Drug development: an introduction to clinical trials

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Drug development process

The process of new drug development, as defined by bringing a new drug to marketing approval by a regulatory agency, can be represented by a three-stage model including:

- Drug discovery and drug design
- Nonclinical development
- Clinical development
Drug discovery and drug design

Work done from the time of the identification of a therapeutic need in a particular disease area to the time the drug candidate deemed most likely to safely affect the desired therapeutic effect.

- Drug discovery: Identification of interesting drug compounds, drug targets and delivery mechanisms with potential for development into products
- Drug design: Identify lead compounds for further development
Nonclinical Research

Three areas of investigation are considered here:

- pharmacokinetics
- pharmacology
- toxicology
Non Clinical Pharmacokinetics

- Pharmacokinetics: study of the effect that the body has on the drug.

- May be helpful when interpreting the data from pharmacological and toxicology studies.

- Nonhuman PK data are not perfect predictors of human PK, they constitute meaningful quantitative data that improve the chances of selecting the correct range of safe doses to test in humans.
Pharmacology studies

Primary pharmacology studies

- The goal is to demonstrate that the drug has pharmacological activity relating to its proposed therapeutic use.
- Can be conducted *in vivo* or *in vitro*.
- Can be useful:
  - In predicting potential safety issue, potential interactions with other drugs,
  - In understanding undesired effects,
  - In understanding the results of toxicological studies.
Secondary pharmacology studies

- Focus on the overall activity of the drug compound, including any activity not directly related to the drug’s proposed therapeutic use.

- Can be conducted *in vivo* or *in vitro*. 
Pharmacology studies

Safety Pharmacology studies

- Investigate potentially undesirable effects of the drug compound on the physiological function.
- Conduct in rat, dog and/or primate
- Single dose studies using the intended therapeutic dose.
- Focus on functional changes in major organs systems within the body.
Indicate the main organs and physiological systems involved, and a quantitative estimation of the drug’s toxicity when administered across a relative short period of time.
Toxicological studies

**Pre-FIH Regulatory Toxicology Studies**
- Twenty-eight day repeated dose toxicology studies in two nonhuman animal species
- Genotoxicity studies
- Reproductive toxicity studies

**Post-FIH Regulatory Toxicology Studies**
- Toxicological studies in two or more nonhuman animal species lasting up to 1 year
- Carcinogenity tests and reproductive toxicology studies lasting up 2 years
- Interaction studies
Clinical Research

Clinical research is research that either directly involves a particular person or group of people or uses materials from humans, such as their behavior or samples of their tissue, that can be linked to a particular living person. This includes:

- Studies of mechanisms of human disease
- Studies of therapies or interventions for disease
- Clinical trials
- Studies to develop new technology related to disease
- Epidemiological and behavioral studies
- Outcomes and health services research
Clinical Trials

The NIH defines a *clinical trial* as a **prospective biomedical** or **behavioral** research study of **human subjects** that is designed to answer **specific questions** about biomedical or behavioral interventions (drugs, treatments, or new ways of using known drugs, treatments, or devices).

Clinical trials are used to determine whether new biomedical or behavioral interventions are **safe, efficacious, and effective**. Behavioral human subjects research involving an intervention to modify behavior (diet, physical activity, cognitive therapy, etc.) fits this definition of a clinical trial. Human subjects research to develop or evaluate clinical laboratory tests (e.g. imaging or molecular diagnostic tests) might be considered to be a clinical trial if the test will be used for medical decision making for the subject or the test itself imposes more than minimal risk for subjects. Biomedical clinical trials of experimental drug, treatment, device or behavioral intervention may proceed through **four phases**.
Classifications of Clinical Trials

- Pharmaceutical clinical trials are often categorized into various phases, with any trial being identified to one of them.

- These categories include phase I, phase II, phase III and phase IV
Classifications of Clinical Trials

*Traditional description of these phases*

- **Phase I**: pharmacologically oriented studies that typically look for the best dose to employ. Comparison to other treatments is not typically built into the study design.

- **Phase II**: trials that look for evidence of activity, efficacy, and safety, at a fixed dose. Again comparison to other treatments is not typically built into the study design.

- **Phase III**: trials in which comparisons with another treatment (e.g., placebo, an active control) is a fundamental component of the design. These trials are undertaken if phase I and phase II studies have provided preliminary evidence that the investigational drug is safe and effective.

- **Phase IV**: these are postmarketing trials, conducted once the drug has been approved and in therapeutic use.
Classifications of Clinical Trials

Phase 0: Micro-dosing Studies

In 2006, FDA has approved testing of small quantities of experimental drugs in human beings to understand the path of drug in the body. US-FDA designated this phase as phase-0 in accordance with US-FDA 2006 Guideline on Exploratory Investigational New Drug Studies.

A phase-0 studies can be considered as micro-dosing studies.

- These studies give no data on safety or efficacy, being by definition, a dose too low to cause any therapeutic effect.

- to rank drug candidates in order to decide which has the best pharmacokinetic parameters in humans to take forward into further development.
### Objectives of trials

<table>
<thead>
<tr>
<th>Human pharmacology</th>
<th>Study examples</th>
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</thead>
<tbody>
<tr>
<td>• Assess tolerance</td>
<td>• Dose-tolerance studies</td>
</tr>
<tr>
<td>• Describe or define PK/PD</td>
<td>• Single-dose and multiple-dose PK and/or PD studies</td>
</tr>
<tr>
<td>• Explore drug metabolism and drug</td>
<td>• Drug interaction studies</td>
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<tr>
<td>interactions</td>
<td></td>
</tr>
<tr>
<td>• Estimate (biological) activity</td>
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<table>
<thead>
<tr>
<th>Therapeutic exploratory</th>
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<tbody>
<tr>
<td>• Explore use for the targeted indication</td>
<td>• Earliest trials of relatively short duration in</td>
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<tr>
<td>• Estimate dosage for subsequent studies</td>
<td>well-defined narrow populations with the</td>
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<tr>
<td>• Provide basis for confirmatory study</td>
<td>disease or condition of clinical concern, using</td>
</tr>
<tr>
<td>design</td>
<td>surrogate of pharmacological endpoints or</td>
</tr>
<tr>
<td></td>
<td>clinical measure</td>
</tr>
<tr>
<td></td>
<td>• Dose-response exploration studies</td>
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</table>
### Objectives of trials

<table>
<thead>
<tr>
<th>Therapeutic confirmatory</th>
<th>Study examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Demonstrate: confirm efficacy</td>
<td>• Adequate and well-conducted studies to establish efficacy</td>
</tr>
<tr>
<td>- Establish safety profile</td>
<td>• Randomized parallel dose-response studies</td>
</tr>
<tr>
<td>- Provide an adequate basis for assessing benefit-risk relationship to support market approval</td>
<td>• Clinical safety studies</td>
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<tr>
<td>- Establish dose response relationship</td>
<td>• Studies of mortality/morbidity outcomes</td>
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<table>
<thead>
<tr>
<th>Therapeutic use</th>
<th>Study examples</th>
</tr>
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<tbody>
<tr>
<td>- Refine understanding of benefit-risk</td>
<td>• Comparative effectiveness studies</td>
</tr>
<tr>
<td>- Relationship in general or special populations and/or environment</td>
<td>• Studies of mortality/morbidity outcomes</td>
</tr>
<tr>
<td>- Identify less common adverse drug reactions</td>
<td>• Studies of additional outcomes</td>
</tr>
<tr>
<td>- Refine dosing recommendations</td>
<td>• Large simple trials</td>
</tr>
<tr>
<td></td>
<td>• Comparative studies</td>
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<td></td>
<td>• Pharmacoeconomic studies</td>
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</tbody>
</table>
ICH 8 classifications (3/3)

Correlation between Development Phases and Types of Study

TYPE OF STUDY

- Therapeutic Use
- Therapeutic Confirmatory
- Therapeutic Exploratory
- Human Pharmacology

PHASES OF DEVELOPMENT

I II III IV

TIME

INDIVIDUAL STUDY

objectives
design
conduct
analysis
report
Phase I (most typically type of study: Human Pharmacology trials)

Assess the safety of the drug

- **Characterizations of the drug’s safety profile:**
  - Pharmacokinetics
  - Structure-activity relationship
  - Mechanisms of action
  - Preferred routes of administration
  - Interactions with other medications

- **Data focus:**
  - Vital signs
  - Plasma and serum levels
  - Adverse events

- **Sample size:** 20 to 80
Phase II (most typically type of study: Therapeutic Exploratory Trials)

- primary objective is to explore therapeutic efficacy in patients.
- Initial therapeutic exploratory studies may use a variety of study designs, including concurrent controls and comparisons with baseline status. Subsequent trials are usually randomised and concurrently controlled to evaluate the efficacy of the drug and its safety for a particular therapeutic indication.
- Studies in Phase II are typically conducted in a group of patients who are selected by relatively narrow criteria, leading to a relatively homogeneous population and are closely monitored.
- An important goal for this phase is to determine the dose(s) and regimen for Phase III trials.
- Confirmatory dose response studies may be conducted in Phase II or left for Phase III. Doses used in Phase II are usually but not always less than the highest doses used in Phase I.
- Additional objectives of clinical trials conducted in Phase II may include evaluation of potential study endpoints, therapeutic regimens (including concomitant medications) and target populations (e.g. mild versus severe disease) for further study in Phase II or III.
Phase III (most typically type of study: Therapeutic Confirmatory Trials)

- Begin with the initiation of studies in which the primary objective is to demonstrate or confirm therapeutic benefit.

- Studies in Phase III are designed to confirm the preliminary evidence accumulated in Phase II that a drug is safe and effective for use in the intended indication and recipient population.

- These studies are intended to provide an adequate basis for marketing approval.

- Studies in Phase III may also further explore the dose-response relationship, or explore the drug's use in wider populations, in different stages of disease, or in combination with another drug.
Phase IV: Therapeutic use

- Phase IV begins after drug approval. Therapeutic use studies go beyond the prior demonstration of the drug’s safety, efficacy and dose definition.

- Studies in Phase IV are all studies (other than routine surveillance) performed after drug approval and related to the approved indication.

- They are studies that were not considered necessary for approval but are often important for optimising the drug’s use.

- They may be of any type but should have valid scientific objectives.

- Commonly conducted studies include additional drug-drug interaction, dose-response or safety studies and studies designed to support use under the approved indication, e.g. mortality/morbidity studies, epidemiological studies.
# Phases and drug development

On average, pharmaceutical companies are spending anywhere between $100 and $800 million per each drug tested.

<table>
<thead>
<tr>
<th>Research Concept &amp; Discover Active Lead Compound</th>
<th>Preclinical Testing</th>
<th>Clinical Trials</th>
<th>Registration, Launch and Sales</th>
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<tbody>
<tr>
<td>2-20 years research</td>
<td>2-3 years development</td>
<td>3-5 years development</td>
<td>2-3 years development</td>
</tr>
<tr>
<td>8,000-10,000 potential Candidate substances</td>
<td>20-30 remaining Substances</td>
<td>20-30 remaining Substances</td>
<td>1 remaining substance</td>
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<tr>
<td></td>
<td>5-10 remaining substances</td>
<td>5-10 remaining substances</td>
<td>1 remaining</td>
</tr>
<tr>
<td>Research Target</td>
<td>Biological Tests</td>
<td>Clinical Trial</td>
<td>Registration with Health Authorities</td>
</tr>
<tr>
<td>Discovery of lead compound</td>
<td>Regulatory clearance</td>
<td>Phase 1</td>
<td>Preparation for Launch</td>
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<tr>
<td>Selection of product candidate</td>
<td>Pharmacy/Chemical Development</td>
<td>Phase 2</td>
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<td>Phase 3</td>
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<tr>
<td></td>
<td>Biological Tests</td>
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</tr>
<tr>
<td></td>
<td>Pharmacy/Chemical Development</td>
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Features of clinical trials

Objectives

The objective(s) of the study should be clearly stated and may include exploratory or confirmatory characterisation of safety and/or efficacy and/or assessment of pharmacokinetic parameters and pharmacological, physiological, biochemical effects.
Features of clinical trials

**Design**

- The appropriate study design should be chosen to provide the desired information. Examples of study design include parallel group, cross-over, factorial, dose escalation, and fixed dose response. (See ICH E4, E6, E9 and E10).

- Appropriate comparators should be utilized and adequate numbers of subjects included to achieve the study objectives. Primary and secondary endpoints and plans for their analyses should be clearly stated.
Features of clinical trials

*Design*

- Type of study
- Selection of subjects
- Selection of control group
- Number of subjects
- Minimize bias
Features of clinical trials

**Conduct**

- The study should be conducted according to the principles described in guidelines.

- Adherence to the study protocol is essential. If modification of the protocol becomes necessary a clear description of the rationale for the modification should be provided in a protocol amendment.

- Timely adverse event reporting during a study is essential and should be documented. Guidance is available on expedited reporting of safety data to appropriate officials and on the content of safety reports and on privacy and confidentiality of data.
Features of clinical trial

Analysis

- The results of a clinical trial should be analysed in accordance with the plan prospectively stated in the protocol and all deviations from the plan should be indicated in the study report.

- Studies are normally expected to run to completion, although in some studies the possibility of early stopping is formally recognised. In such cases this should be clearly described in the protocol with due statistical attention to the overall levels of statistical significance and to the need to adjust the estimates of the size of treatment effects.

- Safety data should be collected for all clinical trials, appropriately tabulated and with adverse events classified according to their seriousness and their likely causal relationship.
Tumor necrosis factor is a proinflammatory cytokine that plays an important role in inflammatory disorders such as rheumatoid arthritis (RA) and psoriatic arthrosis.

**Etanercept** is a receptor TNF antagonist that competitively inhibits the interaction of TNF with cell-surface receptors, preventing TNF-mediated cellular responses and modulating the activity of other proinflammatory cytokines and processes that are regulated by TNF.
Example of drug development

PK

Methods

- 26 healthy volunteers between 19 and 50 years old received single dose of 25 mg of etanercept by SC injection into abdomen
- Serum samples: full PK profile

Results

- Slowly absorbed from the site of injection with a time peak of concentration (±SD) of 51±14 hours; peak of concentration was 1.46 ± 0.72 mg/L.
- The absolute bioavailability of SC-injected etanercept was about 60%
- The AUC was 235 ± 98 mg.h/L
- The apparent clearance was 132 ± 85 mL/h.
- The apparent volume of distribution was 12 ± 6 L
- The half-life was 68 ± 19 h
Example of drug development

PK /PD data

OBJECTIVE:
Our objective was to develop a population pharmacokinetic and pharmacodynamic model of etanercept in patients with rheumatoid arthritis, with the American College of Rheumatology response criterion of 20% improvement (ACR20) used as a binary clinical outcome variable.

METHODS:
Concentration-time profiles from 25 subjects, administered 25 mg subcutaneous etanercept twice weekly for 24 weeks, were pooled with data from 77 subjects, enrolled in a 24-week, randomized, double-blind study comparing 25 mg and 50 mg subcutaneous etanercept twice weekly. The cumulative area under the concentration-time curve (AUC) was used as the exposure variable, and ACR20 was the binomial clinical outcome. ACR20 data from another 80 placebo-treated patients enrolled in a randomized, double-blind phase III study were used to describe the placebo time course of ACR20. A logistic regression analysis with NONMEM was applied to describe the exposure-response relationship, and the 95% confidence intervals (95% CIs) were constructed by bootstrapping 1000 times.
RESULTS:
The population mean apparent clearance was 0.117 L/h (95% CI, 0.108-0.130 L/h) for white female patients and 0.138 L/h (95% CI, 0.118-0.163 L/h) for white male patients. Interindividual variability and interoccasion variability were 41.1% and 27.6%, respectively. The mean absorption half-life was 20.9 hours, and the elimination half-life was 95.4 hours. An improved response profile in male patients was shown, but the multiplicative factor between slope on cumulative AUC between male and female patients was not statistically significant (1.69; 95% CI, 0.37-9.99). The model-predicted percentage of patients achieving ACR20 at 6 months after dosing of 25 mg subcutaneously twice weekly was 54.9%, comparable to the observed 52.9%.

CONCLUSION:
The population pharmacokinetic analysis confirmed that etanercept is slowly absorbed and eliminated after subcutaneous administration. The logistic model linking cumulative AUC with ACR20 adequately characterized the time course of clinical improvement in patients with rheumatoid arthritis receiving etanercept.
OBJECTIVE:
Patients with rheumatoid arthritis (RA) treated with etanercept (Enbrel) in controlled studies of 3 to 6 months' duration had rapid and sustained improvement of their disease, with minimal safety issues. In this study, we examine safety and clinical benefit after longer term treatment with etanercept.

METHODS:
All adult patients with RA with a previously inadequate response to one or more disease modifying antirheumatic drugs, and who received at least one dose of etanercept as monotherapy in controlled or open label clinical trials were evaluated for safety and clinical benefit. Adverse event rates were compared as was evidence of continued benefit over time.

RESULTS:
Etanercept continued to be safe and well tolerated in 628 adult patients treated for a median of 25 mo (maximum 43 mo; 1109 patient-years). Nine percent of patients withdrew due to lack of efficacy and 7% due to adverse events. Most adverse events were mild, and no statistically significant increases in frequency of events were seen when patients received etanercept over longer periods of time. Clinical benefit was maintained with longterm therapy. A 100% improvement in individual disease activity measures was achieved by 17% to 28% of the patients. Fifty-five percent of patients who were taking corticosteroids (mean dose at baseline 6.6 mg/day) decreased or discontinued corticosteroid therapy while maintaining control of their arthritis symptoms.

CONCLUSION:
Etanercept continued to be safe and well tolerated, and its clinical benefit was sustained for a median of 25 mo and for as long as 43 mo in patients with RA.
Example of drug development

**Efficacy Safety**

**METHODS:**
We treated 632 patients with early rheumatoid arthritis with either twice-weekly subcutaneous etanercept (10 or 25 mg) or weekly oral methotrexate (mean, 19 mg per week) for 12 months. Clinical response was defined as the percent improvement in disease activity according to the criteria of the American College of Rheumatology. Bone erosion and joint-space narrowing were measured radiographically and scored with use of the Sharp scale. On this scale, an increase of 1 point represents one new erosion or minimal narrowing.

**RESULTS:**
As compared with patients who received methotrexate, patients who received the 25-mg dose of etanercept had a more rapid rate of improvement, with significantly more patients having 20 percent, 50 percent, and 70 percent improvement in disease activity during the first six months (P<0.05). The mean increase in the erosion score during the first 6 months was 0.30 in the group assigned to receive 25 mg of etanercept and 0.68 in the methotrexate group (P= 0.001), and the respective increases during the first 12 months were 0.47 and 1.03 (P=0.002). Among patients who received the 25-mg dose of etanercept, 72 percent had no increase in the erosion score, as compared with 60 percent of patients in the methotrexate group (P=0.007). This group of patients also had fewer adverse events (P=0.02) and fewer infections (P= 0.006) than the group that was treated with methotrexate.

**CONCLUSIONS:**
As compared with oral methotrexate, subcutaneous [corrected] etanercept acted more rapidly to decrease symptoms and slow joint damage in patients with early active rheumatoid arthritis.
Example of drug development

*Initial approval*

- **Indications:**
  - Rheumatoid arthrisis (RA)
  - Polyarticular Juvenile Rheumatoid Arthritis
  - Psoriatic arthrisis
  - Ankylosing spondylitis
  - Chronic moderate to severe plaque psoriasis

- **Recommended regimen:**
  - Adults: 25 mg twice weekly by subcutaneous (SC) injection
  - 4 to 17 years old: 0.4 mg/kg (up to 25 mg) twice weekly by SC injection
To improve the convenience to adult patient, the sponsor is interested in developing a new dosage regimen for etanercept: 50 mg once weekly.
Additional supportive data

- **PK data**
  - Absolute bioavailability: 60% in adults
  - PK linear at doses up to 50 mg of twice weekly SC injection
  - The steady-state trough concentrations of both regimens were 1 to 2 mg/L (above the concentration yielding 50% of the maximal effect for biomarkers).

- **PD data**
  - Small pilot study shows comparable safety profile with both regimens
Based on the effectiveness guidance, proposed a drug development strategy.

![Flow chart for drug development](image)

**Figure 1.** Flow chart for the development of a new dose, dosage regimen, or dosage form using existing studies based on the Effectiveness Guidance by the FDA.
Is the PK of the 50 mg, once-weekly SC regimen very different from that of 25 mg, twice-daily regimen?
Is the exposure-response relationship of etanercept including its time course well understood?
### Table 1. Strategies to Develop a New Dosage Regimen for Etanercept

<table>
<thead>
<tr>
<th>Drug Development Question</th>
<th>Answer</th>
<th>Strategy</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK of the new regimen not very different from that of the approved regimen?</td>
<td>Expected so, but more data needed</td>
<td>To compare the PK profiles between the 2 regimens</td>
<td>• Conduct a short-term, repeated-dose PK study to compare the regimens</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Conduct a simulation experiment to compare the regimens using a population PK model</td>
</tr>
<tr>
<td>Exposure-response relationship and its time course well understood?</td>
<td>No</td>
<td>To develop the exposure-response relationship</td>
<td>• Conduct a population PK-PD modeling analysis of etanercept in adult patients with RA</td>
</tr>
<tr>
<td>Contingency on possible safety concern</td>
<td>50-mg once weekly will yield a higher peak concentration profile</td>
<td>To address safety concern</td>
<td>• A single safety-oriented clinical trial may be conducted</td>
</tr>
</tbody>
</table>
PK results

Figure 2: Simulated concentrations for 25-mg, twice-weekly SC and 50-mg, once-weekly SC regimens at steady-state in adult patients with rheumatoid arthritis. The mean, 5th and 95th percentiles are represented. Hatched areas denote 5th to 95th percentile for 25-mg twice-weekly regimen. As external validation, observed concentrations from the 2 regimens (○, 50-mg once weekly; △, 25-mg twice weekly) but not used for the model development are also plotted against simulated concentrations. An overlapping PK profile of 50-mg, once-weekly SC regimen with that of 25-mg, twice-weekly SC regimen is clearly shown.
Design

PK
(N=44 patients)

PK
(N=44 patients),
ACR20, safety

PK,
ACR20, safety

Randomization
N=420

Screening

50 mg qw

50 mg qw

25 mg biw

25 mg biw

placebo

25 mg biw

Week 1

Week 8

Week 16

Arthritis & Rheumatism, 50(2),
February 2004, 353-63

27th of September 2012

Drug development: an introduction to clinical trials
Efficacy and safety results

- When evaluated by ACR20, 50% and 49% of the patients receiving 50 mg of etanercept once weekly and 25 mg of etanercept twice weekly, respectively, responded to the treatments, and these were both statistically significant relative to the 19% response in the placebo group (p < 0.0001 for each etanercept group versus placebo).

- The safety profiles were also comparable between the 2 etanercept regimens.
Thank you