Case study: Non clinical study outcomes of fasiglifam (TAK-875) discontinued prior to approval

—Consideration from non-clinical study results

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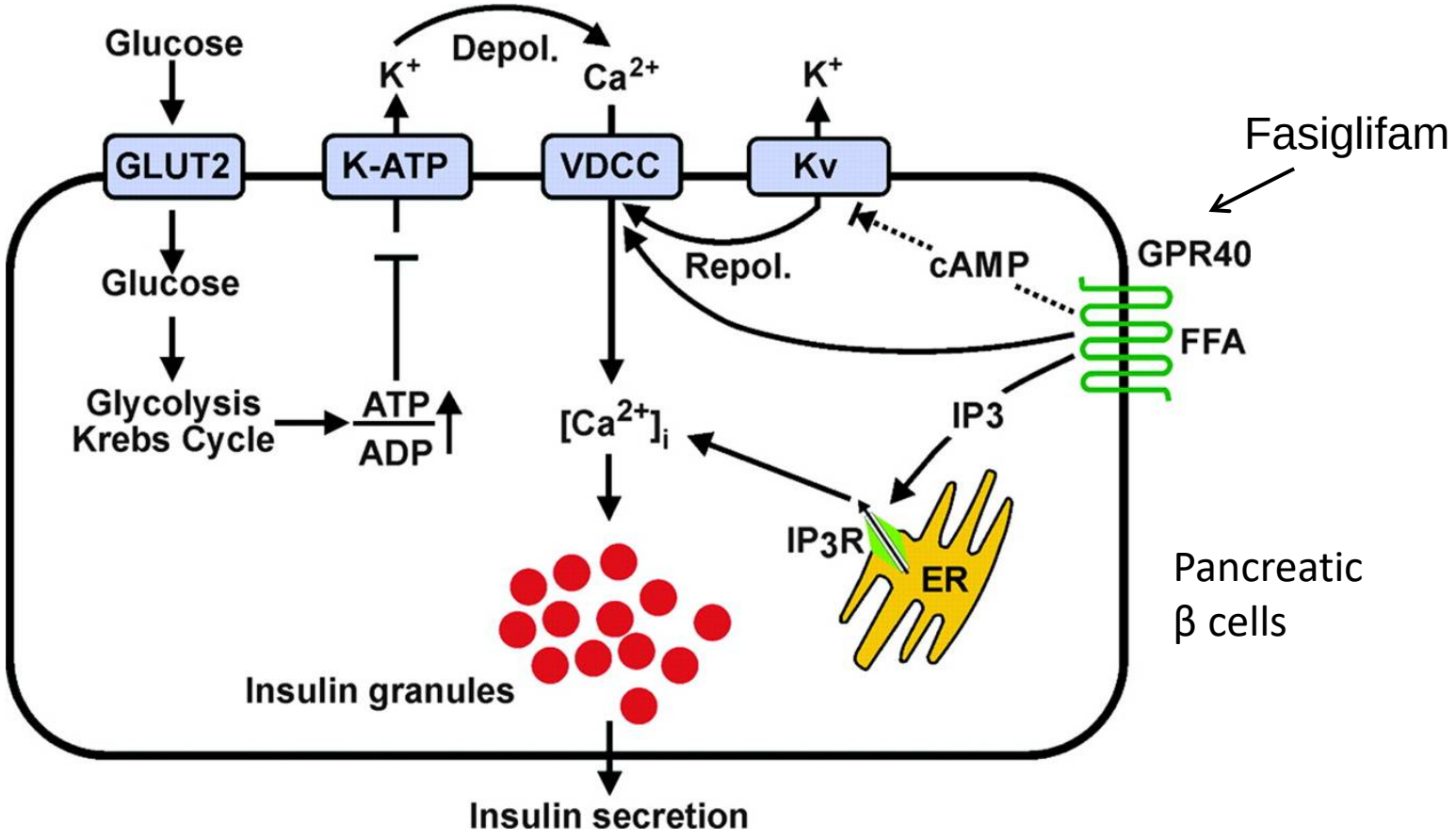
Fasiglifam: Overview of Liver Toxicity Data

Outline

- Pharmacology
- Phase 3 results
- Liver toxicity in repeat-dose studies
  - Rats
  - Dogs
- Pathological changes in dog liver
- Exposure margin

Fasiglifam (TAK-875): Pharmacology

Regulation of insulin secretion by glucose and GPR40



From: Gromada, J. Endocrinology 2006;147:672-673

Clinical development was terminated just before approval in Japan.

What was going on the phase III clinical studies outside Japan?

What is Hy's Law?

Drug-Induced Liver Injury: Premarketing Clinical Evaluation (DILI Guidance, *July 2009)*

- Discontinuation of treatment should be considered if:
  - *stop rules*

	Criteria	Others
ALT/AST	**> 8x ULN**	
ALT/AST	**> 5x ULN**	**over 2 wks**
ALT/AST	**> 3x ULN**	**& T Bilirubin > 2x ULN**
ALT/AST	**> 3x ULN**	**& symptoms** (e.g. fatigue, nausea & vomiting, right upper abdominal discomfort, fever, rash, eosinophilia)

Any potential Hy's Law case should be reported to the FDA promptly.

Overview of liver injury severity in global phase III

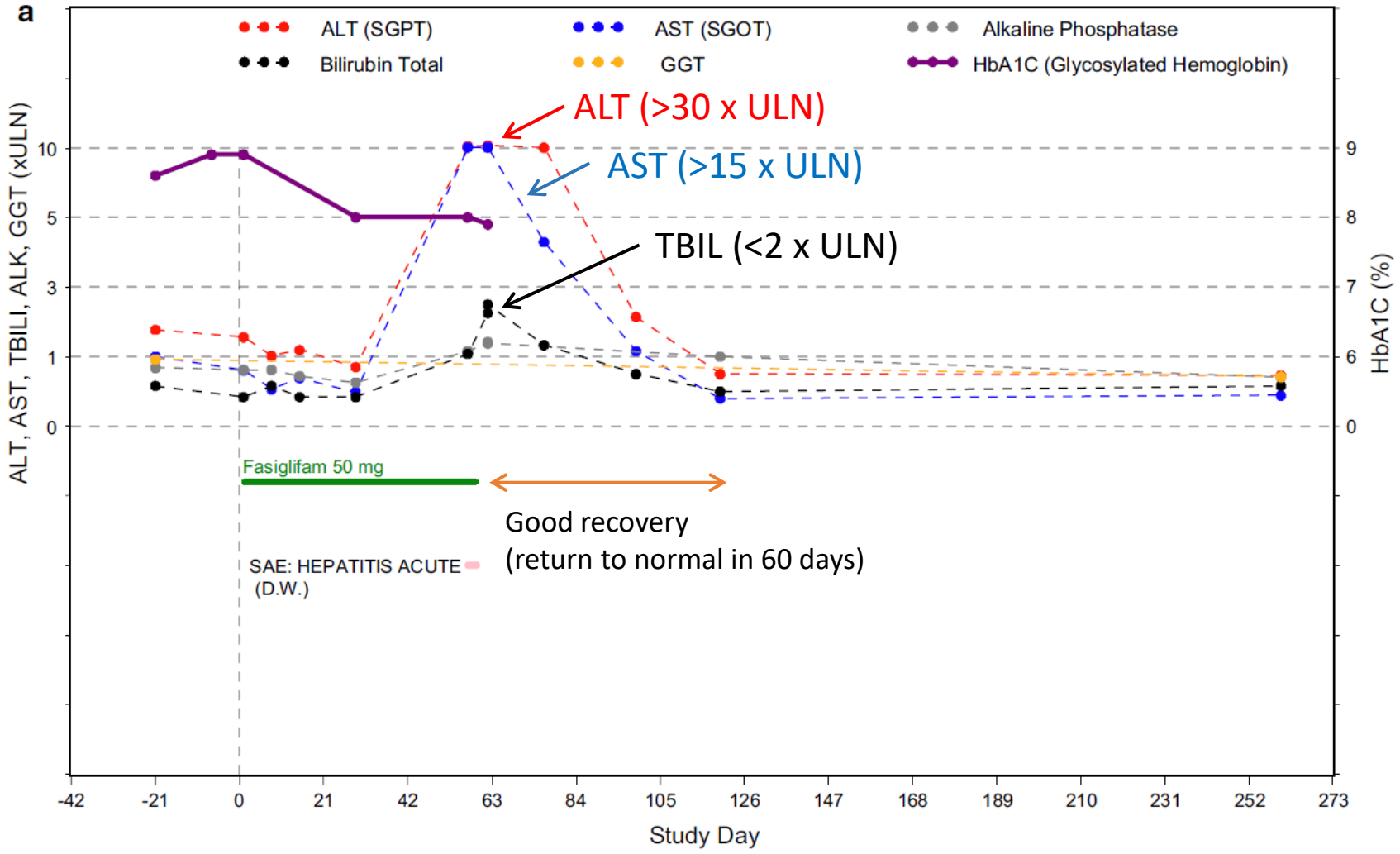
Seriousness category	Placebo	Fasiglifam	Fasiglifam	Sitagliptin	Glimepiride
	[N = 2336] (%)	25 mg [N = 1637] (%)	50 mg [N = 3300] (%)	100 mg [N = 368] (%)	4 mg [N = 953] (%)
ALT >8x ULN	3/2234 (0.1)	10/1624 (0.6)	24/3195 (0.8)	1/360 (0.3)	0
ALT >3x ULN, & TBIL >2x ULN	1/2234 (0.0)	2/1624 (0.1)	5/3195 (0.2)	2/360 (0.6)	0
Hospitalization for the liver injury	2 (<0.1)	4 (0.2)	8 (0.2)	3 (0.8)	4 (0.4)
Liver-related death or transplant	0	0	0	0	0

ALT alanine aminotransferase, ULN upper limit of normal, TBIL total bilirubin, AST aspartate aminotransferase

Marcinak et al. Drug Saf (2018) 41:625–640

Case 1 : Hy's Law Case (Only 1 case)

42-year-old man, fasiglifam 50 mg/day for 2 months



D.W. - Drug Withdrawn, D.I. - Drug Interrupted.

Marcinak et al. Drug Saf (2018) 41:625–640

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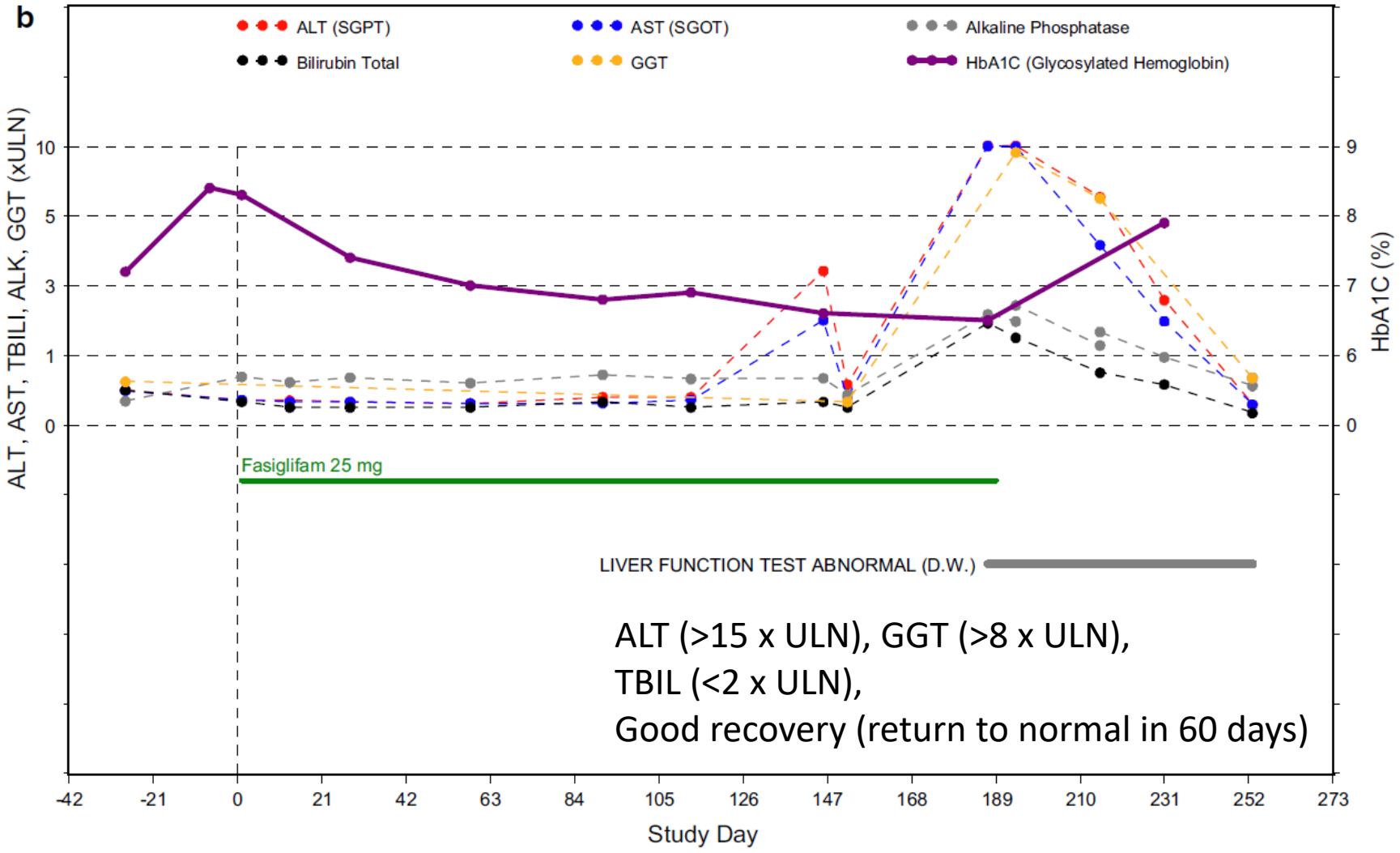
Case 2 : 'Near' Hy's Law Case (1 of 2 cases)

75-year-old man, fasiglifam 25 mg/day for 6 months

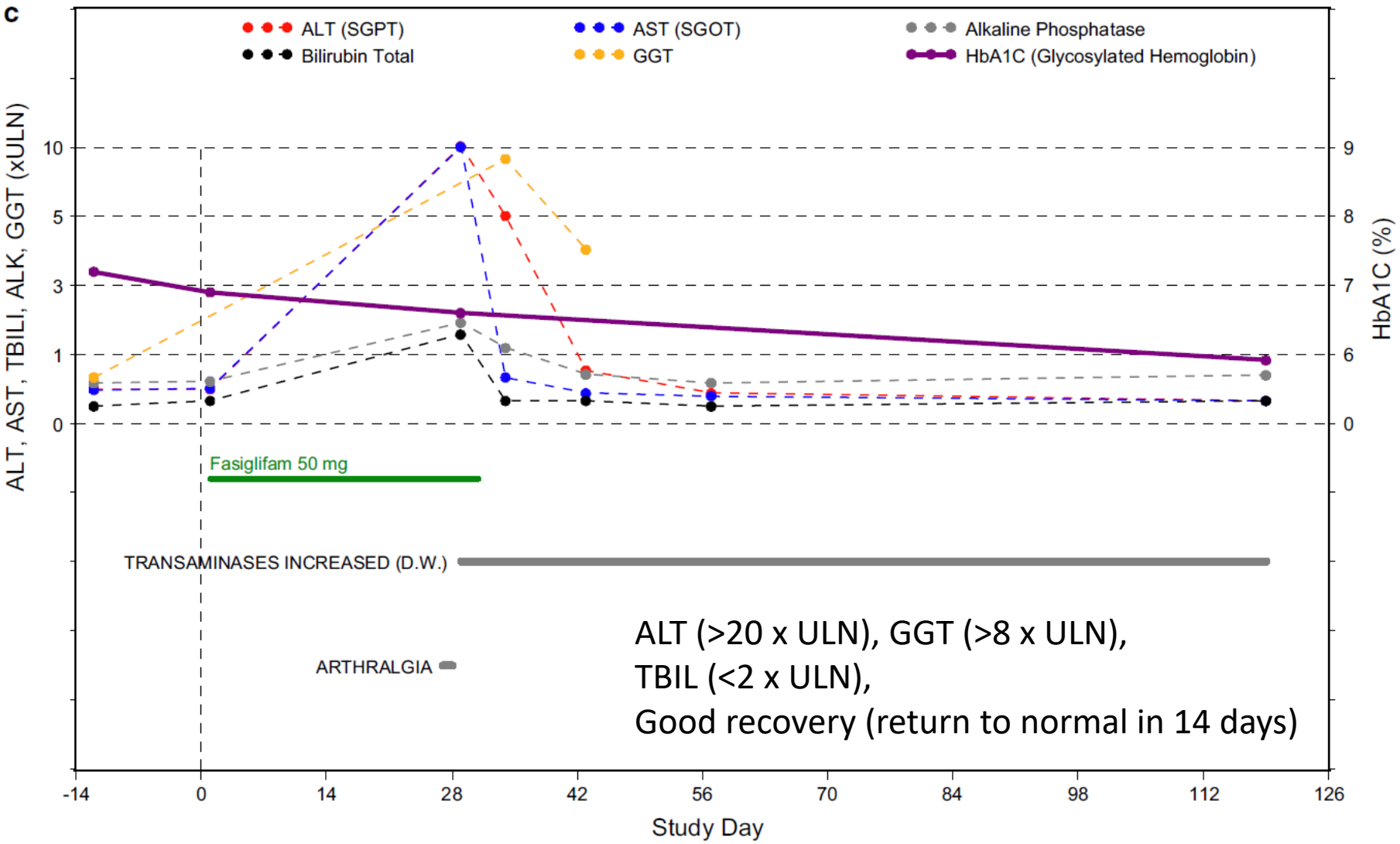


D.W. - Drug Withdrawn, D.I. - Drug Interrupted.

Marcinak et al. Drug Saf (2018) 41:625–640

Case 3 : 'Near' Hy's Law Case (1 of 2 cases)

60-year-old man, fasiglifam 50 mg/day for 1 month



D.W. - Drug Withdrawn, D.I. - Drug Interrupted.

Marcinak et al. Drug Saf (2018) 41:625–640

Clinical development program termination

- The combination of imbalance in ALT elevations with Hy's Law cases led to the termination of the fasiglifam clinical program in late phase III development.

- **Global Phase III:** One definite Hy's Law and two 'near' Hy's Law cases were identified in fasiglifam-treated patients. Three serious liver injuries were attributed to fasiglifam treatment. [**3/5359** patients **(0.05%)** in fasiglifam group]
- **Japanese Phase III:** All studies were completed ahead of the global program. These studies indicated **no Hy's Low cases** in Japanese patients.

- These outcomes resulted in the decision to terminate the clinical development program of fasiglifam.

Marcinak et al. Drug Saf (2018) 41:625–640

Questions?

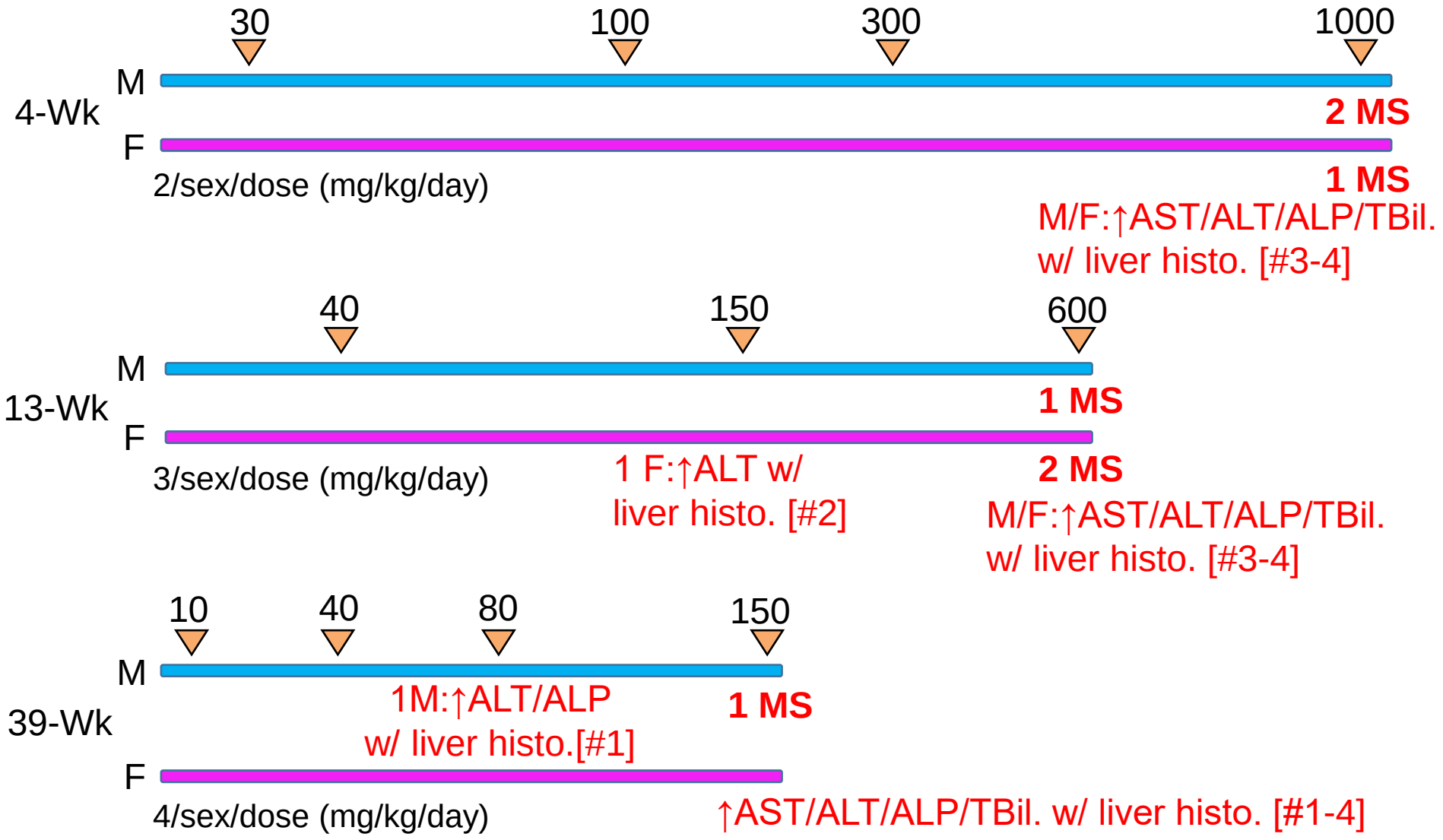
- What had happened in the toxicity studies in animals ?

- Should we predict the outcome of liver toxicity in humans from non-clinical study results?

Fasiglifam: Rat Liver Toxicity

- 4-week (20, 60, 200, 600 mg/kg/day. NOAEL: 60 mg/kg/day)
  - ≥200 mg/kg/day
    - ↑ cholesterol (females)
  - 600 mg/kg/day
    - ↑ liver weight, ↑AST/ALT & bilirubin
    - hypertrophy of centrilobular hepatocytes
- 13-week (20, 60, 600, 2000 mg/kg/day. NOAEL: 60 mg/kg/day)
  - 600 mg/kg/day
    - ↑ liver weight, ↑AST/ALT & bilirubin,
    - hypertrophy of centrilobular hepatocytes
    - Changes resolved/tended to resolve after 13 weeks of recovery
  - 2000 mg/kg/day
    - moribund conditions & mortality (90% by Day 81)
- 26-week (20, 60, 200 mg/kg/day. NOAEL: 60 mg/kg/day)
    - No liver toxicity at up to 200 mg/kg/day

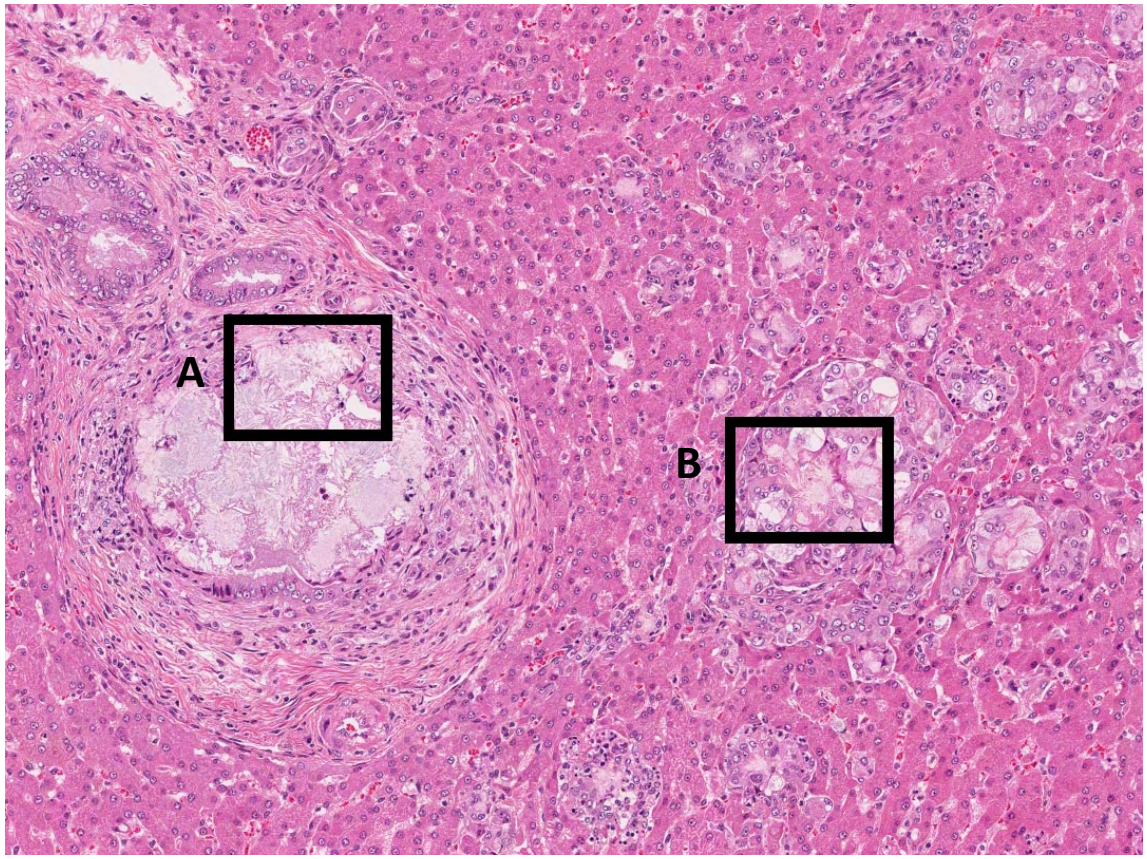
Fasiglifam: Dog Liver Toxicity

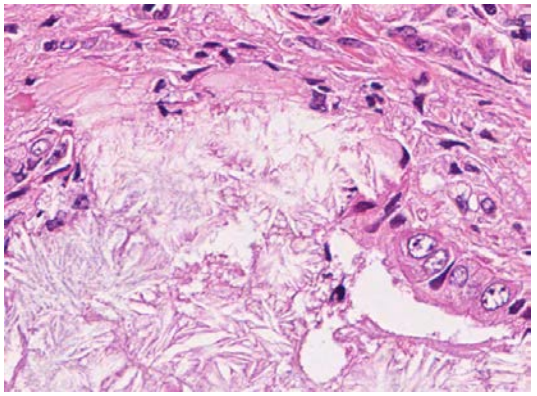


liver histo.=portal/periportal granulomatous inflammation w/ crystal formation, number in [ ] indicates severity grade(s); **MS**: moribund sacrifice.

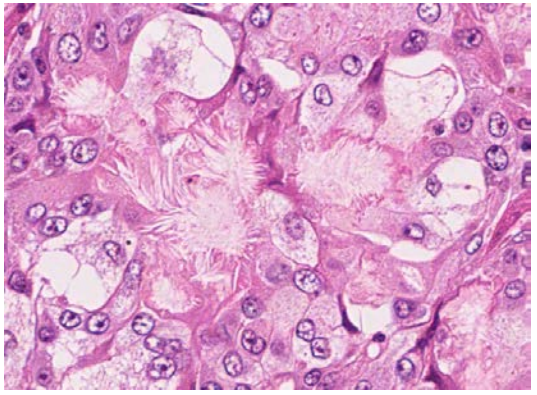
Fasiglifam: Portal/periportal granulomatous inflammation with crystal formation in dogs

Dose: 600 mg/kg





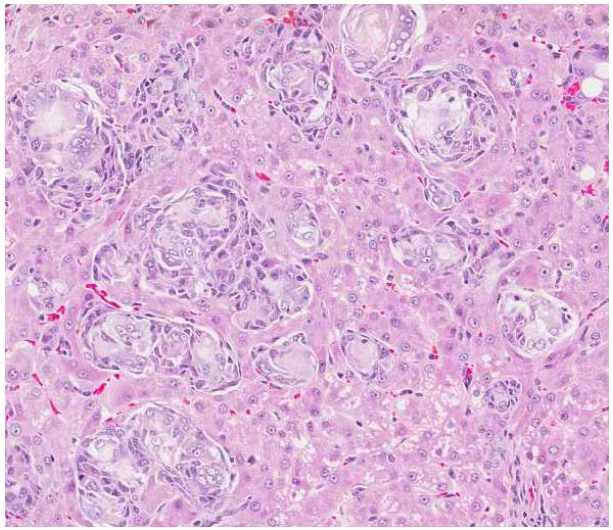
A. bile duct



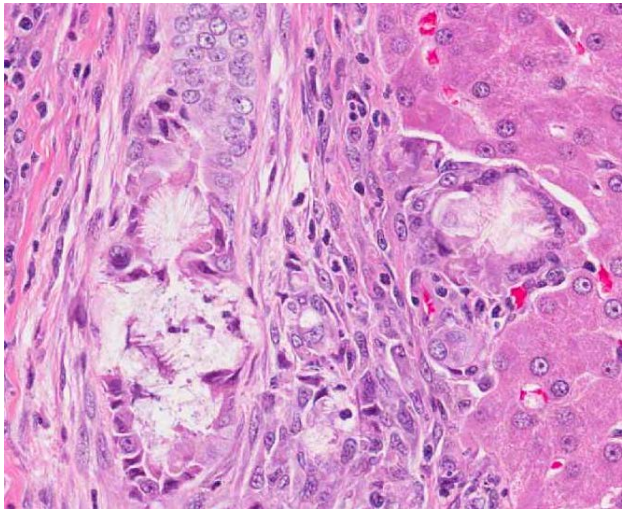
B. parenchyma

The liver toxicity was observed in dogs but not in rats.

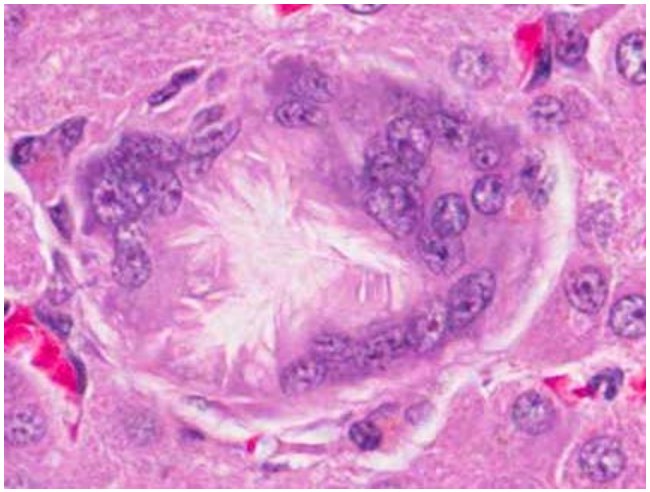
Fasiglifam: Portal/periportal granulomatous inflammation with crystal formation



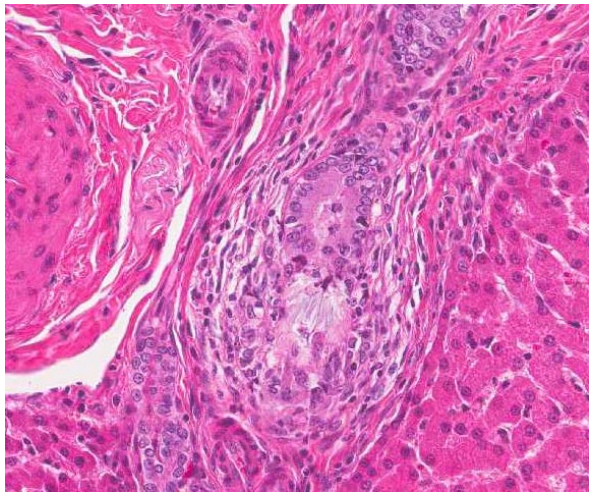
Multiple granuloma [3] (4-week,M,1000 mg/kg/day)



Crystal in bile duct [4] (4-week,M,1000 mg/kg/day)



Granuloma with crystal [4] (4-week,M,1000 mg/kg/day)



Crystal in bile duct [3] (39-week,F,150 mg/kg/day)

M: male; F: female; Number in [ ]: severity grade.

Fasiglifam: Incidence of portal/periportal granulomatous inflammation with crystal formation

Dose (mg/kg/day)	40	80	100	150	300	600	1000
4-Wk 2/sex/dose			-		-		2M/1F MS 1/sex [3] 1/sex [4]
13-Wk 3/sex/dose	-			1F [2]		1M/2F MS 1M [3] 2/sex [4]	
39-Wk 4/sex/dose	-	1M [1]		1M MS 1M [1] 1F [2] 1F [3] 1M [4]			

-: liver appeared normal; M: male; F: female; MS: moribund sacrifice; shaded area: dose not used in the study
Number in [ ]: severity grade 1 (minimal to slight), 2 (mild), 3 (moderate) and 4 (marked to severe).

Process to death due to fasiglifam in dogs

↑ALT, ALP

⇓

↓Food consumption

⇓

↑T-Bil

⇓

Jaundice

⇓

Deterioration in general condition

⇓

Death

Summary: Fasiglifam Dog Liver Toxicity

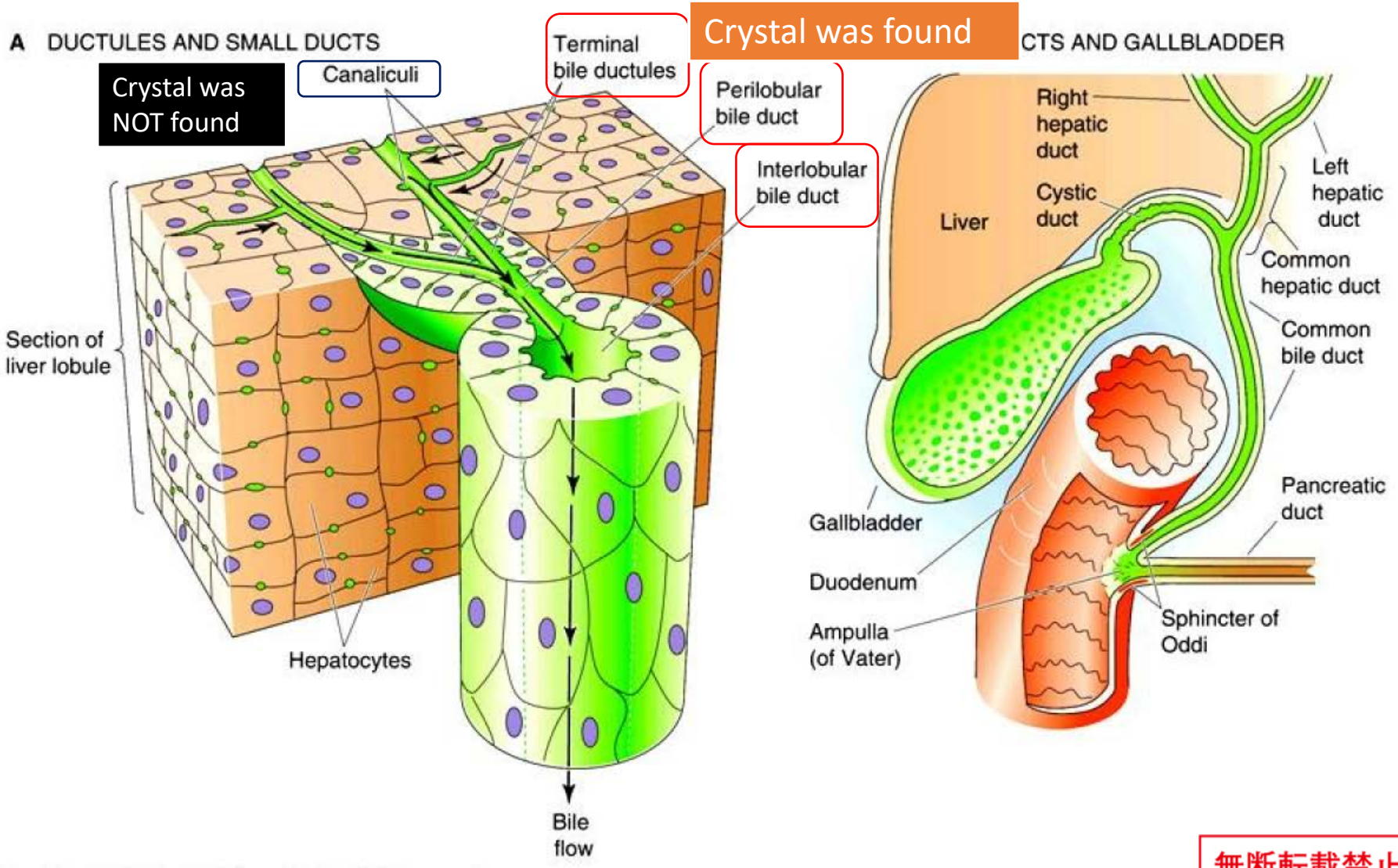
- Dog-specific toxicity in liver/intrahepatic bile ducts
  - Portal/periportal granulomatous inflammation with crystal formation
  - Severity/frequency dose- and time-dependent
  - Liver toxicity at 150 mg/kg/day in the 39-week study resolved/tended to resolve after a 13-week recovery
- Safety margin based on NOAEL in the 39-week dog study for T2DM patients at 50 mg/day
  - 14X

What was the composition of crystal ?

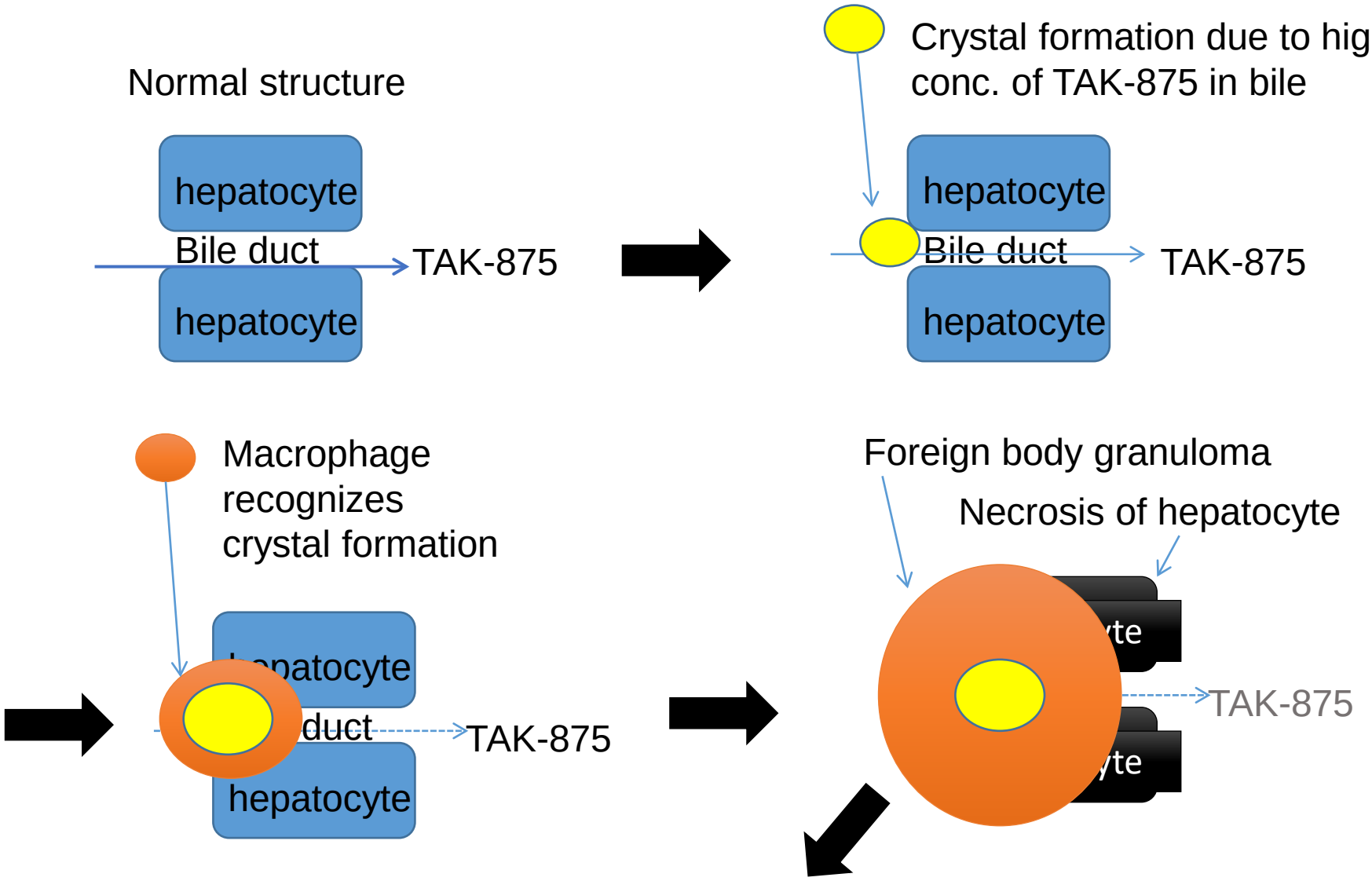
1. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry analysis clarified that the crystalline materials were composed by **fasiglifam and fasiglifam glucuronide**.

2. Hepatotoxicity in dogs is considered due to the precipitation of fasiglifam-related materials in the bile duct.

Bile is secreted by the liver, stored in the gall bladder and ejected into the small intestine



Hypothesis of formation of jaundice with bile stasis



What was safety margin in human bile?

Safety margin in AUC in plasma
- Human Ph3 doses vs NOAEL in dog 39W tox study -

Dose (mg/day)	50
$AUC_{0\text{-}24h}$ (μg.h/mL) in humans	61.4 a)
$AUC_{0\text{-}24h}$ (μg.h/mL) at NOAEL (40 mg/kg/day) in dogs	854 b)
SM (vs AUC in plasma)	**14X**

Estimated Ph3 doses: 50 & 25 mg, AUC at NOAEL in a 39-week tox study in dogs,
a) Mayer, 2014, Drugs R D 14:273–282.
b) Wolenski, 2017, Toxicol Sci 157:50–61.

Possible mechanism of hepatotoxicity in dogs
⇒Precipitation of fasiglifam-related materials in the bile duct.

Consideration of safety margin in bile is more important.

Safety margin in AUC in bile
- Human Ph3 doses vs NOAEL in dog 39W tox study -

Safety margin in estimated conc. in bile: 23X

- Human 50 mg Ph3 doses vs NOAEL in dog 39W tox study -

Next speaker Dr Tagawa explains how to calculate safety margins in bile.

Appropriate SMs (at least 14X in plasma and 23X in bile) would be ensured in consideration of the estimated high dose (50 mg/day) for Ph3.

Conclusion from dog toxicity studies

- Liver toxicity in dogs
  - Unique and likely due to high concentration of TAK-875 and/or metabolites in liver/bile
  - Correlate liver enzyme changes with histopathological changes in affected dogs
- Safety margin based on dog NOAEL is considered adequate (>10X in plasma, >24X in bile, even worst case situation)

TAK-875: KOL and Agency judgment

Key Opinion Leader's opinion:

- Allow clinical monitoring for liver toxicity
- Support progression to Ph.3

In addition, PMDA/FDA/EMA accepted progression to Ph.3.