Global drug development strategies
Philip Hougaard, Lundbeck
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Outline

- Appetizer (extent and reason for globalisation)
- The term “region”
- Bridging approach (first West, then East): Example integrated
- Joint approach: Example; Japan guideline Multi-regional clinical trials; discussion

Why globalised drug development?

- Global registration beneficial for the patients and the company (if patients present)
- Global registration requires inclusion of patients from all regions
- Global development plan can shorten timelines for some countries
- Large study sample size may require global studies

Appetizer (Karlberg, 2011, using clinicaltrials.gov)

Region	% study sites (2006-10)	Trend
N America	45.6	↓
W. Europe	24.6	↓
E. Europe	12.4	↑
Asia	9.1	↑
Latin America	4.5	↓
Africa	1.1	-

Appetizer (2)

- Reasons for trend:
- Quality of sites
- Customer patient population
- Study patient population

- Furthermore, Japan is moving from local to multi-national studies

Multi-...

- We are used to do
- Multi-center trials
- Multi-national trials

- In the future also
- Multi-regional trials (MRCT)
- Multi-regional = multi-continental?
- Not necessarily

What is a region?

- Intrinsic factors:
- Genes … including weight

- Extrinsic factors:
- Medical practice, culture, environment, economy, diet…

- (ICH E5)

What is a region? (2)

- USA vs. North America?
- Japan, China, Korea vs. Asia?
- Eastern Europe, Western Europe vs. Europe?
- EU vs. EMA Europe vs. Europe?

- Regions to be treated equally (symmetrically)?
- "Region" suggests potential difference

Random versus fixed effects?

- Patients
- Centers
- Countries
- Regions

- A single statistical model chooses between random and fixed
- going down the interpretation/thinking gradually switches from random to fixed

Why not random effects models?

- Random effects models are good at describing features varying between regions in a quantitative way, but not good at detecting the occasional outlier
- Can be illustrated with the fact that random effects allow the effect in one region to be estimated, purely by data from other regions

Bridging development scenario

- (Drugs originating in the West):
- Studies in Europe + USA
- Registration in Europe + USA + other countries satisfied with the package
- Studies + registration in Japan
- Studies + registration in other countries (if judged relevant)

Project case

- Drug marketed in Europe + USA, monotherapy and add-on
- 3 Phase III registration studies + one later: all positive
- Now extending into Asia (6 countries)
- Clinical studies in China and Korea, only

ICH E5 guideline “Ethnic factors … foreign clinical data”

- ”…permit adequate evaluation of the influence of ethnic factors while minimizing duplication of clinical studies and supplying medicines expeditiously to patients for their benefit”
- Bridging study definition: Supplemental study in new region that allow extrapolation of foreign data

Mapping existing knowledge

- Ethnic sensitive?
- 4 (/4) positive studies in Western world
- Patients of Asian origin in previous studies
- Exposure after marketing (general as well as patients of Asian origin)
- Safety feedback after marketing
- Genetic comparison of Asian and Western population (target + elimination)

Multi-national efficacy study?

- To include China, Korea + …
- Total size: Combined results statistically significant
- Size in each country: Country-specific results positive according to less restrictive criteria (MRCT)
- Not feasible due to protocol review times

Plan for China

- Add-on: A fully powered efficacy study
- Monotherapy: A study
- PK: A Phase I one-arm study

Korean guideline

- Consider PK study
- If not sensible, consider biomarker study
- If not sensible, make clinical endpoint study; preferably fully powered
- Korea – other Asia – rest of world
- Bridging study: Aims at mimicking a chosen previous study

Mimicking

- Design: Inclusion/exclusion criteria; time points, endpoints, statistical methods as close as possible to the previous study
- Results: Popularly, show the same results as previous study. This phrasing suggests an equivalence type study, but that would be more demanding than showing difference to placebo

Plan for Korea

- Mimicking a previous add-on study, but with placebo as only comparator
- Reduced sample size:
- Significance level: 0.1 (two-sided)
- Power: Less than 0.8
- Chinese PK results will be available at registration

Alternative development scenario

- Multi-regional studies (Europe + USA + Japan + selected other countries)
- Advantages: Faster to Japan and …; Larger study patient pool

MRCT Disadvantages/risk

Case	Comparison (vs. bridging approach)
Drug not useful	Larger sample size
Drug has regionally varying effect	Higher risk of failure
Drug overall useful	Smaller sample size

Stroke

- Ischaemic stroke – blood vessel occlusion (85%)
- Haemorrhagic stroke – bleeding (15%)
- Scanning needed to discriminate
- Acute disease, but symptoms may come slowly
- Current treatment: TPA for ischaemic stroke, within 3 h of onset (registration), 4.5 h (recommendations)
- Onset: Last time known to be healthy

Desmoteplase

- Plasminogen activator (derived from a vampire bat) to treat ischaemic stroke (3-9 h)
- Advantages: reduces risk of bleeding
- No damage to blood-brain barrier
- Not neurotoxic
- Easier administration (longer half life)

Regulator interaction

- Clinical program discussed with EMA (endpoint!) followed by FDA
- Two clinical studies (n=320) agreed upon (identical, except countries)
- One study protocol+SAP went through FDA-SPA process
- n modified to 400

Endpoint: mRS scale

0: No symptoms
1: No significant disability, …
2: Slight disability, …
3: Moderate disability, …
4: Moderately severe disability, …
5: Severe disability, …
6: Dead

Endpoint: Binary (0-2), ordinal, or reduced ordinal (5,6 combined)?

Binary or ordinal response?

- Binary: EMA stroke guideline requests a binary endpoint
- Ordinal: More detailed (efficient); more suitable to broad patient populations; more robust
- The ordinal logistic regression model is based on an assumption of equal odds ratios. What if this is not satisfied?

Country selection

- Why not bridging approach?
- Study A: Europe, Australia, Asia (India, Korea, …)
- Study B: Europe, N.+S.America (USA, Canada,…), S.Africa
- Country selection dynamic - 200 sites
- Treatment window
- Japan: separate program; China?

Japan guideline

- ”Basic principles on global clinical trials” (2007)
- To reduce the Japanese drug lag, Japan can be part of a ”global trial” (essentially MRCT)
- Japan is a region
- “Asia” not mentioned

Steps

- Japanese PK/safety (single dose; exception if similar to existing drugs)
- Japanese dose-finding (possibly in MRCT)
- Japanese confirmatory (MRCT)

Japanese confirmatory

- Planning stage:
- Overall effect statistically significant +:
- Method 1: Prob. 80% of observed effect in Japanese > 50% of overall observed effect (requires at least 20% Japanese patients)
- Method 2: Prob. 80% of estimated effect in each region positive

Japanese experience

- Ando and Hamasaki (2010) – first 5 drugs approved with MRCT

Countries	#Japanese	#total
J+Korea	293	608
J+Korea	197	380
28 globally	96	1513
39 globally	87	3386
J+Europe+N.Am	26	405

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Method 1 critique

- Approach not sensible, Ikeda&Bretz(2010)
- Theoretical example, inspired by the paper

Drug	Effect in Japan	Effect overall	OK according to guideline
A	2	3	OK
B	4	9	Not OK

Alternative approach

- More sensible + better technical performance, Ikeda&Bretz(2010) (still 20% Japanese)
- Overall significance: $p<0.025$ (one-sided)
- Significance in new region: $p<0.25$ (one-sided)

Why not bioequivalence type methods?

- BE: Two drugs (typically two drug formulations) intended to substitute for each other in the same patient
- Multi-regional: One drug intended for use in patients of different types

Why not interaction tests?

- Treatment by region interaction = differential treatment effect over regions
- Often low power (sometimes handled by using significance level 0.1) =>
- Real differences may be overlooked
- Does not discriminate between quantitative interaction (different effect sizes) and qualitative interaction (positive as well as negative regional effects)

What if differential effect?

- A: Persuading or qualitative difference: Fair to evaluate reasons for the difference
- B: Small difference: Could potentially be an unfortunate coincidence. Still fair to consider reasons and potentially perform an additional study

Regulator heterogeneity

- There are differences between regulators in terms of:
- Process
- Timelines
- Scientific requirements

Summary

- Studies have to run globally to allow global registration
- Global multi-regional clinical trials is overall better than a bridging strategy, but also more complex, due to patient heterogeneity as well as regulator heterogeneity

References

- Ando and Hamasaki (2010). Ph. Statist. 9, 190
- Ikeda and Bretz (2010). Ph. Statist. 9, 207
- Karlberg (2011). Clinical Trial Magnifier 4, 7