Rivaroxaban

Cardiovascular and Renal Drugs
Advisory Committee
March 19, 2009

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Peter M. DiBattiste, M.D., F.A.C.C.
Cardiovascular Therapeutic Area Head
Johnson & Johnson
Pharmaceutical Research and Development, L.L.C.

Proposed Indication

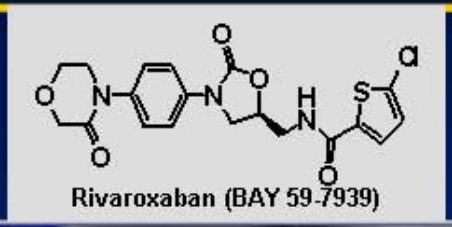
- Rivaroxaban is indicated for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing
  - Hip replacement surgery (THR)
  - Knee replacement surgery (TKR)

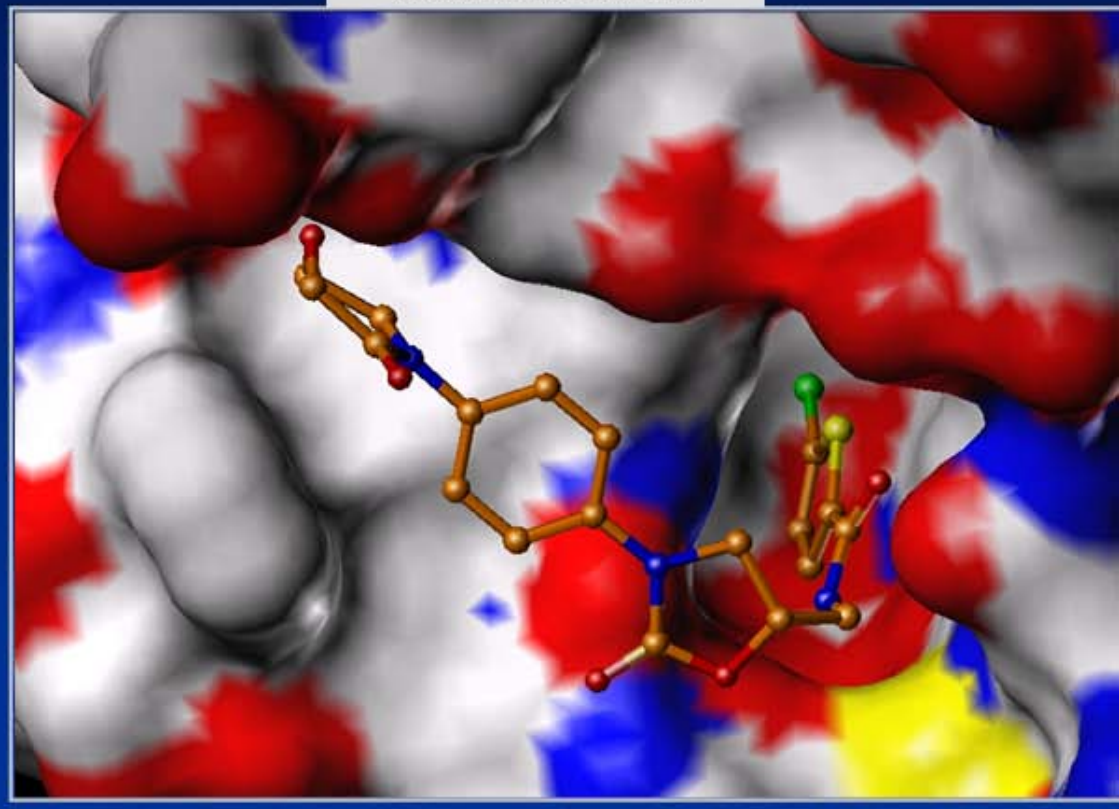
Rivaroxaban Development

- Rivaroxaban is being co-developed through a joint research program between Bayer HealthCare Pharmaceuticals and Johnson & Johnson Pharmaceutical Research and Development, L.L.C.

Rivaroxaban: the first oral direct Factor Xa inhibitor

- Direct, specific, competitive Factor Xa inhibitor
- Inhibits free and clot-bound Factor Xa activity and prothrombinase activity
- Inhibits thrombin generation





Roehrig S *et al. J Med Chem* 2005;48:5900–8; Perzborn E *et al. J Thromb Haemost* 2005;3:514–21.

Rivaroxaban Clinical Development Programs

Program	N
• Phase 2: VTE prophylaxis in THR/TKR	2,787*
• RECORD: VTE prophylaxis in THR/TKR	12,383*

Other studies

• **ATLAS ACS Phase 2** 2° prevention after acute coronary syndrome	3,491*
• **ATLAS 2 ACS Phase 3** 2° prevention after acute coronary syndrome	ongoing
• **MAGELLaN** VTE prophylaxis in hospitalized medically ill	ongoing
• **EINSTEIN** VTE treatment and secondary prevention	ongoing
• **ROCKET AF** Stroke prevention in atrial fibrillation	ongoing

*Completed

Sponsor Presentation

• Total Hip and Knee Replacement: Current Practice	Richard J. Friedman, MD *Medical University of South Carolina*
• Rivaroxaban Development Program	Gary R. Peters, MD
• Hepatic Safety Assessment	Paul B. Watkins, MD *University of North Carolina Chapel Hill*
• Safety Surveillance and Risk Management • Benefit-Risk Assessment • Summary and Conclusions	Peter M. DiBattiste, MD

Experts Available to Advisory Committee

• Eugene Schiff, MD	*University of Miami Miller School of Medicine*
• Willis Maddrey, MD	*University of Texas Southwestern Medical Center*
• Yves Horsmans, MD	*Université Catholique de Louvain*
• Peter Kowey, MD	*Jefferson Medical College*
• Craig Brater, MD	*Indiana University School of Medicine*
• Gerald Faich, MD	*United BioSource Corporation*

Current Use of Anticoagulants in Total Joint Arthroplasty

Richard J Friedman, MD, FRCSC
Clinical Professor of Orthopaedic Surgery
Medical University of South Carolina
Chairman, Department of Orthopaedic Surgery
Roper Hospital, Charleston, SC

Why Prophylax?

- Pulmonary death
- DVT: Proximal & distal

  Primary & recurrent
- Chronic pulmonary hypertension
- Post-thrombotic syndrome

Incidence Of VTE*

	DVT†		PE	
Procedure	Total %	Prox %	Total %	Fatal %
THR	42-57	18-36	0.9-28	0.1-2.0
TKR	41-85	5-22	1.5-10	0.1-1.7

*Control or placebo groups; †Mandatory postoperative venography.
Geerts et al. *Chest* 2008

Total Joint Arthroplasty

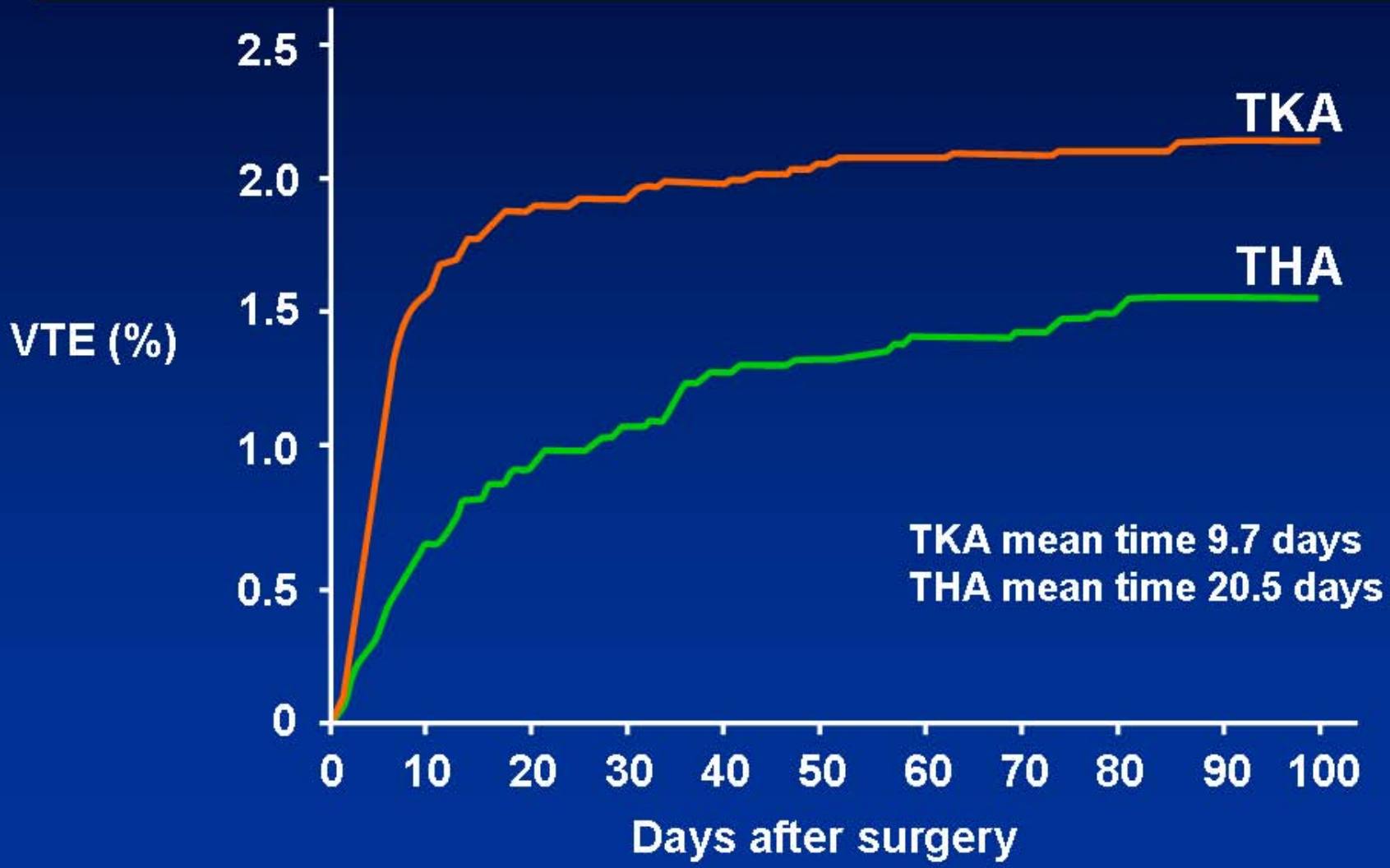
- Over 300,000 THA and 500,000 TKA yearly
- Patients admitted day of surgery
- Mean length of stay 3.1 days
- 25-30% discharged at 2 days
- VTE prophylaxis is mainly an outpatient event

International Comparisons in THR and TKR

- Patient demographics similar between US and rest of world
- Surgical procedures and outcomes similar
- Variations in length of stay
- ASA and warfarin rarely used outside of US
- Similar VTE rates worldwide

Warwick D, Friedman R, *et al. J Bone Joint Surg.* 2007;89-B:799-807
Friedman RJ et al. Curr Med Res Vol 24 No.1, 2008

Cumulative Incidence of Symptomatic VTE after THA or TKA



Warwick D, Friedman R, *et al. J Bone Joint Surg.* 2007;89-B:799-807.

Total Joint Arthroplasty

- Need out of hospital prophylaxis that is safe and efficacious
- VTE most common and serious postoperative complication
- Studies show compliance with ACCP guidelines less than optimal

Drawbacks of Currently Available Agents Limit Their Optimal Use

- Almost all patients in U.S. receive at least some form of recommended prophylaxis
- Full compliance with guidelines (type, duration, start time, dose) achieved in
  - 47% of THR patients
  - 61% of TKR patients
- Compliance rates for LMWHs:
  - 63% of THR patients
  - 72% of TKR patients
- Compliance rates for warfarin:
  - 33% of THR patients
  - 48% of TKR patients

Friedman RJ et al. Curr Med Res Vol 24 No.1, 2008

VTE Prophylaxis

- Oral agents: warfarin
- Advantages
  - Oral
  - Efficacious
- Disadvantages
  - Twice weekly blood draws
  - Food and drug interactions
  - Variable response
  - Slow onset and offset
  - Bleeding complications

VTE Prophylaxis

- Injectable agents: LMWH, fondaparinux
- Advantages
  - Fixed dose qd
  - No monitoring or dose adjustment
  - No food and drug interactions
  - Safe
  - Efficacious
- Disadvantages
  - Injectable
  - Cost increased compared to warfarin

VTE Prophylaxis

- Sequential Pneumatic Compression (IPC)
- Advantages
  - Efficacious in TKA if worn 19 hours/day
  - No effect on bleeding
  - Safe
- Disadvantages
  - No efficacy in THA alone
  - Not efficacious if worn 13 hours/day
  - Restricted to in-hospital use only
  - Limited use with early PT and D/C

Summary

- Important clinical needs exist in DVT/PE prophylaxis in THA and TKA
- Symptomatic and asymptomatic VTE is clinically important
- There are significant costs associated with the management of patients with VTE
- Significant inconsistencies exist between clinical practice and published guidelines
- Deficiencies of existing therapies create the need for new agents with:
  - Improved efficacy
  - More convenient dosing and administration
  - No requirement for anticoagulation monitoring

Rivaroxaban Development Program

Gary R. Peters, M.D., F.A.C.P.
Vice President

Johnson & Johnson
Pharmaceutical Research and Development, L.L.C.

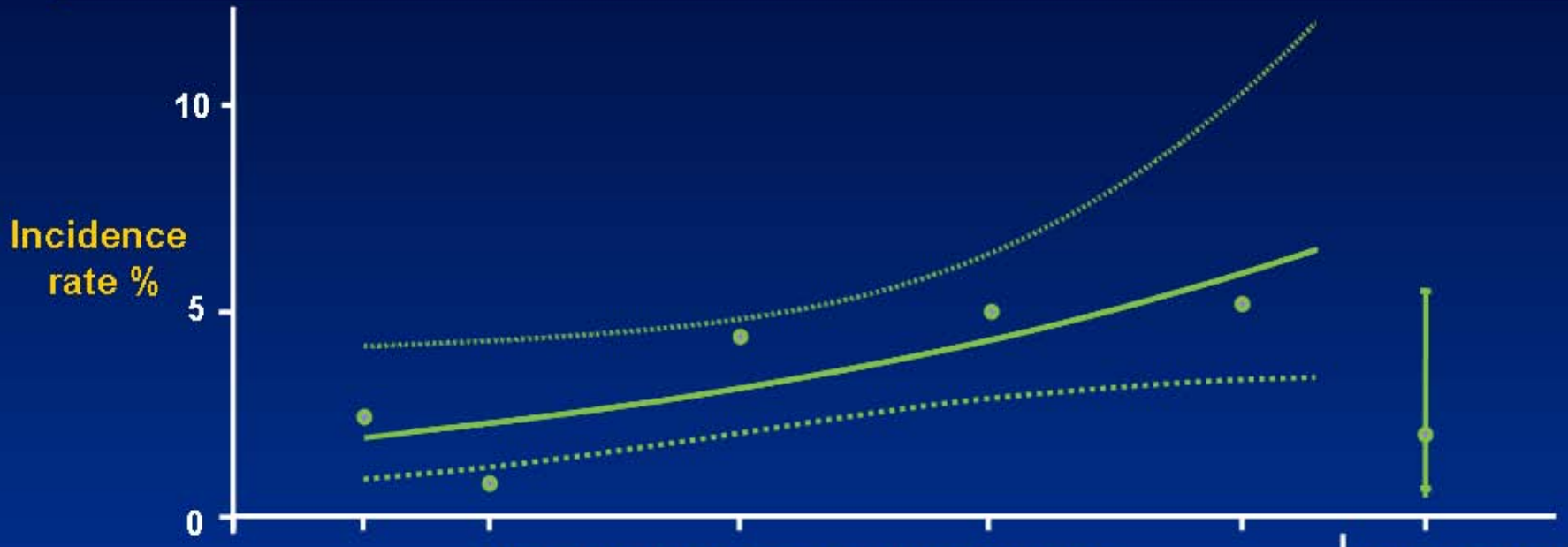
VTE Prophylaxis in THR/TKR: Comprehensive Clinical Program

- Phase 1 - Clinical Pharmacology
  - 52 studies (1129 rivaroxaban)
- Phase 2 - THR and TKR dose finding
  - 4 studies (2232 rivaroxaban)
- Phase 3 - RECORD studies (41 countries)
  - 4 studies (6183 rivaroxaban)
    - RECORD 1 and 2 (THR)
    - RECORD 3 and 4 (TKR)

THR and TKR Dose Finding Summary

- Total daily doses of 5 mg to 60 mg tested
- Once and twice daily dosing regimens with no clear efficacy or safety differences
- Efficacy not strongly related to dose but reduced proximal DVT with increasing dose
- Bleeding dose related but similar to enoxaparin for total daily doses of 20 mg or less
- 10 mg once daily dose selected for Phase 3 evaluation

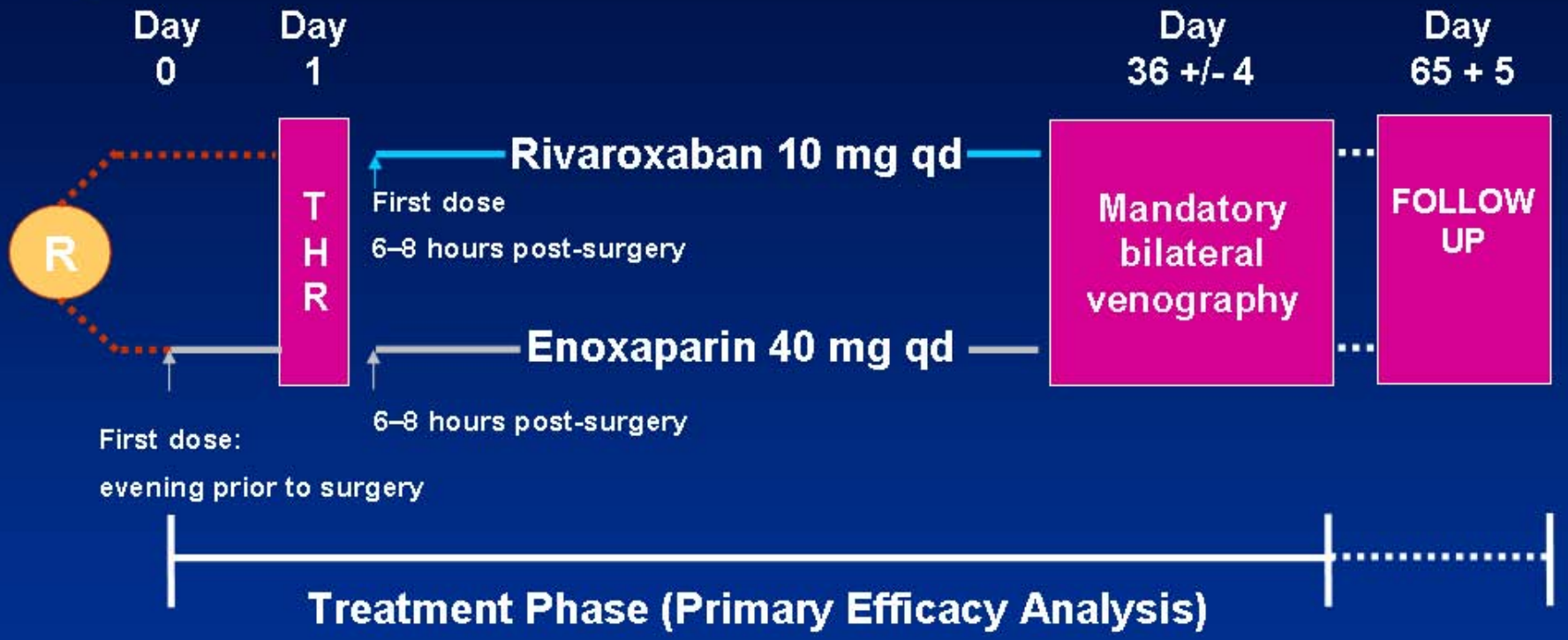
Major Bleeding
Safety Population (Study 11527)



	Total daily dose of Rivaroxaban					Enoxaparin
	5 mg (n=128)	10 mg (n=142)	20 mg (n=139)	30 mg (n=142)	40 mg (n=137)	40 mg (n=157)
n	3	1	6	7	7	3
%	**2.3**	**0.7**	**4.3**	**4.9**	**5.1**	**1.9**
95% CI	0.5, 6.7	0.0, 3.9	1.6, 9.2	2.0, 9.9	2.1, 10.2	0.4, 5.5

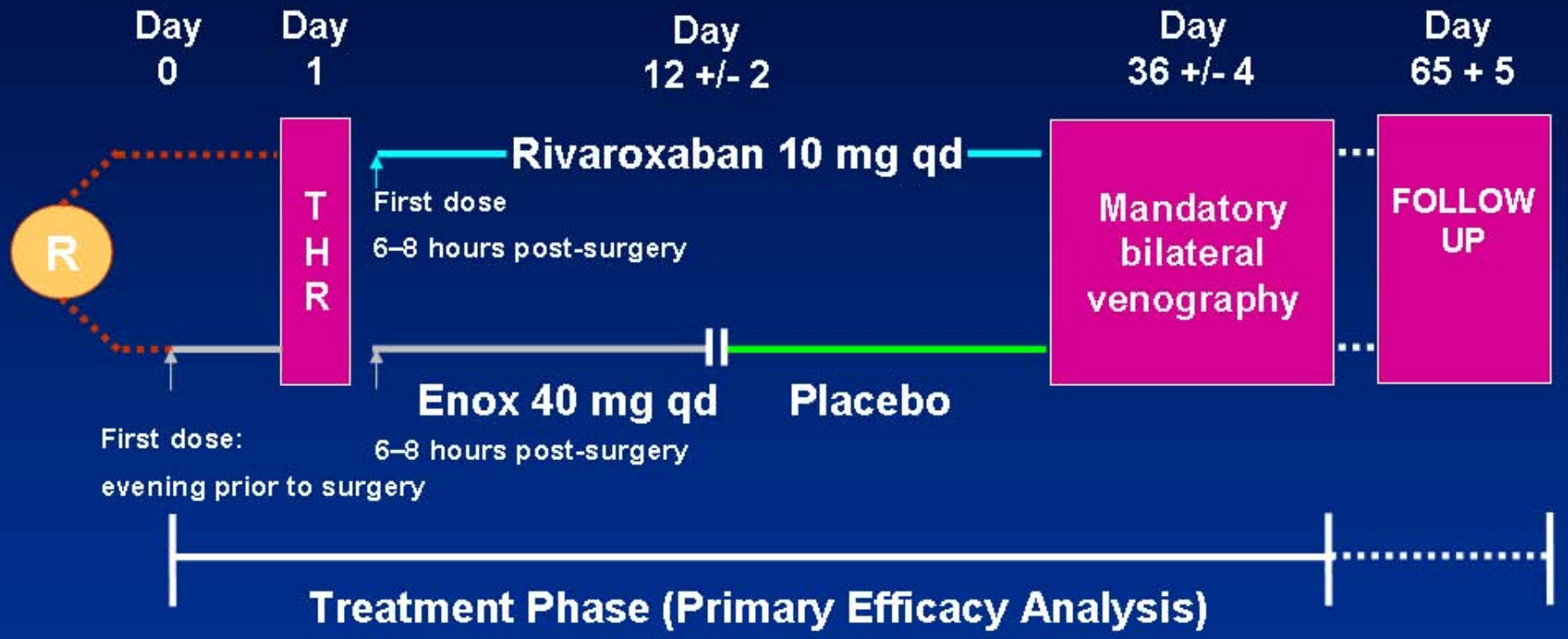
Safety population, n=845. *p*=0.039 for dose trend

RECORD 1 Study Design - THR



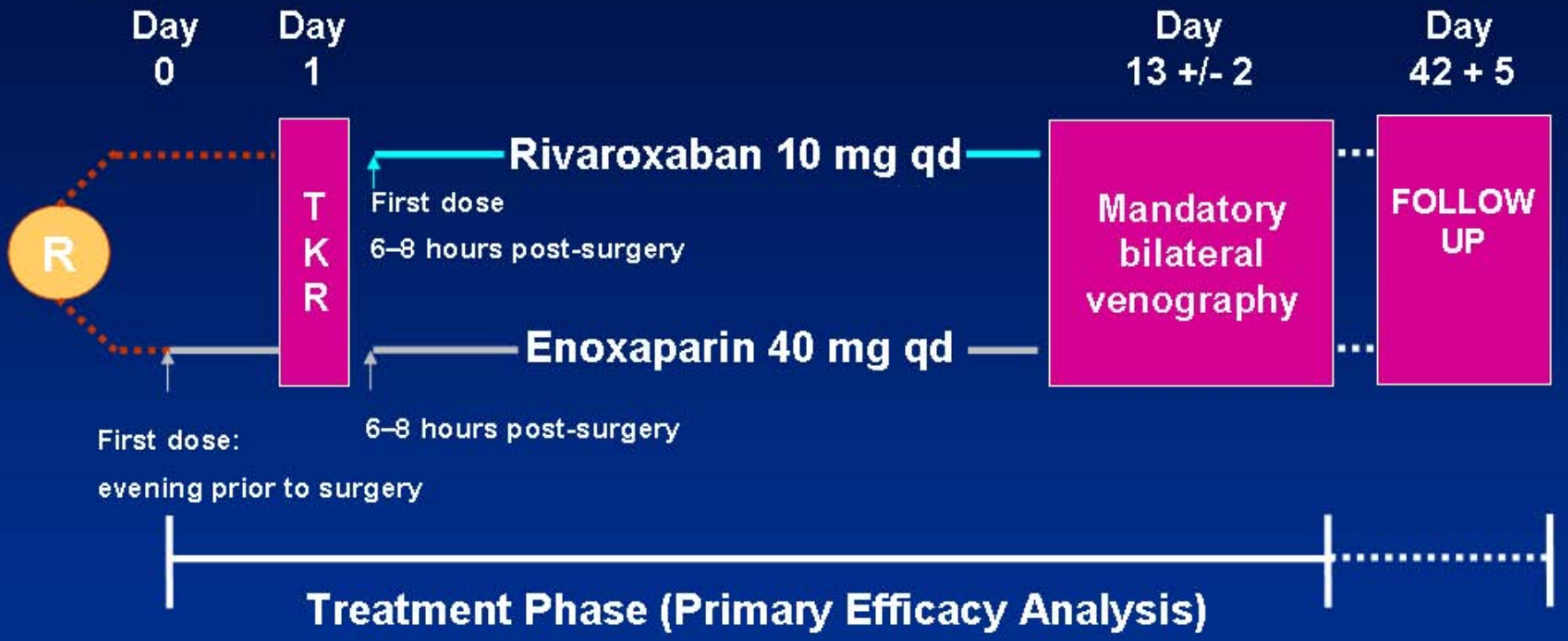
Protocol and analyses agreed upon with FDA

RECORD 2 Study Design - THR



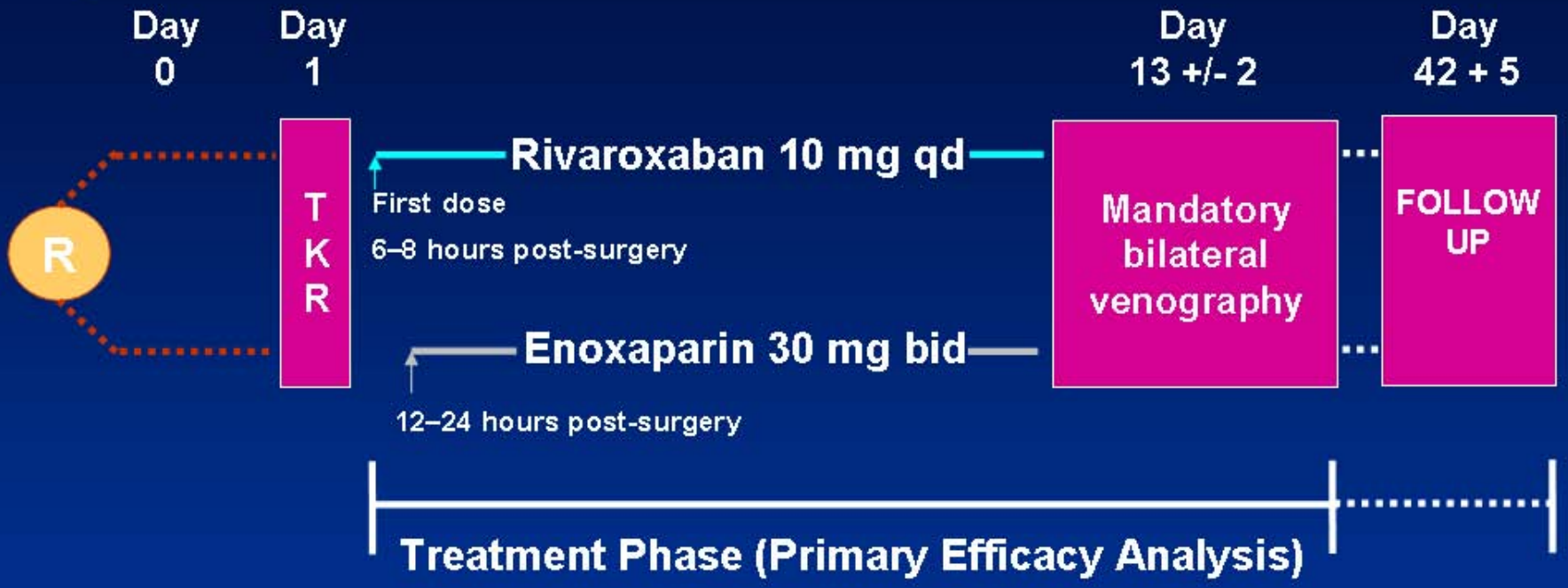
Protocol and analyses agreed upon with FDA

RECORD 3 Study Design - TKR



Protocol and analyses agreed upon with FDA

RECORD 4 Study Design - TKR

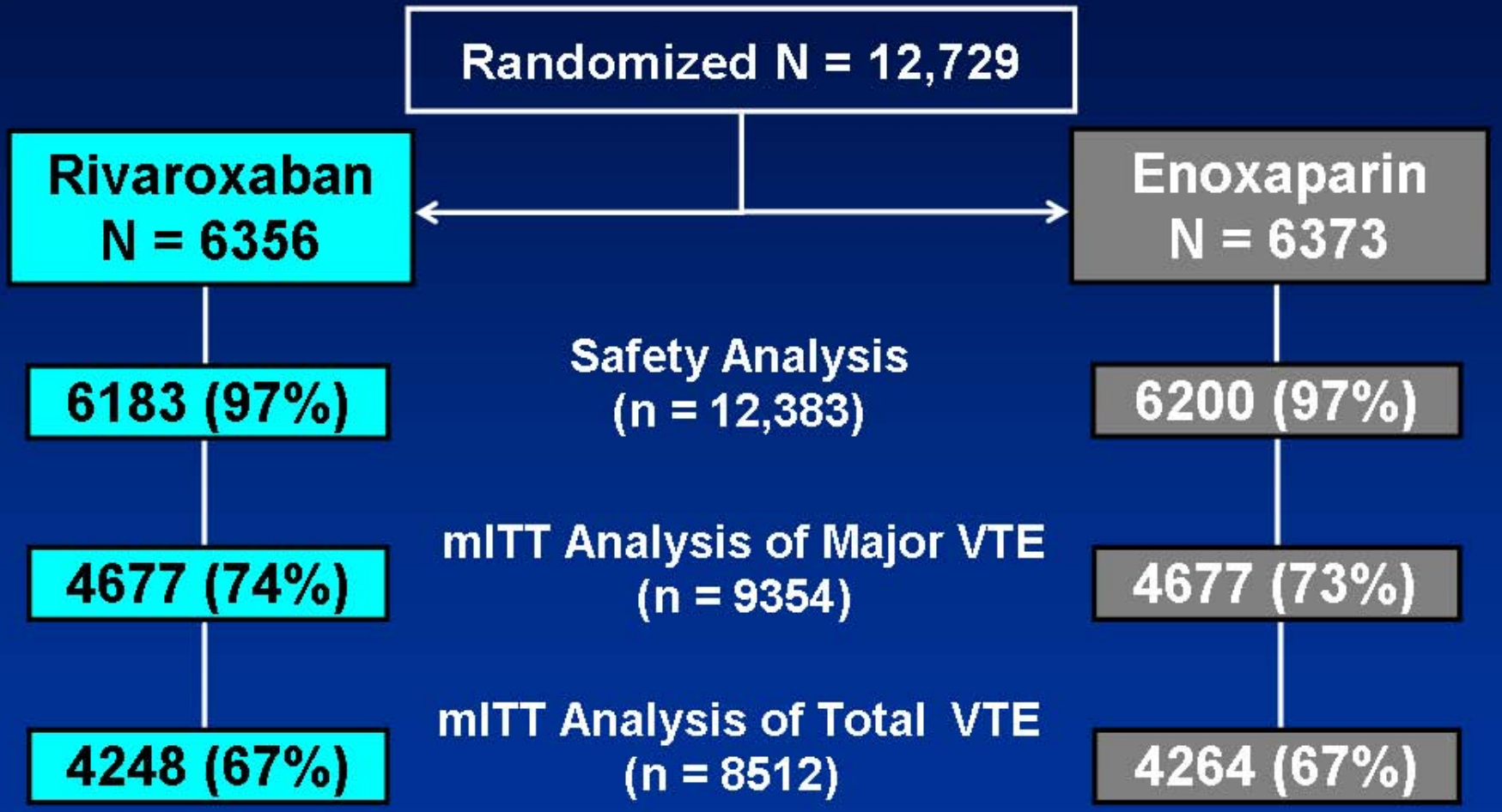


Protocol and analyses agreed upon with FDA

Pre-specified Endpoints

- **Individual Studies – Venography based**
  - Primary: Total VTE
    - All DVT, PE, death
  - Secondary: Major VTE
    - All proximal DVT, PE, VTE death
- **Pooled studies – Symptomatic events**
  - Primary: Symptomatic VTE or death
    - All symptomatic DVT,PE, death

Analysis Populations
Pooled RECORD 1- 4



Demographics
Safety population

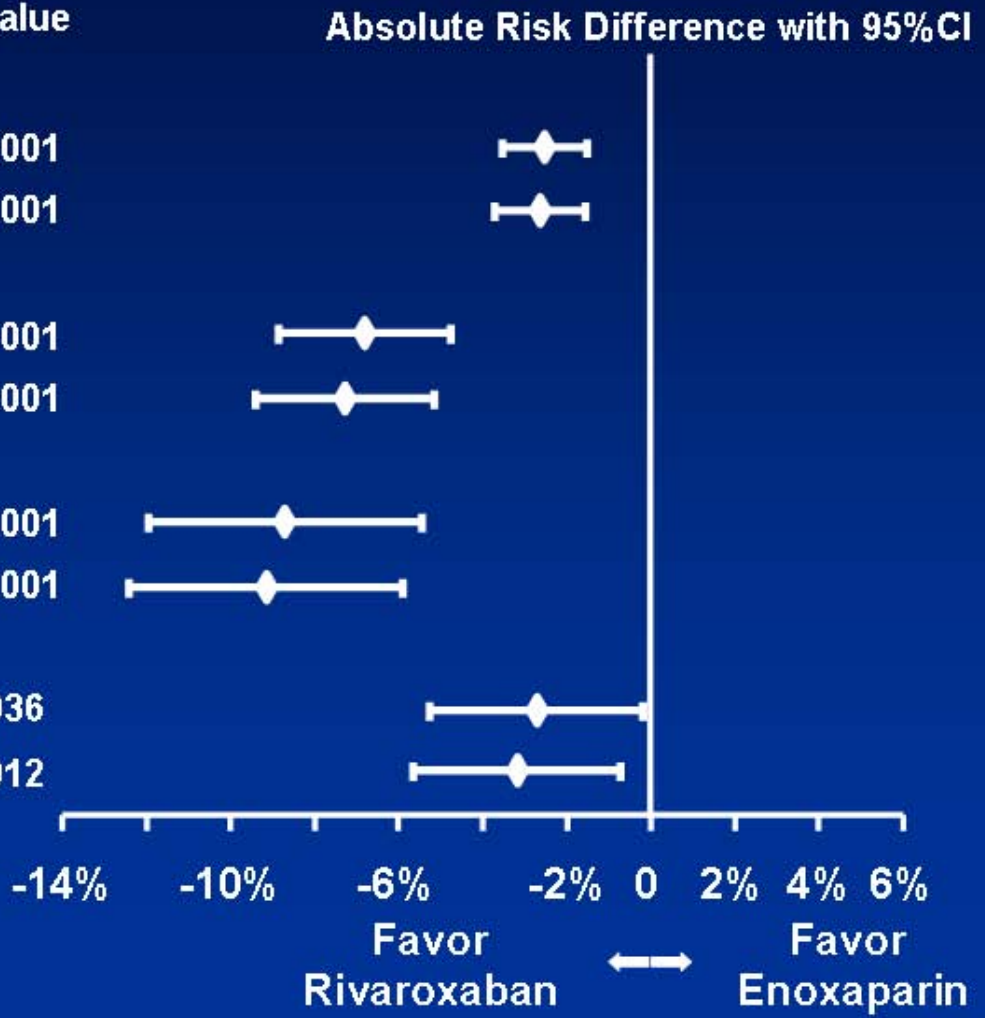
Parameter	RECORD 1-2 THR N = 6890	RECORD 3-4 TKR N = 5493	Total N = 12383
Sex (female)	55%	66%	60%
Race (white)	83%	73%	79%
Age (mean years)	62.6	65.9	64.1
Age > 75 years	13%	17%	15%
Weight (mean kg)	77.0	82.8	79.6
Creatinine clearance			
>80 mL/min	58%	58%	58%
50 to 80 mL/min	34%	34%	34%
30 to <50 mL/min	6%	6%	6%
Fragile Subjects†	18%	21%	19%

†Age > 75 years and/or creatinine clearance < 50 mL/min and/or weight ≤ 50 kg

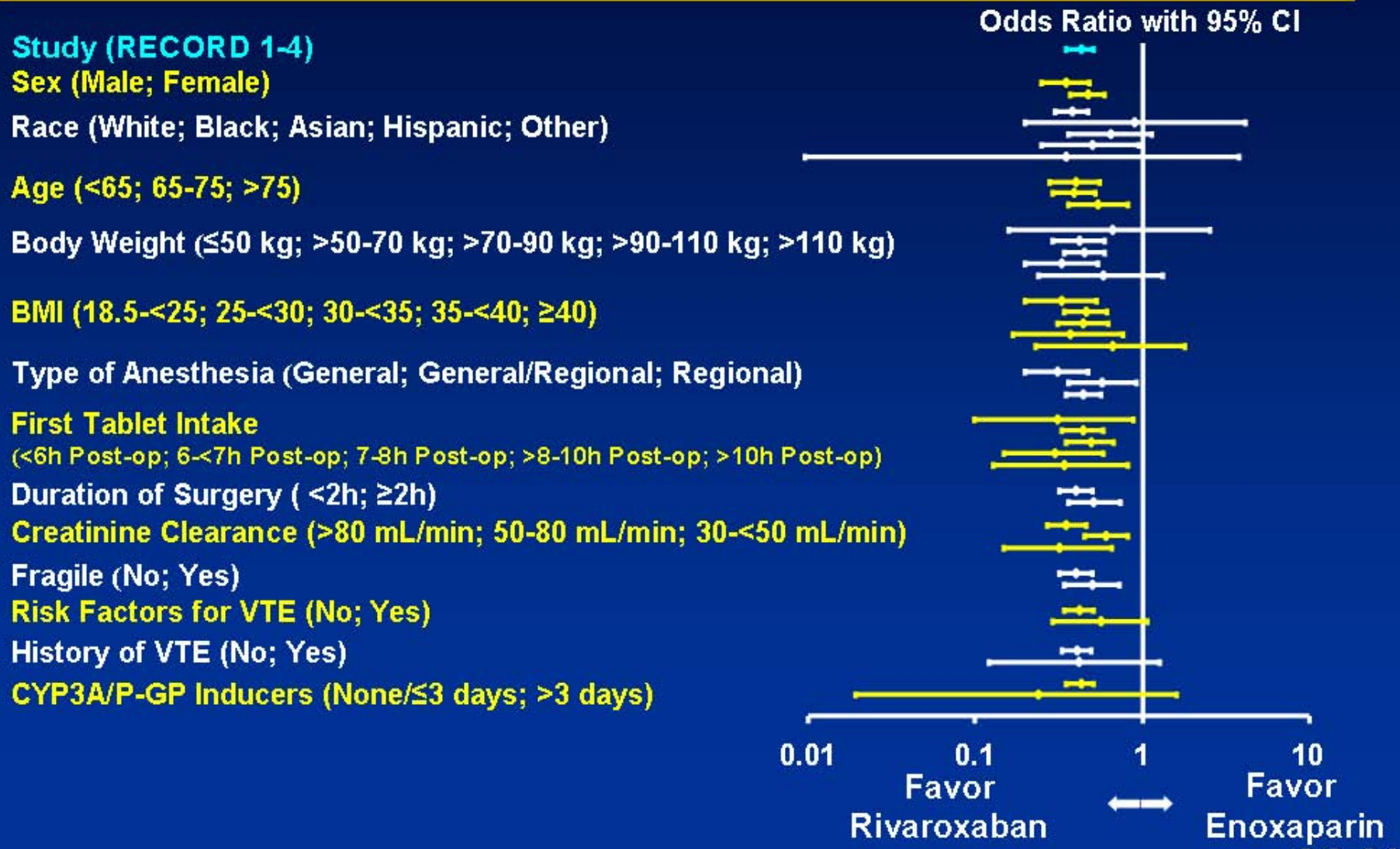
RECORD Efficacy Results

Primary Efficacy Endpoint: Total VTE Per Protocol and MITT Population

RECORD Study	Rivaroxaban n/N (%)	Enoxaparin n/N (%)	p-value
1 (THR)			
PP	13/1537 (0.85)	50/1492 (3.35)	< 0.001
MITT	18/1595 (1.13)	58/1558 (3.72)	< 0.001
2 (THR)			
PP	11/812 (1.35)	66/803 (8.22)	< 0.001
MITT	17/864 (1.97)	81/869 (9.32)	< 0.001
3 (TKR)			
PP	74/793 (9.33)	152/838 (18.14)	< 0.001
MITT	79/824 (9.59)	166/878 (18.91)	< 0.001
4 (TKR)			
PP	58/864 (6.71)	82/878 (9.34)	0.036
MITT	67/965 (6.94)	97/959 (10.11)	0.012



Total VTE by Subgroup
Pooled RECORD 1 - 4 MITT Population

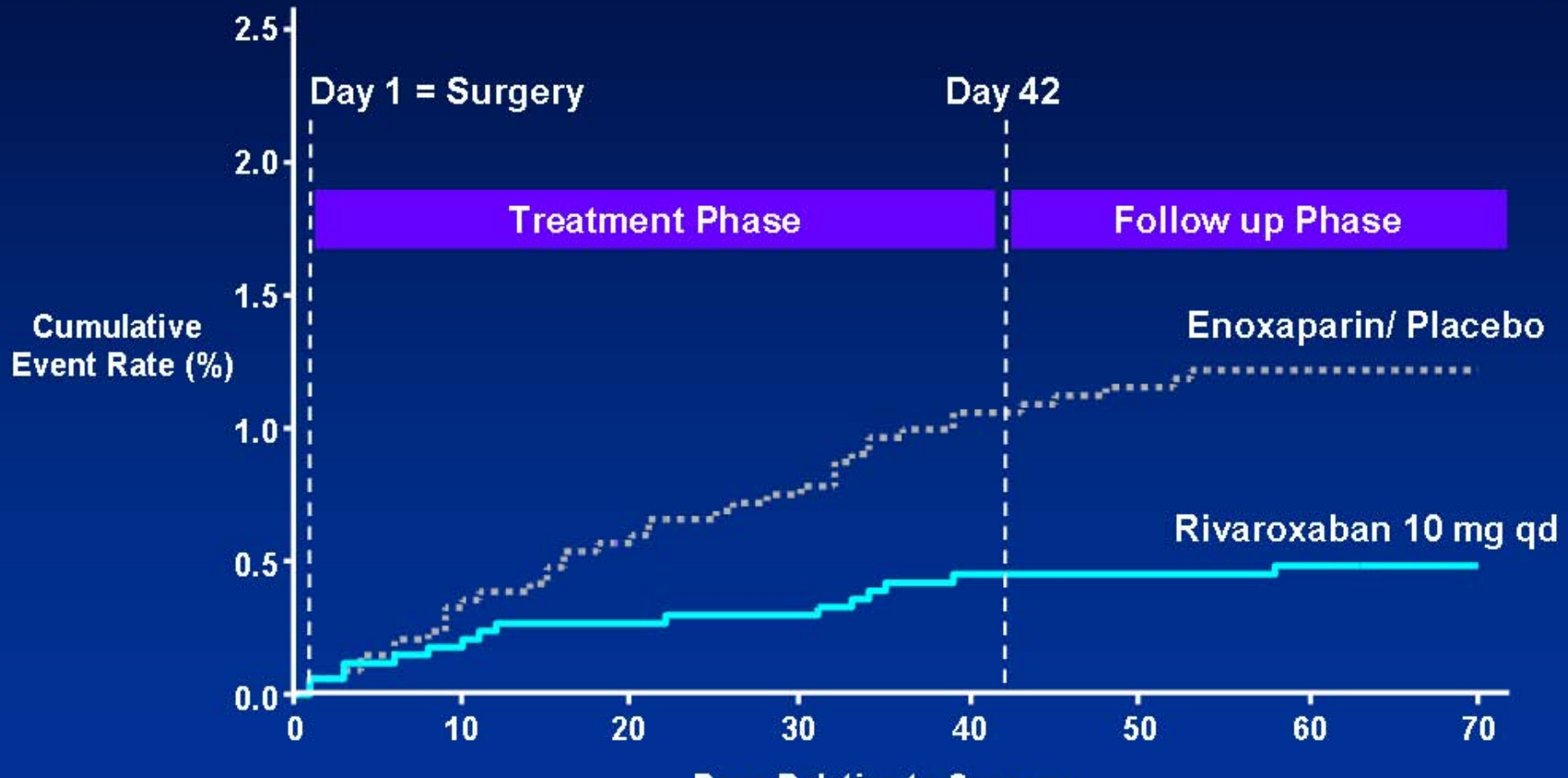


Symptomatic VTE or Death
Pooled Primary Efficacy Endpoint
RECORD 1- 4 Safety Population

	Rivaroxaban N = 6183	Enoxaparin N = 6200	Absolute Risk Difference (95% CI)	Hazard Ratio† (95% CI)
Symptomatic VTE or Death	**0.57% (35)**	**1.32% (82)**	**-0.76% (-1.10, -0.42) p < 0.001**	**0.42 (0.29, 0.63) p < 0.001**
Symptomatic DVT	0.31% (19)	0.79% (49)	-0.48% (-0.74, -0.22)	0.39 (0.23, 0.66)
Symptomatic PE	0.16% (10)	0.31% (19)	-0.15% (-0.32, 0.02)	0.52 (0.24, 1.13)
Death	0.13% (8)	0.26% (16)	-0.13% (-0.28, 0.03)	0.50 (0.21, 1.16)

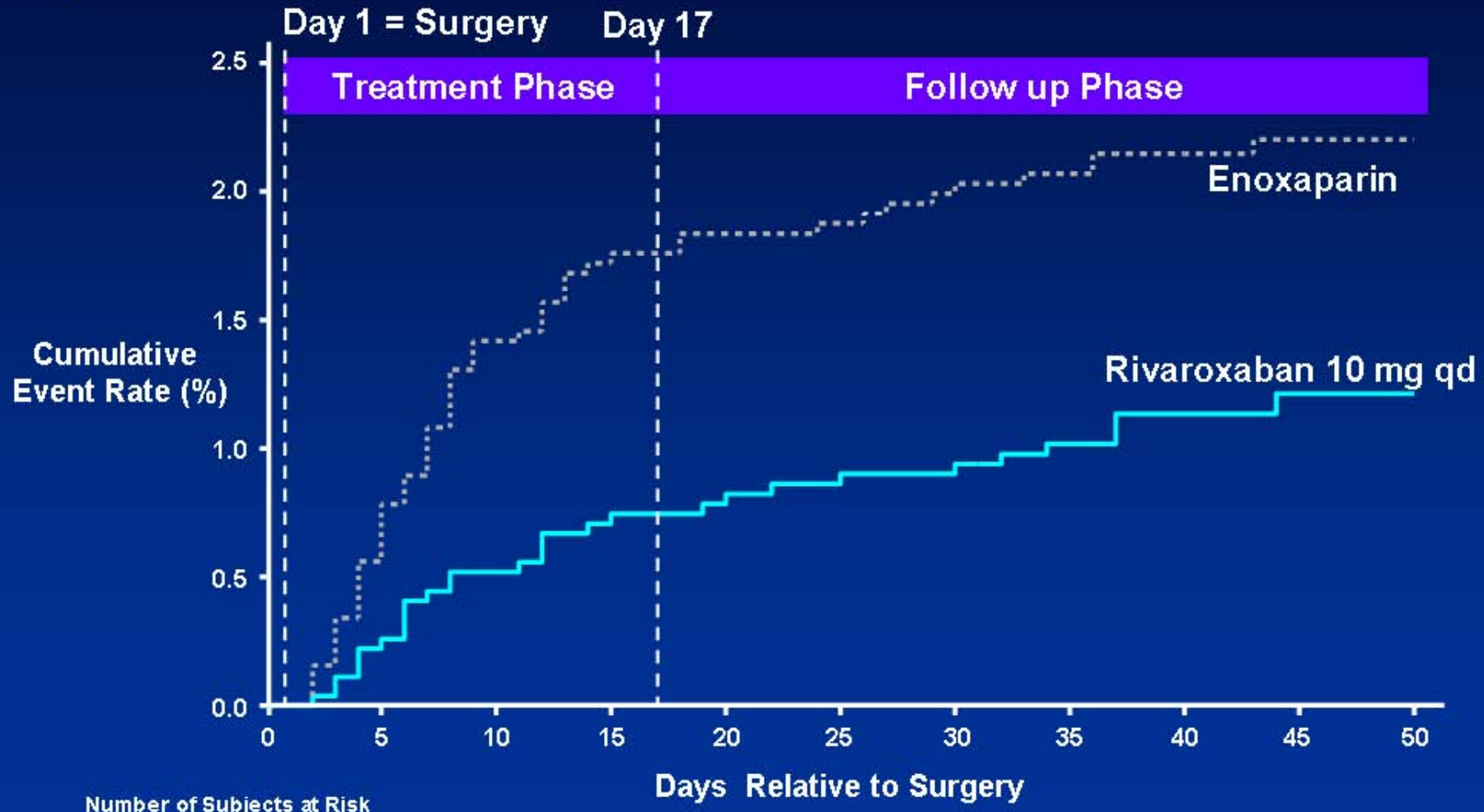
Note: subjects may have more than 1 type of event
†primary analysis

Symptomatic VTE or Death
Treatment and Follow-Up Pooled RECORD 1 - 2 (THR)



Number of Subjects at Risk								
Rivaroxaban	N=3437	N=3328	N=3279	N=3266	N=3141	N=3096	N=3039	N=670
Enoxaparin	N=3453	N=3315	N=3263	N=3235	N=3132	N=3077	N=3018	N=722

Symptomatic VTE or Death
Treatment and Follow-Up Pooled RECORD 3 - 4 (TKR)

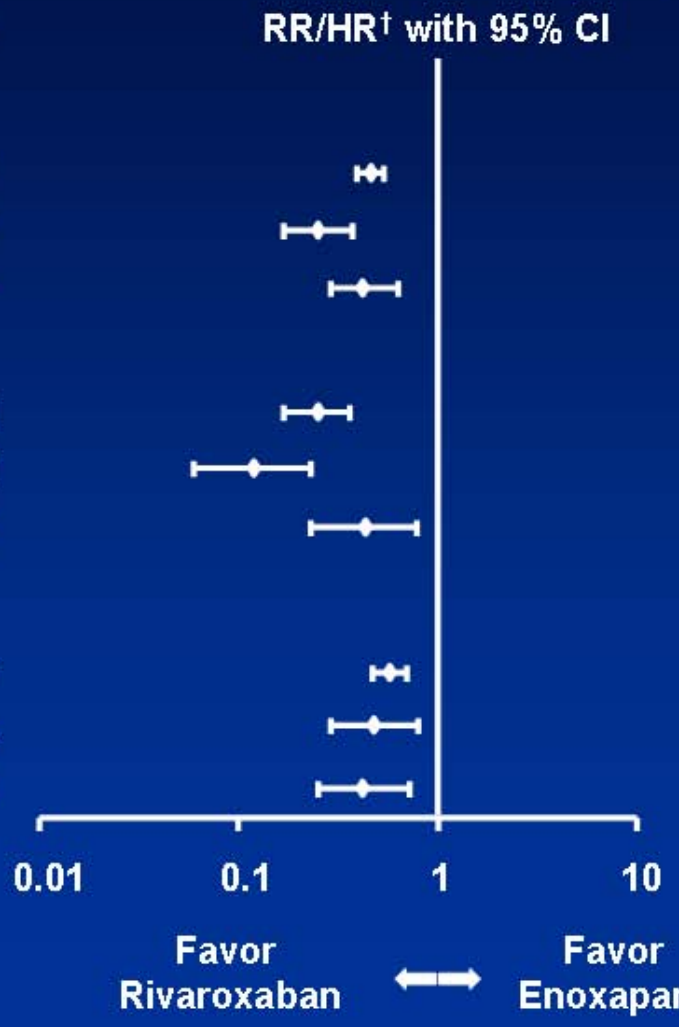


Number of Subjects at Risk

Rivaroxaban	N=2746	N=2695	N=2652	N=2594	N=2564	N=2557	N=2553	N=2540	N=2431	N=846	N=223
Enoxaparin	N=2747	N=2688	N=2626	N=2568	N=2541	N=2537	N=2530	N=2514	N=2403	N=851	N=207

Efficacy Endpoints
Total VTE and Major VTE MITT Population
Symptomatic VTE or Death Safety Population

	RR / HR† (95% CI)	p-value
RECORD 1-4		
Total VTE	0.46 (0.39, 0.54)	<0.001
Major VTE	0.25 (0.17, 0.37)	<0.001
Symptomatic VTE or Death	0.42 (0.29, 0.63)	<0.001
RECORD 1-2 (THR)		
Total VTE	0.25 (0.17, 0.36)	<0.001
Major VTE	0.12 (0.06, 0.23)	<0.001
Symptomatic VTE or Death	0.43 (0.23, 0.78)	0.006
RECORD 3-4 (TKR)		
Total VTE	0.57 (0.47, 0.70)	<0.001
Major VTE	0.48 (0.29, 0.80)	0.004
Symptomatic VTE or Death	0.42 (0.25, 0.72)	0.001



† Relative Risk provided for Total VTE and Major VTE; Hazard Ratio for Symptomatic VTE or Death

RECORD Safety Results

Summary of Adverse Events
Pooled RECORD 1- 4 Safety Population

	Rivaroxaban N = 6183	Enoxaparin N = 6200	Absolute difference† (95% CI)
Any death	0.21% (13)	0.40% (25)	-0.19% (-0.39, 0.00)
Any treatment-emergent serious adverse event	6.57% (406)	8.52% (528)	-1.94% (-2.87, -1.01)
Any adverse event resulting in permanent discontinuation	3.72% (230)	4.65% (288)	-0.93% (-1.63, -0.22)

† Absolute difference analysis done post hoc

Bleeding Event Analyses

- Individual studies – absolute risk differences
  - Primary safety endpoint: Major Bleeding
- Pooled studies – hazard ratio
  - Major bleeding events
  - Major bleeding events or surgical site bleeds
  - Major or non-major clinically relevant bleeding
  - Any bleeding event

Major Bleeding Event Criteria

- Fatal bleeding
- Bleeding into a critical organ
- Extrasurgical site bleeding
  - ≥ 2 g/dL decrease in hemoglobin
  - Transfusion of ≥ 2 units of blood
- Surgical site bleeding that required re-operation

Treatment Emergent Major Bleeding Events Safety Population

STUDY	Rivaroxaban	Enoxaparin	Absolute risk difference† (95% CI)	Hazard ratio (95% CI)
RECORD 1 (THR)	0.27% (6/2209)	0.09% (2/2224)	0.18% (-0.07, 0.44) p = 0.155	3.01 (0.61, 14.92)
RECORD 2‡ (THR)	0.08% (1/1228)	0.08% (1/1229)	0.00% (-0.23, 0.22) p = 0.980	Not calculated due to < 5 total events
RECORD 3 (TKR)	0.57% (7/1220)	0.48% (6/1239)	0.08% (-0.49, 0.66) p = 0.774	1.17 (0.39, 3.49)
RECORD 4 (TKR)	0.66% (10/1526)	0.27% (4/1508)	0.39% (-0.09, 0.88) p = 0.110	2.47 (0.77, 7.87)

†primary analysis

‡ Active comparator included a placebo control period after day 12

Major Bleeding Event Components Pooled RECORD 1- 4 Safety Population

	Rivaroxaban N = 6183	Enoxaparin N = 6200
Any event	0.39% (24)	0.21% (13)
Fatal bleeding event	0.03% (2)†	0% (0)
Critical organ bleeding event	0.05% (3)†	0.08% (5)
Clinically overt extrasurgical site bleeding event (decreased hemoglobin and/or transfusion)	0.13% (8)	0.02% (1)
Surgical site bleeding event requiring re-operation	0.19% (12)	0.11% (7)

†One event before start of Rivaroxaban; active drug never given

Note: subjects may have more than 1 type of event

Major Bleeding Event Components
Pooled RECORD 1- 4 Safety Population

	Rivaroxaban N = 6183	Enoxaparin N = 6200
Any event	0.39% (24)	0.21% (13)
Fatal bleeding event	0.03% (2)†	0% (0)
Critical organ bleeding event	0.05% (3)†	0.08% (5)
Clinically overt extrasurgical site bleeding event (decreased hemoglobin and/or transfusion)	0.13% (8)	0.02% (1)
Surgical site bleeding event requiring re-operation	0.19% (12)	0.11% (7)

†One event before start of Rivaroxaban; active drug never given

Note: subjects may have more than 1 type of event

Treatment Emergent Major or Non Major Clinically Relevant Bleeding Events Safety Population

STUDY	Rivaroxaban	Enoxaparin	Absolute risk difference† (95% CI)	Hazard ratio (95% CI)
RECORD 1 (THR)	3.17% (70/2209)	2.52% (56/2224)	0.63% (-0.35, 1.61) p = 0.206	1.25 (0.88, 1.78)
RECORD 2‡ (THR)	3.34% (41/1228)	2.77% (34/1229)	0.59% (-0.77, 1.95) p = 0.394	1.20 (0.76, 1.89)
RECORD 3 (TKR)	3.28% (40/1220)	2.74% (34/1239)	0.53% (-0.81, 1.87) p = 0.439	1.19 (0.76, 1.88)
RECORD 4 (TKR)	3.01% (46/1526)	2.25% (34/1508)	0.78% (-0.36, 1.92) p = 0.179	1.34 (0.86, 2.09)

†primary analysis

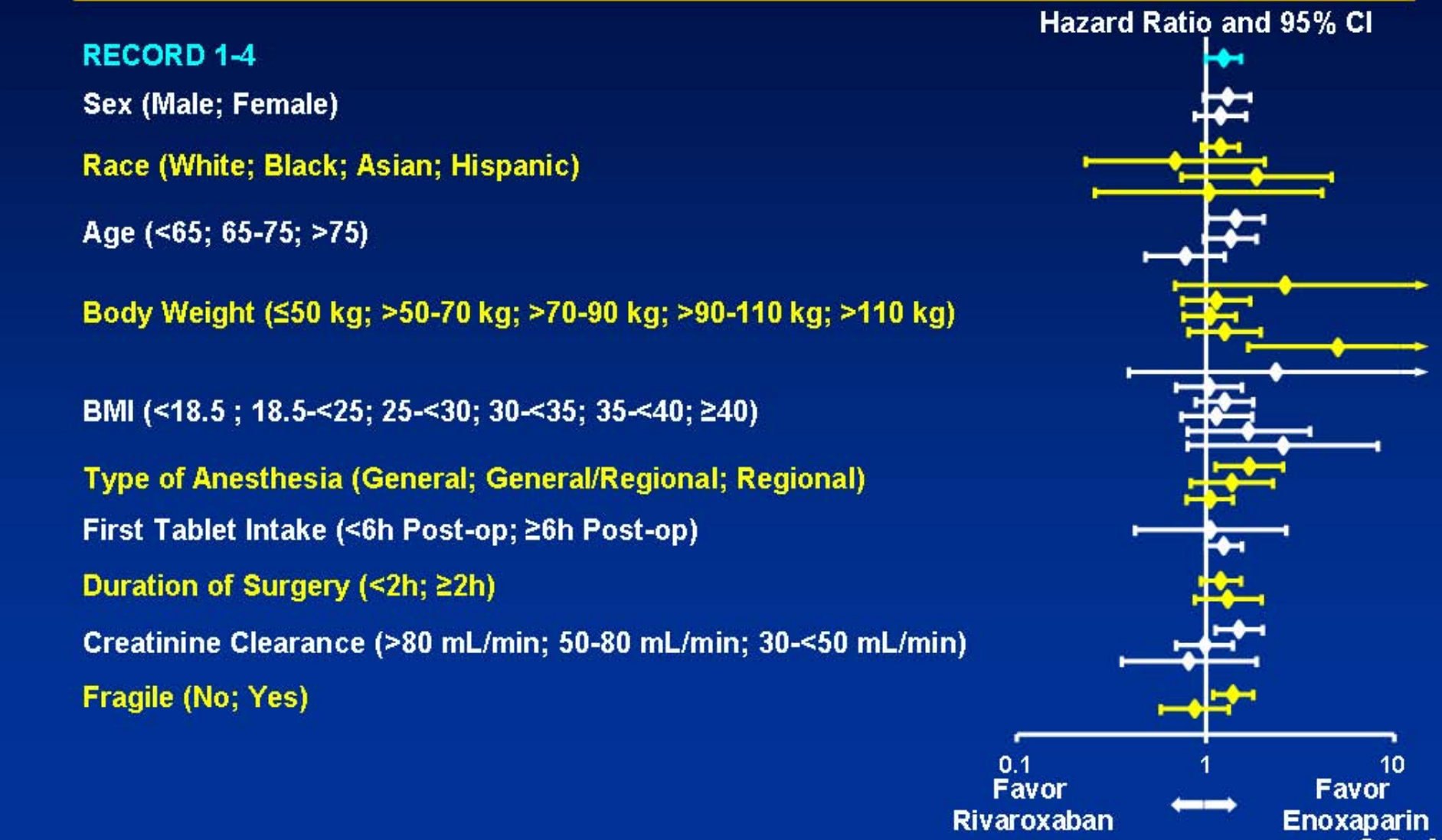
‡ Active comparator included a placebo control period after day 12

Treatment Emergent Bleeding Events Pooled RECORD 1- 4 Safety Population

Endpoint	Rivaroxaban N = 6183	Enoxaparin N = 6200	Absolute risk difference (95% CI)	Hazard Ratio† (95% CI)
Major bleeding event	0.39% (24)	0.21% (13)	0.18% (-0.01, 0.37)	1.84 (0.94, 3.62) p = 0.076
Major bleeding combined with surgical site bleeding events‡	1.80% (111)	1.37% (85)	0.42% (-0.01, 0.86)	1.31 (0.99, 1.73) p = 0.063
Major or non-major clinically relevant bleeding event	3.19% (197)	2.55% (158)	0.64% (0.05, 1.23)	1.25 (1.01, 1.54) p = 0.039
Any bleeding event	7.02% (434)	6.47% (401)	0.53% (-0.35, 1.42)	1.08 (0.94, 1.24) p = 0.255

†primary analysis
‡ associated with hemoglobin decrease or transfusion
Note: subjects may have more than 1 type of event

Major or Non-major Clinically Relevant Treatment Emergent Bleeding Events by Subgroup Pooled RECORD 1-4 Safety Population



Any Treatment Emergent Bleeding Events by Subgroup Pooled RECORD 1-4 Safety Population

RECORD 1-4

Sex (Male; Female)

Race (White; Black; Asian; Hispanic)

Age (<65; 65-75; >75)

Body Weight (≤50 kg; >50-70 kg; >70-90 kg; >90-110 kg; >110 kg)

BMI (<18.5; 18.5-<25; 25-<30; 30-<35; 35-<40; ≥40)

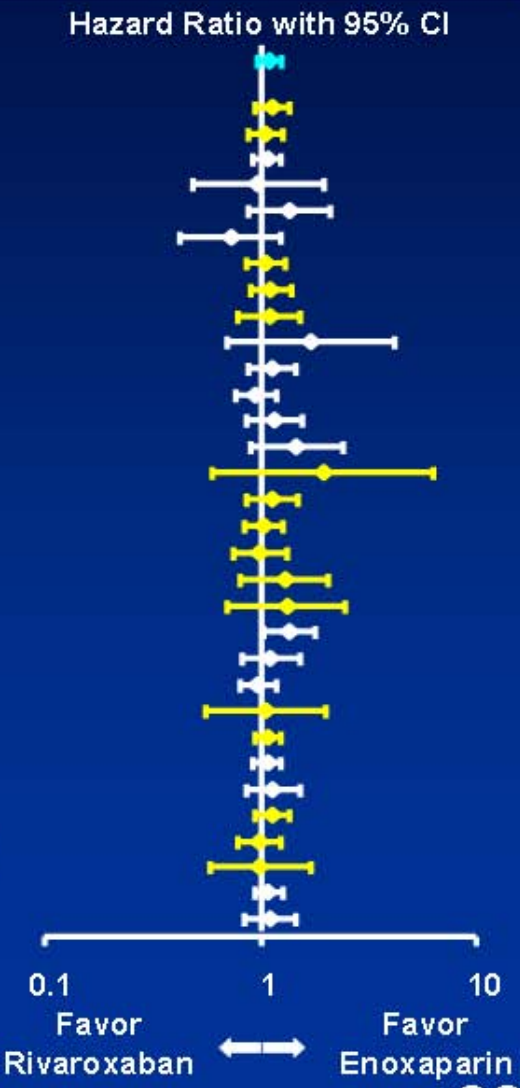
Type of Anesthesia (General; General/Regional; Regional)

First Tablet Intake (<6h Post-op; ≥6 Post-op)

Duration of Surgery (<2h; ≥2h)

Creatinine Clearance (>80 mL/min; 50-80 mL/min; 30-<50 mL/min)

Fragile (No; Yes)



Considerations for Populations with Higher Exposure

- RECORD program shows subgroups with known increases in exposures (fragile, age, moderate renal impairment) have documented efficacy benefit and bleeding risk similar to overall
- Situations with expected exposures over a 2 fold increase are limited in occurrence, and will be addressed with labeling and education

On and Off Treatment Cardiovascular Events RECORD 1- 4 Active Treatment Population

Endpoint	Rivaroxaban N = 6097	Enoxaparin N = 6195
Cardiovascular events on active treatment	0.21% (13)	0.40% (25)
Myocardial infarction	0.11% (7)	0.23% (14)
Ischemic stroke	0.08% (5)	0.10% (6)
Cardiovascular death	0.02% (1)	0.08% (5)
Unexplained death	0.00% (0)	0.00% (0)
Cardiovascular events off active treatment	0.28% (17)	0.23% (14)
Myocardial infarction	0.08% (5)	0.06% (4)
Ischemic stroke	0. 10% (6)	0.02% (1)
Cardiovascular death	0.10% (6)	0.10% (6)
Unexplained death	0.02% (1)	0.06% (4)

Note: A subject can appear in more than one sub-category and 1 subject with an ischemic stroke not in the database is included

Liver Safety Assessments

- Nonclinical assessment
- RECORD studies
  - Liver related laboratory testing
  - Adverse events summarized using a standardized MedDRA dictionary hepatic disorders search
- Other Rivaroxaban studies
  - Longer term exposures
  - Liver related laboratory testing

Nonclinical Safety

- Comparable metabolic profiles in humans, rats, mice and dogs
- Rivaroxaban exposures at least 29 fold higher than for the proposed human dose
- No preclinical signal for liver toxicity based on FDA working group concept paper (November 2000)
- Liver findings did not limit the conduct of the clinical trials

ALT Adverse Events and Serious Adverse Events Pooled RECORD 1-4, Safety Population

Preferred Term	Rivaroxaban (N=6183) n (%)	Enoxaparin (N=6200) n (%)
Treatment-Emergent Events		
ALT increased	134 (2.17)	183 (2.95)
Serious ALT increased	17 (0.27)	11 (0.18)
Treatment-Emergent and Follow-up Events		
ALT increased	144 (2.33)	200 (3.23)
Serious ALT increased	17 (0.27)	14 (0.23)

ALT Abnormalities† Pooled RECORD 1 – 4

ALT Level	Rivaroxaban N = 6131	Enoxaparin N = 6131
>3X ULN	2.48% (152)	3.70% (227)
>5X ULN	0.91% (56)	1.27% (78)
>8X ULN	0.29% (18)	0.33% (20)
>10X ULN	0.16% (10)	0.15% (9)
>20X ULN	0.03% (2)	0.02% (1)

† all after day 0 baseline in safety population with measurement

Combined ALT and Total Bilirubin Abnormalities† Pooled RECORD 1- 4

ALT >3X ULN with total bilirubin >2X ULN	Rivaroxaban N=6131	Enoxaparin N=6131
Central and local laboratory Concurrent and nonconcurrent	0.16% (10^)	0.16% (10)
Central and local laboratory Concurrent	0.15% (9^)	0.13% (8)
Central laboratory only Concurrent	0.15% (9^)	0.11% (7)

^2 cases occurred after surgery and before rivaroxaban administration

† all after day 0 baseline in safety population with measurement

Combined ALT and Total Bilirubin Abnormalities† Pooled RECORD 1-4

ALT >3X ULN with total bilirubin >2X ULN	Rivaroxaban N=6131	Enoxaparin N=6131
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^2 cases occurred after surgery and before rivaroxaban administration

† all after day 0 baseline in safety population with measurement

ATLAS ACS TIMI 46

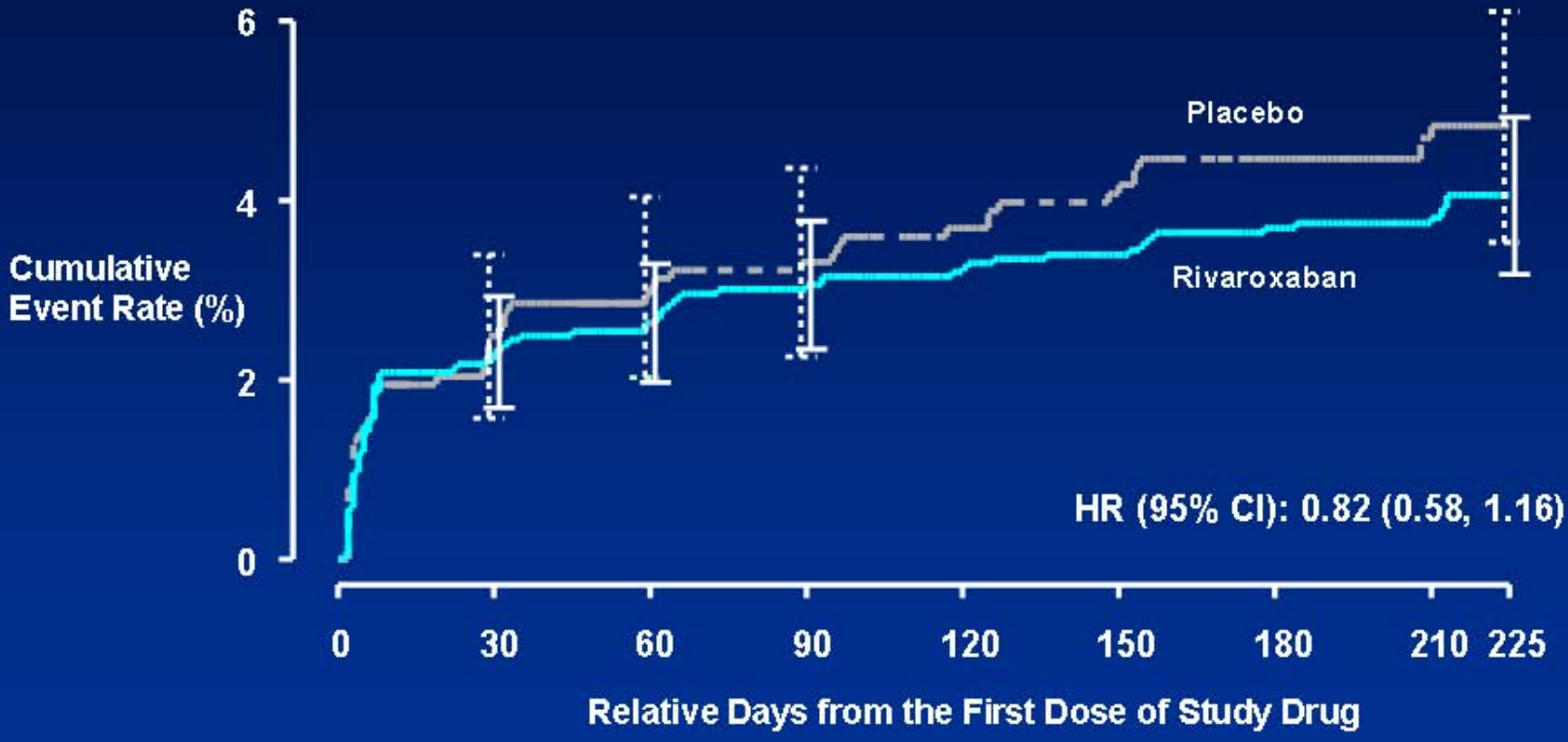
- Phase 2 double blind dose finding study
- Rivaroxaban total daily doses from 5 to 20 mg
- Placebo control (in addition to standard therapy)
- 3491 subjects randomized
  - 2331 rivaroxaban
  - 1160 placebo
- Planned 6 month dosing
- Monthly liver laboratory testing

ATLAS ACS TIMI 46
ALT Abnormalities† - 6 months Dosing Duration

ALT level	Rivaroxaban N = 2270	Placebo N = 1133
>3X ULN	3.74% (85)	4.60% (52)
>5X ULN	0.79% (18)	1.41% (16)
>8X ULN	0.18% (4)	0.35% (4)
>10X ULN	0.13% (3)	0.26% (3)
>20X ULN	0.00% (0)	0.00% (0)

† all after baseline in safety population with central lab measurement

ATLAS ACS TIMI 46
Six Month Placebo Controlled Trial:
Time to the First ALT > 3XULN†



Number of Subjects at Risk:

Placebo	1133	1076	1053	1039	1015	995	964	725	43
Rivaroxaban	2270	2150	2087	2045	2009	1960	1909	1458	1065

† all after baseline in safety population with central laboratory measurement

Combined ALT > 3X ULN with Total Bilirubin > 2X ULN† Studies with Dosing 35 days or Less

Study	Rivaroxaban	Comparator
Phase 2 THR or TKR	0.23% (4/1700)	0.50% (2/379)
Phase 2 AF Japan	0.00% (0/185)	0.00% (0/53)
RECORD 1 - 4	0.15% (9/6131)‡	0.11% (7/6131)
Totals	0.16% (13/8016)‡ 95% CI (0.09 to 0.28)	0.14% (9/6563) 95% CI (0.06 to 0.26)

† all concurrent after baseline in pooled safety populations with central lab measurement

‡ 2 cases occurred postsurgery before rivaroxaban administration

Combined ALT > 3X ULN with Total Bilirubin > 2X ULN† Studies with Dosing 35 days or Less

Study	Rivaroxaban	Comparator
Phase 2 THR or TKR	0.23% (4/1700)	0.50% (2/379)
Phase 2 AF Japan	0.00% (0/185)	0.00% (0/53)
RECORD 1 - 4	0.15% (9/6131)‡	0.11% (7/6131)
Totals	0.16% (13/8016)‡	0.14% (9/6563)
	95% CI (0.09 to 0.28)	95% CI (0.06 to 0.26)

† all concurrent after baseline in pooled safety populations with central lab measurement

‡ 2 cases occurred postsurgery before rivaroxaban administration

Combined ALT > 3X ULN with Total Bilirubin > 2X ULN† Longer Term Dosing Studies

Study	Rivaroxaban	Comparator
Phase 2 DVT Treatment (12 weeks of dosing)	0.12% (1/824)	0.00% (0/235)
ATLAS ACS TIMI 46 (6 months of dosing)	0.00% (0/2270)	0.27% (3/1134)
EINSTEIN DVT/PE (3, 6 or 12 months of dosing)	0.19% (3/1562)	0.00% (0/1549)
Totals	0.09% (4/4656) 95% CI (0.02 to 0.22)	0.10% (3/2918) 95% CI (0.02 to 0.30)

Study	Ximelagatran	Comparator
Long Term Exposure Pool	0.53% (37/6948)	0.08% (5/6230)

† all concurrent after baseline in pooled safety populations with central or local laboratory measurement

Hepatic Safety Assessment

Paul B. Watkins, MD

Safety Surveillance and Risk Management

Peter M. DiBattiste, MD

Risk Assessment and Risk Minimization Strategies

Risk Assessment

- Routine Pharmacovigilance

Risk Minimization

- US Package Labeling
- Education and Outreach Programs

Risk Assessment and Risk Minimization Strategies

Risk Assessment

- Routine Pharmacovigilance
- Enhanced Pharmacovigilance
- Post-Marketing Observational Study
- Post-Marketing Utilization Study
- Monthly Prescription Tracking – IMS Database

Risk Minimization

- US Package Labeling
- Education and Outreach Programs
  - Targeted Education
- Patient Package Insert
- Drug Packaging Strategies
- Targeted Education

Benefit Risk Assessment

Peter M. DiBattiste, MD

Benefit-Risk Assessments

- Total VTE vs. Major or Non-major Clinically Relevant Bleeding
- Major VTE vs. Major Bleeding
- Symptomatic VTE vs. Major Bleeding
- Serious Adverse Events

RECORD 1–4: Excess Number of Events
(Total VTE* vs. Major/Non-Major Clinically Relevant Bleeding)

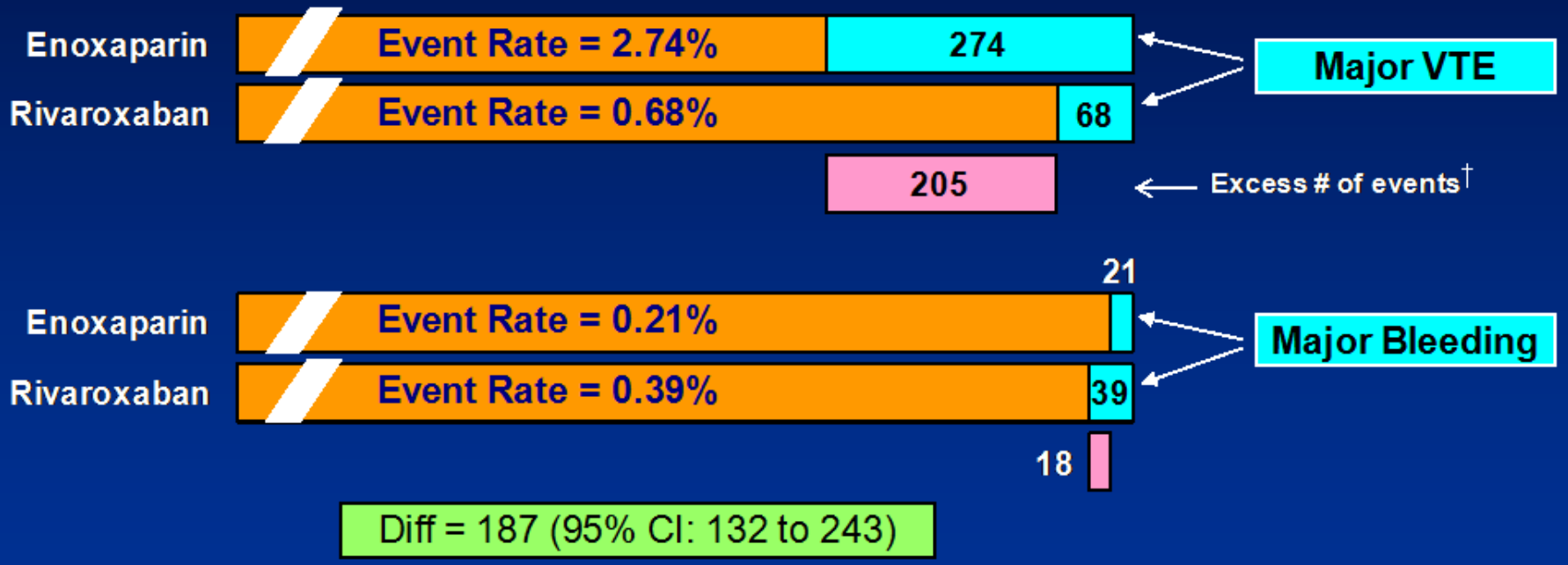
Treating 10,000 patients in each group:

† Excess # of events is based on Mantel-Haenszel-weighted treatment difference and is not identical to crude rate difference.

* Total VTE was a prespecified primary efficacy endpoint in the individual RECORD studies and is based on the MITT population for Total VTE; Bleeding results from safety population.

RECORD 1–4: Excess Number of Events (Major VTE* vs. Major Bleeding)

Treating 10,000 patients in each group:

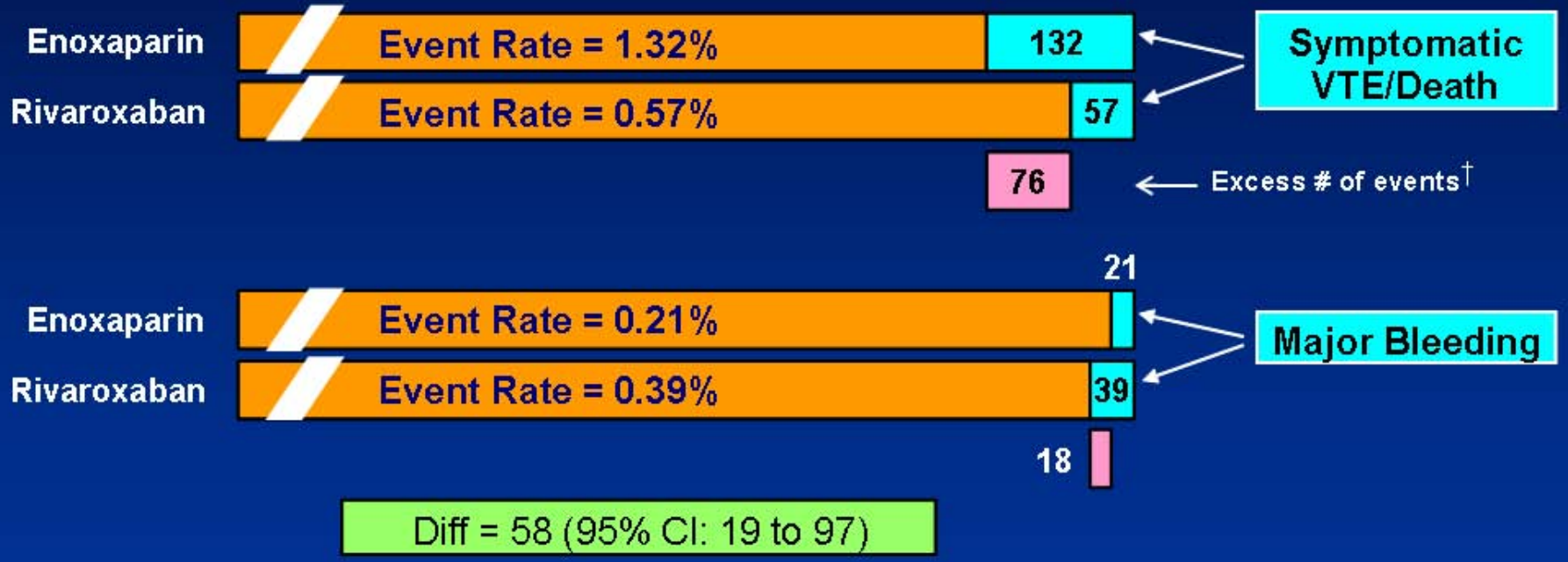


† Excess # of events is based on Mantel-Haenszel-weighted treatment difference and is not identical to crude rate difference.

* Major VTE was a prespecified secondary efficacy endpoint in the individual RECORD studies and is based on the MITT population for major VTE; Bleeding results from safety population.

RECORD1–4: Excess Number of Events (Symptomatic VTE/Death* vs. Major Bleeding)

Treating 10,000 patients in each group:



† Excess # of events is based on Mantel-Haenszel-weighted treatment difference and is not identical to crude rate difference.

* Symptomatic VTE/death from all causes was the primary endpoint in pooled analysis of RECORD studies; Efficacy and bleeding results from safety population

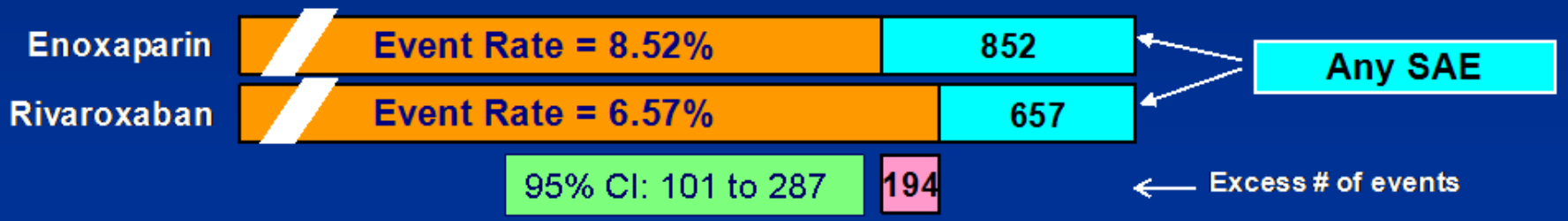
Clinical Impact Comparison of Symptomatic VTE Events vs. Bleeding Events Pooled RECORD 1-4 – Treatment Period

Parameter*	Symptomatic VTE	Major Bleeding	Clinically-relevant, non-major bleeding
	N=97	N=37	N=349
Severe intensity	26.8%	27.0%	8.0%
Serious event	**99.0%**	**70.3%**	**21.5%**
Hospitalization	53.6%	54.1%	13.5%
Outcome unresolved	**50.5%**	**13.5%**	**9.5%**
Transfusion	NA	73.0%	38.4%
Action – permanent d/c	71.1%	45.9%	16.3%
Action- remedial Rx	**85.6%**	**29.7%**	**24.9%**
Duration of event – median days	**29.0**	**2.0**	**4.0**
Onset time from surgery- median days	**7.0**	**2.0**	**3.0**

*** As identified by the investigator in case report forms and adverse event reports**

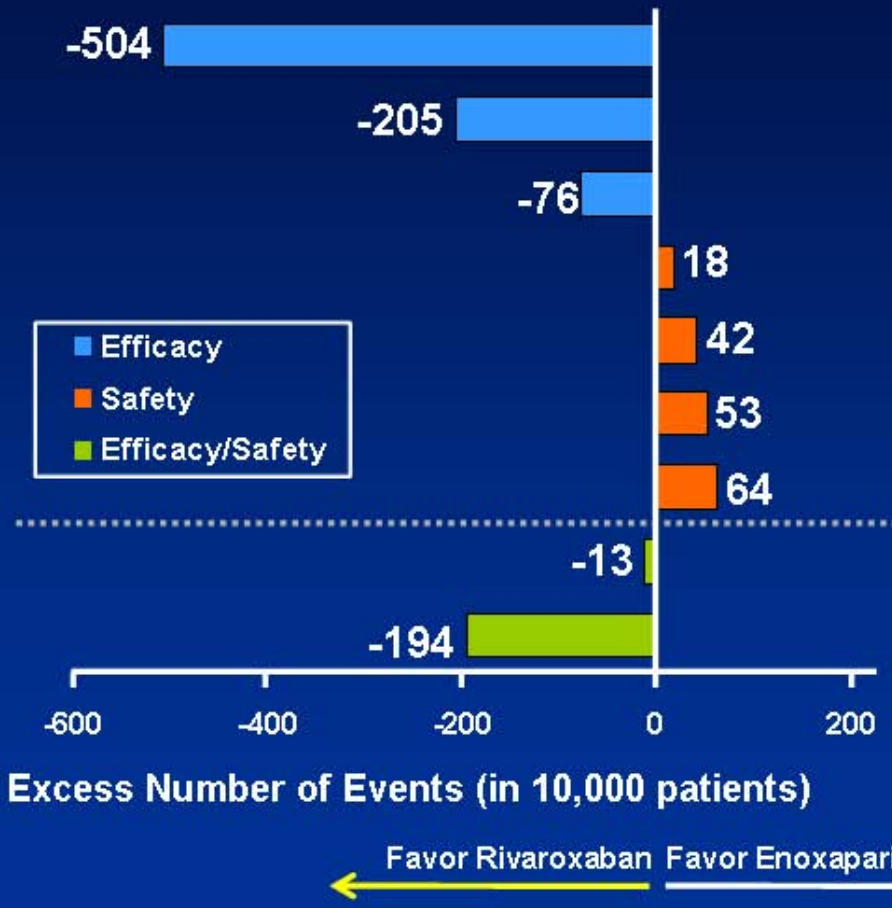
Summary of Adverse Events (RECORD 1-4 Pooled, Safety Population)

	Rivaroxaban N = 6183	Enoxaparin N = 6200	Absolute difference† (95% CI)
Any death	0.21% (13)	0.40% (25)	-0.19% (-0.39, 0.00)
Any treatment-emergent serious AE	6.57% (406)	8.52% (528)	-1.94 (-2.87, -1.01)
Any AE resulting in permanent discontinuation	3.72% (230)	4.65% (288)	-0.93 (-1.63, -0.22)



† Post hoc analysis

Excess Number of Events Pooled RECORD 1 – 4



Total VTE

Major VTE

Symptomatic VTE & All-Cause Mortality

Major Bleeding

Major bleeding + Surgical Site Bleeding

Any bleeding

Major or Non-Major Clin Rel Bleeding

Death from all causes

Any treatment-emergent serious AE

Excess # of events is based on Mantel-Haenszel-weighted treatment difference and is not identical to crude rate difference.

Total VTE and major VTE were based on the MITT populations and were prespecified endpoints; Symptomatic VTE, all cause deaths, treatment emergent bleedings and SAEs were based on the safety population; Total Duration Pool was used during treatment phase.

Conclusions

Peter M. DiBattiste, MD

RECORD Program: Conclusions

- Important reductions in total, major, and symptomatic VTE vs. a highly effective active comparator

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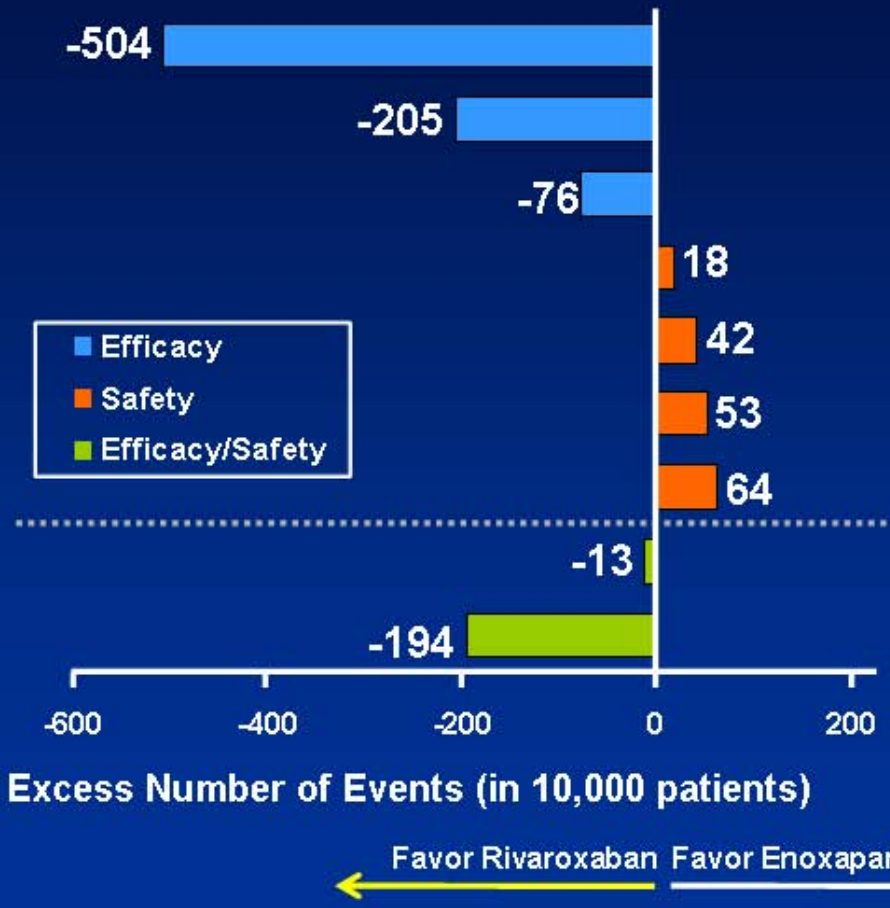
- Important reductions in total, major, and symptomatic VTE vs. a highly effective active comparator
- Well-tolerated with only modest increases in bleeding
- No liver signal apparent in RECORD studies or across program
- Compelling benefit to risk for rivaroxaban when used for prophylaxis of DVT and PE in patients undergoing elective THR or TKR surgery

Excess Number of Events
Pooled RECORD 1 – 4



Total VTE

Major VTE

Symptomatic VTE & All-Cause Mortality

Major Bleeding

Major bleeding + Surgical Site Bleeding

Any bleeding

Major or Non-Major Clin Rel Bleeding

Death from all causes

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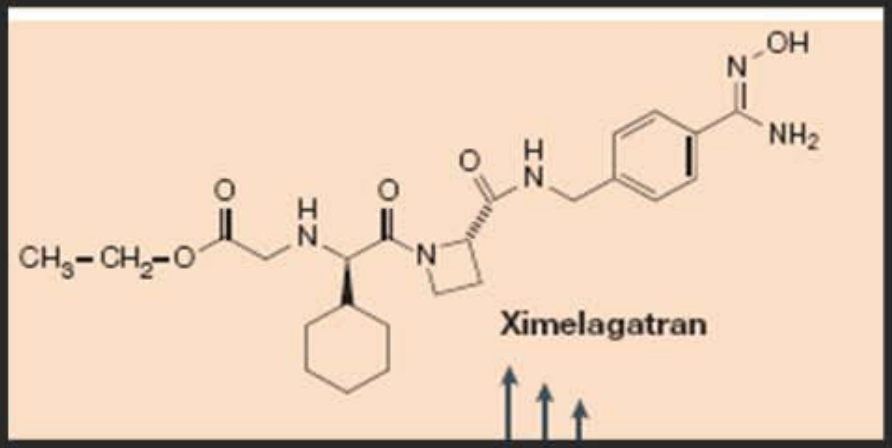
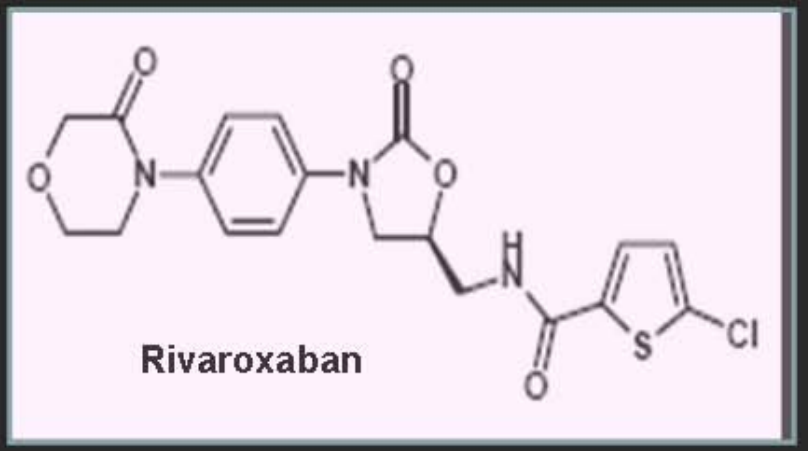
Assessment of the Liver Safety of Rivaroxaban

Paul B. Watkins, MD
Verne S. Caviness Professor of Medicine
Director,
Hamner Center for Drug Safety Sciences
University of North Carolina
Chapel Hill

Rivaroxaban and Ximelagatran differ in structure, mechanism of action and metabolism





Direct thrombin inhibitor

Prodrug metabolized to melagatran

Factor Xa inhibitor

Not prodrug

Outline of Presentation

1). “Liver related” deaths

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5). Conclusions

Deaths preceded by ALT >3x ULN concurrent with TB >2x ULN within 30 days – All Rivaroxaban Studies

Treatment group and Subject ID	Study (Randomization Ratio)	Key demographics	Causality assessment	Controversy
Rivaroxaban 220134004	EINSTEIN DVT/PE (1:1)	71 y/o Italian man with gastric cancer	Gastric cancer with liver metastases	none
Rivaroxaban 160183005	EINSTEIN DVT/PE (1:1)	63 y/o French woman with a history of hypertension, asthma and emphysema	Ischemic hepatitis	No documented hypotension
Rivaroxaban 11223-506006	Phase 2 VTE treatment (4:1)	72 y/o Czech woman with uterine cancer s/p chemo	Acute Hepatitis B infection	No inflammation on liver biopsy
Rivaroxaban 10944-84008	Phase 2 THR prophylaxis (4:1)	79 y/o German woman with hypertension and Parkinson's Disease	Cholestatic reaction, deteriorated after ERCP procedure	Contribution of liver failure to death
Placebo 200039	ATLAS ACS TIMI 46 (2:1)	44 y/o Australian woman	Sepsis, alcoholic hepatitis	
Enoxaparin 280130001	MAGELLAN (1:1)	72 y/o Belgian woman	Cardiac and renal failure	

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Expert Consensus Statement

"This patient most likely had an ischemic injury leading to hepatocellular necrosis in the setting of multiorgan failure. There is a distant possibility, albeit much less likely, for a role of rivaroxaban in the initiation or worsening of the event".

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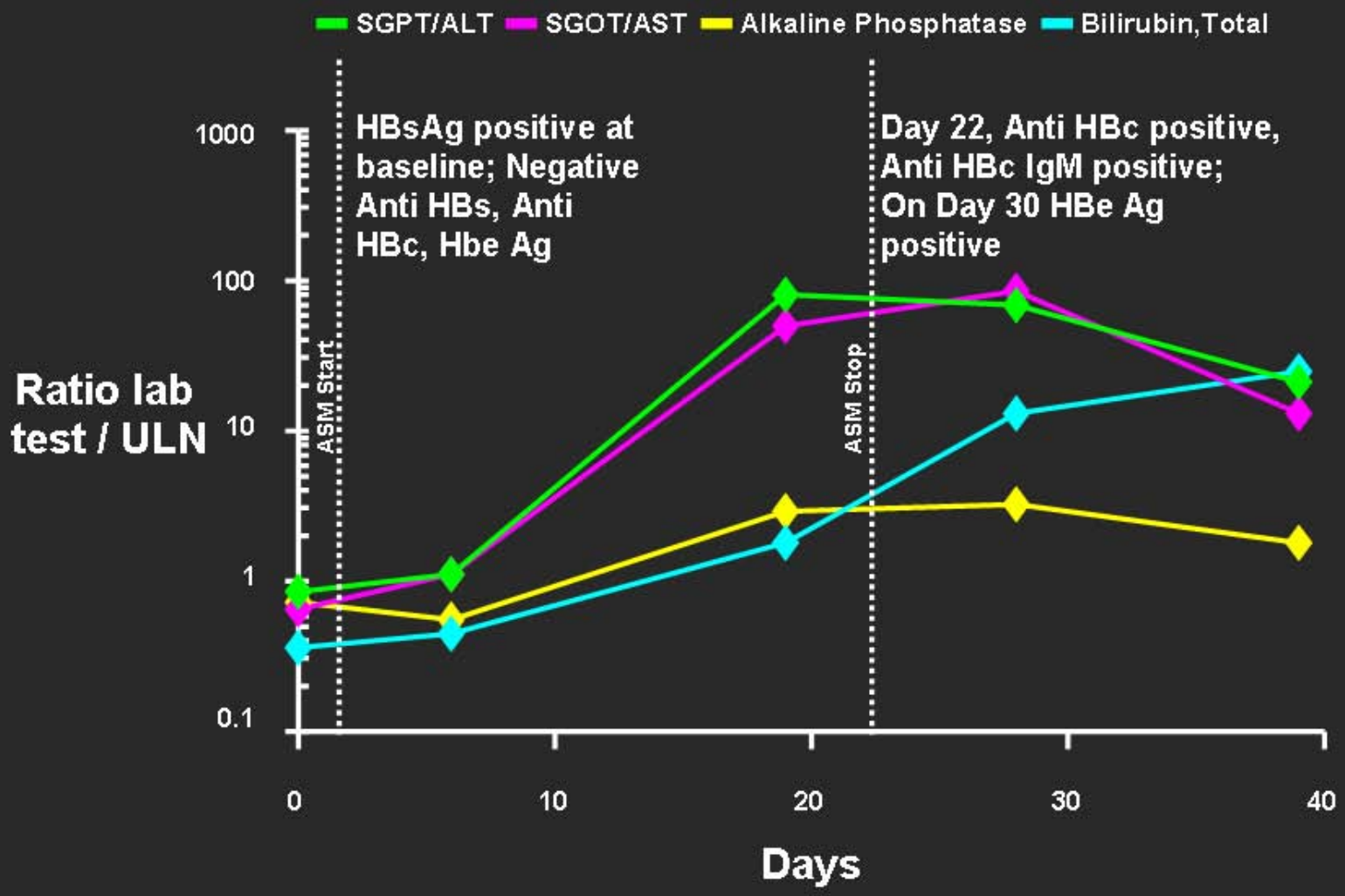
Rivaroxaban Phase 2 Hepatitis B case (11223-506006) 72 years old; Female; Czech Republic



WC-8

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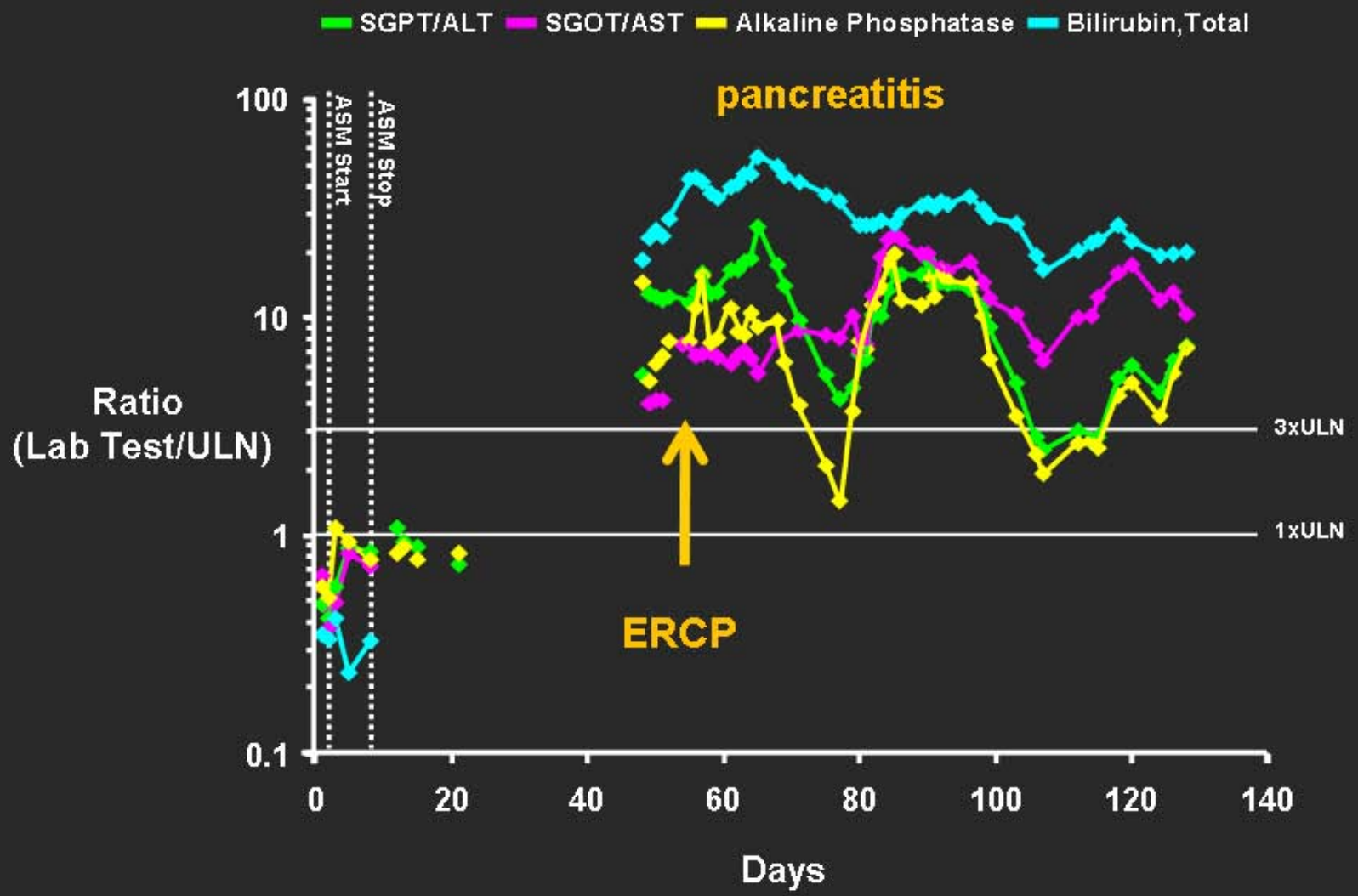
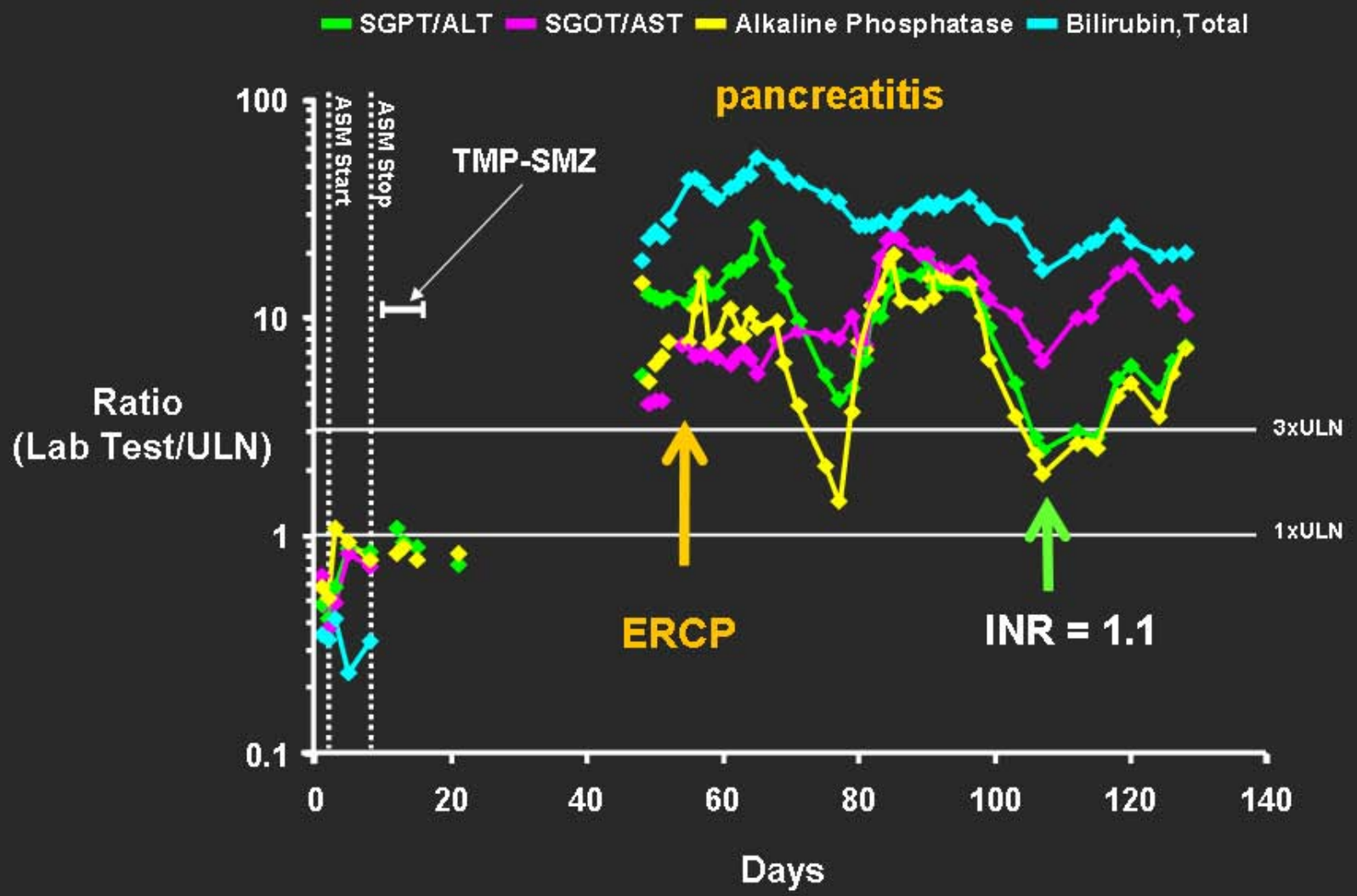
Rivaroxaban (10944-084008)
79 year old; Female; Germany



WC-10

Rivaroxaban (10944-084008)
79 year old; Female; Germany



WC-11

Conclusion

It is unlikely that rivaroxaban-induced liver injury caused these fatalities.

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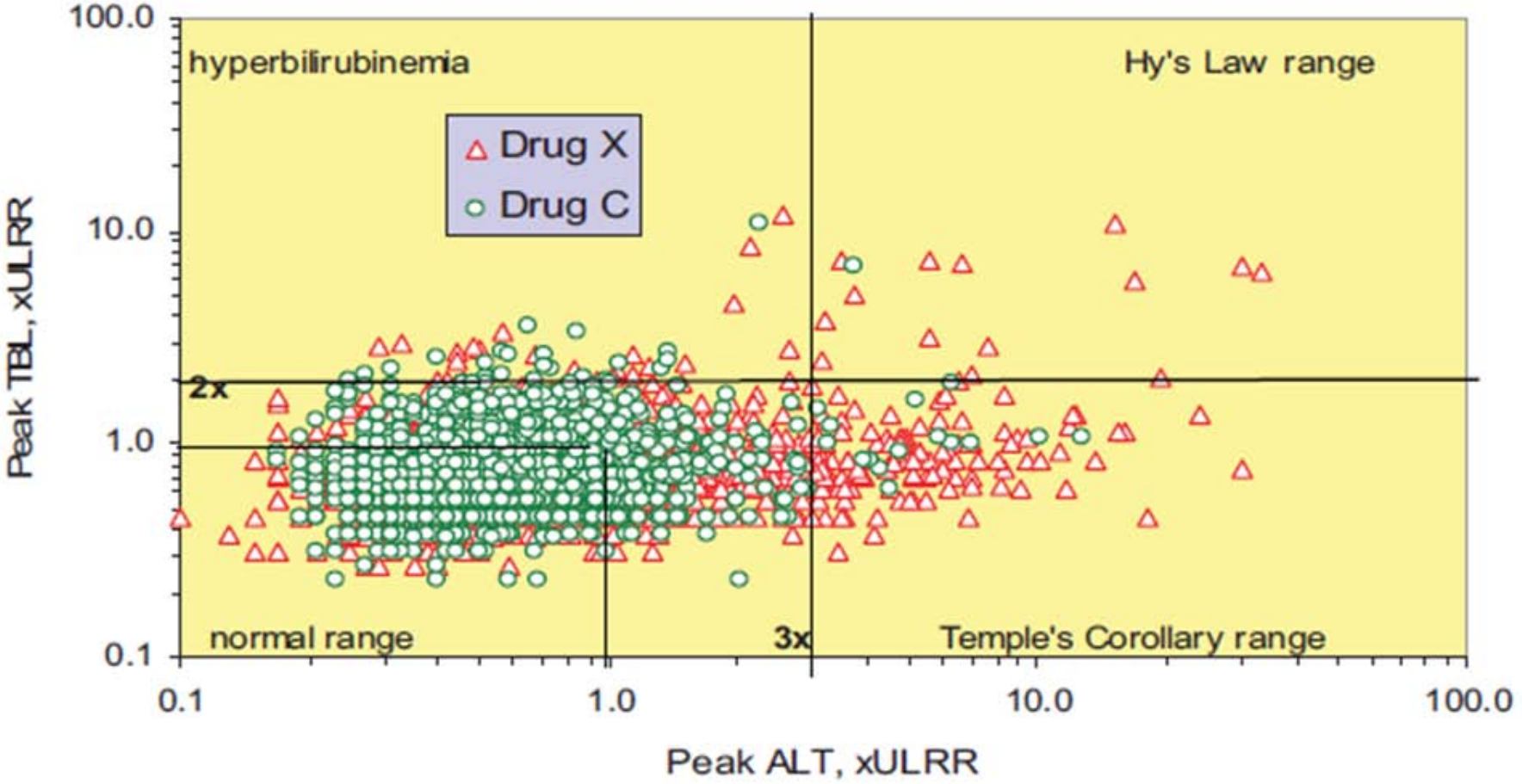
† all after day 0 baseline in safety population with measurement

Peak ALT vs peak total bilirubin observed in each subject in a phase 3 clinical trial of a drug that can cause acute liver failure (not rivaroxaban)



Edish plot from: Hepatology 48(5):1680-9,2008

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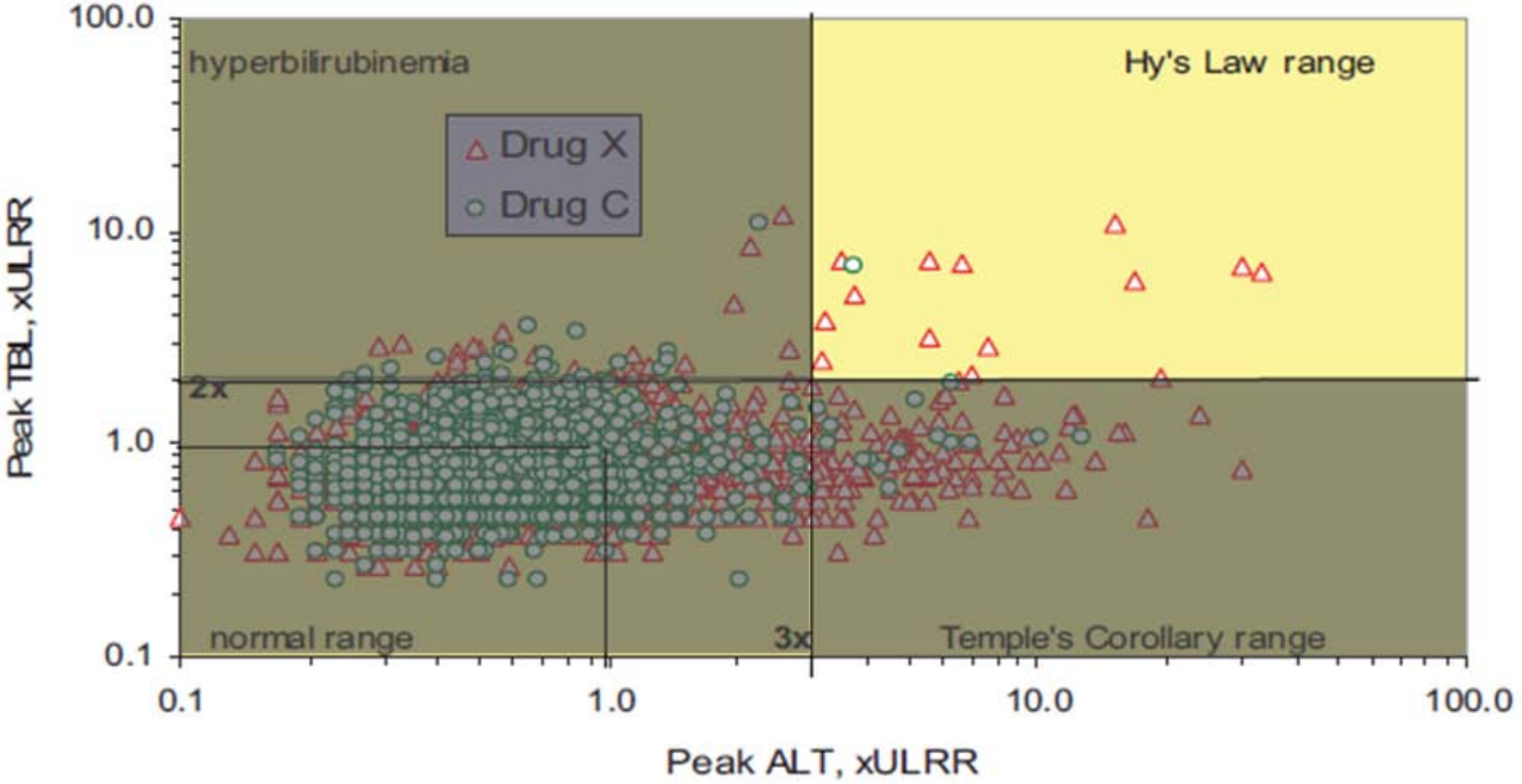

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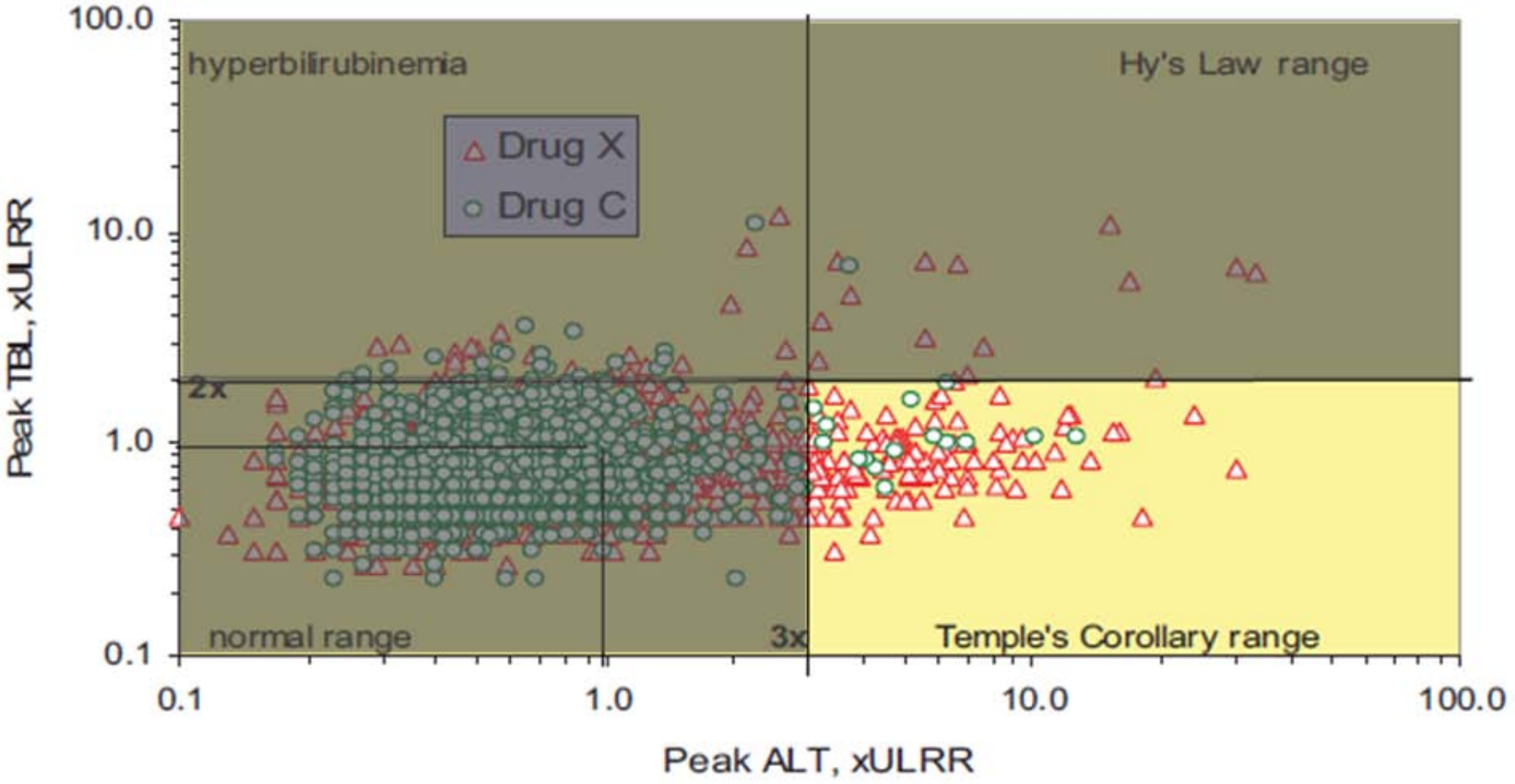

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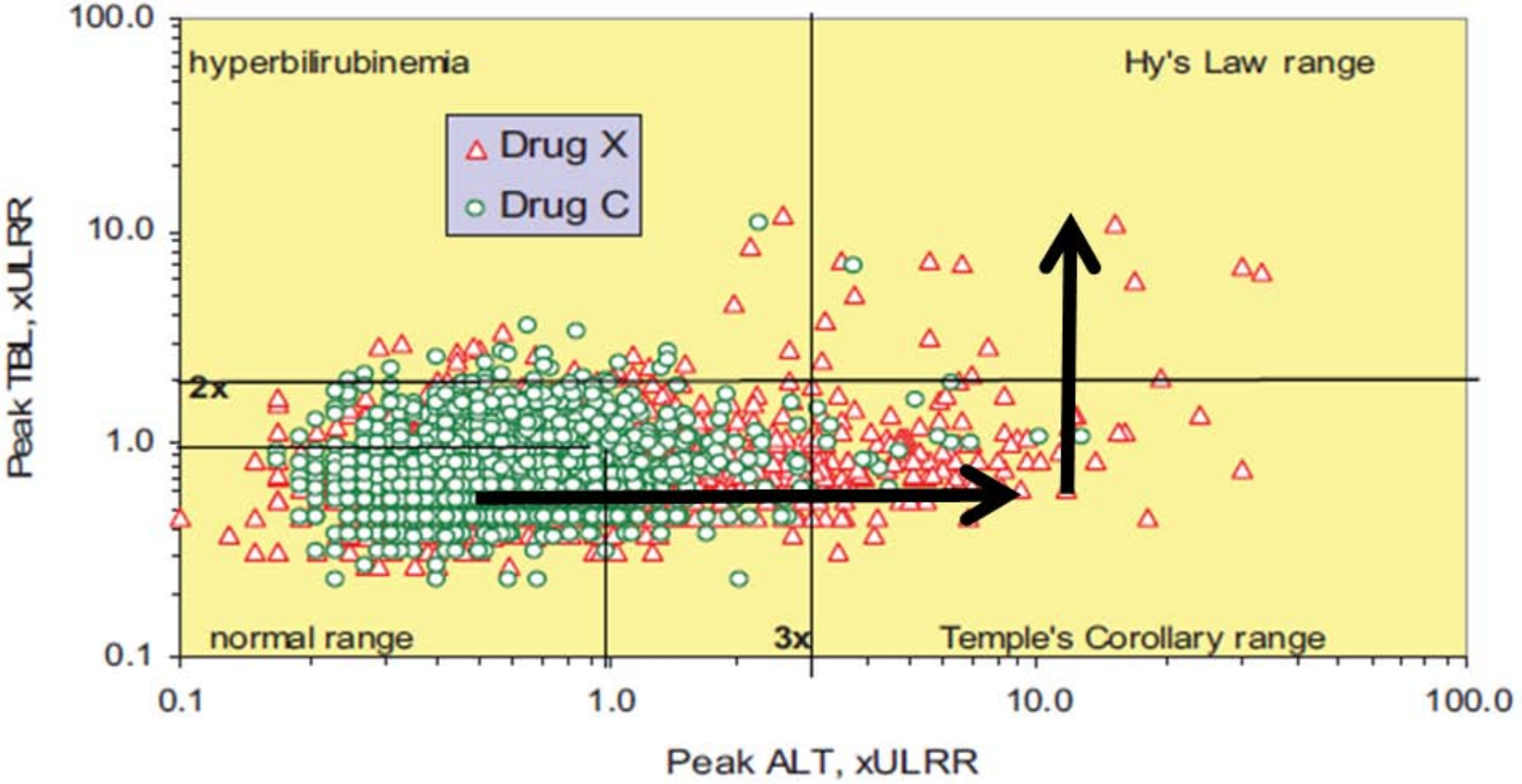

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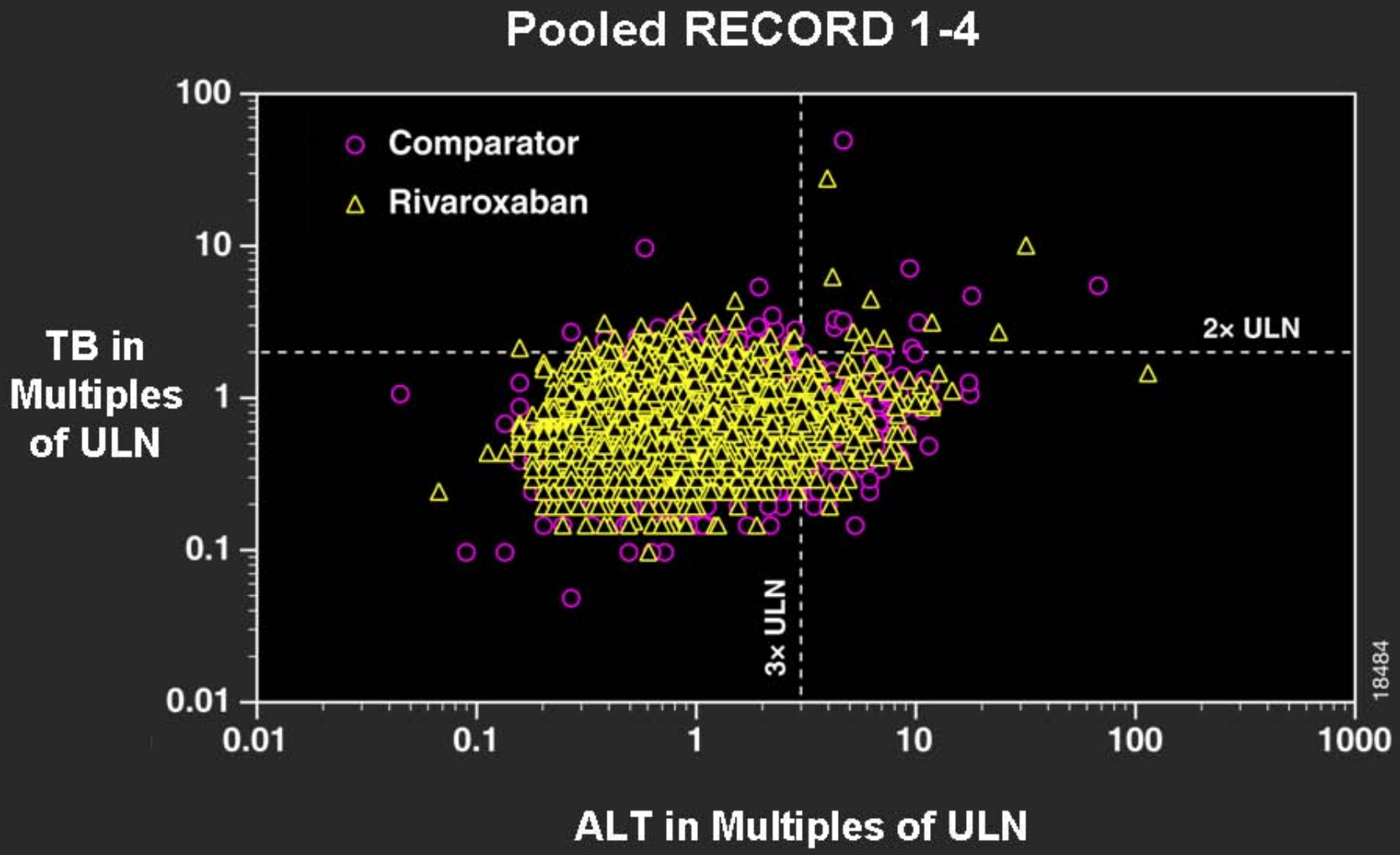
eDISH Pooled RECORD 1-4
(treatment and follow-up; central and local labs)



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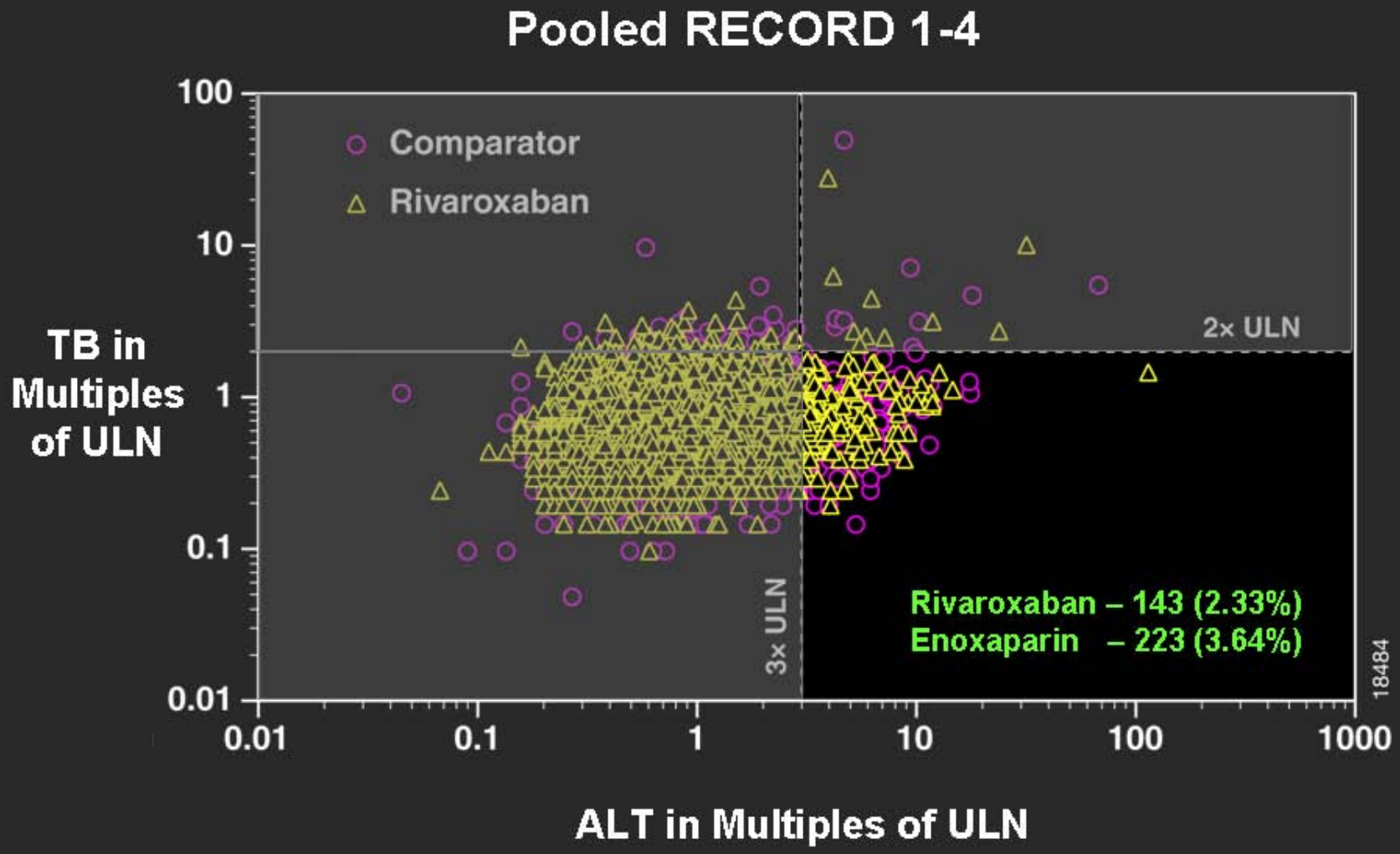
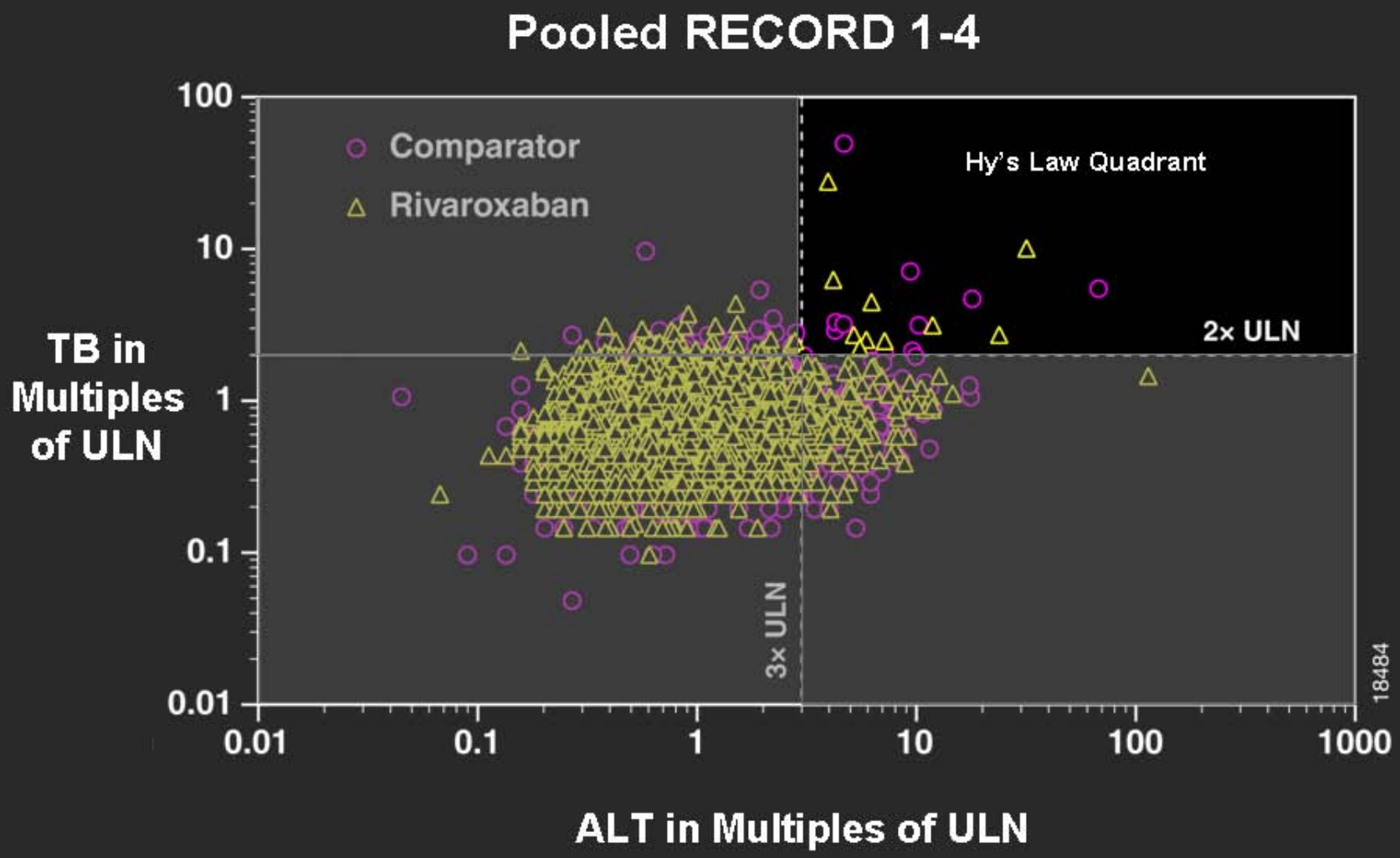
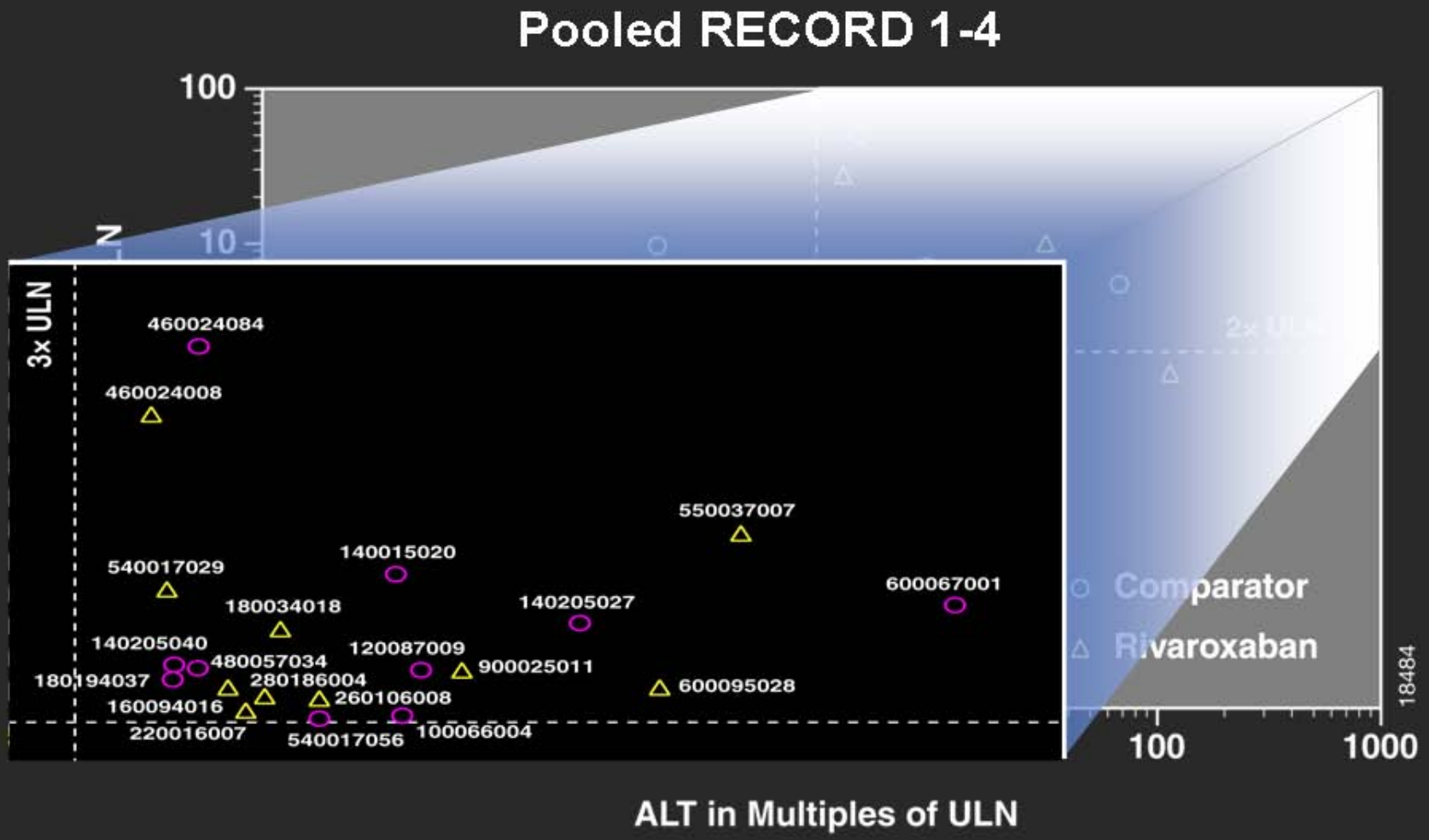


eDISH Pooled RECORD 1-4
(treatment and follow-up; central and local labs)

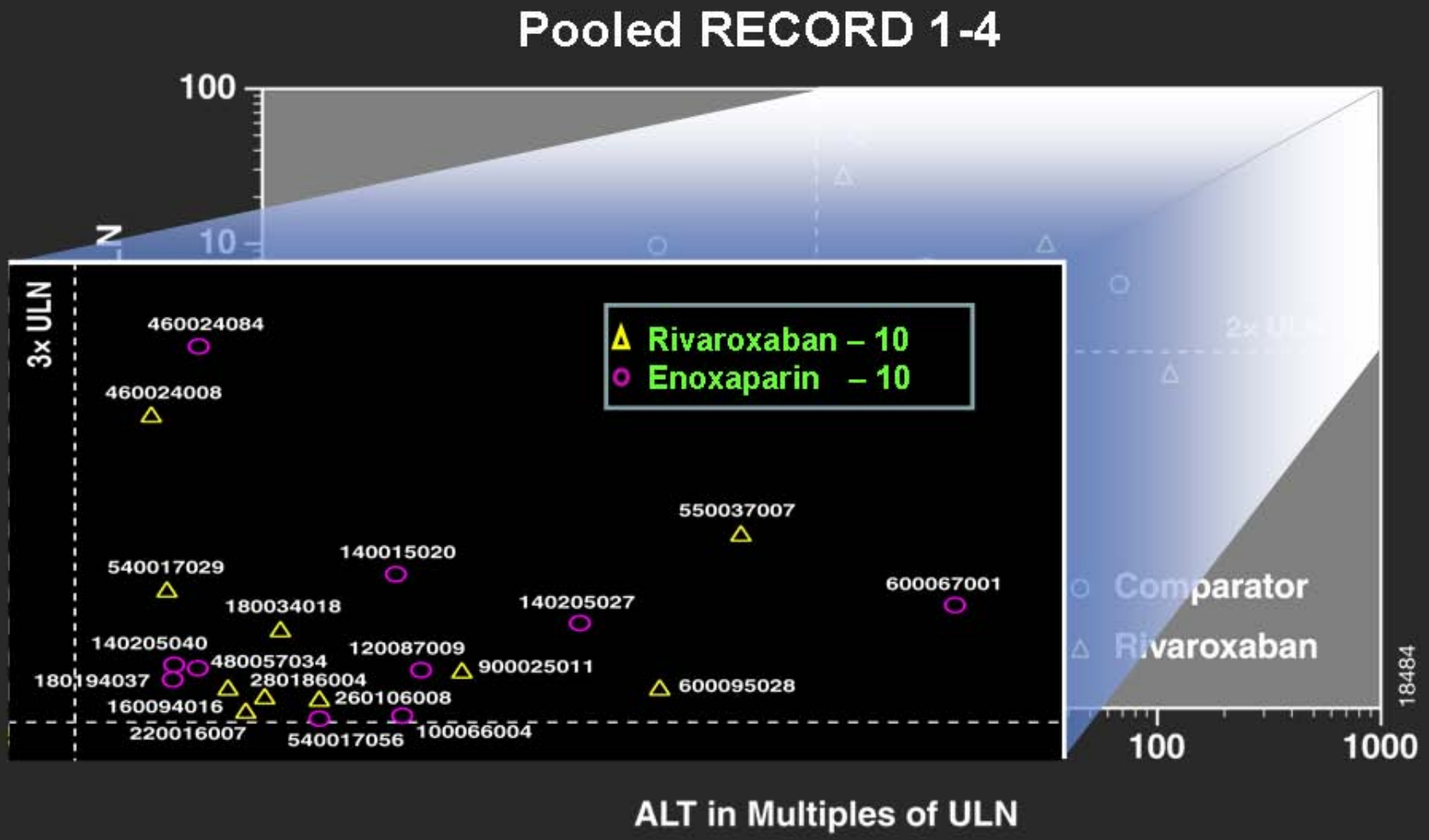


eDISH Pooled RECORD 1-4
(treatment and follow-up; central and local labs)

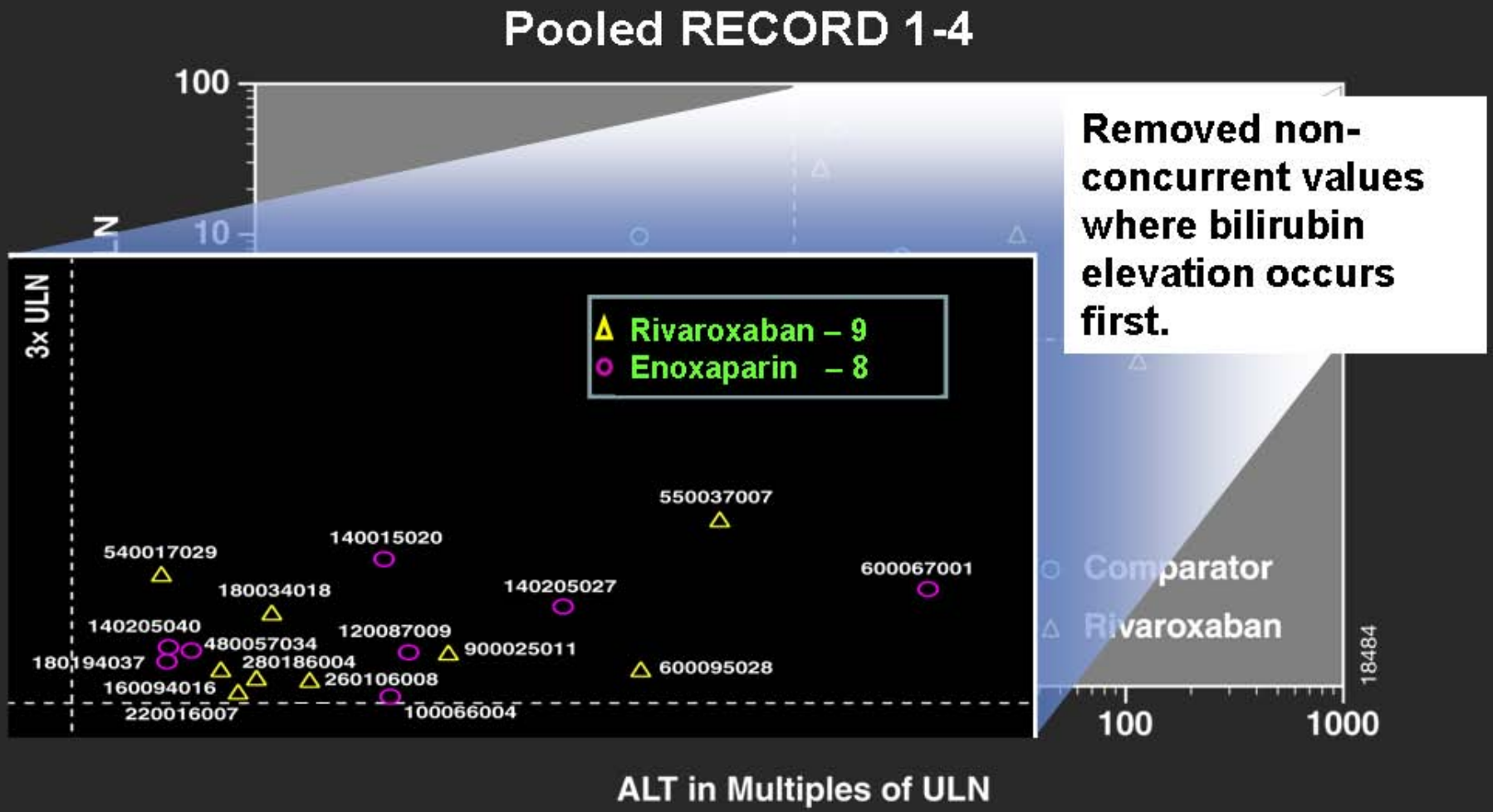


WC-23

eDISH Pooled RECORD 1-4
(treatment and follow-up; central and local labs)



eDISH Pooled RECORD 1-4
(treatment and follow-up; central and local labs)



Hy's Law Case Definition*

Subjects in a clinical trial who experience ALT >3xULN and TBL >2xULN and satisfy the following three criteria:

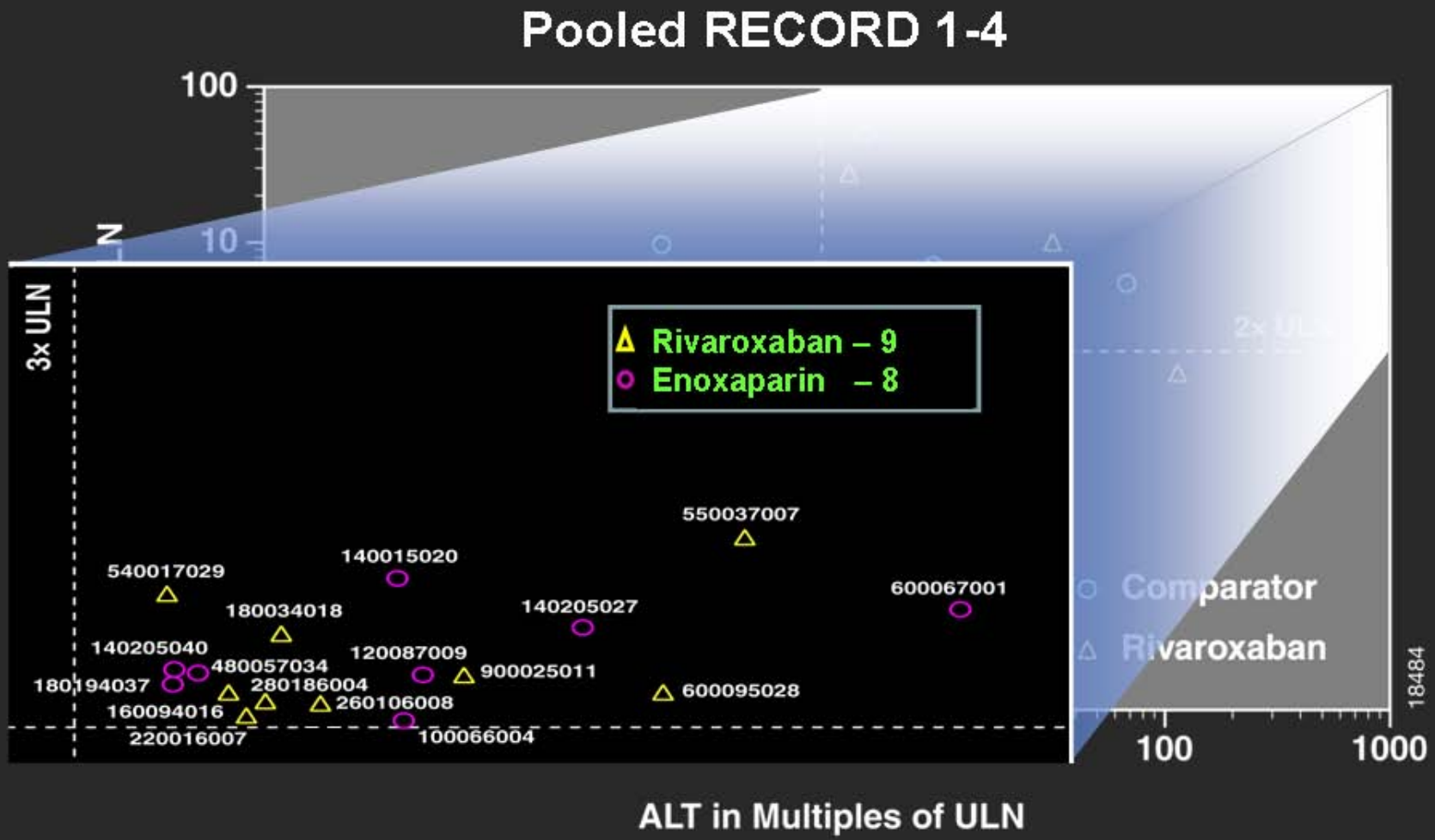
1) the liver injury should be hepatocellular in nature (alkaline phosphatase < 2 X ULN)

2) there should be no more likely alternative cause than DILI

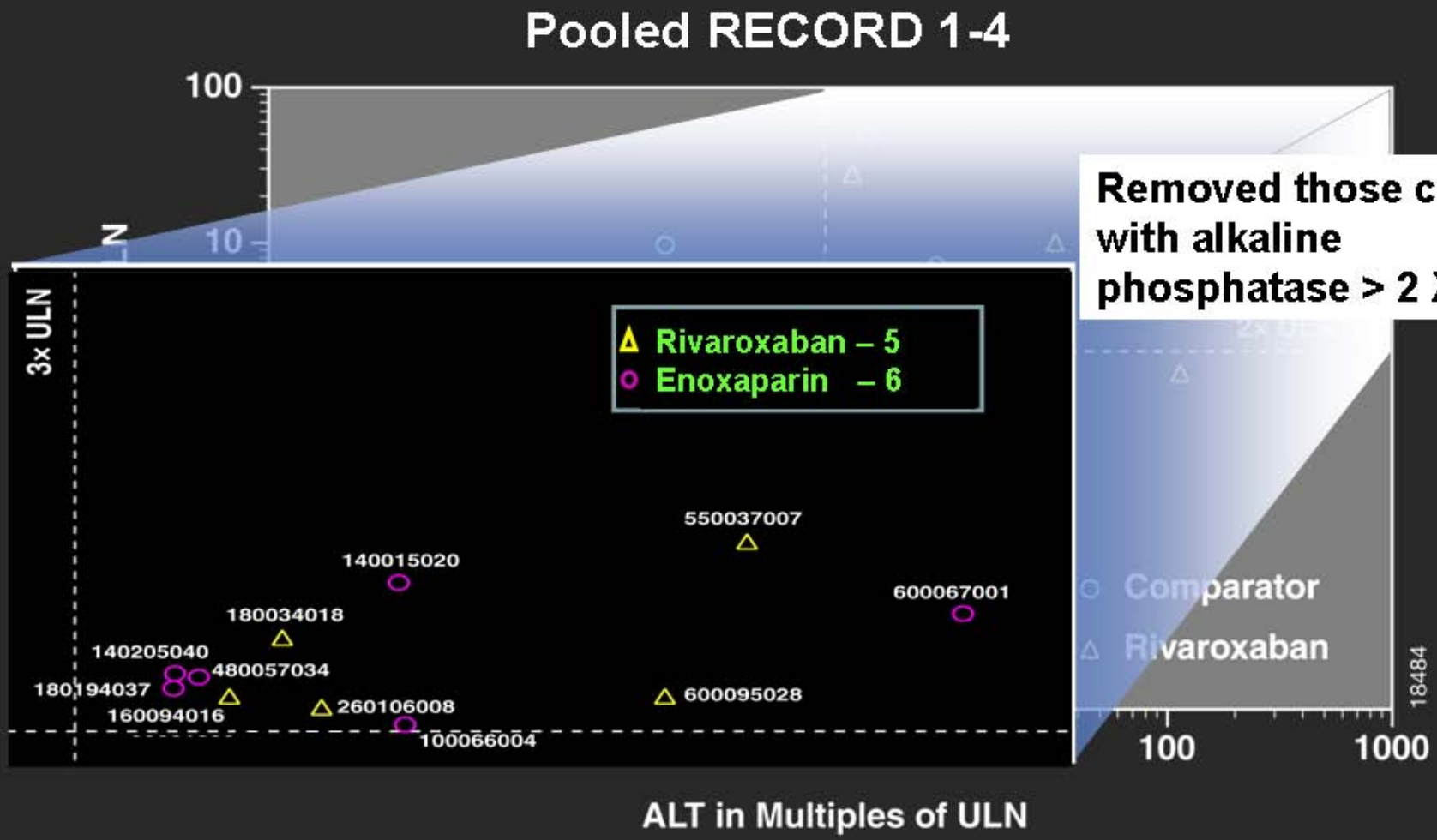
3) there should be more frequent ALT elevations >3 xULN in the treated group relative to the group on control treatment ("Temple's Corollary")

** FDA Draft Guidance for Industry - Drug-Induced Liver Injury: Premarketing Clinical Evaluation October 2007*

eDISH Pooled RECORD 1-4
(treatment and follow-up; central and local labs)

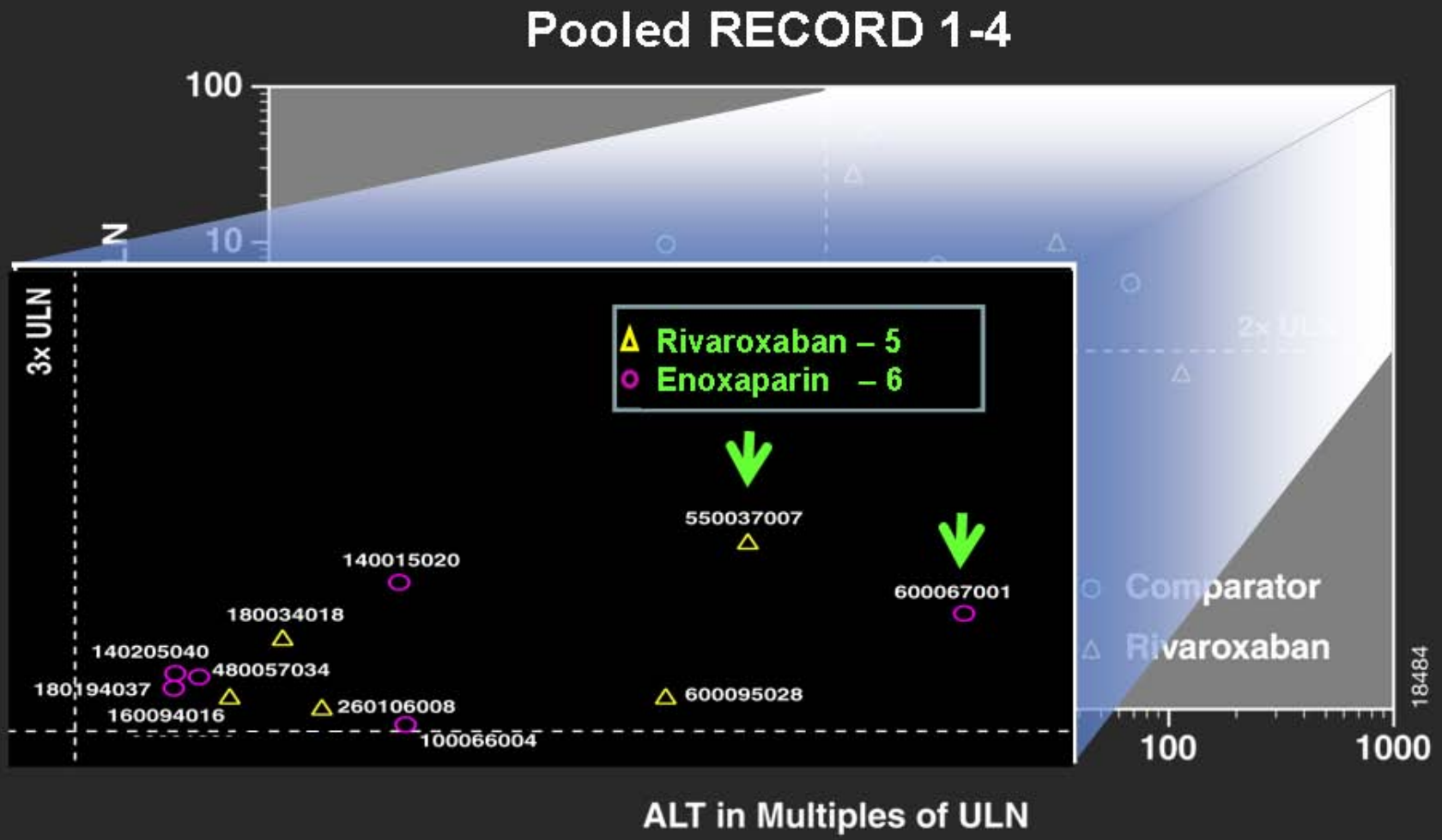


eDISH Pooled RECORD 1-4
(treatment and follow-up; central and local labs)

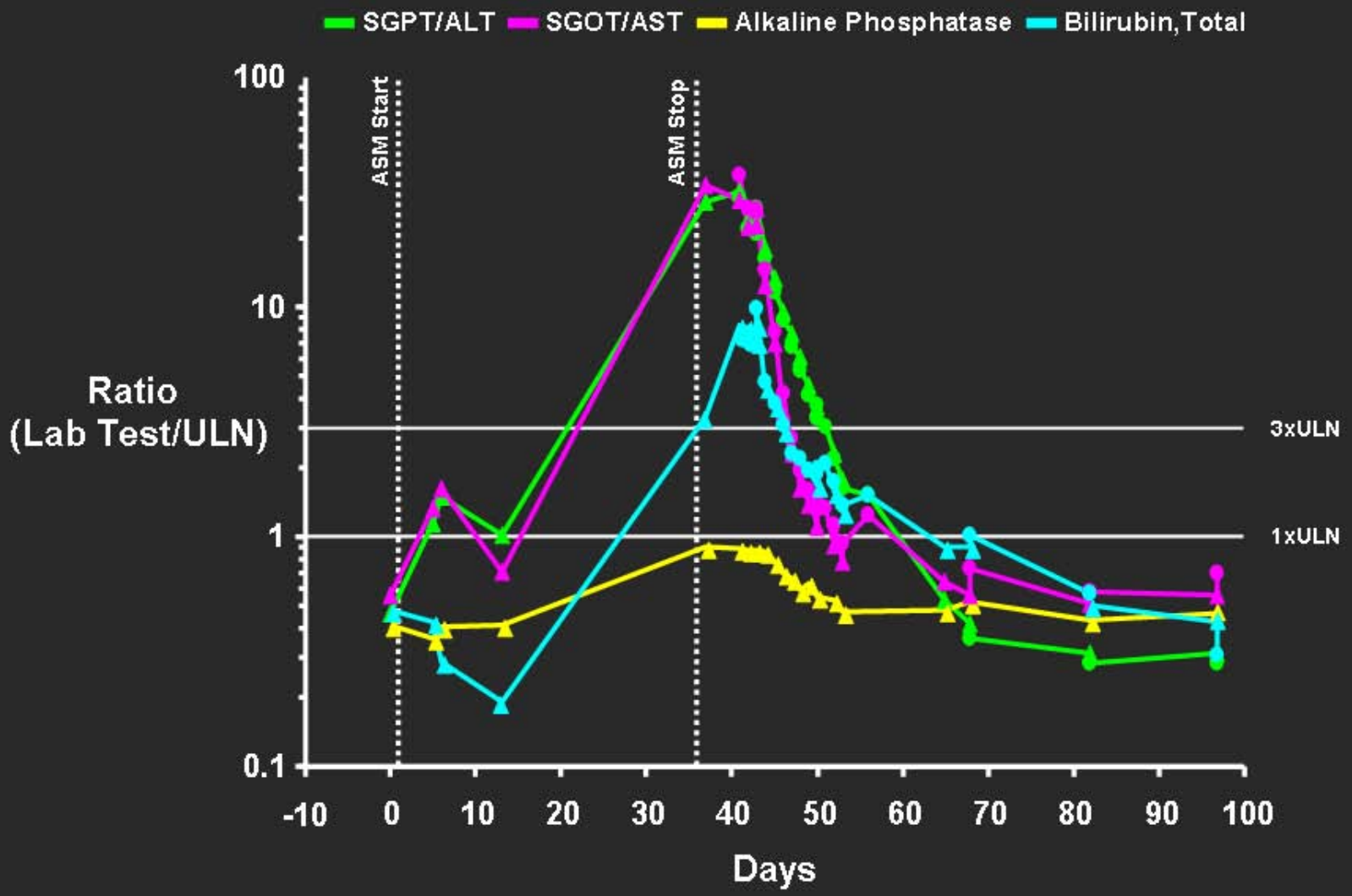


Removed those cases with alkaline phosphatase > 2 X ULN

eDISH Pooled RECORD 1-4
(treatment and follow-up; central and local labs)

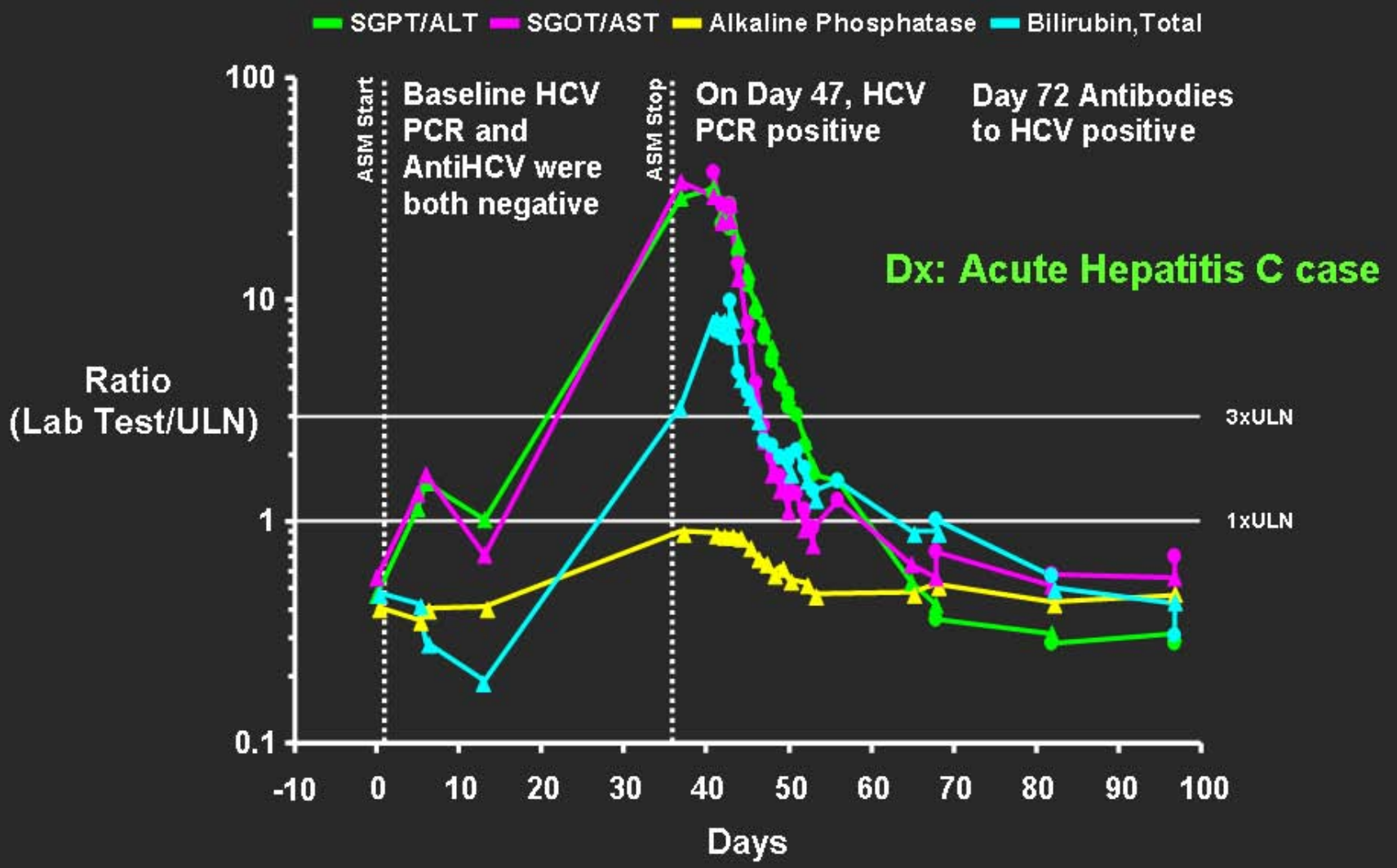


Rivaroxaban (11357/55003-7007)
52 year old; Male; Indonesia



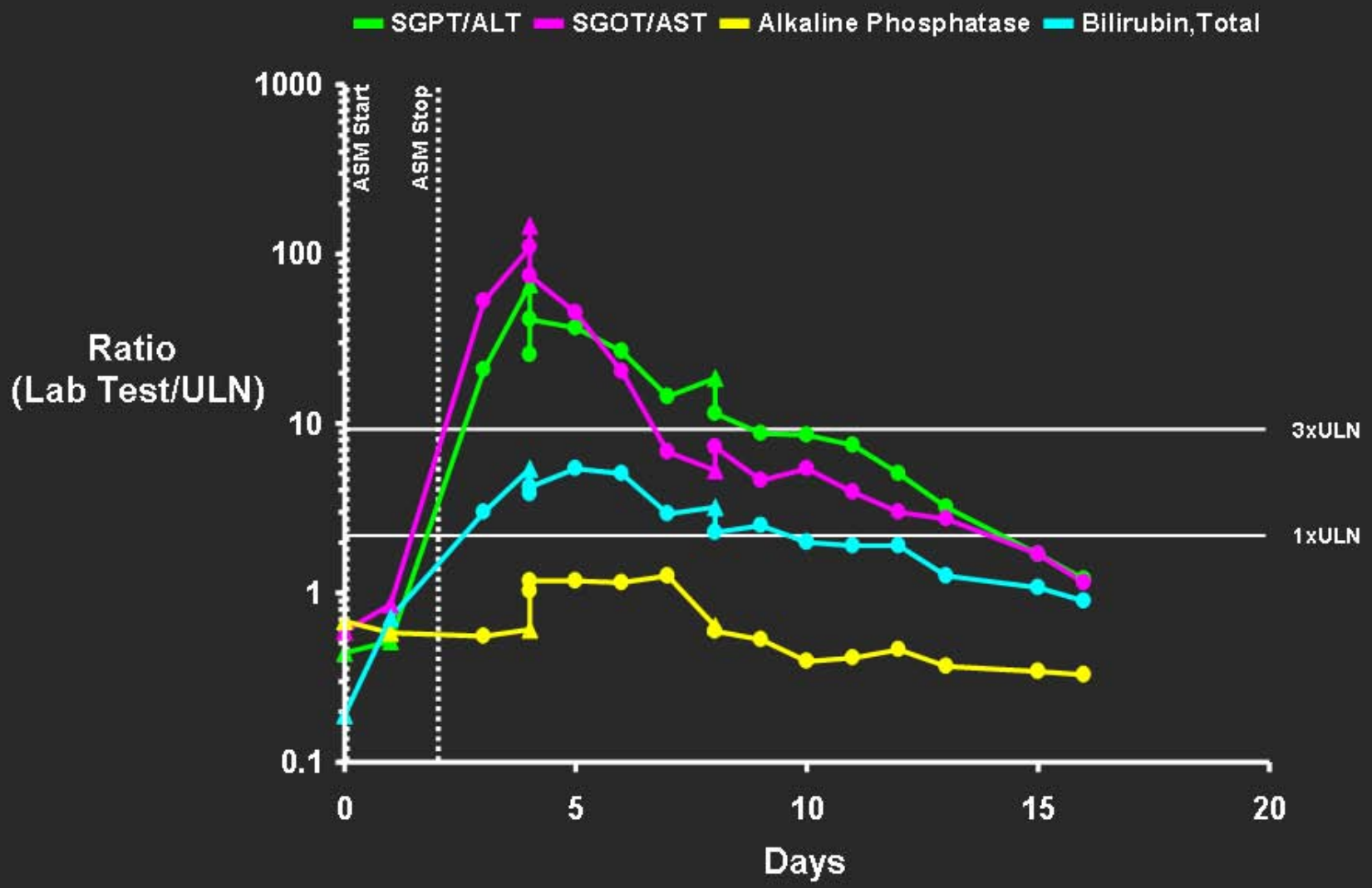
WC-30

Rivaroxaban (11357/55003-7007)
52 year old; Male; Indonesia



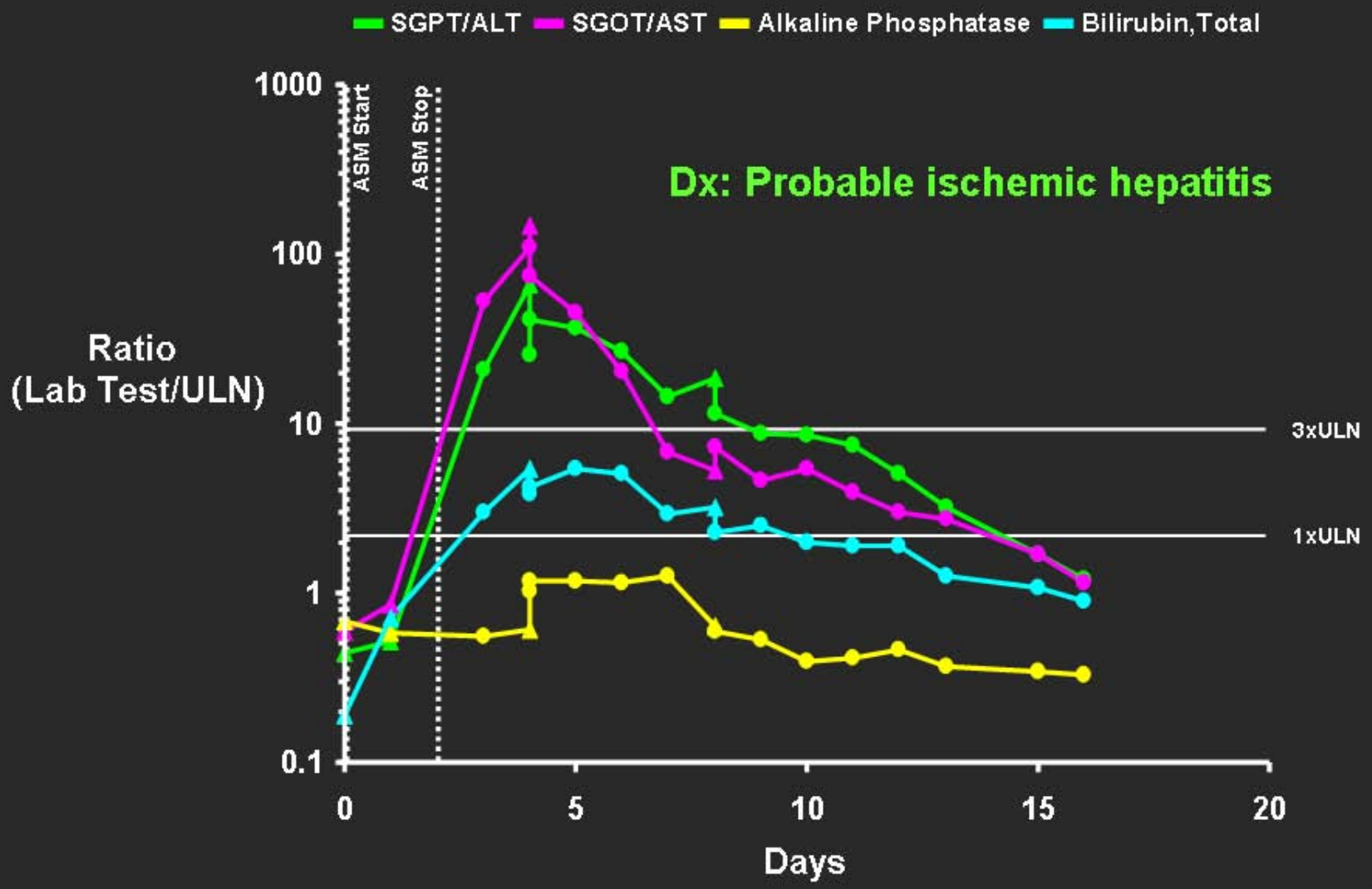
WC-31

Enoxaparin case (11357/60006-7001)
40 year old; Female; India



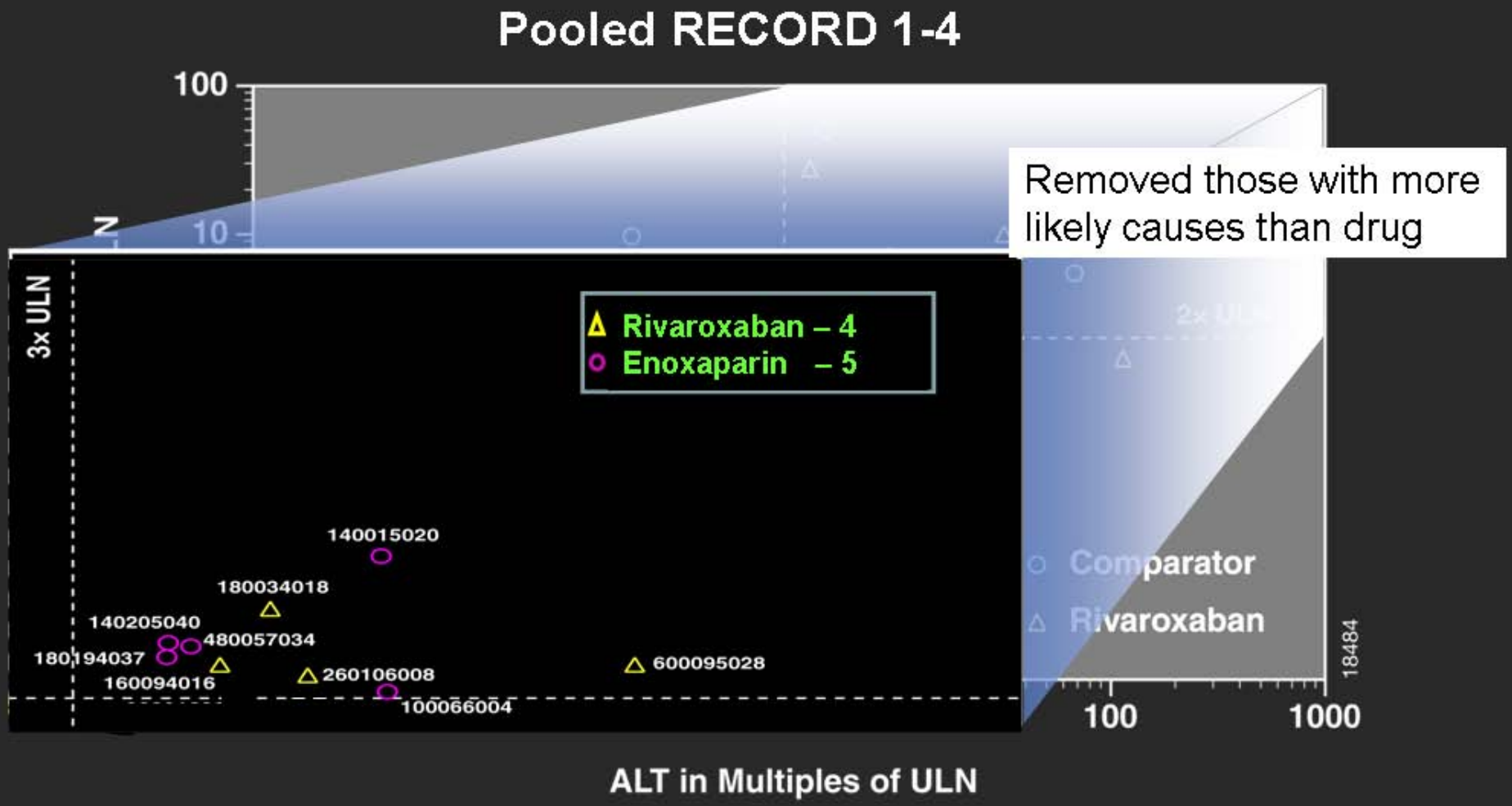
WC-32

Enoxaparin case (11357/60006-7001)
40 year old; Female; India

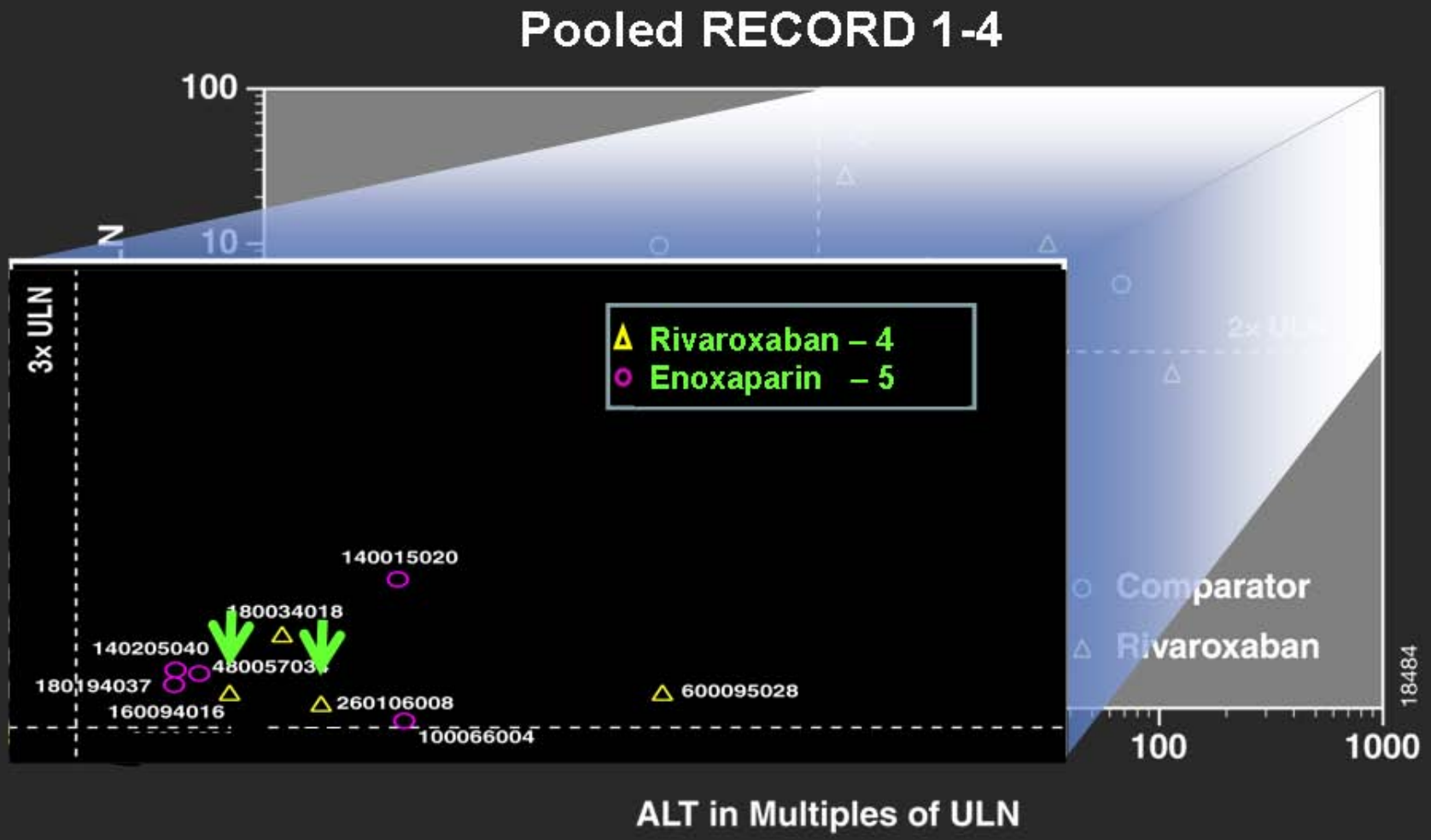


WC-33

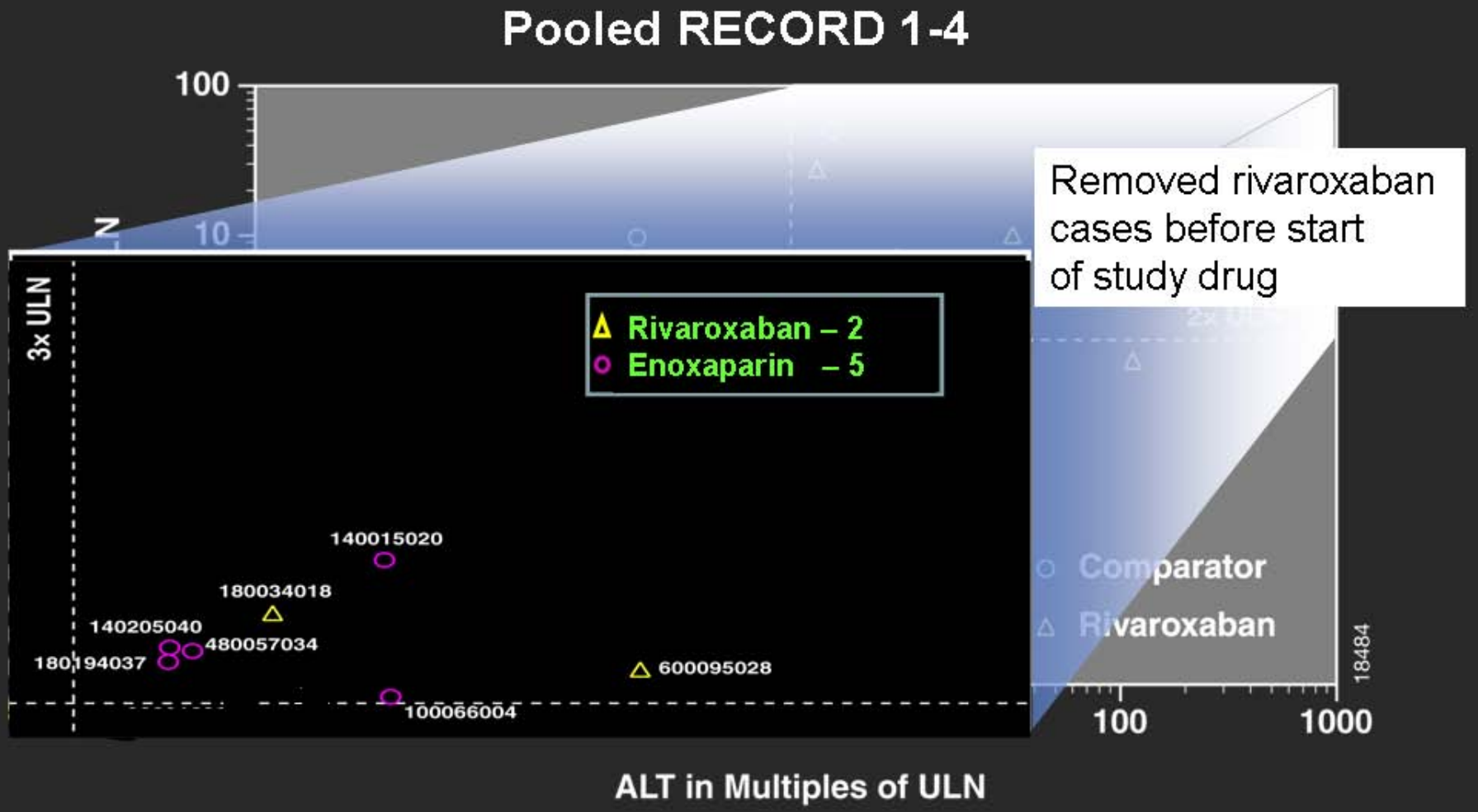
eDISH Pooled RECORD 1-4
(treatment and follow-up; central and local labs)



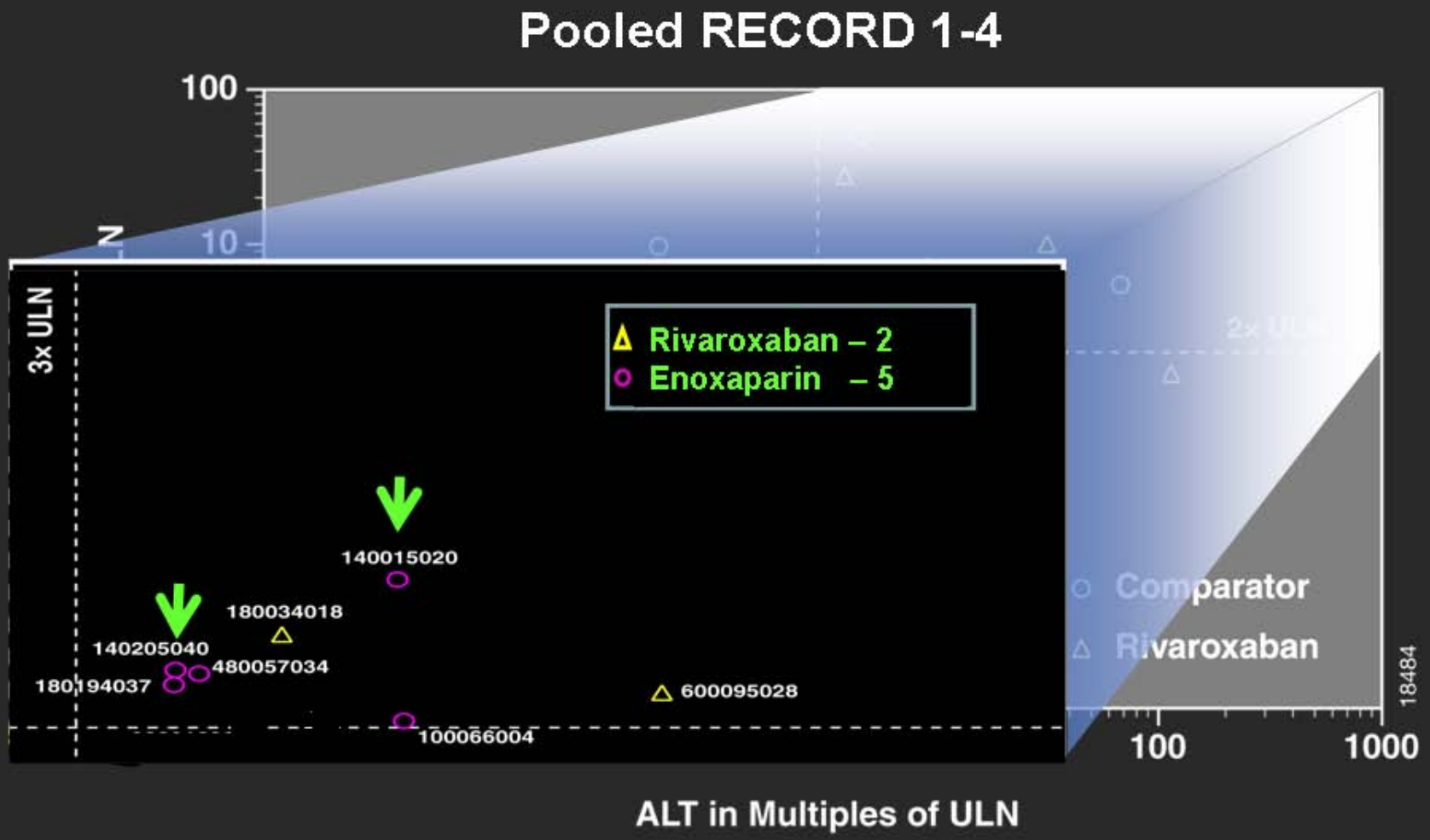
eDISH Pooled RECORD 1-4
(treatment and follow-up; central and local labs)



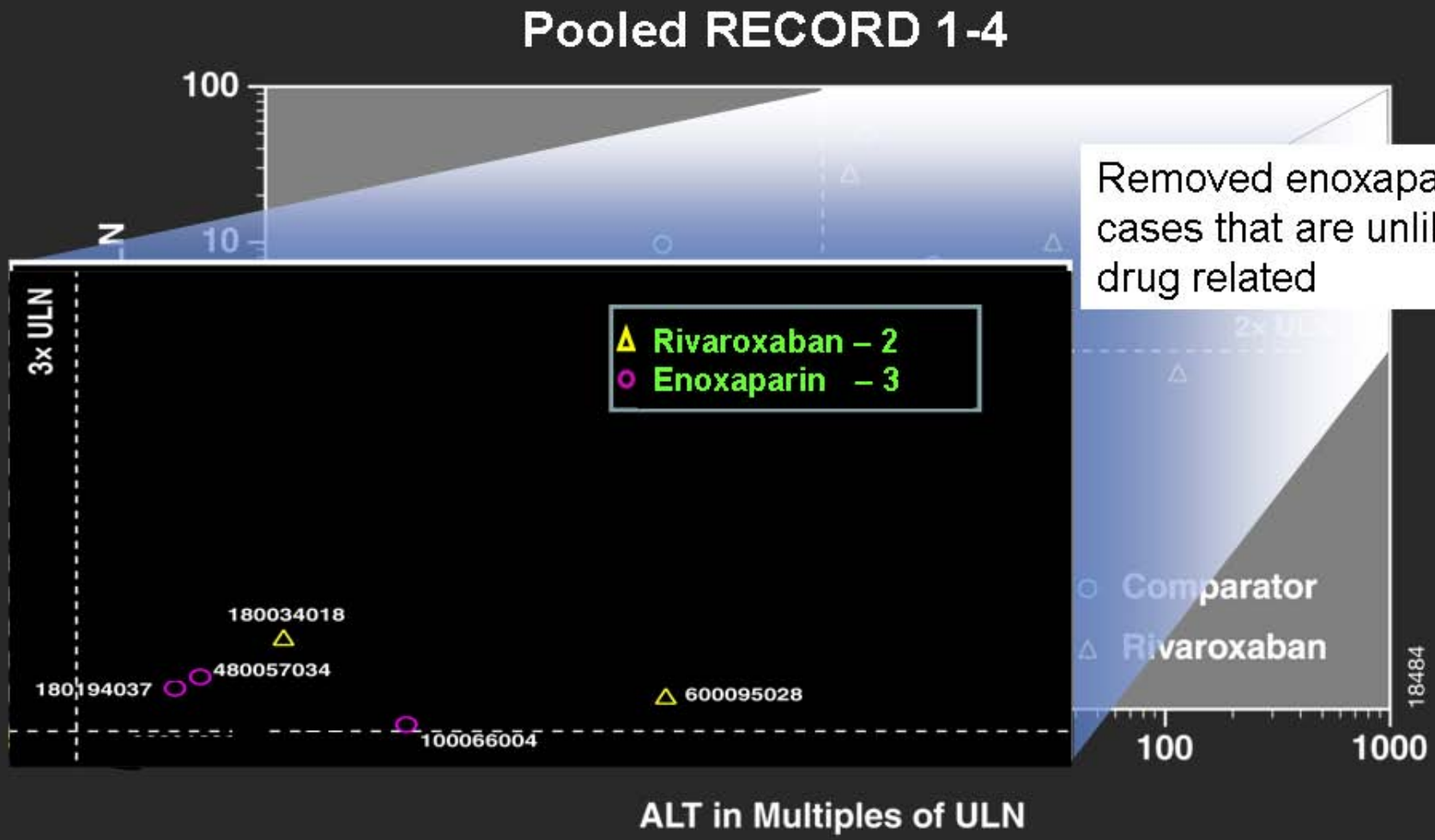
eDISH Pooled RECORD 1-4
(treatment and follow-up; central and local labs)



eDISH Pooled RECORD 1-4
(treatment and follow-up; central and local labs)

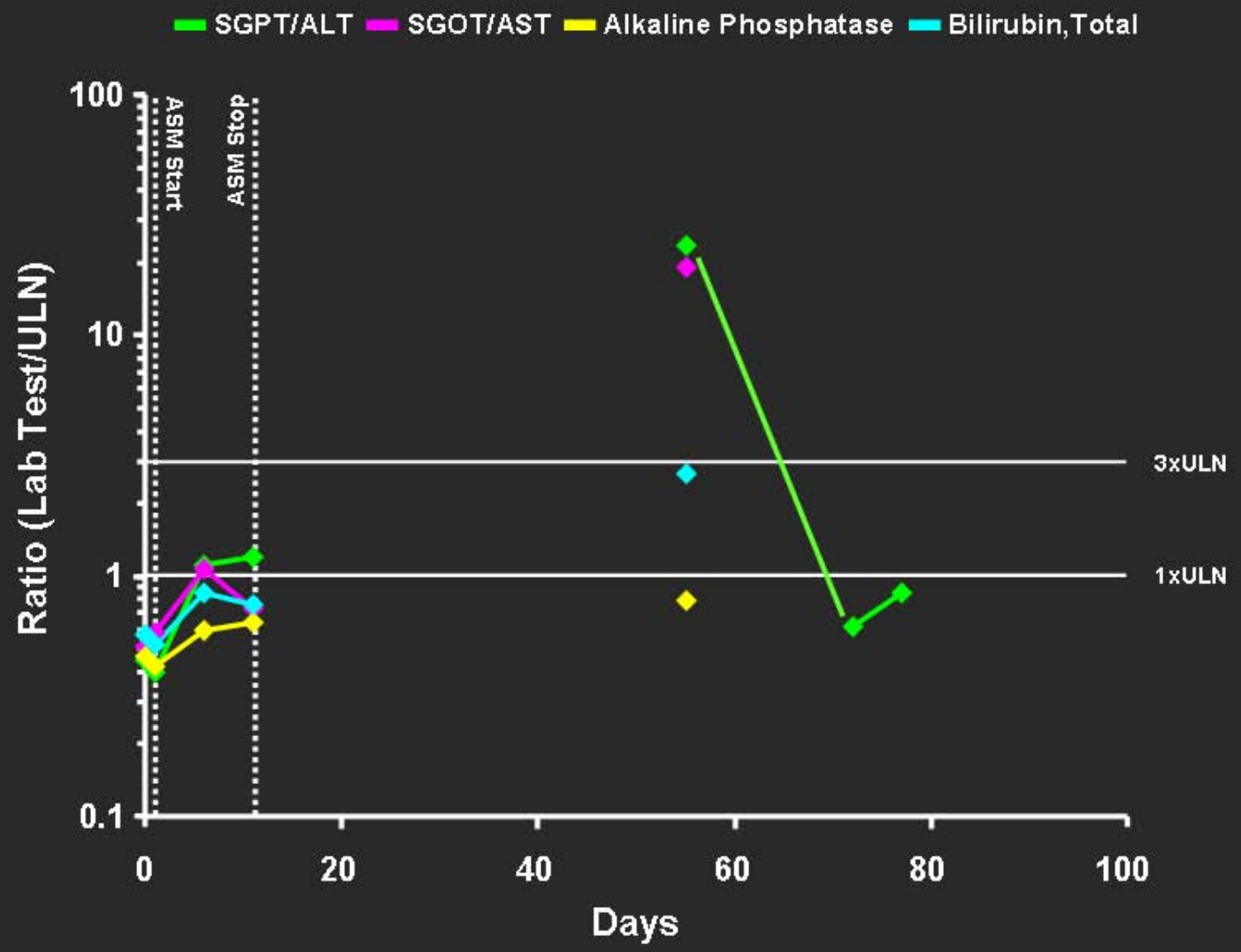


eDISH Pooled RECORD 1-4
(treatment and follow-up; central and local labs)

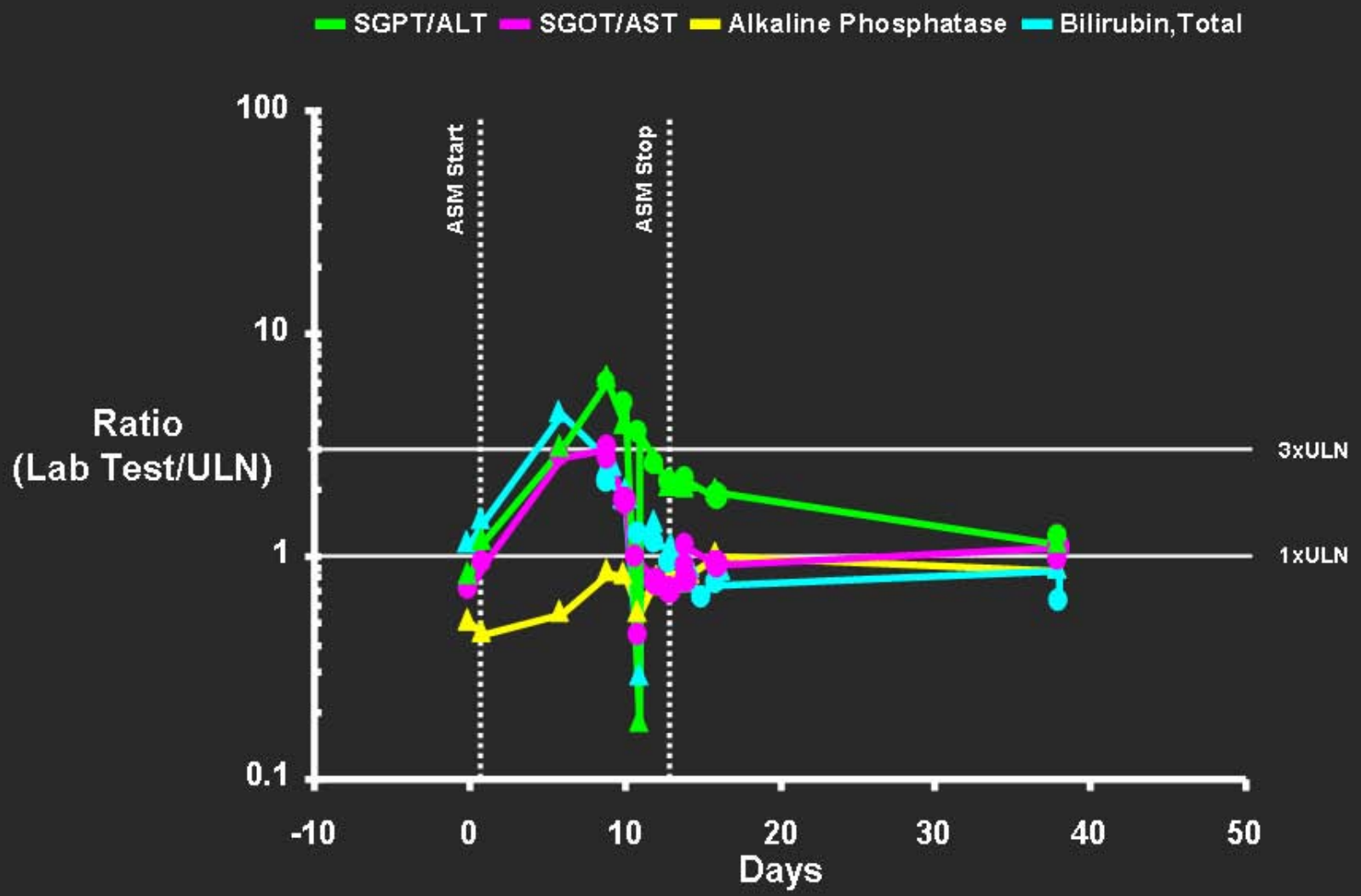


Removed enoxaparin cases that are unlikely drug related

Rivaroxaban (11355/60009-5028)
72 year old; Male; India

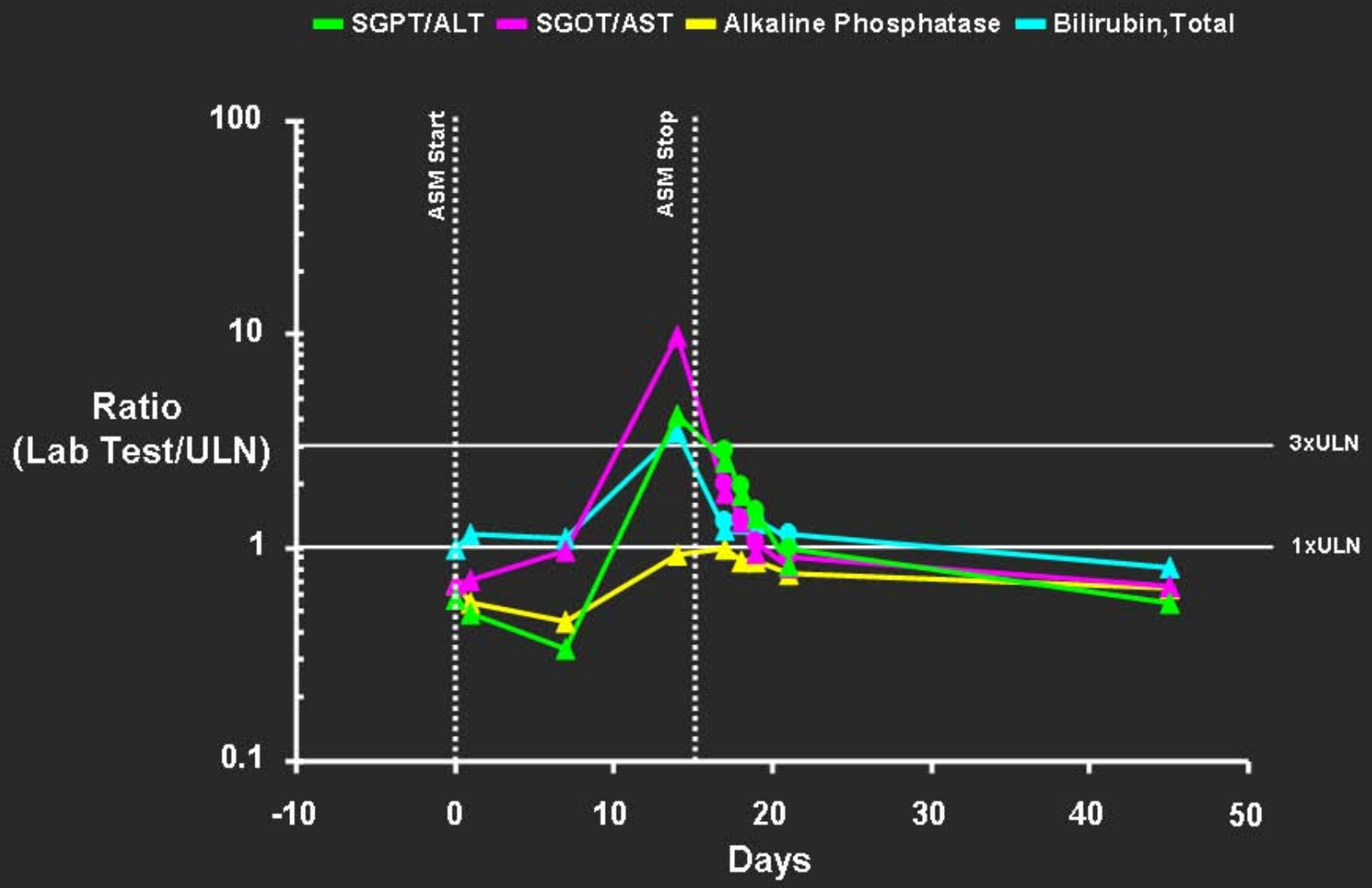


Rivaroxaban (11354/18003-4018)
49 year old; Female; Poland



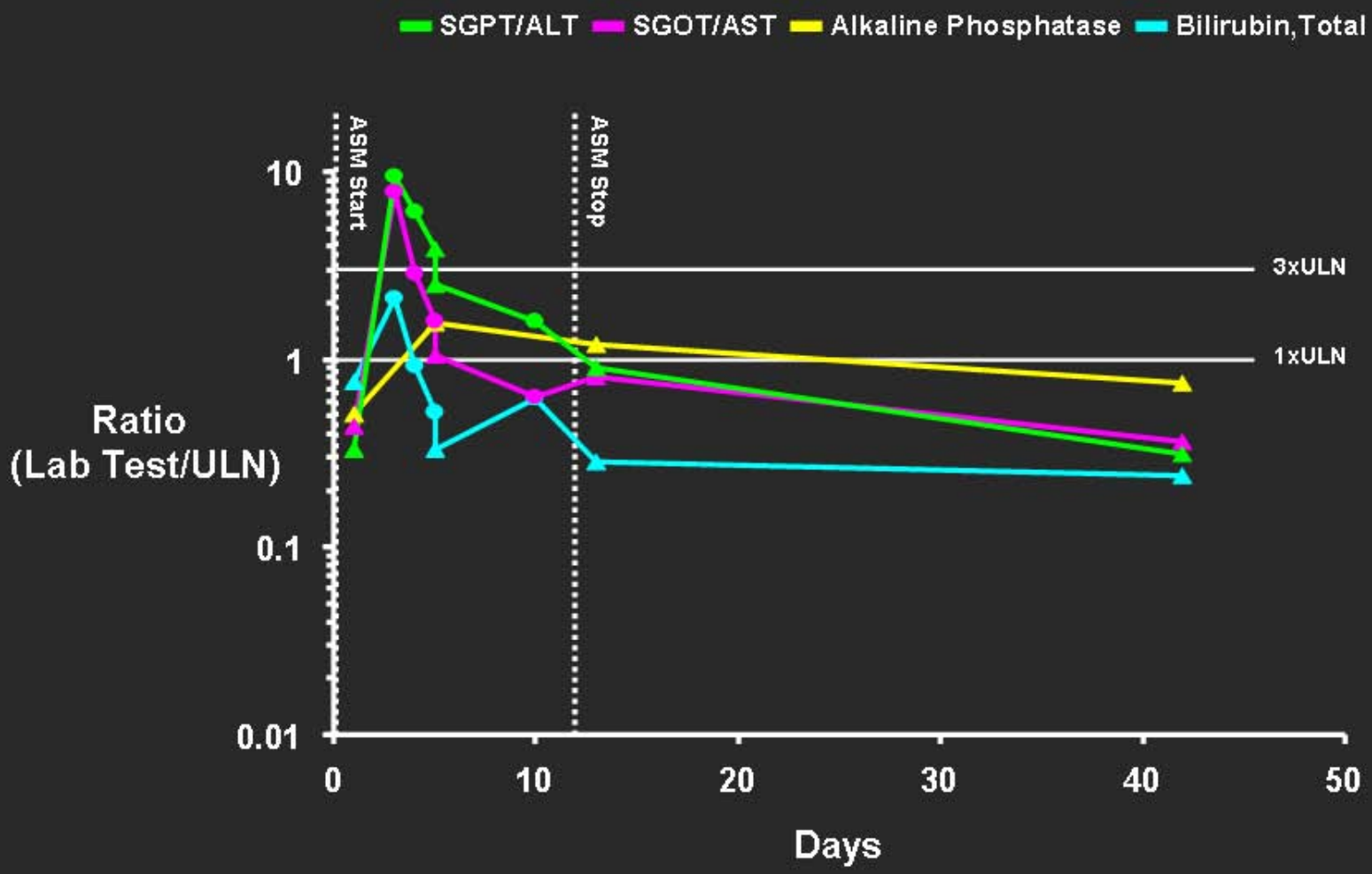
WC-40

Enoxaparin case (11354/18019-4037)
74 year old; Male; Poland



WC-41

Enoxaparin Case 11356-10006-6004
64 Year Old; Male; Germany



Local Source = ● Central Source = ▲

In the RECORD trials:

No evidence of an imbalance in clinically important liver injuries.

Temple's corollary hard to interpret since enoxaparin causes ALT elevations.

But……Relatively short term data

Outline of Presentation

1). “Liver related” deaths.

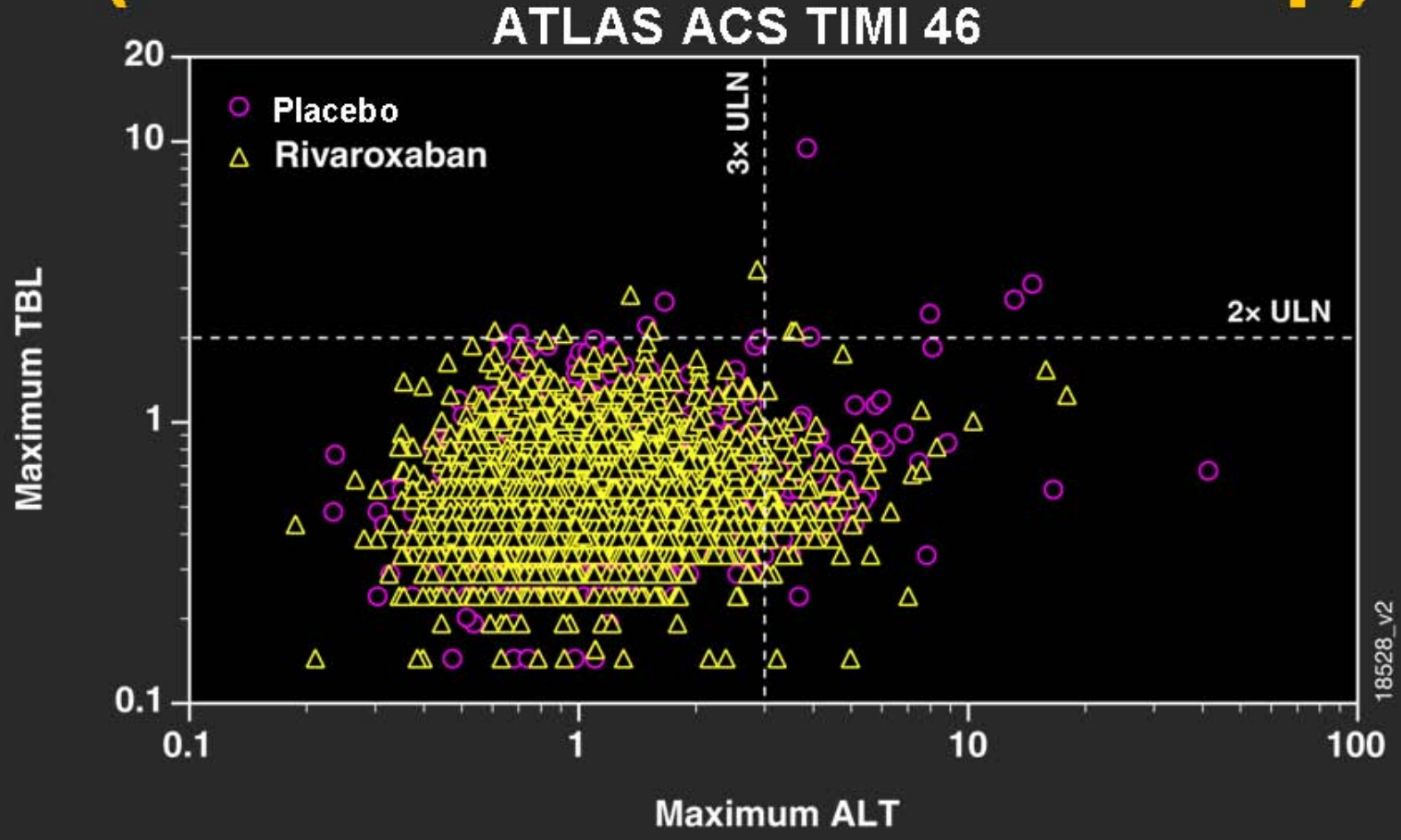
2). The Edish plot

3). The RECORD liver safety database

4). The ATLAS liver safety databases.

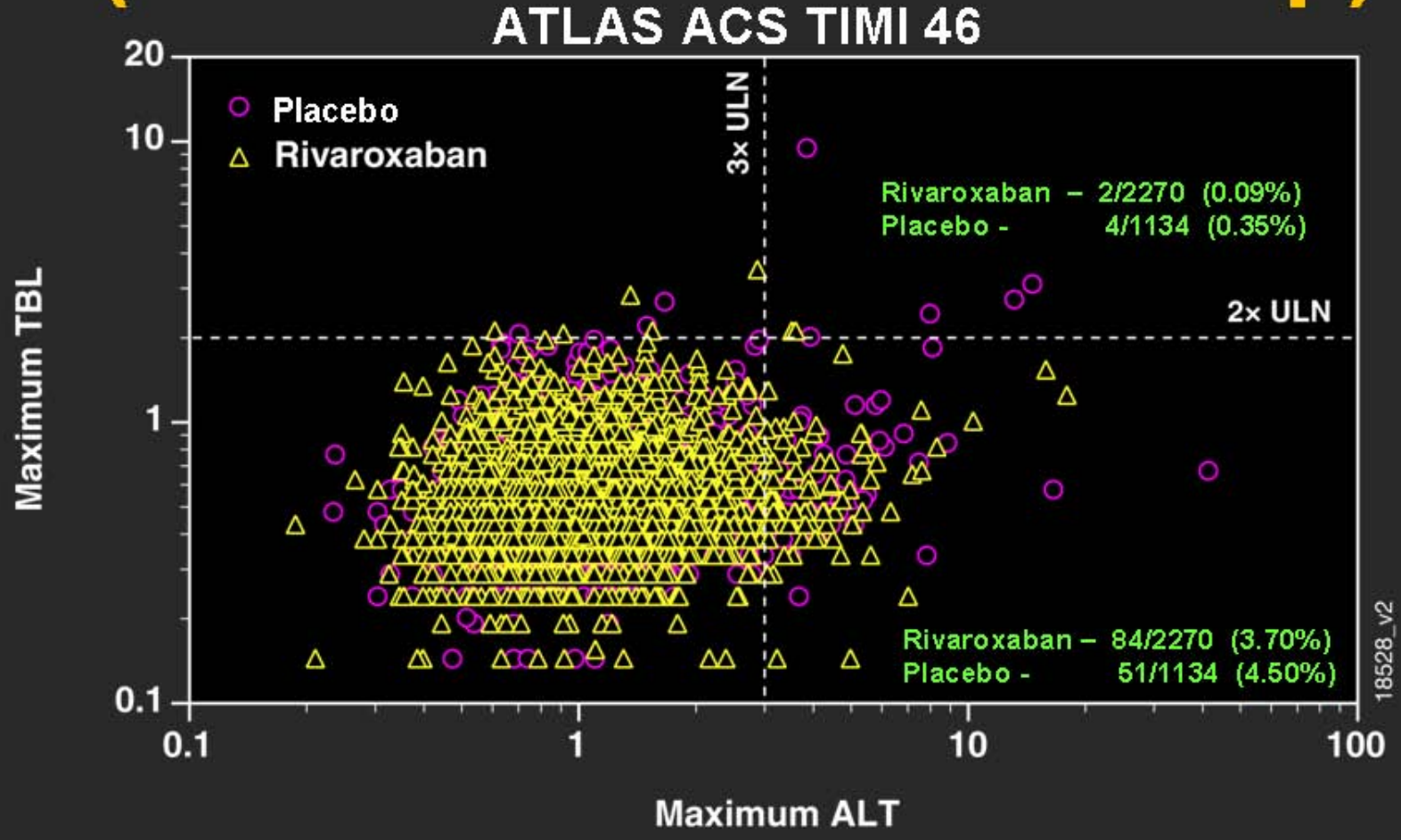
5). Conclusions

eDISH plot ATLAS study (Treatment and follow-up)



*For Subject 200012, the lab value units for Total Bilirubin were incorrectly entered into Medidata EDC as g/dl instead of mg/dl.

eDISH plot ATLAS study (Treatment and follow-up)



*For Subject 200012, the lab value units for Total Bilirubin were incorrectly entered into Medidata EDC as g/dl instead of mg/dl.

Summary

1). No deaths attributed to rivaroxaban liver toxicity.

2). No imbalance in clinically important liver injuries between rivaroxaban vs enoxaparin in the RECORD or vs true placebo in the ATLAS clinical trial.

3). No evidence of increased ALT elevations relative to placebo in the ATLAS trial.

Conclusion

A liver safety signal is not evident in the clinical trials database for rivaroxaban.