European Federation of Pharmaceutical Industries and Associations

Global Development of Drugs and Cooperation Among East Asian Countries

Global Clinical Trials and Development: EFPIA Japan's Perspective

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EFPIA Japan Mission

Bring innovative drugs to Japanese patients

EFPIA Japan
2008 Policy Objectives

1. Reward innovation

2. Emphasize the role of drugs and vaccines in health maintenance

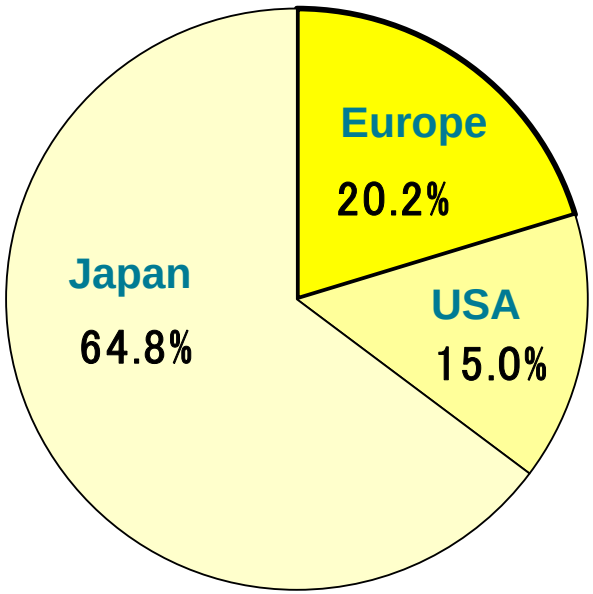
3. Move the debate from pricing to funding

4. Reduce the drug lag to serve patients better

5. Make Japan a dynamic and attractive place to invest for pharmaceutical companies

Presence of European Pharmaceutical Companies in Japan

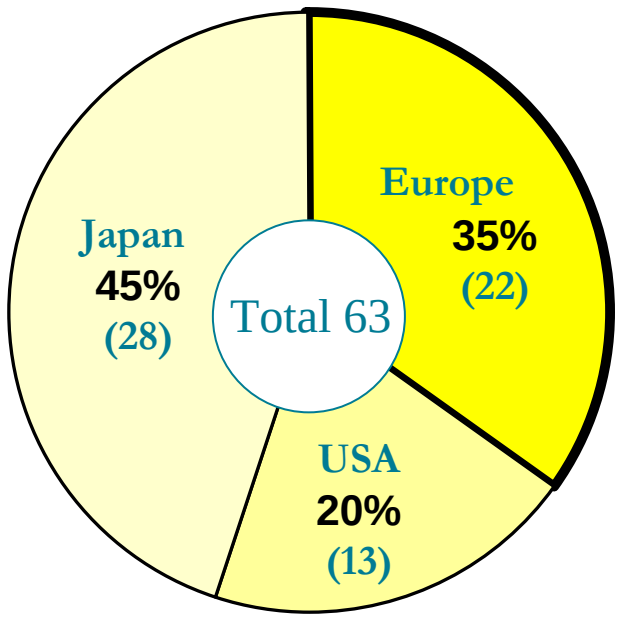
Sales Amount (2006)
1.6 trillion yen (10 billion euro)



Total Sales: 7.7 trillion yen (48 billion euro)

Source: IMS Jan-Dec 2006

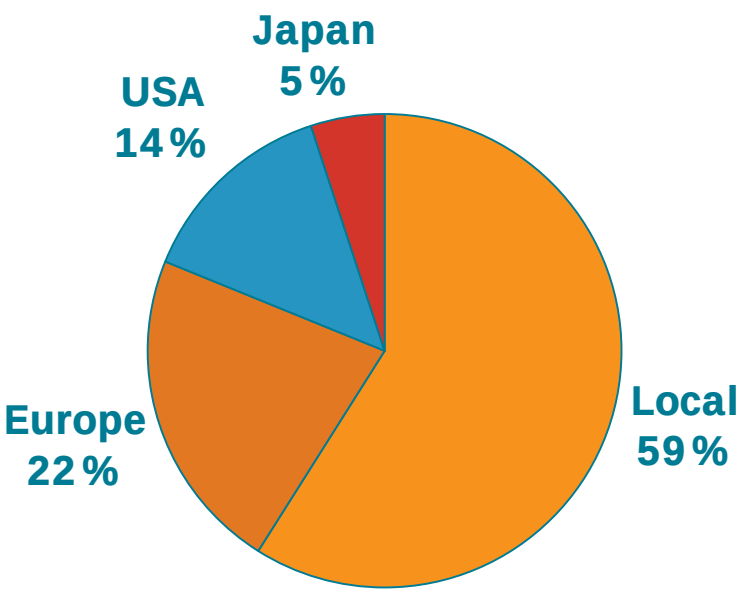
Number of Newly Launched Drugs
(2003 - 2005)



Source: Chuikyo Official Data

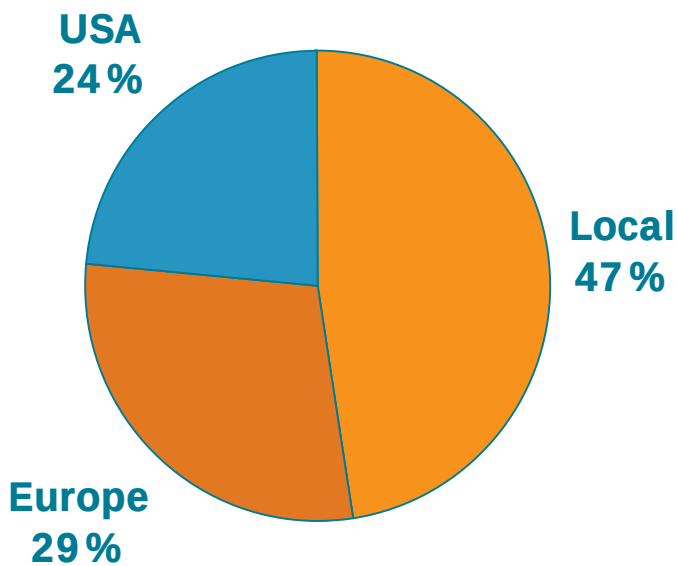
Presence of European Pharmaceutical Companies in Korea

2006 Korea ETC Market
4.0 Bil GBP



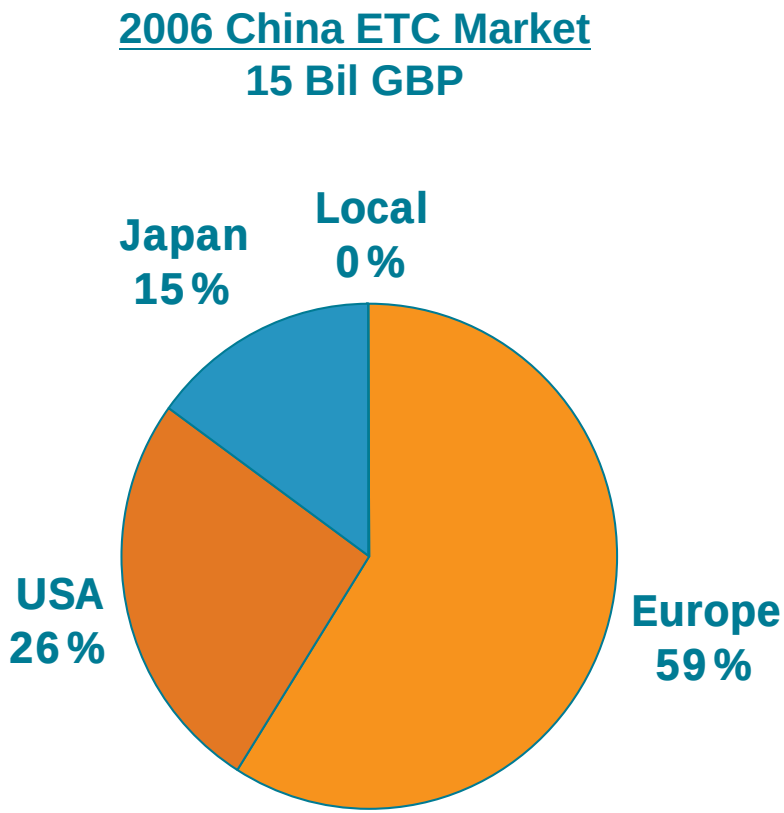
[2006 Korea ETC Sales share]

2005-2007 New Products
Total 76 products



[New products in 2005-2007]

Presence of European Pharmaceutical Companies in China



Survey of the Status of Multinational Studies

EFPIA Japan Technical Committee

- 13 member companies in Japan provided information
- 51 protocols have been analyzed
- 10 Asian locations were involved:

C: China, H: Hong Kong, I: India, In: Indonesia, J: Japan, K: Korea, M: Malaysia, P: Philippines, S: Singapore, T: Taiwan, Th: Thailand

Number of Companies and Multinational Clinical Trials

- Conducted 4
- On-going 4
- In preparation 2
- No plan 3
- Total 13 companies

Breakdown of 51 Protocols Surveyed

- Completed: 12
- On-going: 26 (17 in oncology)
- Planned: 13

What Type of Multinational Studies?

1. Non-Asia plus Japan alone
2. Non-Asia and Asia
3. Asia alone
4. (Non-Asia only)

Twelve studies have been completed

Stage	Area	# of Countries	Study size	Asia	Non—Asia
Ph III	T2DM	2	390	JK	None
Ph II	Af	17	673	J(74)	16(599)
Ph II	T2DM	5	120	J	4
Ph II	Oncology	8	200	J(100)	7(100)
Ph III	Stroke	23	3407	J(217) H(52) M(51) P(36) T(40)	18(3011)
Ph III	Oncology	26	660	J(60)	25(600)
Ph III	Oncology	8	450	J(100)	7(350)
Ph II	Oncology (gynecology)	30	240	J(6) T(15) I(15)	27(200)
Ph III	Oncology (urology)	41	8256	J	40(8199)
Ph II	Transplant	11	270	J(57)	9(193)
Ph II	CV/Metabolism	7	355	J(44)	6(311)
Ph IV	Transplant	15	690	J(10)	14(680)

Thirteen studies are being planned

Stage	Area	# of Countries	Study size	Asia	Non-Asia
Ph III	T2DM	16	630	JKCT	12
Ph III	DM	8	395	J(75)	7(320)
Ph III	CV	47	7397	J(200) C(400) I(187) K(90) In(70)	42(6450)
Ph I	Oncology	3	36	J(12) K(18) C(6)	None
Ph I/II	Oncology	3	180	J(126) K(39) C(15)	None
Ph III	Imaging	7	280	J(70)	6(210)
Ph III	GI (ulcerative colitis)	TBD	TBD	TBD	TBD
Ph III	Respiratory	3	540	J(270)	2(270)
Ph II	CV	TBD	TBD	TBD	TBD
Ph III	DM	TBD	TBD	TBD	TBD
Ph III	Urology	23	2700	J(200) C	21
Ph III	DM	TBD	TBD	TBD	TBD
Ph III	DM	TBD	TBD	TBD	TBD

Reasons for “No plan”

- Regulatory requirements, speed of patient enrolment and difference in clinical practice would result in the difference in trial completion, thereby affecting the overall global development schedule

- No plan for development of products which require multinational clinical trials

- No appropriate products

Questions from the Survey

- What exactly is the scope of East Asia? Is East Asia a homogeneous unit?
- How important is the issue of ethnic sensitivity in drug development and clinical practice?
- Should dose-finding studies (DFS) always be conducted in East Asia? Are global DFS not always sufficient?
- Can regulatory requirements and processes be unified within the region?

Unified or mutually recognized requirements and processes for new drug approval are desired/requested with respect to:

- Drug development consultation
- IND/CTA/CTN
- Clinical samples
- Language

Other Feedback

- Basic research sponsored by governments for the study of similarity or lack thereof of PK in populations in Asia

Similar Genetic Backgrounds Between Chinese and Japanese

MtDNA haplogroup	DNA sample* YRI (60)	CEU (60)	CHB (45)	JPT (44)
L1	0.22	–	–	–
L2	0.35	–	–	–
L3	0.43	–	–	–
A	–	–	0.13	0.04
B	–	–	0.33	0.30
C	–	–	0.09	0.07
D	–	–	0.22	0.34
M/E	–	–	0.22	0.25
H	–	0.45	–	–
V	–	0.07	–	–
J	–	0.08	–	–
T	–	0.12	–	–
K	–	0.03	–	–
U	–	0.23	–	–
W	–	0.02	–	–

Y chromosome haplogroup	DNA sample* YRI (30)	CEU (30)	CHB (22)	JPT (22)
E1	0.07	–	–	–
E3a	0.93	–	–	–
F, H, K	–	0.03	0.23	0.14
I	–	0.27	–	–
R1	–	0.70	–	–
C	–	–	0.09	0.09
D	–	–	–	0.45
NO	–	–	0.68	0.32

The International HapMap Consortium. A haplotype map of the human genome. Nature 2005;437:1299-320

Recent experience preparing for the Compound X development for T2DM in the region has shown that the China-Japan-Korea collaboration is an effective way for drug development in the region.

Development of Compound X for T2DM in the Region (1)

- In 2006, 180 million people worldwide were suffering from diabetes, and this number is estimated to double by 2030. The greatest increase in prevalence is expected to occur in Asia and Africa.
- The diabetes market potential in the region is large: 2.8 billion USD in 2016 in Japan only.
- Substantial clinical data from Japanese patients with diabetes are required for JNDA.

Development of Compound X for T2DM in the Region (2)

- Clinical data from Asia seem to be acceptable by the Japanese and Asian authorities as far as type 2 diabetes is concerned.
- Development of Compound X in China and Korea in addition to Japan was considered.
- The data obtained can be used for registration in all three countries.

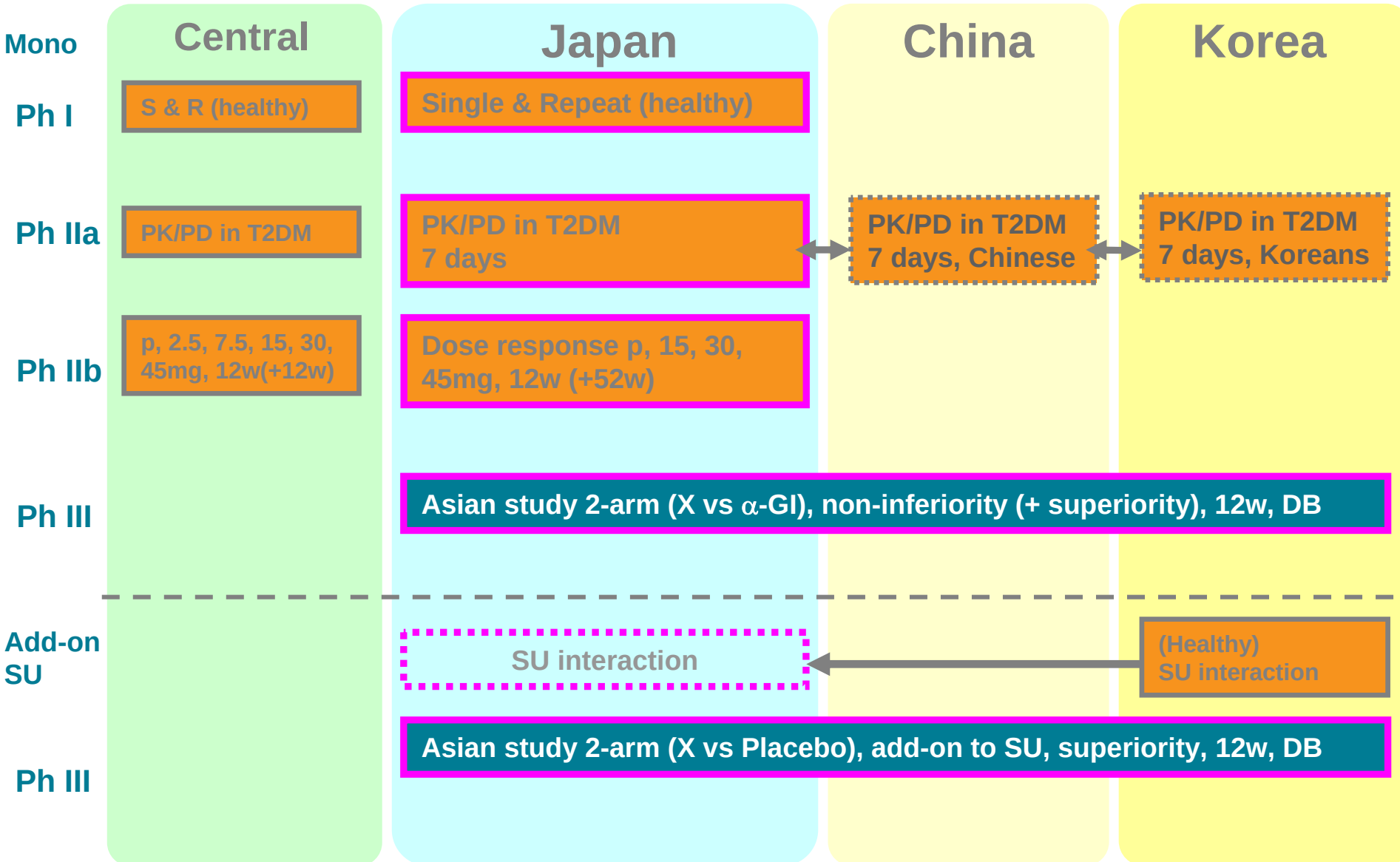
NDA Requirements for Compound X

- **Japan**
  - Full development
  - Ph I, Ph IIa (7 days; n=30), Ph IIb (12 wks + 52 wks; n=200) and Ph III (mono, SU combo; n= 348+258=606)
- **China**
  - Category: Class 3
    - PK: 20 - 30 pts
    - Ph III: 100 pairs (total 200 pts) for each indication
    - Certificate of pharmaceutical product of a sourcing country
- **Korea**
  - Major logic of approval is based on the concept of bridging
  - At least one bridging study (local or global)
  - Certificate of pharmaceutical product of a sourcing country

Comparison: Speed and Cost

	CHN / JPN / KOR	Japan Only
Monotherapy		
# of Pts	n=348 (n=116/each region)	n=348
Enrolment speed	4 months	9 months
Add-on to SU		
# of Pts	n=258 (n=86/each region)	n=258
Enrolment speed	3 months	7 months

Complete Clinical Data Package



Items/Issues Discussed by the Collaboration in Preparing the Plan

- **Requirements for initiating dosing to patients vary:**
  - Japan requires data from PI and DFS before PIII but not other countries.
- **Time between CTN and FSI varies:**
  - A few weeks to several months
- **Approved dose range of comparator drugs varies; need to agree on the range to be specified in the protocol:**
  - Many SUs with different dose ranges
- **Use of a generic drug to be used as a comparator drug varies:**
  - A generic drug approved in one country may not be approved in the other.

Items/Issues Discussed by the Collaboration in Preparing the Plan (cont'd)

- Safety reporting: via the central safety department; arrangements may be needed to consolidate the safety data in the region.
- Use of an EDC system in English is doable in the two-byte environment.

Conclusion

Background of Asian Collaboration

- Genetically very close (*Nature* report)
  - China/Hong Kong/Taiwan, Japan, Korea, ･･･
- Pathogenesis and prevalence of diseases are similar.
  - Metabolic disease, CV, ID, oncology, ･･･
- Dietary habits/social factors are similar.
- Clinical study productivity is high.

Rationale of the Collaboration

1. Indications of diseases that are prevalent and relevant in the region can be jointly investigated and developed.
2. New drugs can be launched without delay; Japan will benefit from data from China and Korea, which in turn will benefit the two countries for new drug applications.
3. Better development economics are realized by leveraging China, Korea and other parts of the region.

Regulatory Considerations

- Patient/volunteer safety are of paramount concern.
- Clearly defined regulatory requirements and procedures will help efficient drug development.
- Efficient ethics approval procedure is conducive to the smooth initiation of clinical trials.
- Regulatory procedural timelines, when pre-defined and followed up closely, will expedite drug development.
- Mechanisms to manage change during drug development including that for CMC (chemistry and manufacturing controls) should be defined for eliminating unnecessary use of development resources.

Recommendation

- The major players in East Asia such as China, Japan and Korea to agree that the data on PK, PD, safety, efficacy generated in the region either jointly or separately are acceptable across the region.
  - There is diversity within Europe but Pan-European data are accepted in Europe.

Additional Comments

- Standards for the acceptability of the data from the region should be established so that Pan-East Asian studies can be planned and implemented (e.g. implementation of ICH E5- type guideline)
  - Adoption of common regulatory requirements (e.g. EU harmonized to Investigational Medicinal Product Dossier) may help the process.
- Regulatory systems may first be aligned and then unified later with respect to requirements, processes and timelines to promote multinational trials in East Asia.
- For non-ethnically sensitive products, submission of data from East Asian population should not be a requirement for the registration of medicines with data from non-East Asian countries.
- If a product does display ethnic sensitivity, then data generated in a comparable population should be accepted and a separate local study in that comparable population should not be required.
- Such an agreement will result in more clinical data regarding East Asians that will be of relevance to the region and will also facilitate the placement of early phase work in the region.

Thank you very much for your attention!

Back up slides

Seventeen oncology studies are on-going

Stage	Area	# of Countries	Study size	Asia	Non-Asia
Ph III	Oncology	2	464	J(414) K(50)	None
Ph III	Oncology	24	1400	J(140) CKVMSInI(300)	16(960)
Ph III	Oncology	32	1500	J(120) OAsia(300)	27(1200)
Ph III	Oncology	34	600	J(70) CISKT(120)	28(480)
Ph III	Oncology	9	1200	J(230) CHKTTHSMPIn(970)	None
Ph II	Oncology	4	260	J(40)	3(220)
Ph III	Oncology	16	760	J(150) KCT(?)	12
Ph III	Oncology	40	4500	J(140) C(180) T(160) K(40) S(15)	24(3800)
Ph III	Oncology	24	584	J(100) K(90) C(77)	10(150)
Ph III	Oncology	34	3450	J(20) C(108) K(121) T(32) Th(32) S(32) H(25)	20(2800)
Ph III	Oncology (gynecology)	70	8000	J(140) K(130) Th(130) T(80) C(60) H(10) S(10) Oasia(200)	60(7340)
Ph III	Oncology (GI)	5	260	J(80) C(100) K(50) T(20) H(10)	None
Ph III	Oncology	21	4000	J(300) C(40) K(30)	18(3630)
Ph II	Oncology	5	115	J(50) S(5)	3(60)
Ph III	Oncology	34	770	J(60) K(40) Th(10) T(10) S(4)	24(500)
Ph II	Oncology	10	415	J(24)	9(391)
Ph II	Oncology	17	586	J(15) K(25) C(20) S(5)	13(521)

Nine non-oncology studies are on-going

Stage	Area	# of Countries	Study size	Asia	Non-Asia
Ph III	CV (lower limb ischemia)	31	490	JKSM	25(442)
Ph III	CV (Af)	44	18,118	J (300) I(584) C(500) T(350) K(340) M(184) Th(157) P(153) H(92) S(59)	34(15,399)
Ph III	Parkinson's	15	500	J(90) T(36) M(20) I (20)	11(334)
Ph III	Ophthalmology	24	1563	J(203) I (169)	22(1191)
Ph III	CNS	2	400	J(150) K(250)	None
Ph III	CNS	19	1500	J(130)	18(1370)
Ph III	Transplant/immunology	10	180	J(45)	9(150)
Ph IV	Transplant/immunology	18	300	J(16) T(10)	16(274)
Ph II	Respiratory	3	80	J(25)	2(55)