The importance of Clinical Pharmacology Study for Successful Implementation of ICH E17 Guideline

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Mar.02, 2018 Hong Kong

Outline

- **CFDA's reform**
- **ICH E17 Overview**
- **The importance of Clinical Pharmacology Study**
- **Concluding remarks**

CFDA 国家食品药品监督管理总局
China Food and Drug Administration

国家食品药品监督管理总局关于开展药物临床试验数据自查核查工作的公告（2015年第117号）

2015年07月22日 发布

为落实党中央、国务院用“最严谨的标准、最严格的监管、最严厉的处罚、最严肃的问责，确保广大人民群众饮食用药安全”的要求，从源头上保障药品安全、有效，国家食品药品监督管理总局决定对附件所列已申报生产或进口的待审药品注册申请开展药物临床试验数据核查。有关事宜公告如下：

一、自本公告发布之日起，所有已申报并在总局待审的药品注册申请人，均须按照《药物临床试验质量管理规范》等相关要求，对照临床试验方案，对已申报生产或进口的待审药品注册申请药物临床试验情况开展自查，确保临床试验数据真实、可靠，相关证据保存完整。

国家食品药品监督管理总局 CFDA
China Food and Drug Administration

国家食品药品监督管理总局成为国际人用药品注册技术协调会成员

2017年06月19日 发布

2017年5月31日至6月1日，国际人用药品注册技术协调会（ICH）2017年第一次会议在加拿大蒙特利尔召开。会议通过了国家食品药品监督管理总局的申请，正式批准总局成为其成员。6月14日，经报国务院批准，国家食品药品监督管理总局局长毕井泉致函ICH管理委员会主席穆林博士，正式确认总局加入ICH，成为其全球第8个监管机构成员。

国家食品药品监督管理总局 CFDA
China Food and Drug Administration

中共中央办公厅 国务院办公厅印发《关于深化审评审批制度改革鼓励药品医疗器械创新的意见》

来源： 新华社

2017年10月08日 发布

当前，我国药品医疗器械产业快速发展，创新创业方兴未艾，审评审批制度改革持续推进。但总体上看，我国药品医疗器械科技创新支撑不够，上市产品质量与国际先进水平存在差距。为促进药品医疗器械产业结构调整和技术创新，提高产业竞争力，**满足公众临床需要**，现就深化审评审批制度改革鼓励药品医疗器械创新提出以下意见。

国家食品药品监督管理总局 CFDA
China Food and Drug Administration

中共中央办公厅 国务院办公厅印发《关于深化审评审批制度改革鼓励药品医疗器械创新的意见》

来源： 新华社

2017年10月08日 发布

1. **改革临床试验管理**
2. **加快上市审评审批**
3. **促进药品创新和仿制药发展**
4. **加强药品医疗器械全生命周期管理**
5. **提升技术支撑能力**
6. **加强组织实施**

支持临床试验机构和人员开展临床试验

- 将临床试验条件和能力评价纳入医疗机构等级评审
- 开展临床试验的医疗机构建立单独评价考核体系
- 鼓励医疗机构设立专职临床试验部门，配备职业化的临床试验研究者
- 完善单位绩效工资分配激励机制
- 对临床试验研究者在职务提升、职称晋升等方面与临床医生一视同仁
- 允许境外企业和科研机构在我国依法同步开展新药临床试验

国家食品药品监督管理总局 CFDA
China Food and Drug Administration

中共中央办公厅 国务院办公厅印发《关于深化审评审批制度改革鼓励药品医疗器械创新的意见》

来源： 新华社

2017年10月08日 发布

- **临床试验机构资格认定实行备案管理**

  激发潜力，释放活力，回归责任，竞争机制

Outline

- CFDA’s reform
- ICH E17 Overview
- The importance of Clinical Pharmacology Study
- Concluding remarks

ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

GENERAL PRINCIPLES FOR PLANNING AND DESIGN OF MULTI-REGIONAL CLINICAL TRIALS

E17

Final version

Adopted on 16 November 2017

Objectives of the Guideline

- The purpose of this guideline is to describe general principles for the planning and design of MRCTs with the aim of increasing the acceptability of MRCTs in global regulatory submissions.

Basic Principles

1. Strategic use of MRCTs can increase efficiency of drug.
2. The intrinsic and extrinsic factors should be identified early before the design of confirmatory MRCTs.
3. Strategic allocation of the sample size to regions allows an evaluation of the extent to which this assumption holds.
4. Facilitate the assessment of consistency in treatment effects across regions, and support regulatory decision-making.
5. A single primary analysis approach for hypothesis testing and estimation of the overall treatment effect should be planned so that it will be acceptable to all concerned regulatory authorities.
6. Ensuring high quality of study design and conduct in accordance with ICH E6 in all regions is of paramount importance to ensure the study results are interpretable.
7. Efficient communication among sponsors and regulatory authorities is encouraged at the planning stage of MRCTs.

The Value of MRCTs in Drug Development

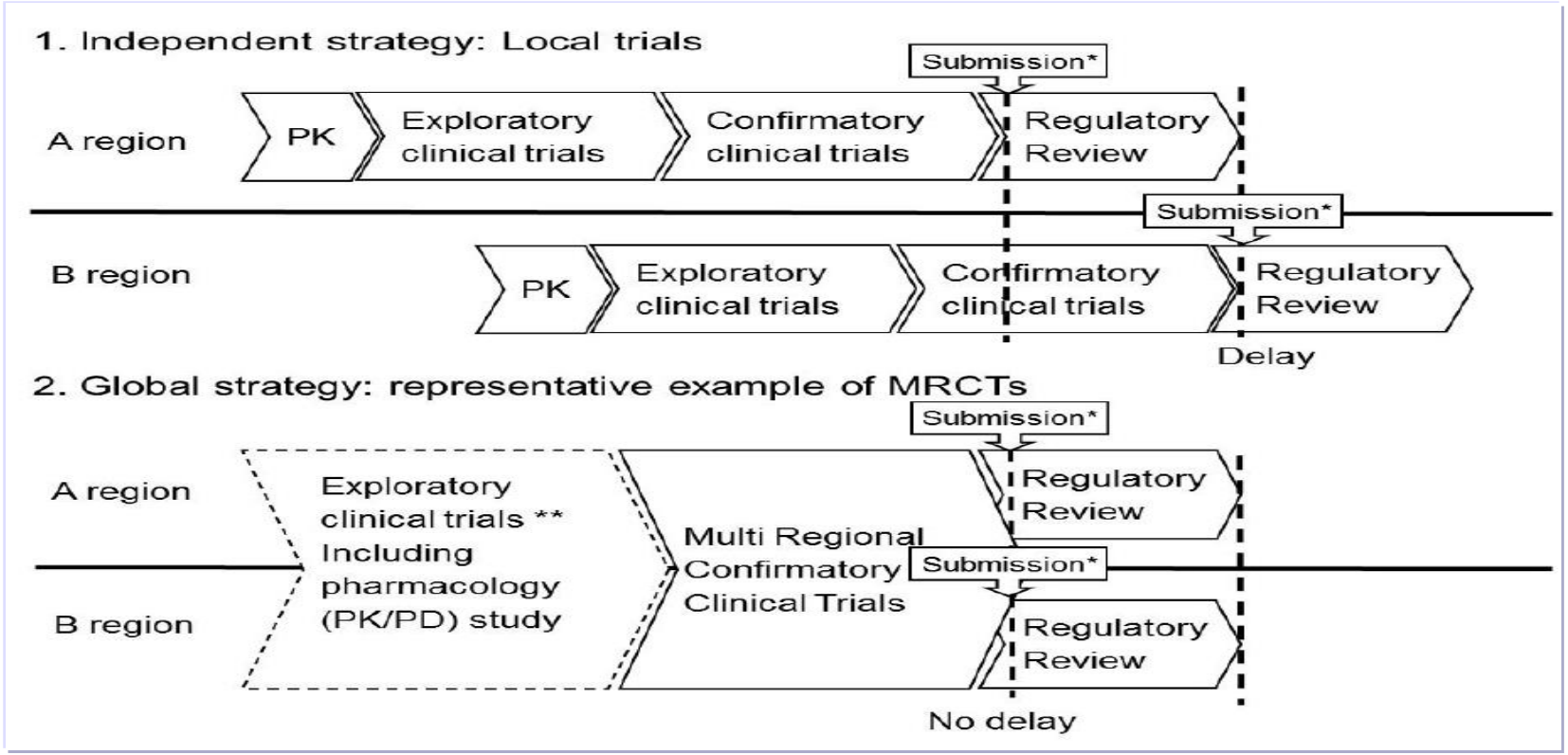
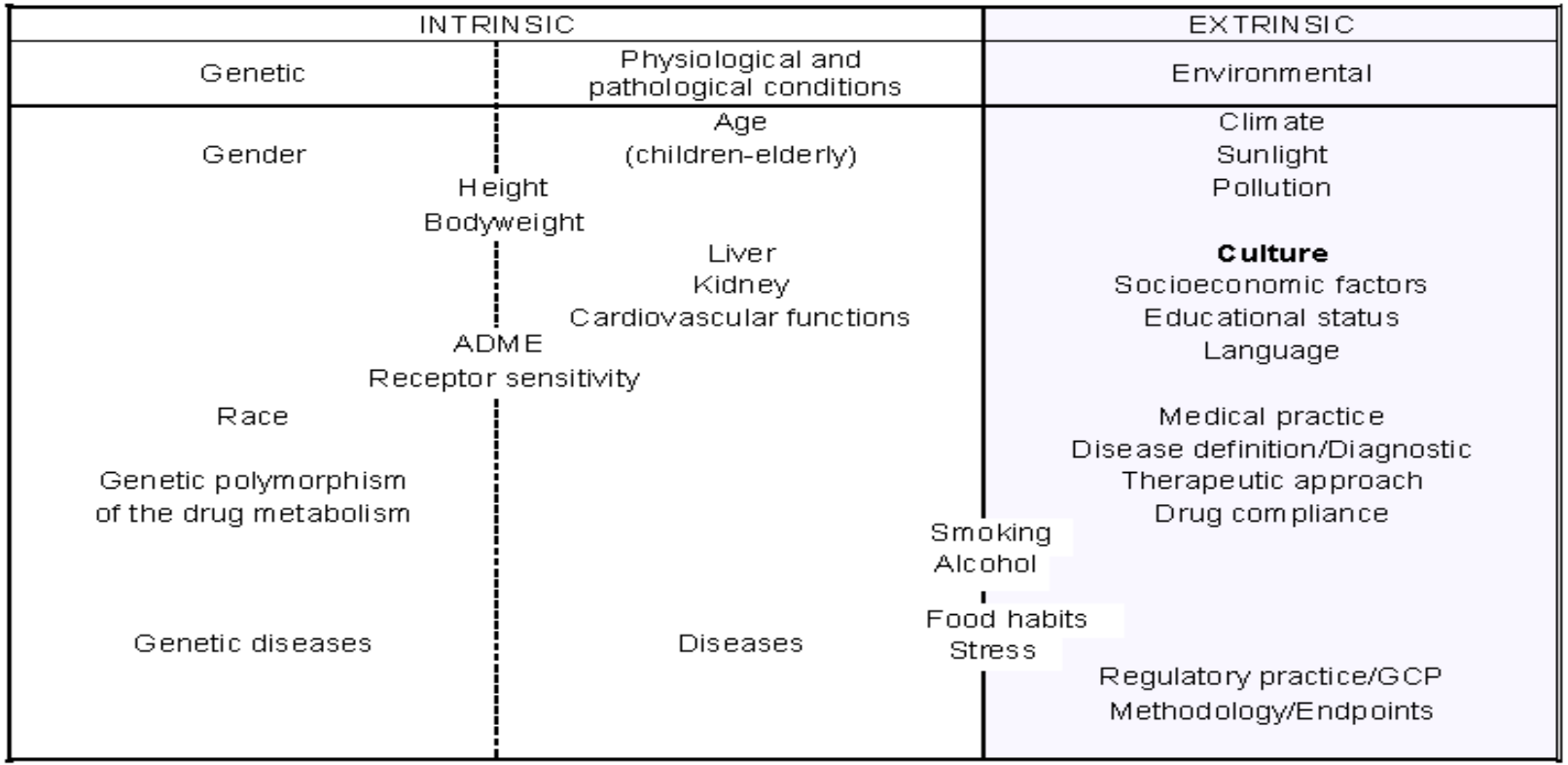


Figure 1. Illustrations of clinical drug development workflow across regions for drug submission and regulatory review in independent and global strategies

Classification of intrinsic and extrinsic factors—ICH E5 APPENDIX A



E17 and E5 should be used in combination.

Collecting and learning intrinsic/extrinsic factors are the key for design success

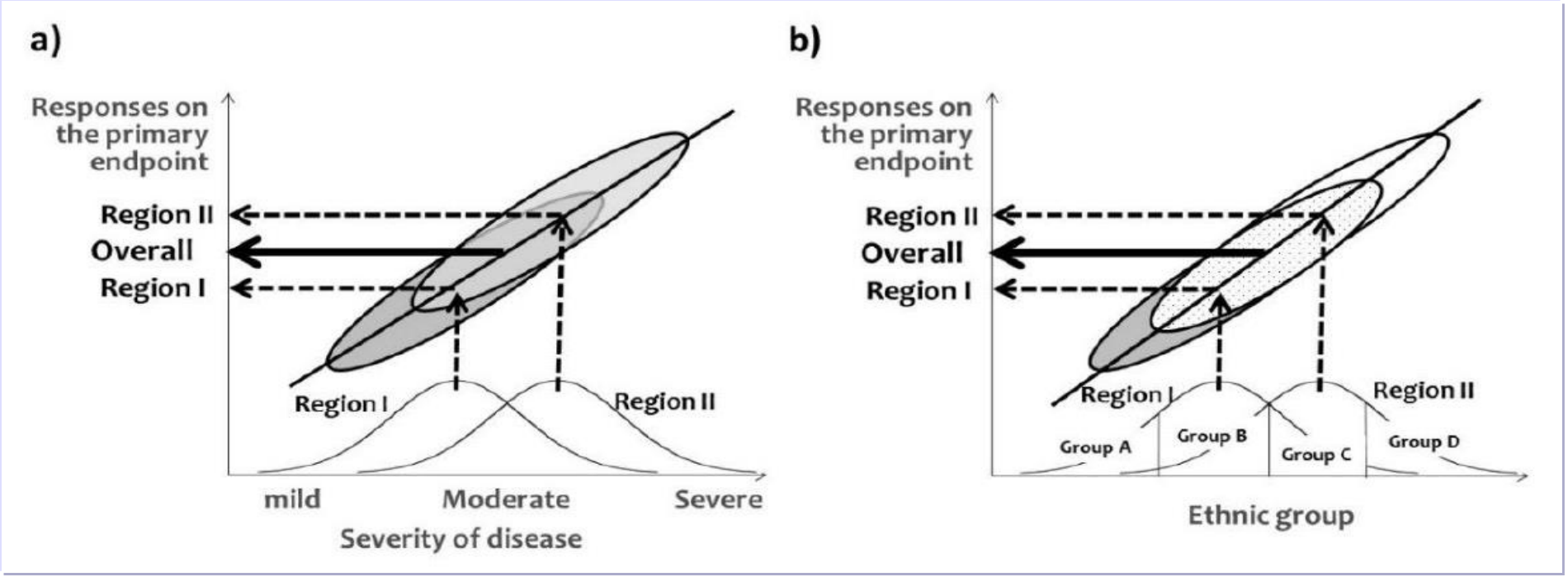


Figure 2. Illustration: primary endpoint modulated by intrinsic and extrinsic factors across regions; (2a) by severity of disease, (2b) by ethnic group.

PK and/or PK-PD studies-E17

It is important to execute well-planned early development programmes.

- PK studies should be undertaken in the major ethnic groups most relevant to the regions to be included in MRCTs.
- If differences in PK, will allow for decisions with respect to the need for PD studies and dose-response studies in different regions and/or subpopulations.
- Dose-response studies should cover a broad range of doses and generally include the populations to be enrolled in confirmatory MRCTs.
- It may not be necessary to obtain PK-PD or dose-response data from subjects in all regions planned to be included in confirmatory MRCTs.
- The dose regimens in confirmatory MRCTs should in principle be the same in all participating ethnic population. However, if earlier trial data show a clear difference in dose-response and/or exposure-response relationships for an ethnic population, it may be appropriate to use a different dosing regimen, provided that the regimen is expected to produce similar therapeutic effects with an acceptable safety margin.

Deepening the Drug Innovation Ecosystem Reform – A Plan to Design and Build China's Clinical Research System

R&D-based Pharmaceutical Association Committee (RDPAC)

Committee of Drug Clinical Evaluation and Research, Chinese Pharmaceutical Association

Peking University Asia Pacific Economic Cooperation Regulatory Sciences Center of Excellence (PKU APIRB Regulatory Sciences CoE)

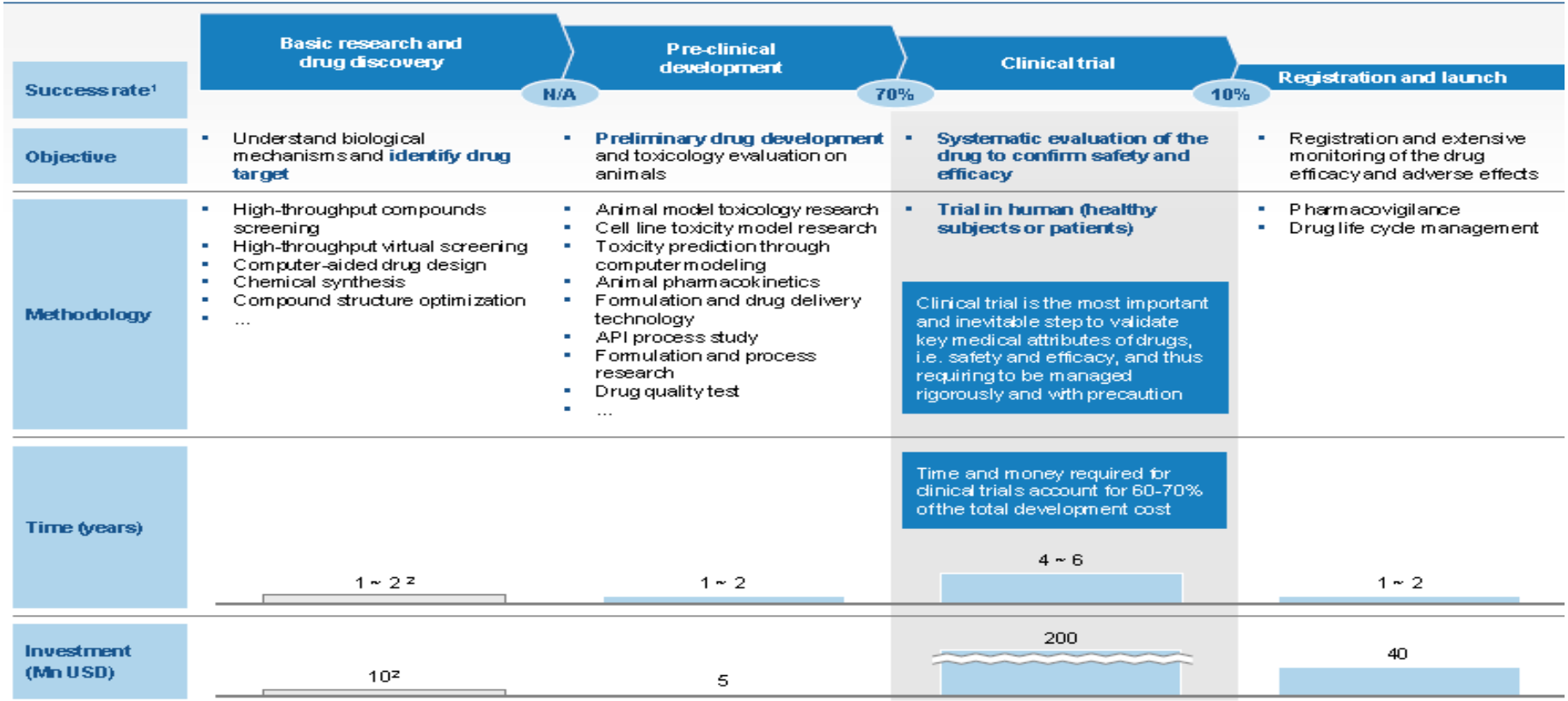
Peking University Clinical Research Institute (PUCRI)

China Pharmaceutical Enterprises Association (CPEA)

China Pharmaceutical Industry Association (CPIA)

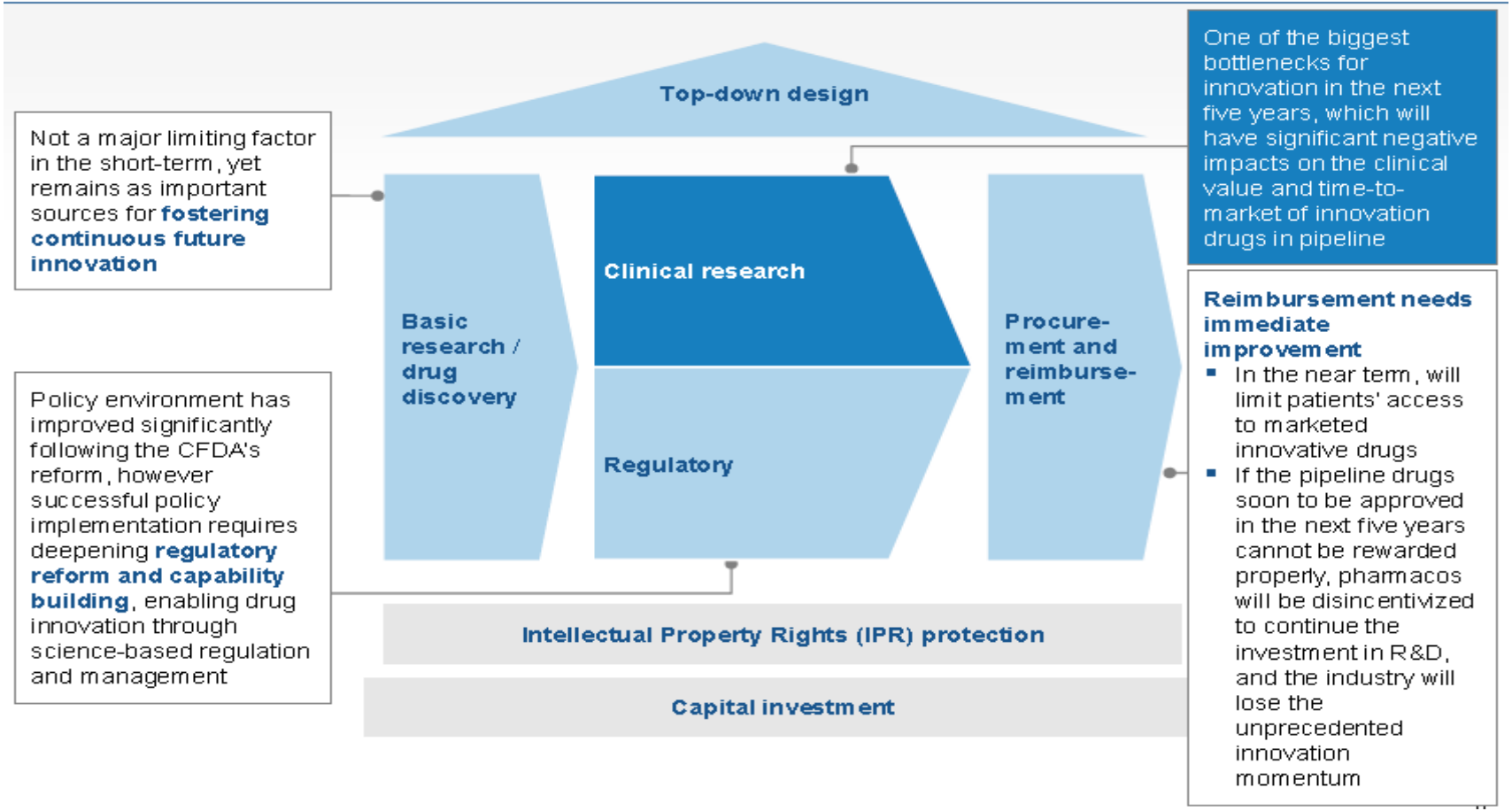
China Chamber of Commerce for Import & Export of Medicines & Health Products (CCCMHPIE)

Clinical trial is the most crucial drug development stage, accounting for a large part of the time spent and total investment



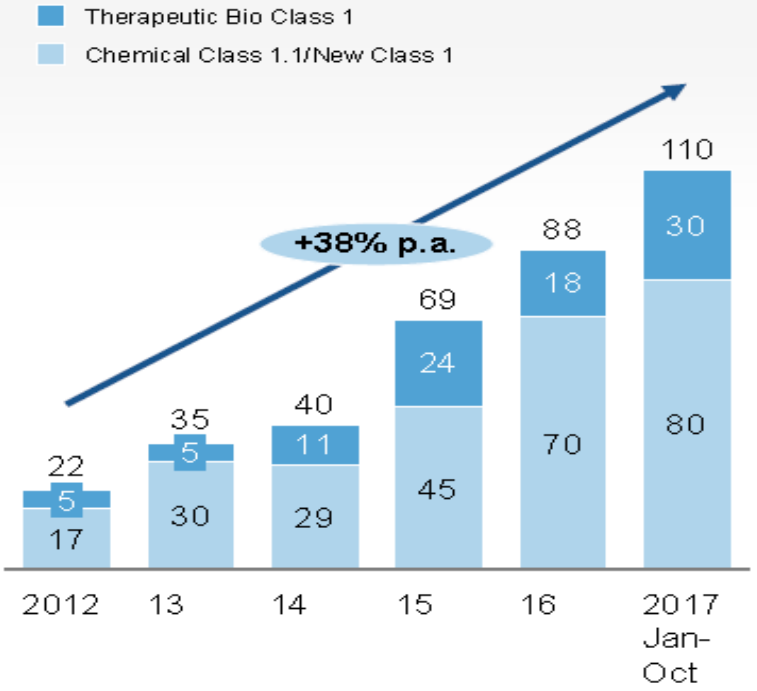
1 Probability of success for a drug compound enter the next development stage from the previous stage
2 Only covering active substance identification, synthesis of lead compounds, and lead compound optimization phase
SOURCE: McKinsey report (Trends in Attrition); literature research

Clinical research has become one of the most significant bottlenecks for China's drug innovation

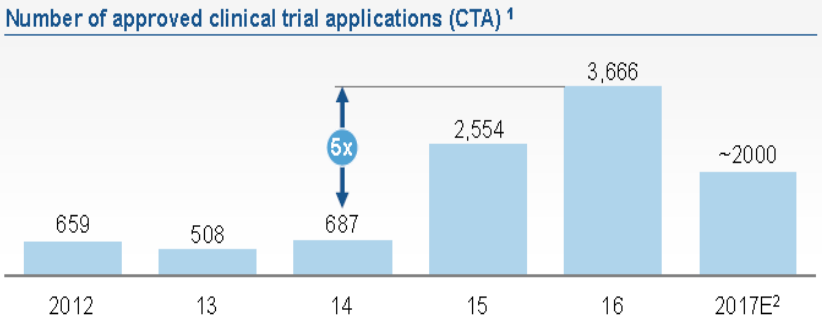


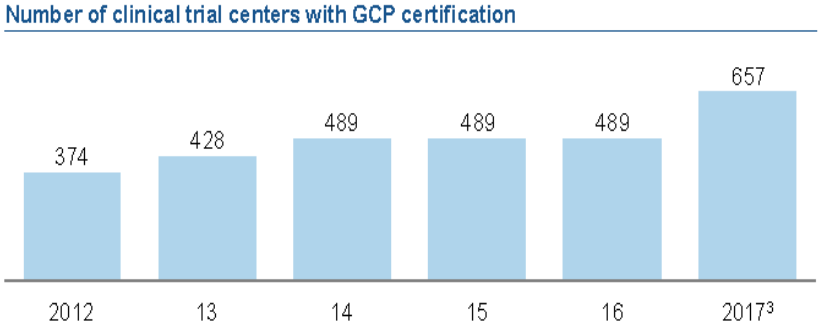
More innovative compounds are entering clinical development stage in China, creating increasing demand for clinical trial resources

Number of Chem Class 1[1] and Biologics Class 1 molecules newly approved for clinical trials each year in China



Rapid increase of the number of CTAs approved further highlights resource constraints in clinical research





Overall assessment: China currently ranks No. 9 amongst leading drug innovation countries in clinical research capabilities

Scores indicate: in each dimension, the country with the highest value (No.1) is indexed as 100 points, and other countries' scores = value of the indictor of that country / No.1's value * 100

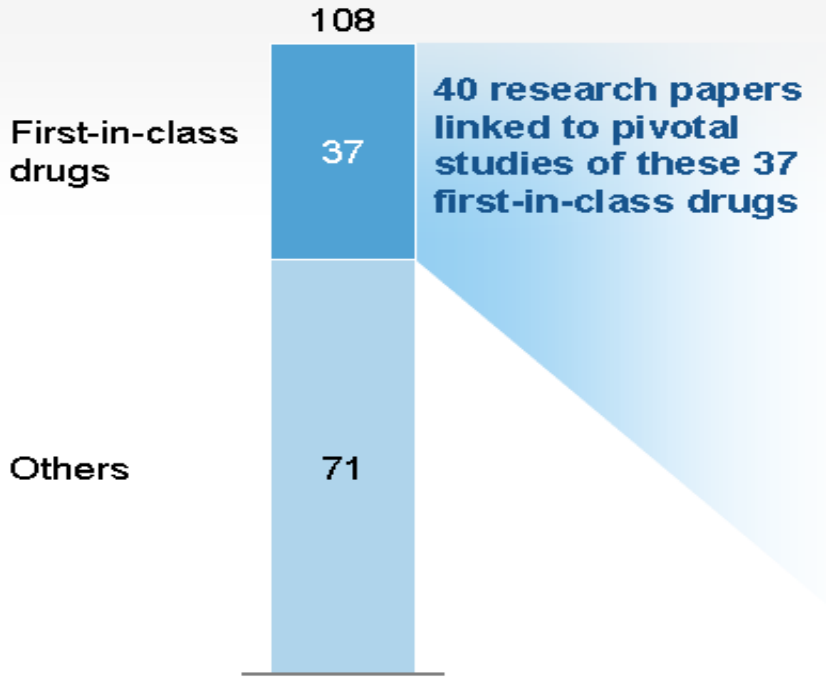
	No.1 US	No.2 UK	No.3 Germany	No.4 Canada	No.5 France	No.6 Australia	No.7 S. Korea	No.8 Japan	No.9 China	No.10 Switzer-land	No.11 Denmark	No.12 India
No. of interventional clinical trials initiated between 2014-2016	100	23	23	23	23	11	18	11	22	6	7	3
No. of Phase I clinical trials[1] in interventional trials initiated in 2016	100	50	37	18	21	21	24	27	17	6	5	0
No. of Phase II/III MRCT (interventional trials) initiated in 2016 by sponsors	100	59	68	62	49	34	29	24	4	14	15	4
No. of research articles published in JAMA, Lancet, and NEJM between 2014-2016	100	38	7	10	9	9	0	2	3	7	2	1
Overall score of clinical trial capabilities	100	42	34	28	25	19	18	16	12	8	7	2

1 Excluding trials for generics such as bioequivalence trials

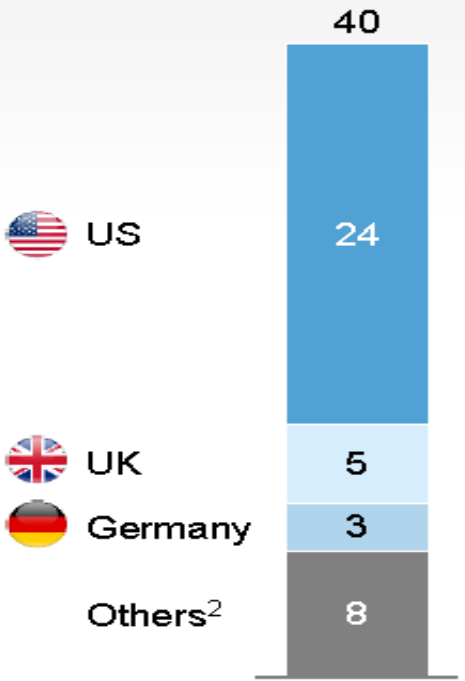
SOURCE: ClinicalTrials.gov; ANZCTR database; Asuno Shinyaku database; CTRI database; DKRS database; Health Canada's Clinical Trials database; EU Clinical Trials Register; UK Clinical Trial Gateway; South Korea's CRIS database; Web of Science database; GBI Metrix database

Few pivotal studies of First-in-Class drugs are led by Chinese PIs in the last 3 years

First-in-Class drugs approved by US FDA[1] (2014-2016)



By country break-down of the 40 publications



1 Drugs with new pharmaceutical mechanisms as defined by US FDA Novel Drug Approval Annual Report
2 Including France, Switzerland, Spain, the Netherlands, Australia, Greece, Russia, Belgium

SOURCE: FDA Novel Drug Approval Annual Report; FDA Drug Trials Snapshot; Clinicaltrials.gov; PubMed; literature search

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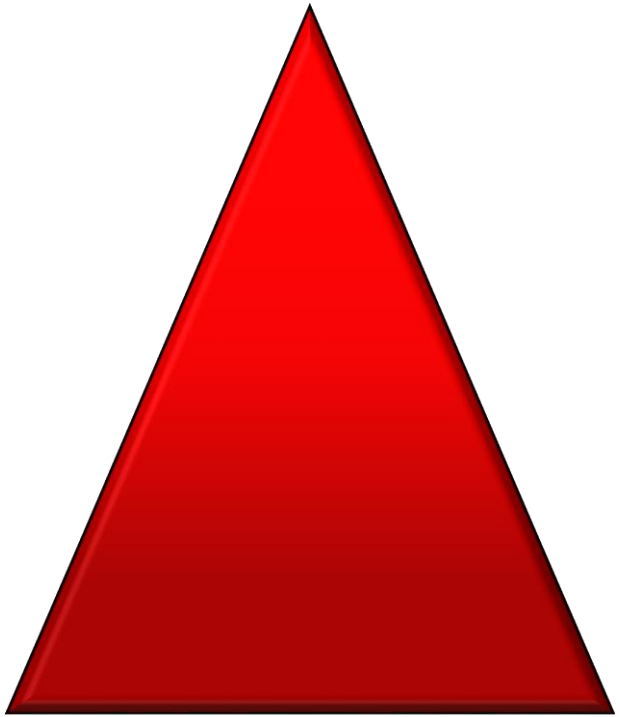
Ticagrelor Clinical Development



PLATO (n = 18,624)--MRCT

4 phase 2 studies (n=1380)

- *DISPERSE*
- *DISPERSE 2*
- *ONSET/OFFSET*
- *RESPOND*

41 Clinical pharmacology studies

205 Non-clinical studies

Clinical Pharmacology

I. ADME

In vitro study:

- *Absorption,Distribution,Metabolism*
- *Enzyme Inhibition,Enzyme Induction*

In vivo Metabolite Identification-14C

II. PHARMACOKINETICS

- *Single Ascending Dose (FIH)*
- *Multiple Ascending Dose*
- *Age/Gender*
- *Japanese/Caucasian :Single and Multiple*
  Chinese （2008）
- *Food Effect*
- *Mass Balance Study*
- *Clopidogrel BE*（over-encapsulated）
- *TQT*

III. SPECIFIC POPULATION

- *Renal Impairment (*2007)
- *Hepatic Impairment(2007)*

IV. DRUG-DRUG INTERACTIONS

- *Ketoconazole ,Diltiazem, Rifampin, Desmopressin, Oral Contraceptive, Midazolam, Tolbutamide*
- *Aspirin, Simvastatin, Atorvastatin, Digoxin, Heparin,Enoxaprin*

V. BIOPHARMACEUTICS

- *Absolute Bioavailability（2007）*

VI. PHARMACODYNAMICS--POC

- *Onset Offset*
- *RESPOND*
- *Ticagrelor + ASA vs. Clopidogrel + ASA*
- *Loading Dose*
- *Uric Acid*
- *Respiratory Parameters*

MRCT Design

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022433orig1s000clinpharmr.pdf

Pharmacokinetics-FIH

single-dose: (0.1, 0.3, 1, 3, 10, 30 and 100 mg), 30–400mg, 900–1260mg

Ticagrelor Pharmacokinetic Parameters, Mean (%CV)						
Dose (mg)	N	C_{max} (ng/mL)	T_{max}(h) Median (range)	AUC (ng h/mL)	$t_{1/2}$ (h)	CL/F (mL/min/kg)
30	7	161 (20.5)	1.5 (1-2)	1005 (14.3)	7.77 (13.0)	6.72 (17.7)
100	9	586 (28.8)	1.5 (1-4.1)	3683 (20.4)	7.30 (18.9)	6.52 (22.4)
200	8	1295 (32.2)	1.49 (1-3)	8213 (25.7)	8.09 (14.1)	5.71 (24.0)
300	8	1746 (18.2)	1.5(1-3.05)	13170 (22.6)	7.57 (14.0)	5.31 (23.5)
400	7	2711 (21.0)	1.5 (1-2)	18547 (23.8)	7.88 (13.2)	5.03 (25.8)

AR-C124910XX Pharmacokinetic Parameters, Mean (%CV)						
Dose (mg)	N	C_{max} (ng/mL)	T_{max}(h) Median (range)	AUC (ng h/mL)	$t_{1/2}$ (h)	CL/F (mL/min/kg)
30	7	42.1 (31.7)	2.0 (1.03-3)	376 (26.1)	9.39 (22.5)	18.25 (15.5)
100	9	166 (27.2)	3.0(1.5-4.1)	1460 (27.9)	8.63 (19.9)	16.71 (21.8)
200	8	367 (34.9)	1.5(1.5-3)	3722 (44.8)	10.05 (17.7)	13.10 (23.9)
300	8	462 (32.2)	2.49 (1.5-4)	4611 (25.4)	8.54 (17.3)	14.99 (16.7)
400	7	713 (21.8)	1.97 (1.47-3)	6577 (32.3)	8.77 (15.1)	14.13 (18.2)

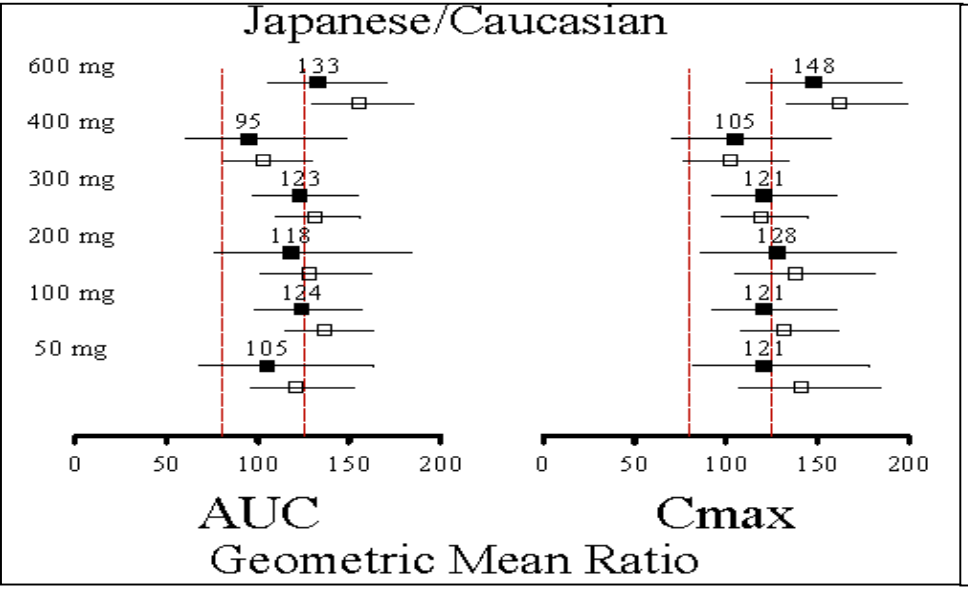
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022433orig1s000clinpharmr.pdf

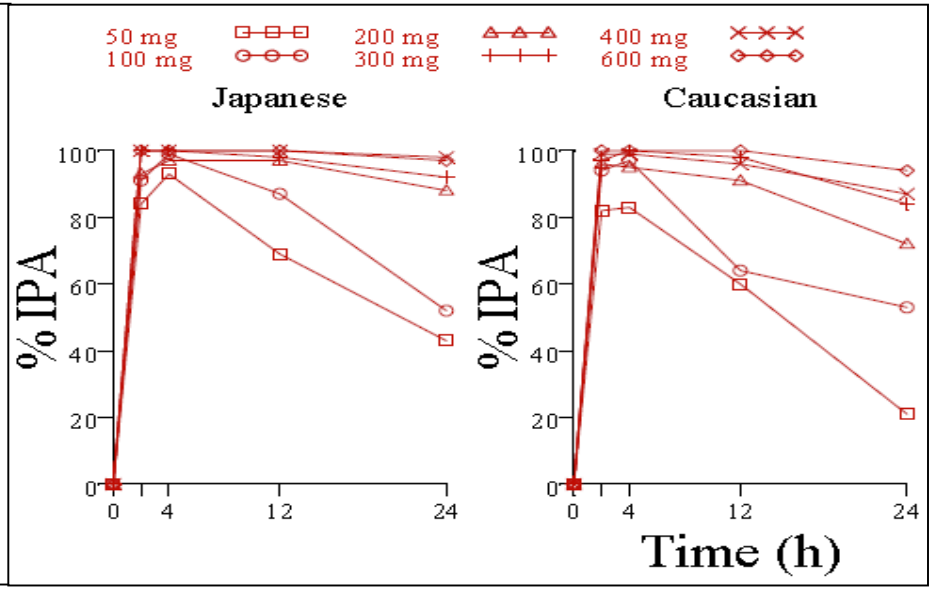
Ticagrelor – pharmacokinetic parameters

Absorption	• Rapidly absorbed in the small intestine
Distribution	• ~99.7% bound to human plasma protein
Metabolism	• Predominantly metabolized by CYP3A4/5 in the liver, which may account for drug/drug interactions • Metabolized to active metabolite (AR-C124910XX) and/or inactive metabolites
Elimination	• Primarily eliminated via biliary secretion • Less than 1% excreted in urine
Pharmacokinetics	• Peak plasma concentrations and steady state are dose-proportional and occur between 1.5 and 3 hours • Half life ~8 hours • Dosing with food increases the area under the curve (AUC) ~20% • AR-C124910XX (half-life ~10 hrs) accounts for ~30% to 40% of total activity

Husted S , et al. *Cardio Ther.* 2009;27**:**259-274; Butler K et al, *Can J Clin Pharmacol.* 2008;15:e684-e685 [Abstract 562];
Teng R. *Eur J Clin Pharmacol.* 2010;66:487-496. Data on File, Investigator's Brochure.

Ethnic Differences：Japanese/Caucasian





Ticagrelor (■)and AR-C124910XX (□)

Systemic exposure is significantly higher (by median ~ 20%) in healthy Japanese
%IPA is slightly higher in healthy Japanese. There is no need to adjust ticagrelor dose in Japanese subjects.

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022433orig1s000clinpharmr.pdf

Pharmacokinetics and Tolerability of Single and Multiple Doses of Ticagrelor in Healthy Chinese Subjects

An Open-Label, Sequential, Two-Cohort, Single-Centre Study

Haiyan Li,[1] *Kathleen Butler*,[2] *Li Yang*,[1] *Zhenghua Yang*[1] and *Renli Teng*[2]

1 Peking University Third Hospital, Beijing, China
2 AstraZeneca LP, Wilmington, DE, USA

	Chinese	Caucasian		
	Healthy volunteers (n=10)	Healthy volunteers (n=13)	DISPERSE CHD (n=34)	DISPERSE2 ACS (n=16)
Steady state	90 bd	100 bd	100 bd	90 bd
Ticagrelor		Geometric mean (%CV)		Mean±SD
C_{max}, ng/ml	915 (32)	626 (46)	810 (41)	770±411
AUC, ng.h/ml	**7168 (35)**	4108 (43)	**5530 (48)**	4762±2443
AR-C124910XX				
C_{max}, ng/ml	311 (25)	219 (49)	261 (41)	257 ±139
AUC, ng.h/ml	**3511 (31)**	1701 (47)	**2108 (40)**	1961±946

Li H et al. Clin Drug Investig 2012;32:87-97

REVIEW

Cardiovascular Therapeutics

Ticagrelor: The First Reversibly Binding Oral $P2Y_{12}$ Receptor Antagonist

Steen Husted[1] & J.J.J. van Giezen[2]

1 Department of Medicine and Cardiology, Aarhus University Hospital, Aarhus, Denmark

Table 3 Mean IPA (20 μM ADP, final extent) over 24 h at specified testing times in healthy subjects receiving ticagrelor 50–300 mg bid, clopidogrel 300-mg loading dose or 75 mg/day, or placebo

Treatment group	n	Inhibition (%), mean (range) 4 h	8 h	12 h	24 h
Ticagrelor					
50 mg bid, day 1	14	92 (55–100)	82 (19–100)	66 (0–100)	88 (45–100)
50 mg bid, day 5	14	95 (62–100)	90 (27–100)	87 (13–100)	79 (3–100)
100 mg bid, day 5	13	97 (72–100)	95 (63–100)	93 (43–100)	93 (65–100)
200 mg bid, day 5	13	98 (85–100)	98 (89–100)	96 (79–100)	97 (76–100)
300 mg bid, day 5	7	100 (100–100)	100 (100–100)	99 (97–100)	100 (100–100)
Clopidogrel					
300-mg loading dose, day 1	14	67 (0–100)	52 (0–98)	57 (0–100)	56 (0–100)
75 mg, day 14	14	90 (35–100)	82 (14–100)	83 (30–100)	77 (11–100)
Placebo	39	7 (0–25)	8 (0–38)	8 (0–48)	5 (0–28)

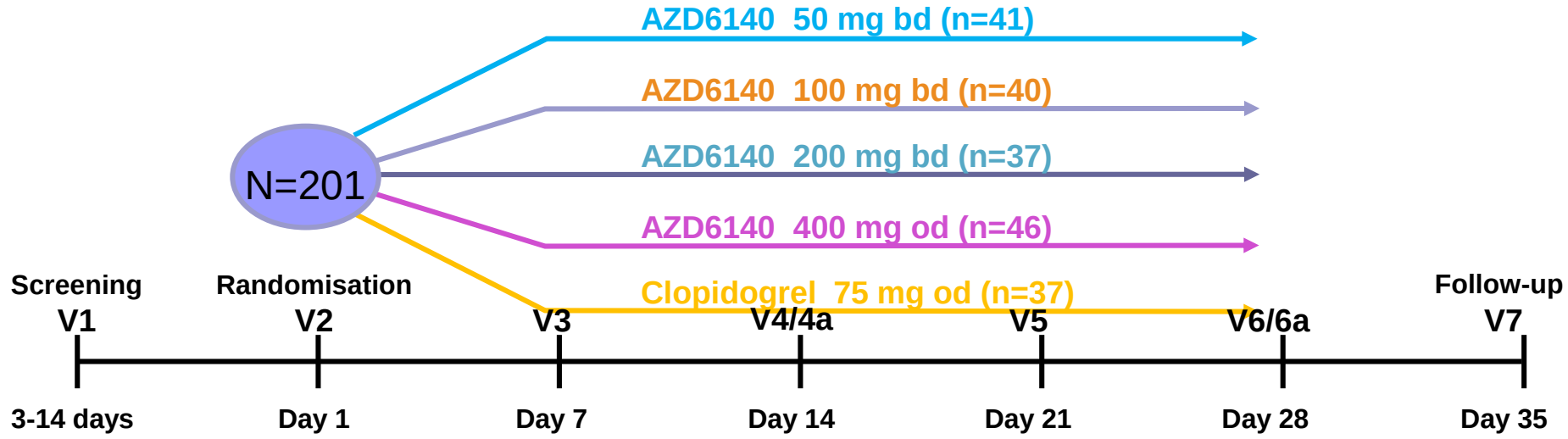
From Peters et al. [48], Butler et al. [44].
Day refers to day within treatment group, not day within study.

IPA--Inhibition of Platelet Aggregation

DISPERSE 1 Study Design

Objective:

To assess the PD, PK, safety, and tolerability of AZD6140 relative to those of clopidogrel in patients with stable atherosclerotic disease



Aspirin 75-100 mg qd in all arms

bd = twice daily; od = once daily.

Husted SE, et al. *Eur Heart J.* 2006;27:1038-1047.

Dose response relationship

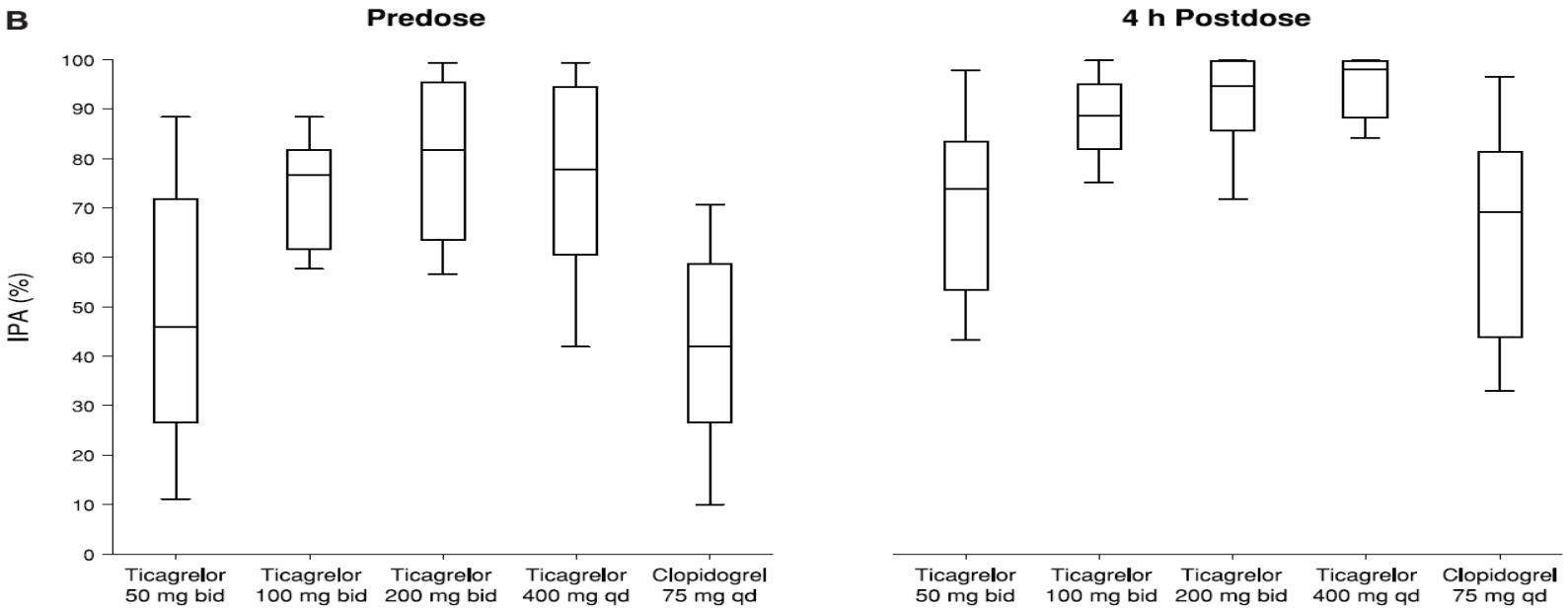
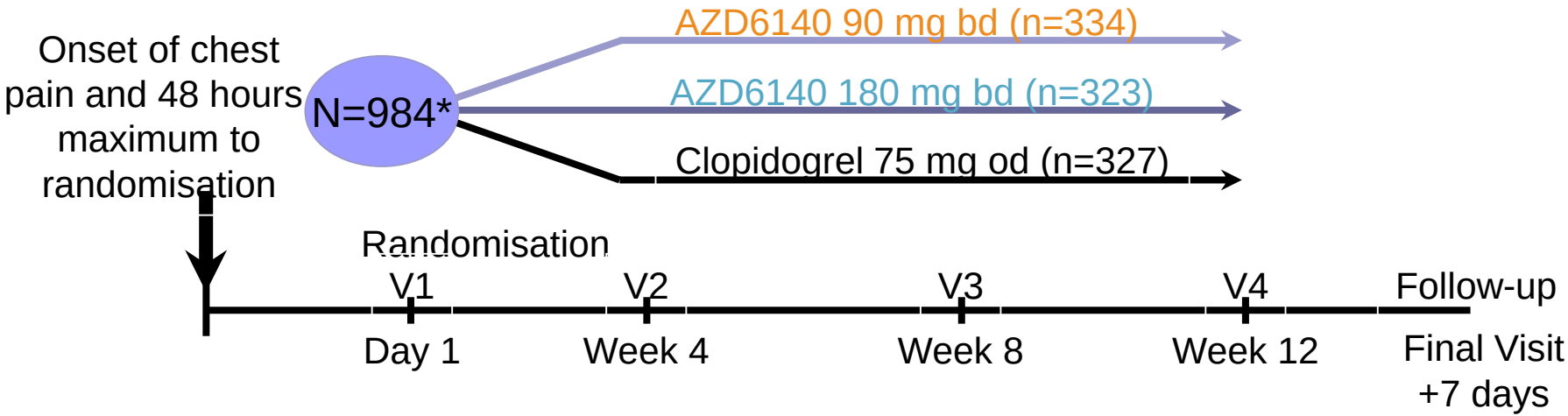


Figure 4 (**A**) Mean IPA (20 μM ADP, final extent) in patients in DISPERSE receiving ticagrelor 50, 100, or 200 mg bid or 400 mg qd or clopidogrel 75 qd on day 1, day 14, and day 28. *No second dose of ticagrelor was given on day 28. Error bars indicate standard deviation, shown only for IPA sample space. (**B**) Median (line in box), 25–75% percentile (box), and 10–90% percentile (whiskers) IPA predose and 4-h postdose on day 14 (final extent). Adapted with permission from Husted et al. [50].

DISPERSE 2 Study Design

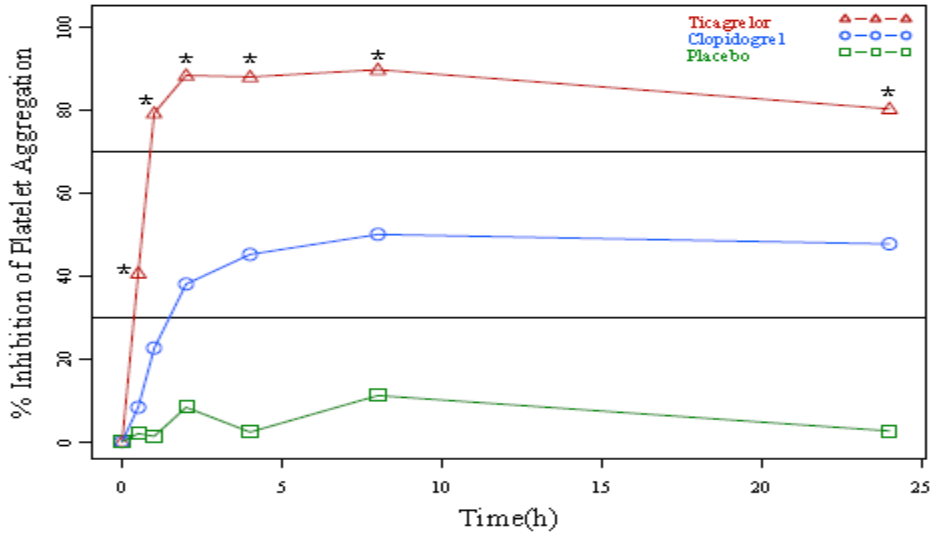
Objective : To assess the safety, tolerability, and preliminary efficacy of different dosing strategies of AZD6140 vs clopidogrel in NSTE-ACS patients



All patients received aspirin (≤325 mg first dose, then 75-100 mg od) and heparin/LMWH and/or a GP IIb/IIIa antagonist。

*Randomised patients who received ≥1 dose of study drug.
GP = glycoprotein; LMWH = low-molecular-weight heparin.

Onset: In patients with stable coronary artery disease, onset of action (measured by 20 µM ADP induced %IPA) is faster following the administration of 180 mg loading dose of ticagrelor compared to a 600 mg loading dose of clopidogrel (Figure 2)



https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022433orig1s000clinpharmr.pdf

The NEW ENGLAND JOURNAL of MEDICINE

Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes

Lars Wallentin, M.D., Ph.D., Richard C. Becker, M.D., Andrzej Budaj, M.D., Ph.D., Christopher P. Cannon, M.D., Håkan Emanuelsson, M.D., Ph.D., Claes Held, M.D., Ph.D., Jay Horrow, M.D., Steen Husted, M.D., D.Sc., Stefan James, M.D., Ph.D., Hugo Katus, M.D., Kenneth W. Mahaffey, M.D., Benjamin M. Scirica, M.D., M.P.H., Allan Skene, Ph.D., Philippe Gabriel Steg, M.D., Robert F. Storey, M.D., D.M., and Robert A. Harrington, M.D., for the PLATO Investigators*

N Engl J Med 2009;361.

Study of Platelet Inhibition and Patient Outcomes (PLATO)

PLATO Study Objectives

- PLATO was designed to

- Demonstrate superiority vs. clopidogrel on the primary endpoint of CV death, MI or stroke

- Quantify bleeding risk compared to clopidogrel

- Characterize safety and tolerability of ticagrelor

- Enhance knowledge of platelet biology and human disease

- To meet these goals: 18,624 patients, 43 countries, 862 sites,academic governance, extensive infrastructure

PLATO: Study Design

NSTE-ACS (moderate-to-high risk) STE-ACS (if primary PCI)
Randomized within 24 hours of symptom onset
(N=18,624)

Clopidogrel
300 mg loading dose unless pre-treated
then 75 mg qd maintenance;
(additional 300 mg allowed pre-PCI)

Ticagrelor
180 mg loading dose, then
90 mg bid maintenance;
(additional 90 mg pre-PCI)

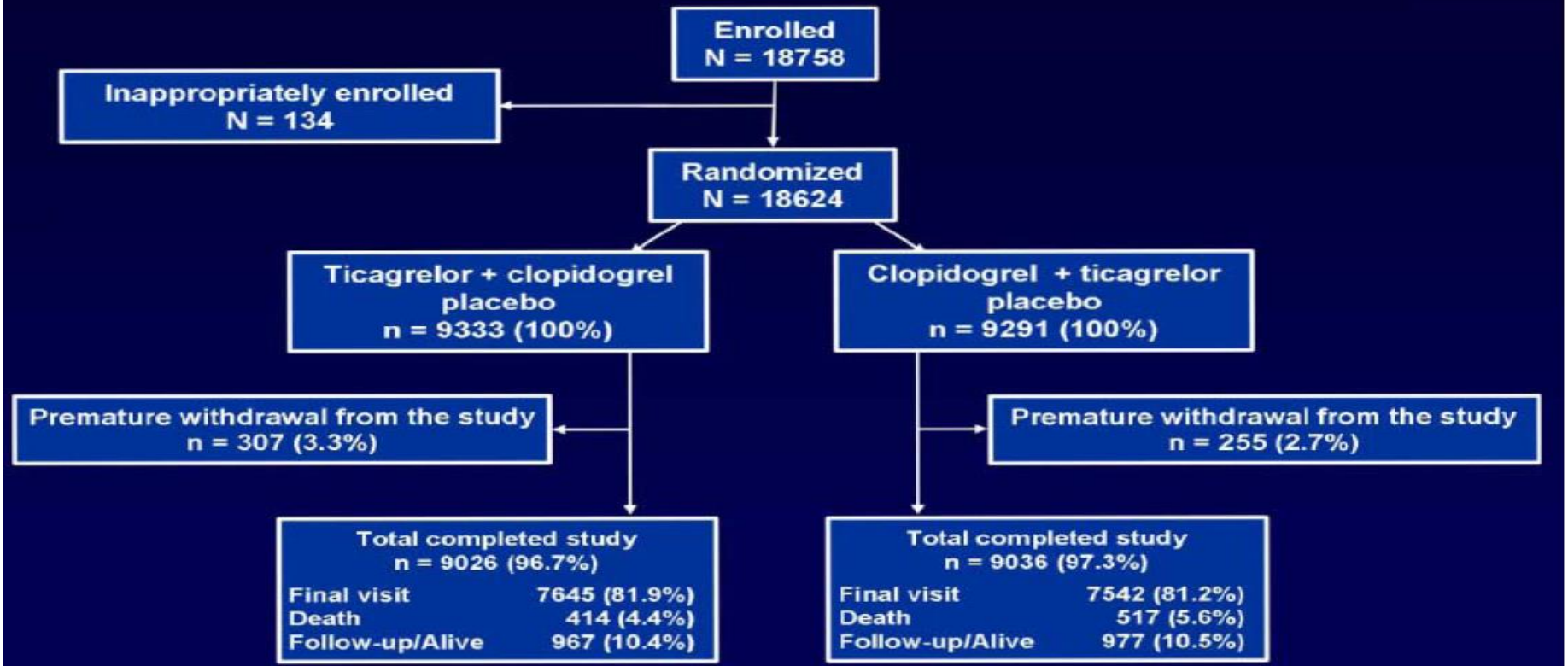
6-12 month exposure (min, max by design)

Primary efficacy endpoint: CV death + MI + Stroke
Primary safety endpoint: Total Major bleeding

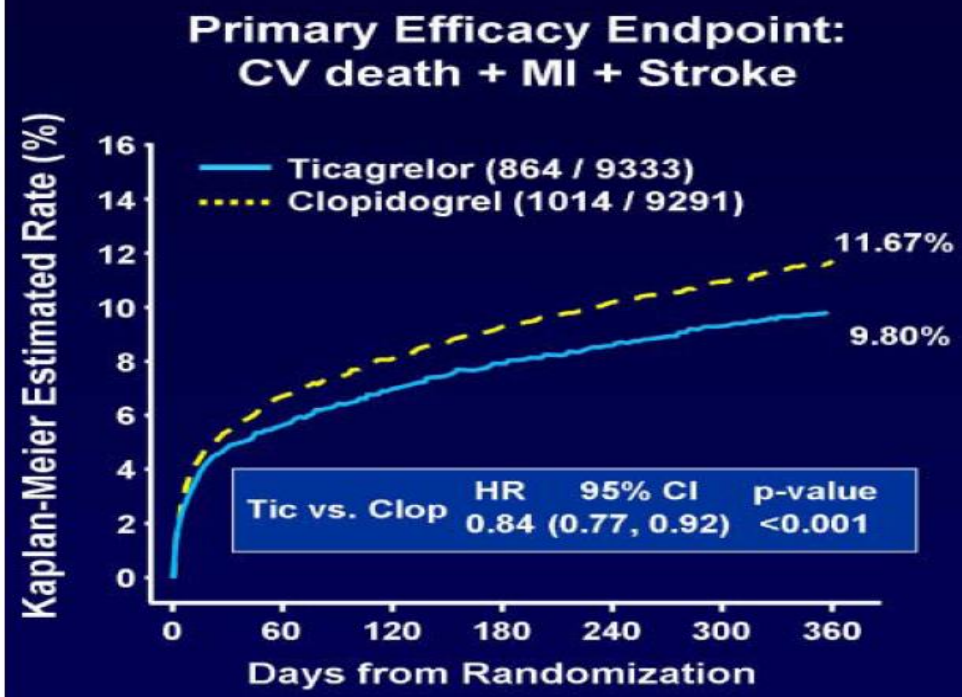
Sample Size Calculation

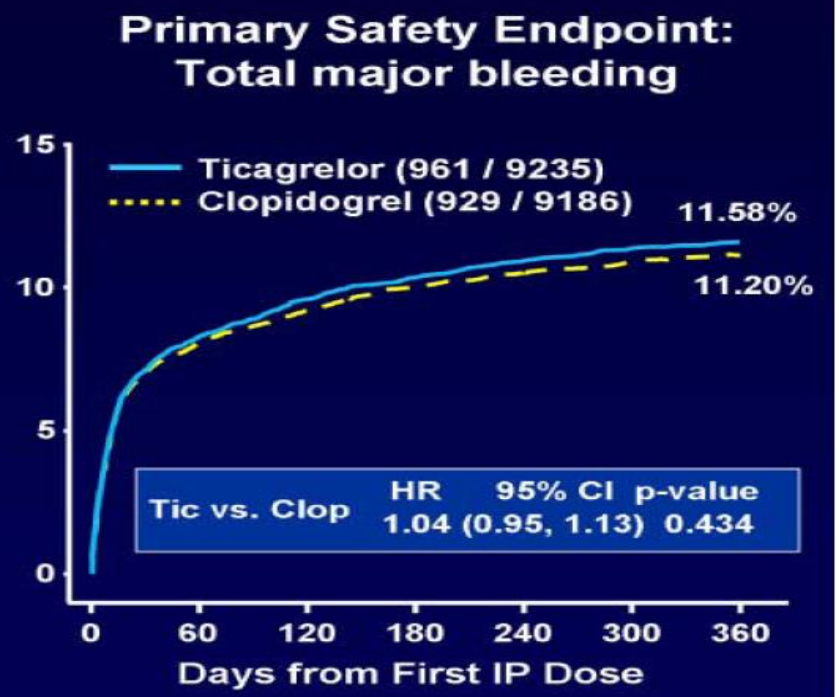
- We estimated that 1780 such events would be required to achieve 90% power to detect a relative risk reduction of 13.5% in the rate of the primary end point in the ticagrelor group as compared with the clopidogrel group, given an event rate of 11% in the clopidogrel group at 12 months.

PLATO: Patient Disposition in Study



Main Ticagrelor Results from PLATO



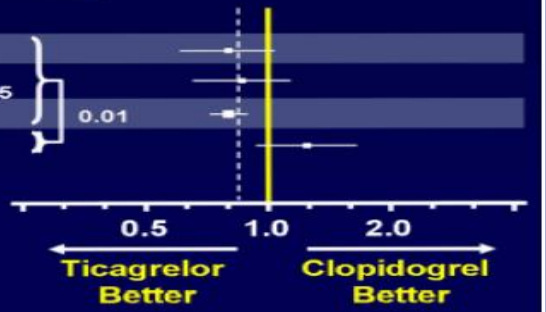


PLATO Efficacy by Region

PLATO: Ticagrelor Effect Apparently Inconsistent Across Geographic Regions

- 31 pre-specified subgroup tests conducted for consistency
- No α-level adjustment for multiplicity
- Indication of qualitatively different outcomes by region
- Results in NA appear to be driven by US: HR 1.27 (0.92, 1.75)

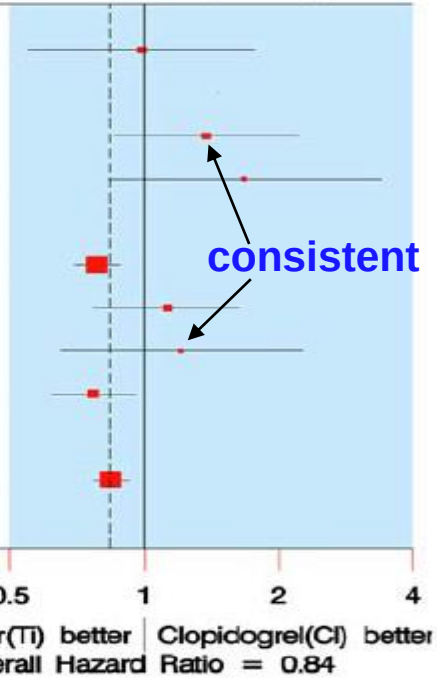
Characteristic	Total Patients	KM at Month 12 Tic	KM at Month 12 Clop	HR (95% CI)	Interaction p-values
Geographic Region					
Asia / Australia	1714	11.4	14.8	0.80 (0.61, 1.04)	0.045
Cent / Sth America	1237	15.2	17.9	0.86 (0.65, 1.13)	
Euro / Md E / Afr	13859	8.8	11.0	0.80 (0.72, 0.90)	0.01
North America	1814	11.9	9.6	1.25 (0.93, 1.67)	



source：CCDRS

Figure 10: Primary efficacy endpoint by aspirin dose category and treatment for USA and non-USA

Region	ASA Dose (mg)	Ticagrelor N	Ticagrelor E	Clopidogrel N	Clopidogrel E	HR (95% CI)
US	<=100	281	24	251	22	0.99 (0.55, 1.76)
	>100 – <300	21	2	15	1	1.47 (0.13, 16.20)
	>=300	305	39	330	31	1.38 (0.86, 2.21)
	Unknown	100	19	110	13	1.68 (0.83, 3.40)
Non-US	<=100	7225	553	7231	701	0.78 (0.70, 0.88)
	>100 – <300	476	57	483	52	1.13 (0.77, 1.64)
	>=300	117	21	124	18	1.21 (0.65, 2.27)
	Unknown	808	149	747	176	0.77 (0.62, 0.96)
Overall		9333	864	9291	1014	0.84 (0.77, 0.92)



https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022433orig1s000clinpharmr.pdf

BJCP British Journal of Clinical Pharmacology
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Clinical Trials

Pharmacodynamics, pharmacokinetics, and safety of ticagrelor in Chinese patients with stable coronary artery disease

Haiyan Li, Jingchuan Guo, Glenn F. Carlson, Renli Teng

First published: 9 June 2016 Full publication history

Pharmacokinetics of ticagrelor and AR-C124910XX

Table 1. Ticagrelor and AR-C124910XX PK parameters following a single dose (Day 1) and multiple (Day 7) doses of ticagrelor.

	Ticagrelor 45 mg bid (n = 12)		Ticagrelor 60 mg bid (n = 12)		Ticagrelor 90 mg bid (n = 12)	
PK parameter[a]	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
Ticagrelor						
C_{max} (ng/mL)	464 (38)	616 (37)	414 (34)	689 (34)	822 (37)	1273 (43)
AUC_{0-12h} (ng·h/mL)	2114 (42)	3882 (42)	2313 (30)	4351 (37)	3983 (42)	8206 (51)
AUC (ng·h/mL)	3220 (51)	–	3633 (32)	–	6234 (54)	–
t_{max} (h)[b]	2.00 (1.00–2.00)	2.00 (1.00–3.03)	3.00 (1.00–6.00)	2.00 (1.00–3.00)	2.00 (1.00–3.03)	2.00 (1.00–3.00)
$t_{½}$ (h)	10.72 (16.18)	–	9.42 (13.53)	–	10.14 (17.54)	–
R_{ac}	–	1.84 (23.6)	–	1.88 (20.7)	–	2.06 (22.8)
AR-C124910XX						
C_{max} (ng/mL)	88.3 (24.6)	144 (26)	77.1 (54)	180 (50)	139 (38)	301 (32)
AUC_{0-12h} (ng·h/mL)	464 (19)	1069 (25)	504 (55)	1314 (41)	836 (30)	2254 (37)
AUC (ng·h/mL)	922 (29)[c]	–	1108 (35)[c]	–	1644 (31)	–
t_{max} (h)[b]	2.00 (2.00–3.00)	2.00 (1.00–6.00)	3.00 (2.00–6.00)	2.00 (2.00–3.00)	3.00 (2.00–3.03)	2.54 (2.00–3.10)
$t_{½}$ (h)	12.65 (22.94)[c]	–	11.38 (24.27)[c]	–	11.62 (24.64)	–
R_{ac}	–	2.30 (24.7)	–	2.61 (28.3)	–	2.70 (27.4)

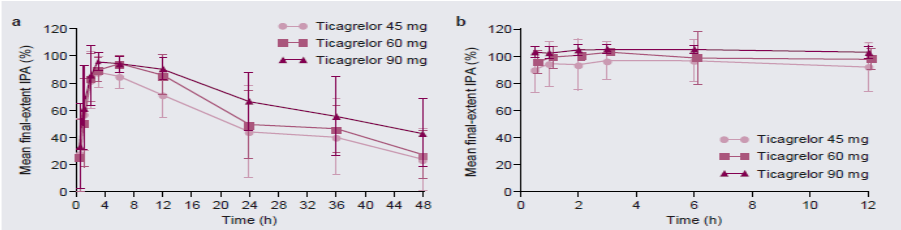
[a]Values are geometric mean (percentage coefficient of variation) unless otherwise indicated; [b]Median (range); [c]n = 11
AUC, area under the plasma-concentration time curve; AUC_{0-12h}, AUC from time 0 to 12 h; C_{max}, maximum plasma concentration $t_{1/2}$, half-life; t_{max}, time to C_{max}
R_{ac}, accumulation ratio.

Pharmacodynamics

Inhibition of platelet aggregation

- **Day 1**: IPA over time was dose dependent (**Figure 1a**).
  - IPA was evident within 30 min of dosing: mean ± standard deviation (SD) final-extent IPA was 27 ± 26%, 26 ± 27%, and 33 ± 31% for the 45, 60, and 90 mg doses, respectively.
  - IPA was maximal at 3 h with 45 and 90 mg ticagrelor (88 ± 12% and 96 ± 6%, respectively), and at 6 h with 60 mg ticagrelor (94 ± 6%).
- **Day 7**: after multiple bid dosing with ticagrelor, the mean final-extent IPA was >85% (45 mg bid), >90% (60 mg bid), >95% (90 mg bid) (**Figure 1b**).
  - Between the three ticagrelor doses, differences in mean IPA were small.

Figure 1. Mean (± SD) final-extent IPA following (a) a single dose (Day 1) and (b) multiple doses (Day 7) of ticagrelor.



Outline

- CFDA’s reform
- ICH E17 Overview
- The importance of Clinical Pharmacology Study
- Concluding remarks

Concluding remarks

Proactive, Structured and Innovative statistical thinking, as illustrated in the ICH E17, can be the linchpin to make these happen.—William Wang,PHD


北医三院
Thank you very much
for your attention