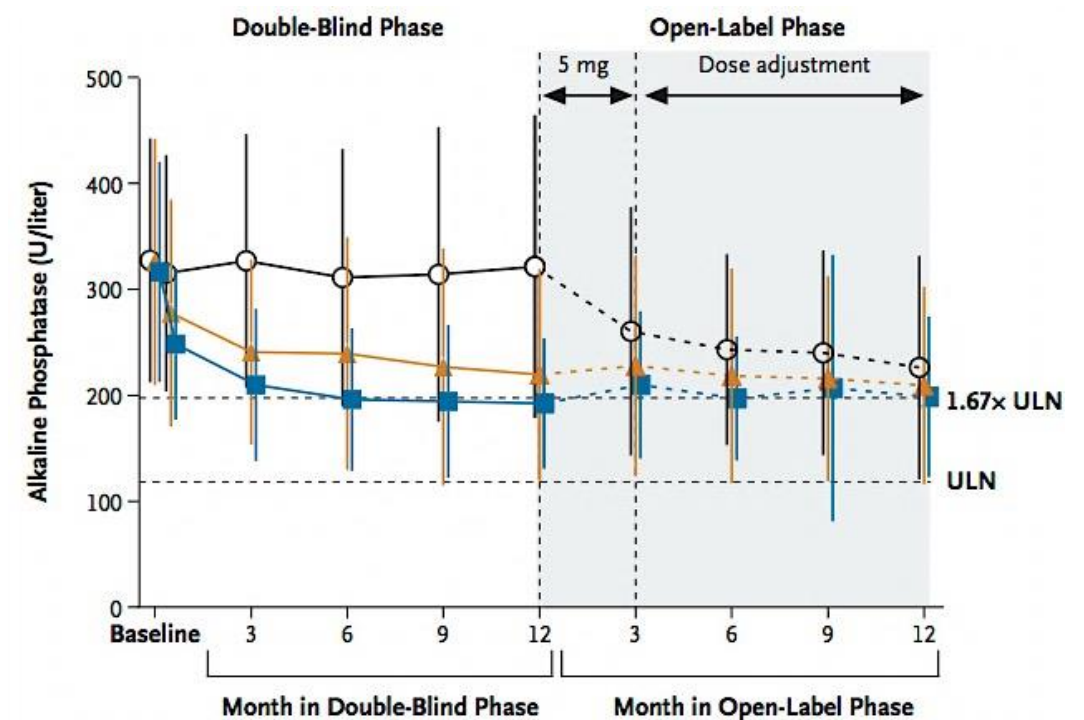
# ACIDE OBÉTICHIQUE: ÉTUDE POISE (CBP)

## Étude de Phase 3 de 12 mois avec période d'extension

Response rate: ALP < 1.67N and  $\Delta$ ALP > 15%



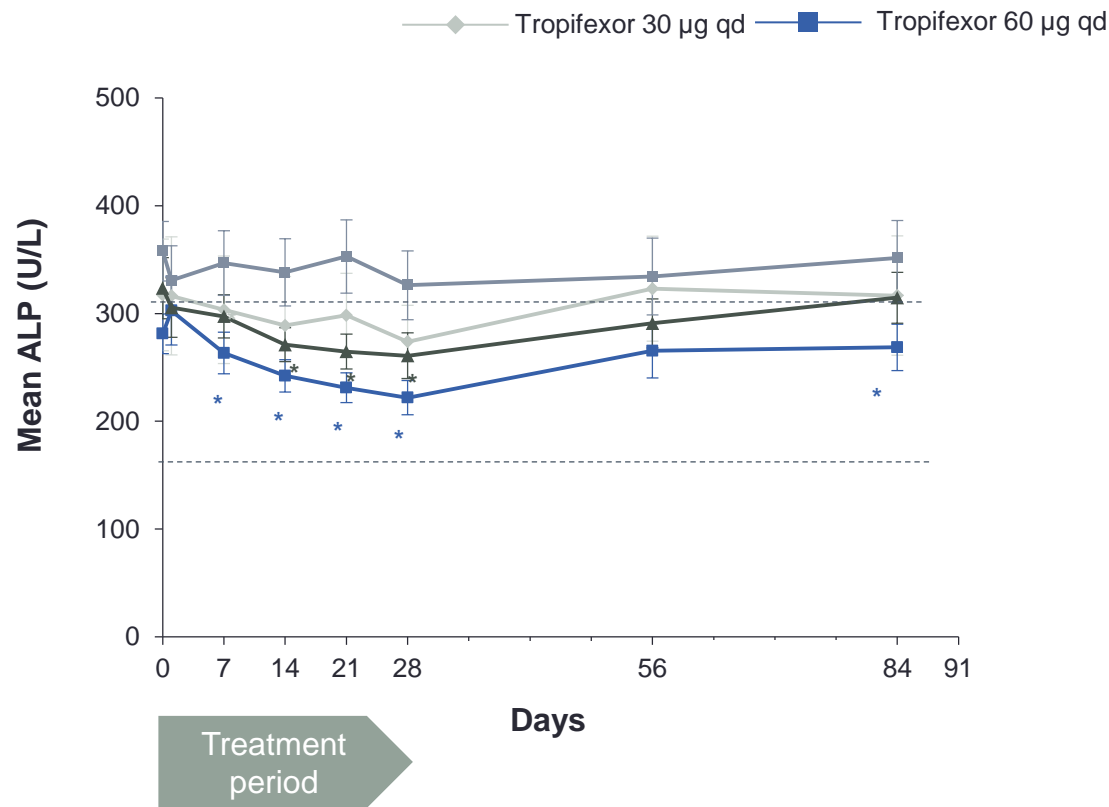
Absolute ALP levels over time



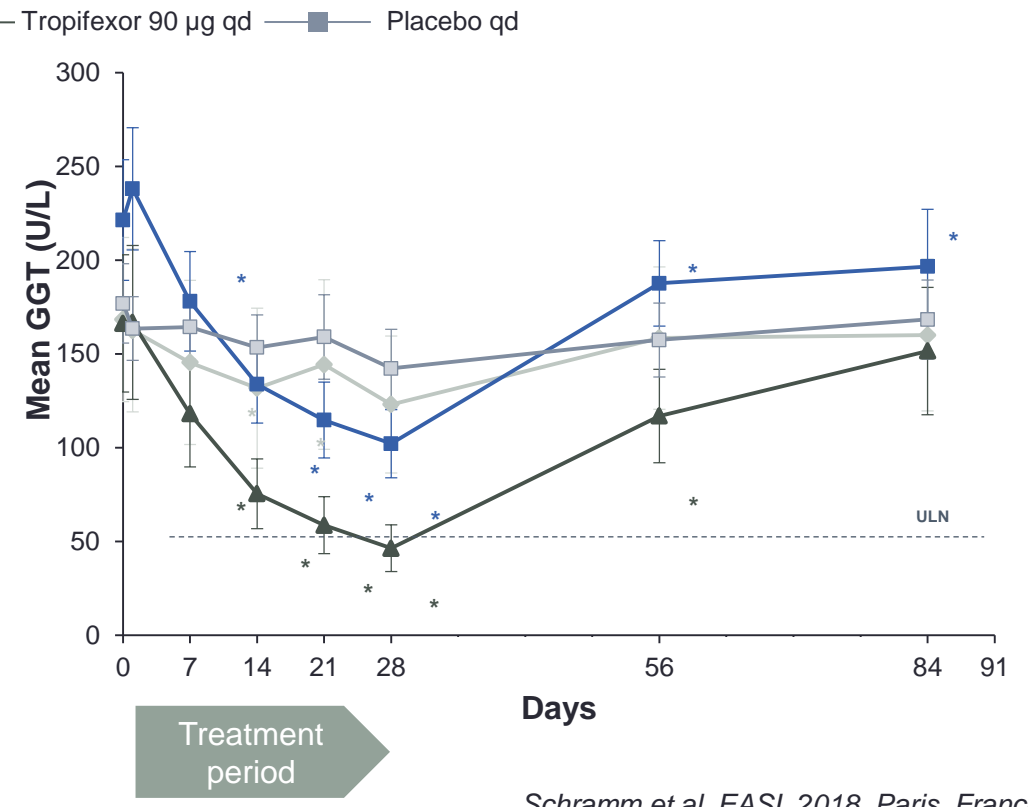
# TROIPIFEXOR: ÉTUDE DE PHASE 2 (CBP)

## Étude de Phase 2 de 4 semaines

Absolute ALP levels over time



Absolute GGT levels over time



# PEROXYISOME PROLIFERATOR-ACTIVATED RECEPTORS

## PPAR- $\alpha$

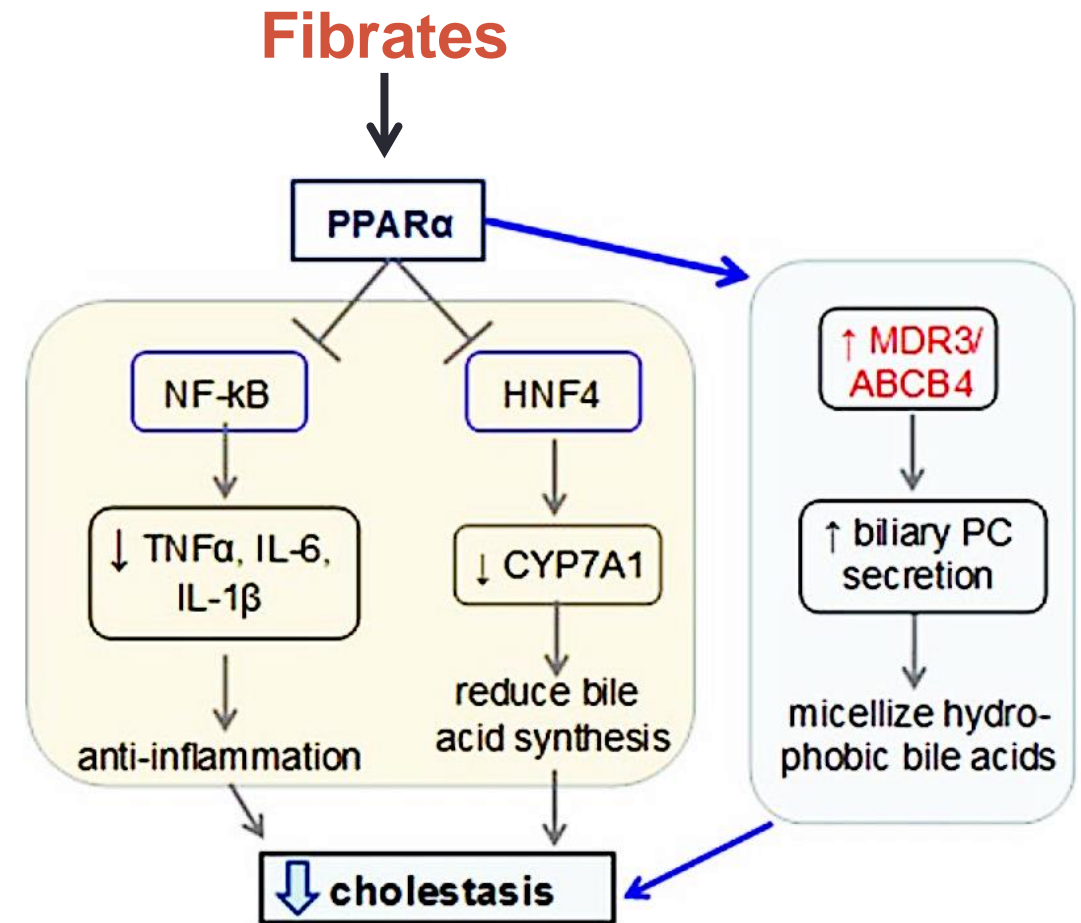
- Métabolisme lipidique
- Forte expression dans le foie
- Agonistes: **Fibrates**

## PPAR- $\delta$

- Métabolisme glucido-lipidique
- Expression ubiquitaire
- Agonistes: Acides gras

## PPAR- $\gamma$

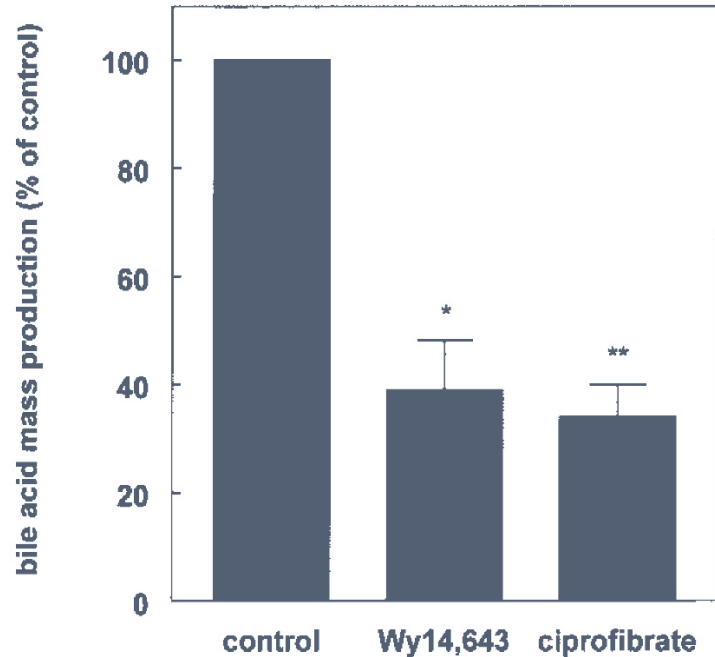
- Métabolisme glucido-lipidique
- Forte expression tissu adipeux
- Agonistes: Thiazolidinediones





# FIBRATES ET SÉCRÉTION BILIAIRE

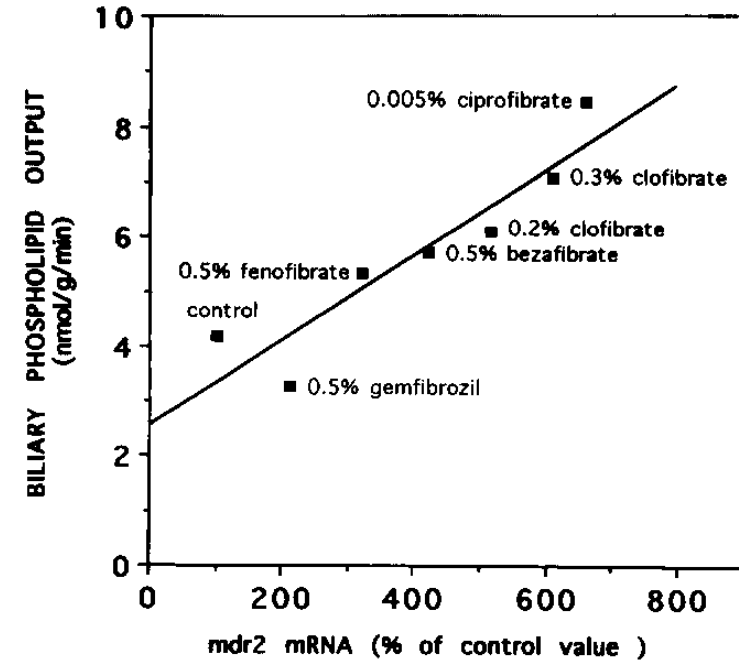
↓ Synthèse des AB



Inhibition de CYP7A1 et NTCP

Post et al. Arterioscler Thromb Vasc Biol 2001

↑ Sécrétion des PL



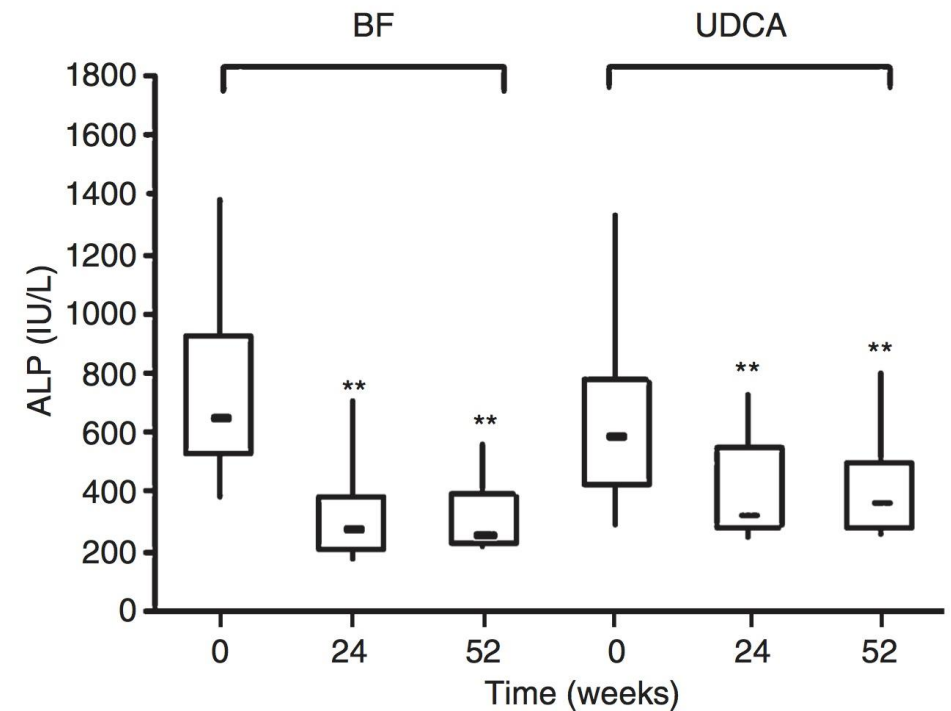
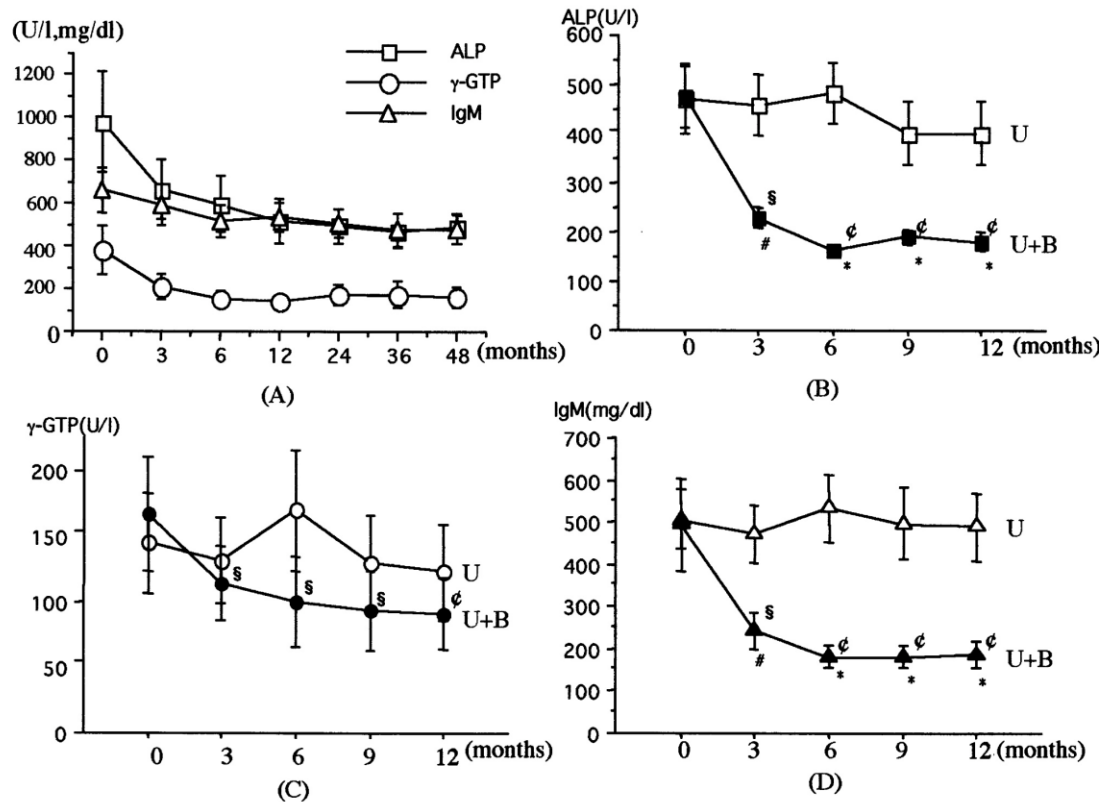
Induction de ABCB4 (MDR3)

Chianale et al. Biochem J 1996

# FIBRATES ET CHOLESTASE: ÉTUDES PILOTES (CBP)

En association à l'AUDC (résistance à l'AUDC)

En monothérapie (patients naïfs d'AUDC)



# BÉZAFIBRATE dans la CBP

*The NEW ENGLAND JOURNAL of MEDICINE*

ORIGINAL ARTICLE

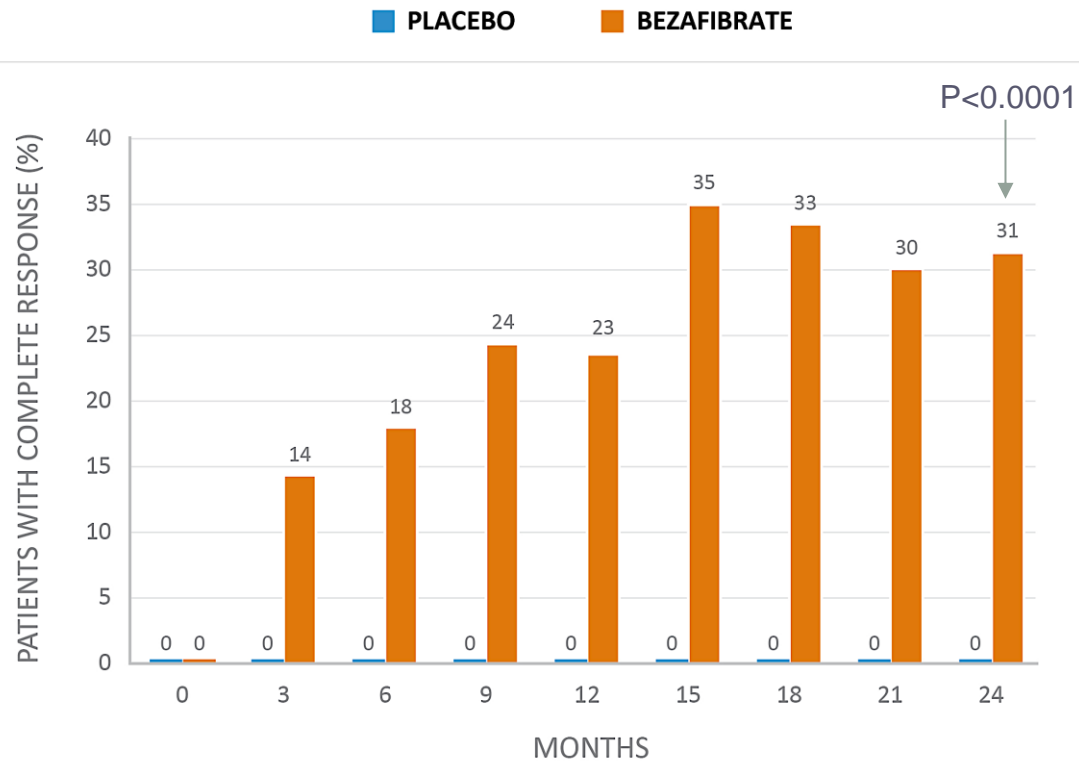
## A Placebo-Controlled Trial of Bezafibrate in Primary Biliary Cholangitis

C. Corpechot, O. Chazouillères, A. Rousseau, A. Le Gruyer, F. Habersetzer, P. Mathurin, O. Gorla, P. Potier, A. Minello, C. Silvain, A. Abergel, M. Debette-Gratien, D. Larrey, O. Roux, J.-P. Bronowicki, J. Boursier, V. de Ledinghen, A. Heurgue-Berlot, E. Nguyen-Khac, F. Zoulim, I. Ollivier-Hourmand, J.-P. Zarski, G. Nkontchou, S. Lemoine, L. Humbert, D. Rainteau, G. Lefèvre, L. de Chaisemartin, S. Chollet-Martin, F. Gaouar, F.-H. Admane, T. Simon, and R. Poupon

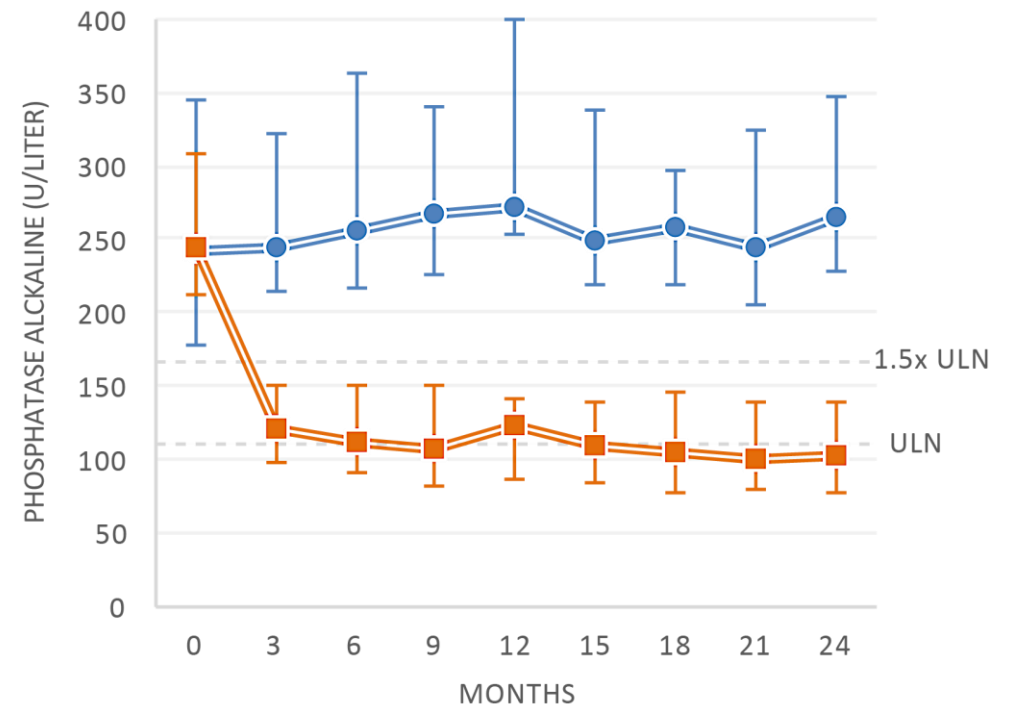
# BÉZAFIBRATE: ÉTUDE BEZURSO (CBP)

## Étude de Phase 3 de 24 mois

Response rate: normal bilirubin, ALP, AST, ALT, albumin, and PT

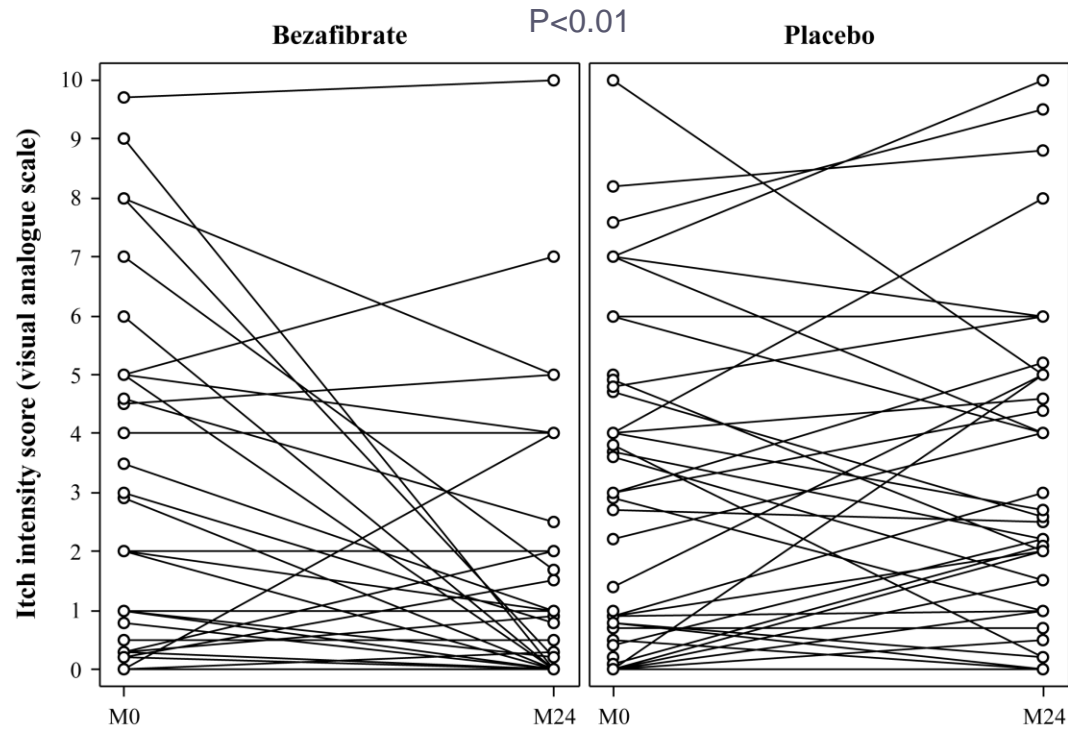


Absolute ALP levels over time

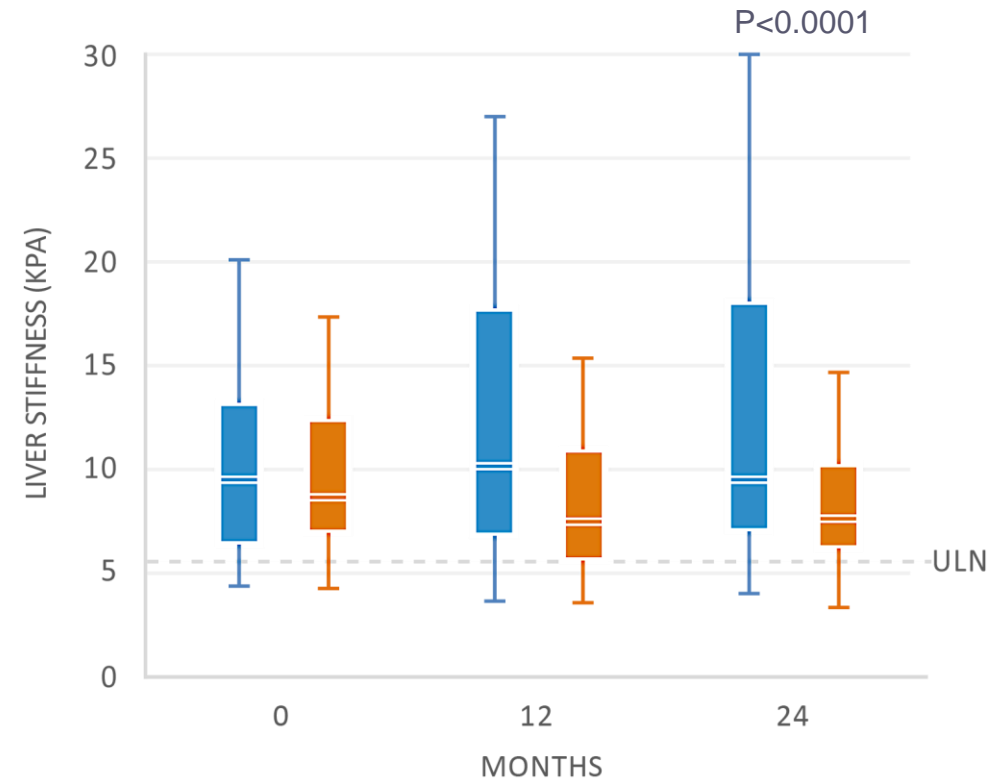


# BÉZAFIBRATE: ÉTUDE BEZURSO (CBP)

Absolute itch intensity levels over time



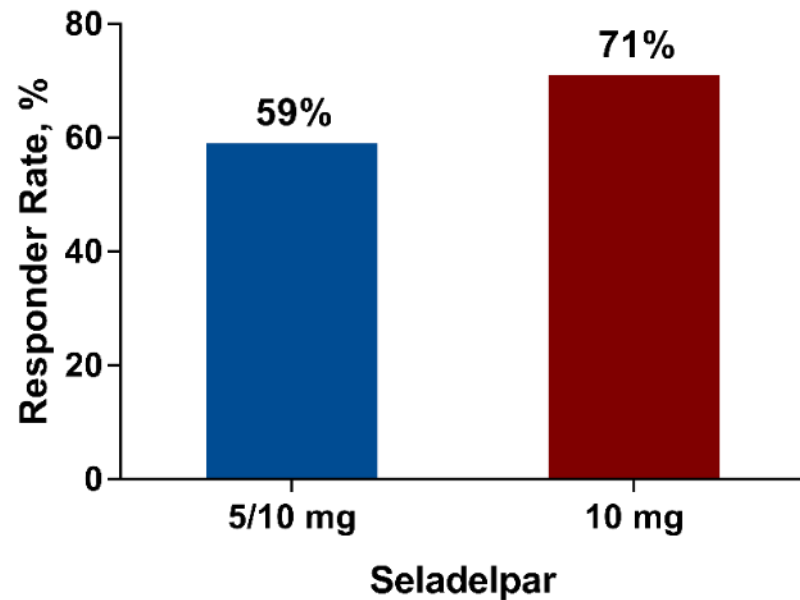
Absolute Liver stiffness levels over time



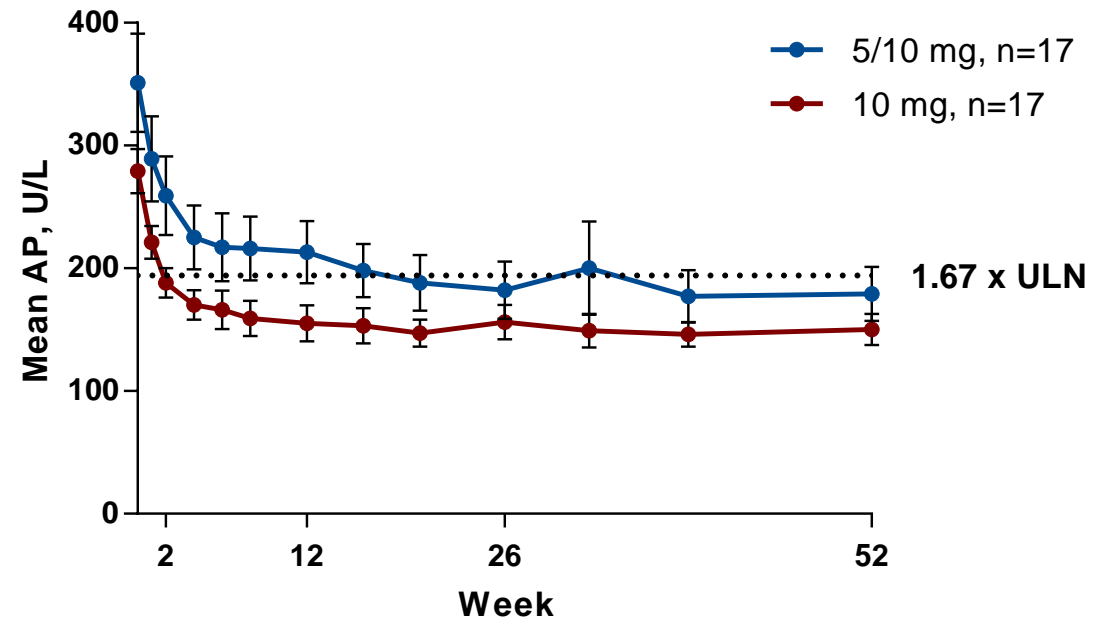
# SELADELPAR: AGONISTE PPAR- $\delta$ SÉLECTIF

## Étude de Phase 2 de 52 semaines

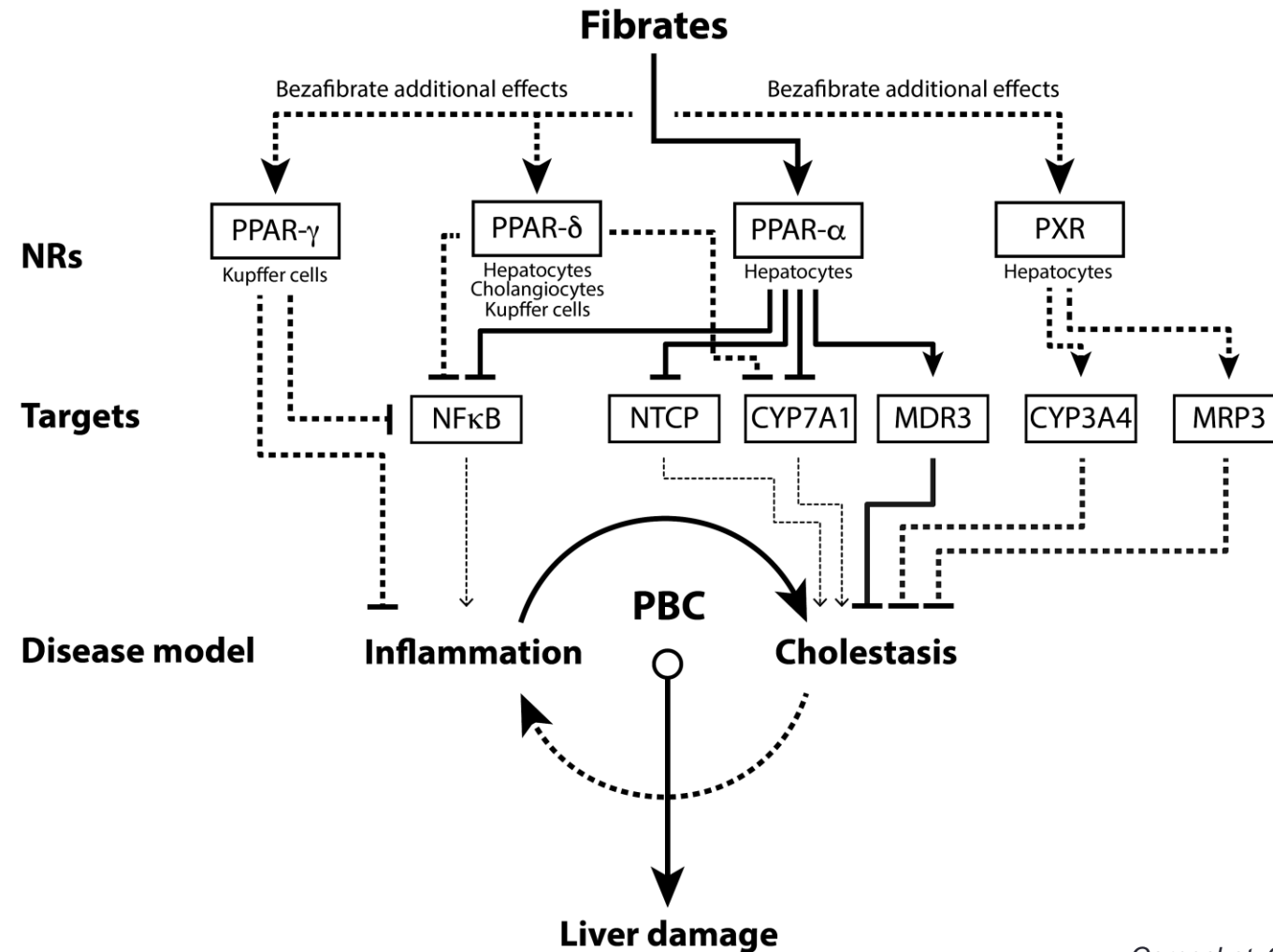
Response rate: ALP < 1.67N and  $\Delta$ ALP > 15%



Absolute ALP levels over time



# AGONISTES PPAR ET CBP



# DÉVELOPPEMENTS THÉRAPEUTIQUES

## CBP

## CSP

PHASE 3

AUDC  
OBETICHOLIC  
BÉZAFIBRATE

BUDÉSONIDE \*

PHASE 2

SÉLADELPAR  
TROIIFEXOR  
NGM282



AUDC \*

NOR-AUDC  
OBETICHOLIC  
NGM282 \*  
CILOFEXOR

\* Selon le critère de jugement considéré



# CONCLUSION ET PERSPECTIVES

- **Agonistes FXR et agonistes PPAR** = nouveaux traitements de la cholestase
- **Indication** = traitement de 2<sup>ème</sup> ligne de la CBP (AMM conditionnelle pour l'acide obéticholique, hors AMM actuellement pour le bézafibrate)
- **Questions en suspens:**
  - Efficacité sur la morbi-mortalité hépatique?
  - Tolérance et effets secondaires à le long terme?
  - Synergie de ces traitements?
  - Efficacité dans les autres maladies cholestatiques?