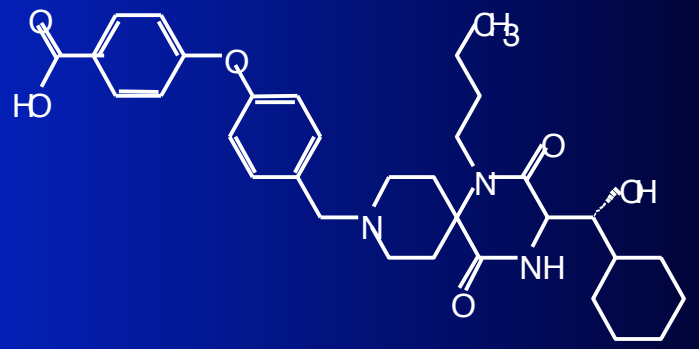
Hepatotoxicity observed in clinical trials of aplaviroc (APL, 873140)

WG Nichols[1], HM Steel[1], TM Bonny[1], SS Min[1],
L Curtis[1], K Kabeya[2], N Clumeck[2]
[1] GlaxoSmithKline, Research Triangle Park, USA;
[2] CHU-Saint-Pierre, Brussels, Belgium.

Aplaviroc (APL, 873140, Ono 4128)



- Specific CCR5 antagonist
- Potent HIV entry inhibitor
  - mean 1.66 $\log_{10}$ decline at nadir in HIV-RNA after 10d monotherapy[1]
- Safety profile supported further study in humans

[1] Lalezari J et al. AIDS 2005;19:1443–1448.

Aplaviroc Phase 2b Program

CCR100136

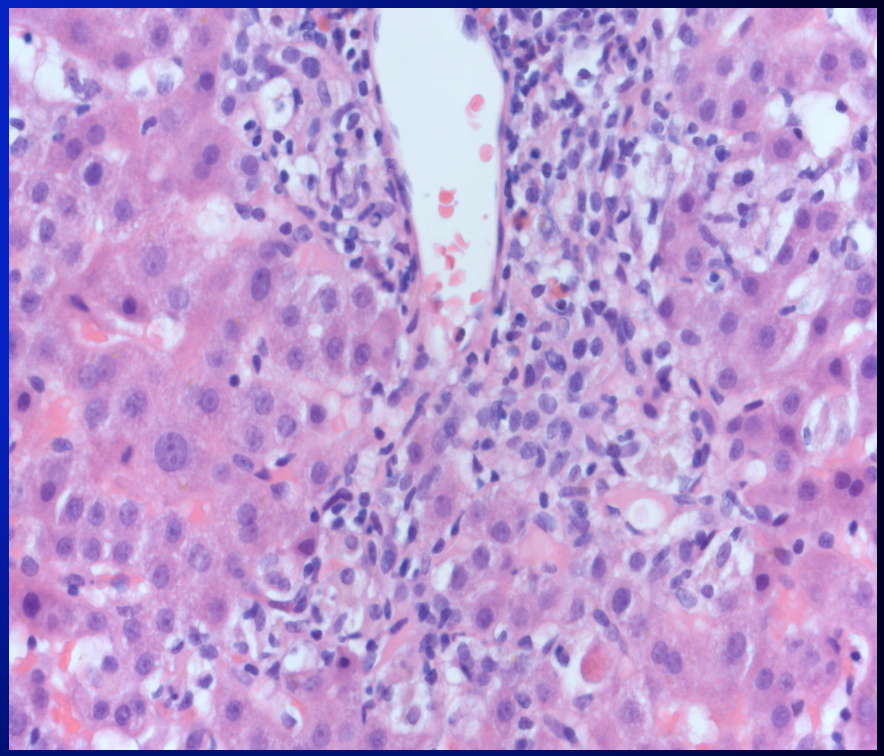
- 195 treatment-naïve subjects randomized to
  - APL 200mg BID / LPV/r
  - APL 400mg BID / LPV/r
  - APL 800mg QD / LPV/r
  - LPV/r / Combivir
  - 2:2:2:1 randomization

CCR102881

- 147 treatment-naïve subjects randomized to
  - APL 600mg BID / Combivir
  - APL 800mg BID / Combivir
  - Combivir / efavirenz
  - 2:2:1 randomisation

Sentinel case: Severe hepatitis

- 39 year old HIV+ male
  - CD4 283 cells/mm^3
  - HBV/HCV negative
  - Normal AST/ALT/bilirubin
- APL 800mg BID + COM
- Day 59: developed severe hepatic cytolysis
- Liver biopsy:
  - Chronic inflammatory infiltrate, mod intensity
  - Consistent with drug-induced hepatotoxicity



Liver biopsy (portal area)

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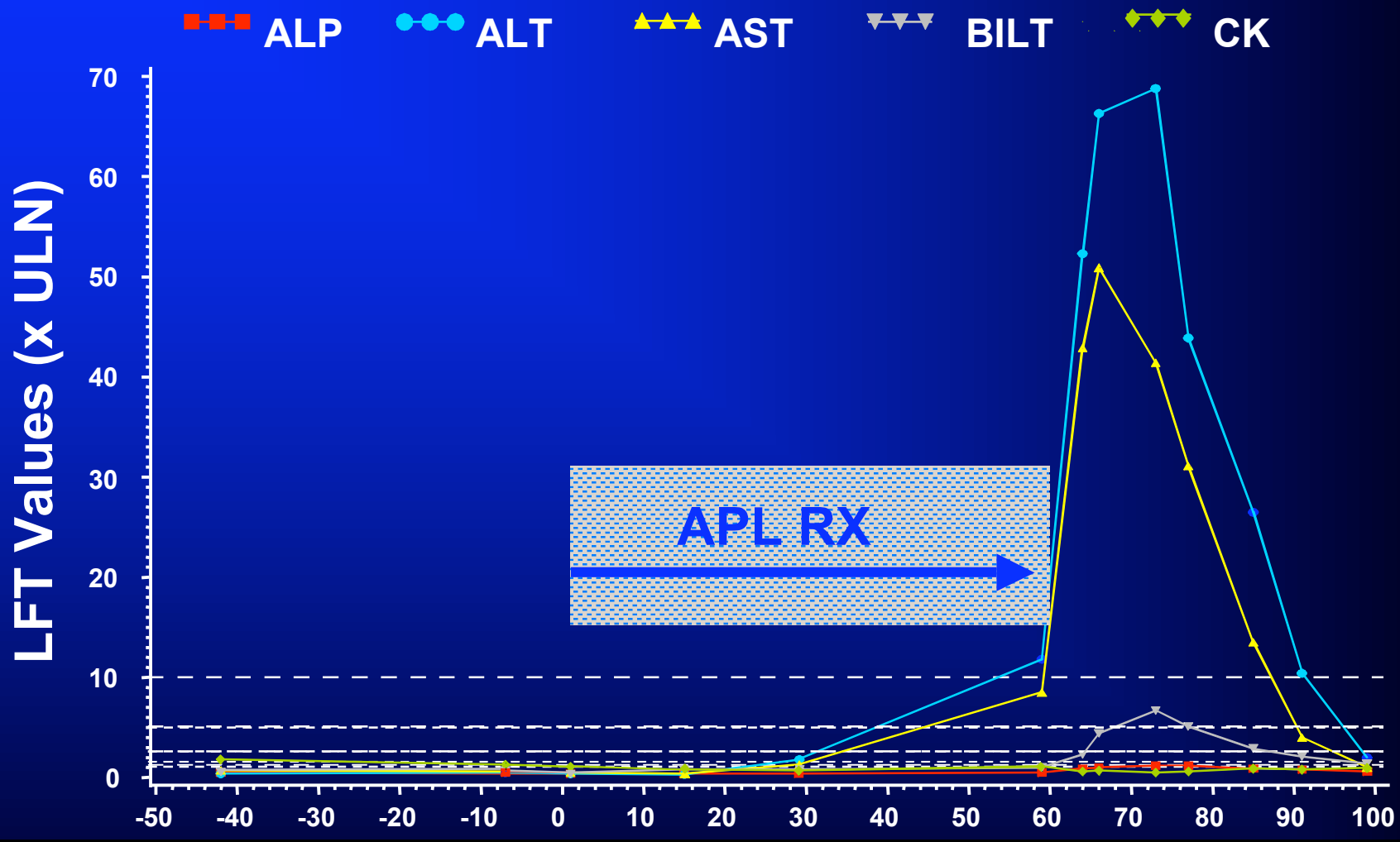
Individual Patient LFT Plots



Review of Liver Enzyme Elevations in APL Phase IIb trials

- 336 subjects received treatment
  - 282 subjects on APL
  - median duration of therapy: 13 wks
- Central Lab database query to identify
  - any Grade 3/4 elevation in ALT, AST or bilirubin
- 13 subjects identified
  - 3 BL abnormalities (2 APL, 1 control) improved
  - **10 treatment-emergent cases, all on APL**

Cases of Grade 3/4 Liver Enzyme Elevations NOT Attributed to APL (N=6)

- 3 cases: exercise induced
  - transient AST with concurrent elevation in CPK
- 2 cases: increased bilirubin related to other drugs
  - 1 after APL withdrawal and switch to ATZ/rtv
    - (max 5X ULN)
  - 1 with concomitant prochlorperazine and alcohol
    - (max 3X ULN)
- 1 case: grade 2 bilirubin at screen
  - fluctuations on APL
    - grade 3 at single time point, max 2.7X ULN

Cases of Clinical Concern (N=4)

1. Severe hepatitis
   - sentinel case (APL 800mg BID + COM)
   - reported as Serious Adverse Event (SAE)
2. Hepatitis
   - underlying hepatic disease (APL 400mg BID + LPV/r)
   - symptomatic ↑ in ALT (12x ULN) and bilirubin (3x ULN)
3. Asymptomatic hepatitis
   - no underlying liver disease (APL 400mg BID + LPV/r)
   - elevations in ALT/AST (max 9X ULN) without elevation in bilirubin
   - positive de-challenge and re-challenge
4. Hyperbilirubinaemia
   - HBV co-infected subject (APL 200mg BID + LPV/r)
   - Grade 3 elevations in bilirubin (max 5X ULN)
   - reported as SAE

Actions Taken to Protect Patient Safety

- Risk:benefit deemed unfavourable for therapy naïves
  - investigators notified
  - all subjects in Phase 2b studies stopped dosing
  - studies amended to collect additional follow-up data
- Ongoing phase 3 studies in treatment-experienced subjects (on OBT with APL 400mg BID or Placebo)
  - Screening and randomisation halted
  - Subjects already randomised (N=46) allowed to continue
    - few treatment options
    - intensive 2 weekly monitoring after re-consent of all subjects

APL Phase 3 Safety Findings

- 1 of 26 subjects randomized to APL developed grade 4 ALT at Week 4
  - max 24X ULN
  - slight ↑ bilirubin
    - background ATV/r therapy
  - 57-year-old Caucasian man
  - asymptomatic at all visits
  - stopped all study medication

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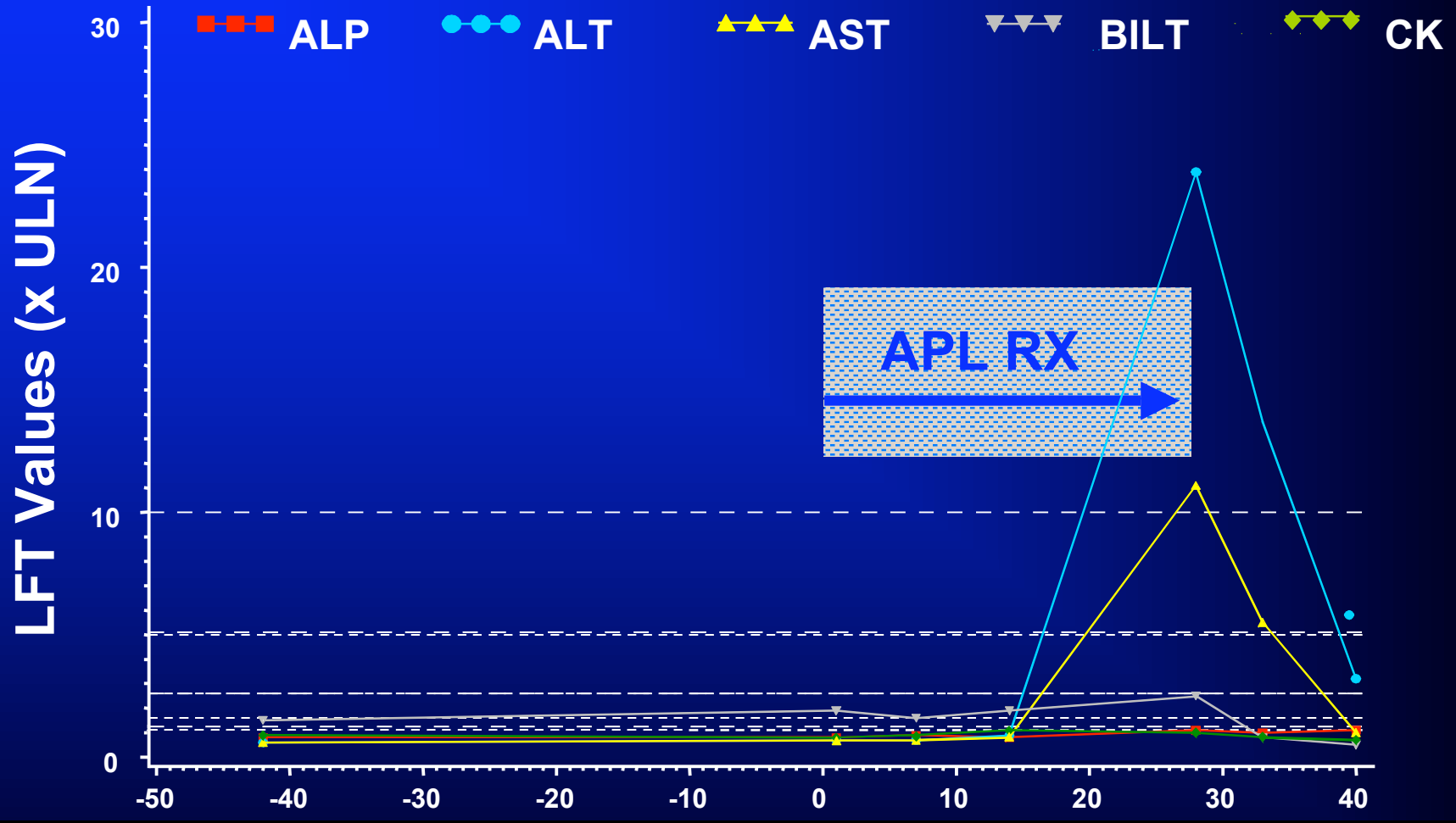
APL Phase 3 Safety Findings

Individual Patient LFT Plots



APL Phase 3 Safety Response

- Phase 3 studies terminated; treatment unblinded
  - Subjects on APL, deemed to be gaining clinical benefit, allowed to continue Tx with intensive 2 weekly monitoring

"Hy's Law"

- 10-50% patients with hepatocellular jaundice will have fatal liver failure[1]
- ↑ ALT *or* total bilirubin are relatively common (particularly in HIV/AIDS)
  - **BUT combination** is rare in drug development
- FDA: combination of "ALT >3xULN and total bilirubin >1.5xULN" as an indicator of clinical concern[2]
- Clinical relevance validated:
  - 12.7% incidence of mortality/liver transplantation in subjects with hepatocellular jaundice[3]

Hyman Zimmerman

[1] Zimmerman HJ. Hepatotoxicity (New York: Appleton-Century Crofts), 1978.
[2] FDA, www.fda.gov/cder/livertox/clinical.pdf-04-17-2001
[3] Bjornsson and Olsson, Hepatology 2005;42:481-9.

Summary: Observations of Hepatotoxicity in APL Clinical Trials

- 4 of 308 (1%) subjects dosed with APL had combined elevations in ALT (>3xULN) and bilirubin (>1.5xULN), meeting Hy's Law criteria
- No deaths or cases of liver failure
  - all subjects have fully recovered
- Clinical development of APL has been discontinued

Acknowledgements

- Investigators
- Sites/Patients involved in APL Clinical Program
- Chris Hunt and GSK Hepatotoxicity board
- External consultants (Watkins, Lewis, Kaplowitz)
- Aplaviroc Development Team

"Hepatotoxicity has been the most common single adverse effect.….causing major drug problems, including withdrawals and refusals to approve"

–Bob Temple, FDA CDER, 2002