

# Consideration of Factors Affecting the Safety Index in Early Clinical Drug Development

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## Abstract

### Consideration of Factors Affecting the Safety Index in Early Clinical Drug Development

In drug development, a “safety index”, the ratio of the highest exposure which does not induce toxicity to the exposure which exerts efficacy, is used to quantify the balance between the safety and efficacy of a test drug. Here, the Phase 1 Index (maximum area-under-the-curve [AUC] in Phase 1/therapeutic AUC) and no observed adverse effect level (NOAEL) Index (AUC at NOAEL/therapeutic AUC) of recently approved drugs in Japan were calculated and characterized by drug attributes such as therapeutic areas, molecular features (biopharmaceuticals versus chemicals) and indications. For both indices, large variation was observed with a median of 3.2 for the Phase 1 Index and 3.5 for the NOAEL Index. Further, the safety indices were smaller in drugs used to treat infectious diseases and disorders of the nervous system, which might be attributed to the difference in unmet medical needs for certain diseases. Other factors affecting the safety indices would be qualitative aspects of toxicological findings such as severity, seriousness, reversibility, and translatability of the observed toxicities. In a decision-making process regarding further drug development based upon the Phase I results, we need to appropriately interpret the safety indices by considering qualitative aspects of toxicological findings, and then to evaluate the potential benefit-risk balance in light of the target product profile of a test drug, where its clinical positioning is clarified and the acceptable benefit and risk balance is elucidated. This study provides a qualitative measure for interpreting the Phase 1 Index versus the NOAEL Index and might help inform the decision-making process following Phase 1.

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## List of Abbreviations

Abbreviation	Definition
ATC	Anatomical Therapeutic Chemical
AUC	Area-under-the-curve
AUC inf	AUC extrapolated to infinity
AUC ss	AUC over a dose interval at a steady state
CNS	Central Nervous System
CTD	Common Technical Documents for New Drug Application
DDI	Drug-drug interaction
MAD	Multiple ascending dose
NMEs	New molecular entities
NOAEL	No observed adverse effect level
PD	Pharmacodynamics
PK	Pharmacokinetics
PMDA	Pharmaceutical and Medical Device Agency
SAD	Single ascending dose
TI	Therapeutic index



## 1. Introduction

In clinical development, Phase 1 is the first stage where safety, tolerability, pharmacokinetics (PK) and possibly pharmacodynamics (PD) of a test drug are investigated in humans, following required preclinical studies on toxicology, pharmacology and drug metabolism/pharmacokinetics (1). Phase 1 studies are generally conducted in healthy subjects with dose levels increasing in single and multiple administrations. Following Phase 1, we have to decide whether or not safety and tolerability is ensured sufficiently to further advance development, typically to move on to a Proof of Concept study. This decision-making process requires multi-disciplinary knowledge and sometimes raises tough argument from standpoints of research, clinical development and marketing.

To quantify the balance between the safety and efficacy of a test drug, we use a “safety index”, which is the ratio of the highest exposure which does not induce toxicity to the exposure which exerts efficacy. The decision to advance development of a test drug is often undertaken with reference to the safety index throughout the research and clinical development stage, and Phase 1 is the first key milestone in clinical development to decide whether a test drug is worth further developing.

The results of Phase 1 and toxicology studies often challenge us whether or not the obtained safety index is sufficient to advance development, or in other words, whether or not the safety and tolerability when administering a dosage exceeding the therapeutic exposure is sufficiently ensured to proceed with further clinical development. Related to a safety index, the ICH E14 guideline addresses the use of a supratherapeutic dose in the context of the design of a thorough QT/QTc study (2). A thorough QT/QTc study is intended to determine whether or not a test drug has a threshold pharmacological effect on cardiac repolarization, as detected by QT/QTc prolongation. As a supratherapeutic dose, the guideline recommends a

dose that produce concentrations similar to those observed under conditions that produce maximum exposure. Generally, it is needed that the highest Phase 1 dose covers the supratherapeutic dose range. With respect to drug developability, however, no regulatory guidance or systematical research has been drafted to specifically address a standard or appropriate safety index. Muller and Milton previously investigated therapeutic index (TI) determination and interpretation with some examples, along with the progression through drug research and development (3). They emphasized the need to understand the preliminary TI from the lead identification stage onwards, and the fact that TIs should be continuously refined as a test drug progresses from *in vitro* to animal to human studies. Further, they indicated that decisions based on the TI depend on multiple factors that characterize an acceptable risk-benefit profile for the targeted indication of a test drug.

Here, in order to systematically explore factors affecting the safety index, I calculated and characterized the safety indices of recently approved drugs in Japan by attributes such as therapeutic area and indications, and then discussed “point to consider” to interpret the safety indices. Further, I tried to clarify how the safety indices would contribute to the decision-making process following Phase 1.

## 2.Methods

### 2.1. Data Source

I analyzed drugs classified as new molecular entities (NMEs) that were recently approved in Japan. Summary NDA dossiers, review reports and package inserts of NMEs approved between 2008 and 2012 in Japan were obtained from the website of Pharmaceutical and Medical Device Agency (PMDA) (<http://www.pmda.go.jp>). Of the 174 NMEs approved during the period, I excluded the following categories of drugs:

- Anti-cancer drugs
- Endogenous substances, such as hormones and peptides, and their analogues, for which there is previous clinical experience with similar products
- Enantiomer, pro-drugs, or active metabolites of approved drugs
- Drugs not intended for systemic administration
- Drugs with little or no absorption
- Vaccines
- Drugs approved in other countries before 2000
- Drugs with a scarcity of research data

I excluded anti-cancer drugs, as cancer patients are normally subjects for Phase 1 studies, and evaluation on safety versus potential benefit is generally different with anti-cancer drugs from drugs in other therapeutic areas (4).

Then the following information was collected:

- Highest tolerable AUC extrapolated to infinity (AUC inf) from single ascending dose (SAD) studies conducted.

- Highest tolerable AUC/day over a dose interval at a steady state (AUC ss) for multiple ascending dose (MAD) studies conducted.
- Approved maximum dose in Japan and AUC ss at that dose. I collected the AUC ss from the contents of CTD (Common Technical Documents for New Drug Application) 2.6.6 for each drug if exposure comparison between humans and animals was performed in that section. When that was not the case, we collected the AUC ss from PK studies with patients or healthy volunteers.
- NOAEL and AUC ss at the NOAEL (rodent and non-rodent) were determined in 13 weeks of repeated toxicology studies. If these data were not available, data were then collected from 4 weeks or more than 13 weeks of studies.

The AUC of an unchanged drug was basically used in this study. I also used the highest AUC tested if no information on tolerability was obtained. A Phase 1 study was adopted regardless of the countries in which the study was carried out.

## 2.2. Data Analysis

Figure 1 shows the general relationship of the dose range of a Phase 1 first-in-human study, target therapeutic dose, and NOAEL in animal toxicology studies. From a safety viewpoint, NOAEL and toxicological findings with toxicokinetics obtained from repeated toxicology studies are the major determinants for setting the dose range in first-in-human studies. From an efficacy viewpoint, the target therapeutic dose is generally obtained prior to first-in-human studies via translation of information on the pre-clinical PK-PD relationship into humans. The target therapeutic dose is then modified based on the clinical PK and PD data.

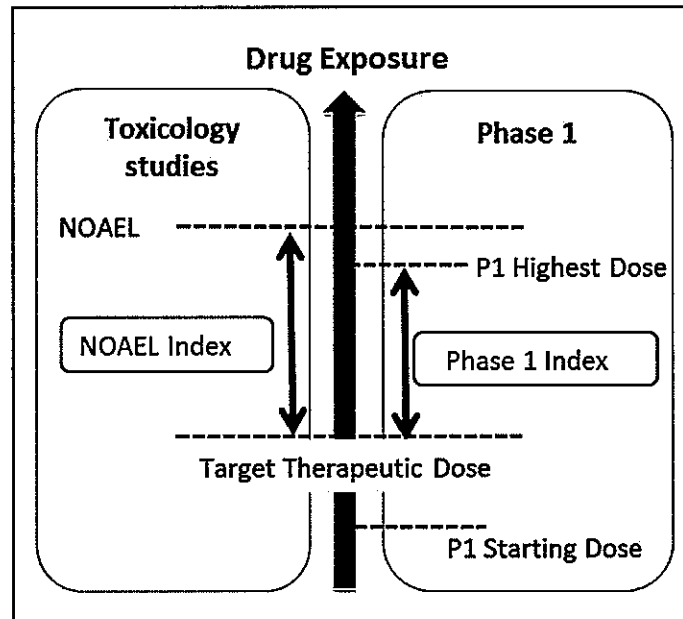
I utilized the NOAEL Index and Phase 1 Index as safety indices and each index was calculated as follows:

Phase 1 Index = maximum AUC in Phase 1<sup>1)</sup>/AUC ss at the maximum approved dose

NOAEL Index = AUC ss at NOAEL<sup>2)</sup>/AUC ss at the maximum approved dose

<sup>1)</sup> Highest AUC of the AUC inf for SAD or the AUC ss for MAD

<sup>2)</sup> AUC of the most sensitive animal species (the mean of male and female)



**Figure 1. Relationship of Phase 1 dose range, target therapeutic dose and no observed adverse effect level (NOAEL).**

### 2.3. Analysis of the Phase 1 Index and NOAEL Index

Summary statistics of the Phase 1 Index and NOAEL Index were calculated, and the relationship between the two indices was investigated. The obtained Phase 1 Index and NOAEL Index were stratified based on the drug attributes of the Anatomical Therapeutic Chemical (ATC) code, therapeutic indication, administration route, molecular features (biopharmaceuticals versus chemicals), and “orphan drug” designation. Classification by the ATC code was applied when at least 5 drugs had the same ATC code. Drugs for which no ATC code had been assigned were categorized to the appropriate ATC main group for research purpose. Analysis was performed via StatsDirect statistical software (version 2.7.9, StatsDirect Ltd., Cheshire, U.K.).

### 3. Results

#### 3.1. New molecular entities (NMEs) analyzed in this study

Of the 174 NMEs approved in Japan between 2008 and 2012, 60 were analyzed in the present study (Table 1). The breakdown of the excluded drugs was as follows: anti-cancer drugs, 24; endogenous substances, 8; enantiomer, pro-drugs, or active metabolites of approved drugs, 11; drugs not intended for systemic administration, 14; drugs with no or little absorption, 3; vaccines, 14; drugs for no main therapeutic purpose, 9; drugs approved in other countries before 2000, 25; and drugs lacking sufficient research data, 6.

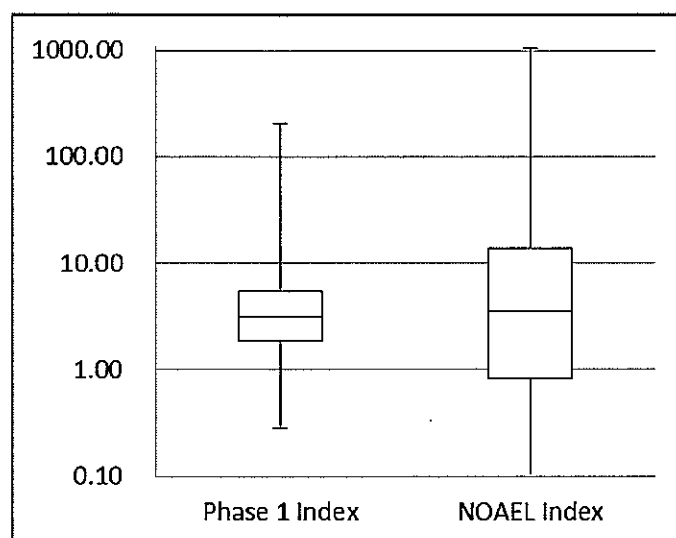


**Table 1. New molecular entities (NMEs) analyzed in this study**

Abatacept	Daptomycin	Lubiprostone	Rivaroxaban
Adalimumab	Duloxetine	Maraviroc	Rivastigmine
Aliskiren	Edoxaban	Memantine	Romiplostim
Alogliptin	Eltrombopag	Minodronic acid	Rotigotine
Ambrisentan	Etravirine	Mirabegron	Sitafloxacin
Anagliptin	Exenatide	Nalfurafine	Sitagliptin
Apixaban	Febuxostat	Omalizumab	Tebipenem pivoxil
Aprepitant	Fingolimod	Palonocetron	Telaprevir
Azilsartan	Galantamine	Peramivir	Teneligliptin
Bazedoxifene	Golimumab	Pirfenidone	Teriparatide
Blonanserine	Iguratimod	Pregabalin	Thrombomodulin alfa
Canakinumab	Indacaterol	Raltegravir	Tigecycline
Caspofungin	Laninamivir octanoate	Ramelteon	Tolvaptan
Certolizumab pegol	Linagliptin	Rasburicase	Ustekinumab
Dabigatran etexilate	Liraglutide	Rilpivirine	Vildagliptin

### 3.2. Phase 1 Index and NOAEL Index

Summary statistics of the Phase 1 Index and NOAEL Index are shown in Table 2 and their boxplots in Figure 2. Both indices exhibited large variation, and the geometric mean and median for each were as follows: Phase 1 Index, 3.7 and 3.2 and NOAEL Index, 3.8 and 3.5. The inter-quartile range of the Phase 1 Index was 1.9 to 5.4 and that of the NOAEL Index was 0.8 to 13.8. The relationship between the NOAEL Index and the Phase I Index is shown in Figure 3. Linear regression analysis for NOAEL Index and Phase 1 Index showed no statistically significant correlation (spearman's rank correlation coefficient = 0.238, p value = 0.0888).

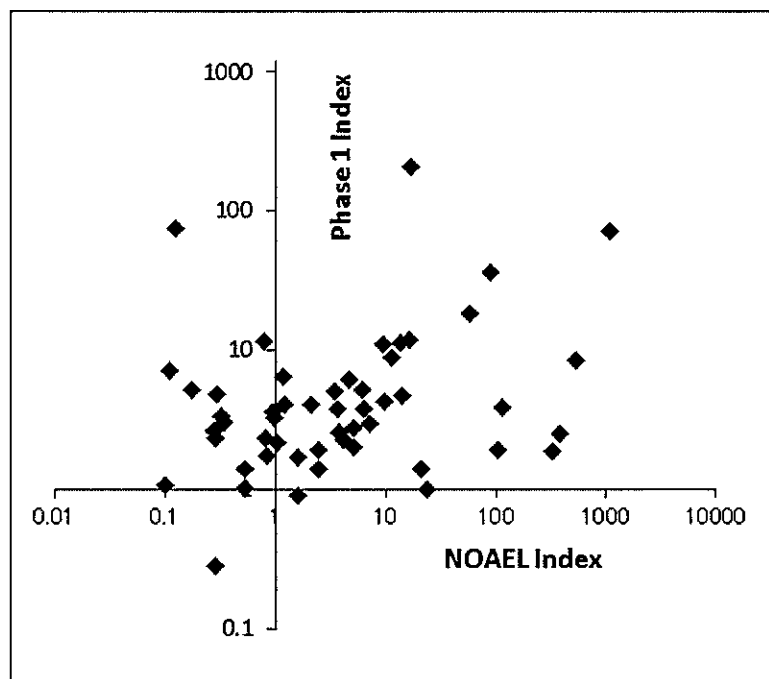


**Figure 2. Phase 1 Index and NOAEL Index for drugs investigated.**

**Table 2. Phase 1 Index and NOAEL Index**

	Phase 1 Index (n=60)	NOAEL Index (n=52) <sup>1)</sup>
<b>Geometric mean</b>	3.7	3.8
<b>Median (minimum-maximum)</b>	3.2 (0.3-204.7)	3.5 (0.1-1067.3)

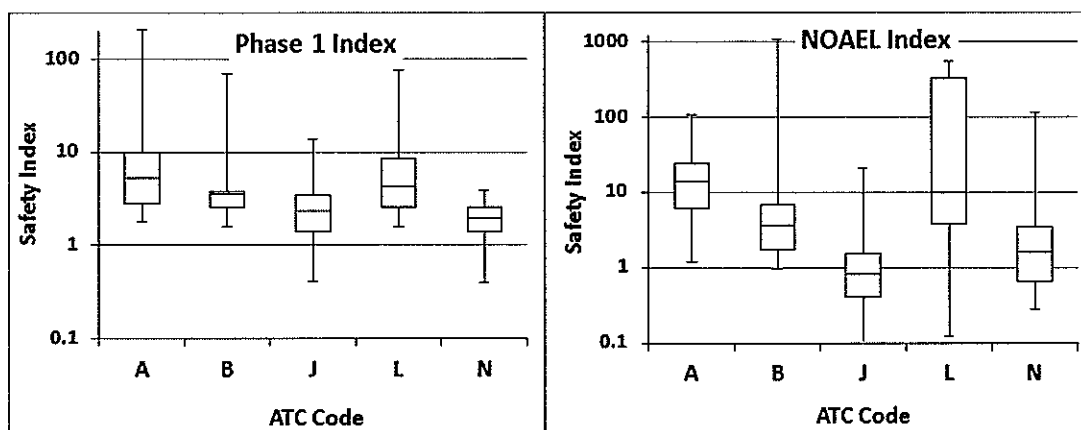
<sup>1)</sup> NOAEL Index of 8 drugs out of 60 could not be determined.



**Figure 3. Plot of Phase 1 Index versus NOAEL Index of the 52 drugs.**

### 3.3. Classification by ATC code

The indices were classified by ATC code as shown in Figure 4, and the median of the Phase 1 Index for each was as follows: A, alimentary tract and metabolism (5.2); B, blood and blood-forming organs (3.6); J, anti-infectives for systemic use (2.3); L, antineoplastic and immunomodulating agents (4.2); and N, nervous system (2.0). In contrast, the median of the NOAEL Index for indices as classified by ATC code were as follows: A, alimentary tract and metabolism (13.7); B, blood and blood forming organs (3.6); J, anti-infectives for systemic use (0.8); L, antineoplastic and immunomodulating agents (9.8); and N, nervous system (1.6). Although a high degree of variation was observed in the Phase 1 Index and NOAEL Index, the median of the Phase 1 Index and NOAEL Index were smaller in drugs used to treat infectious diseases and disorders of the nervous system.

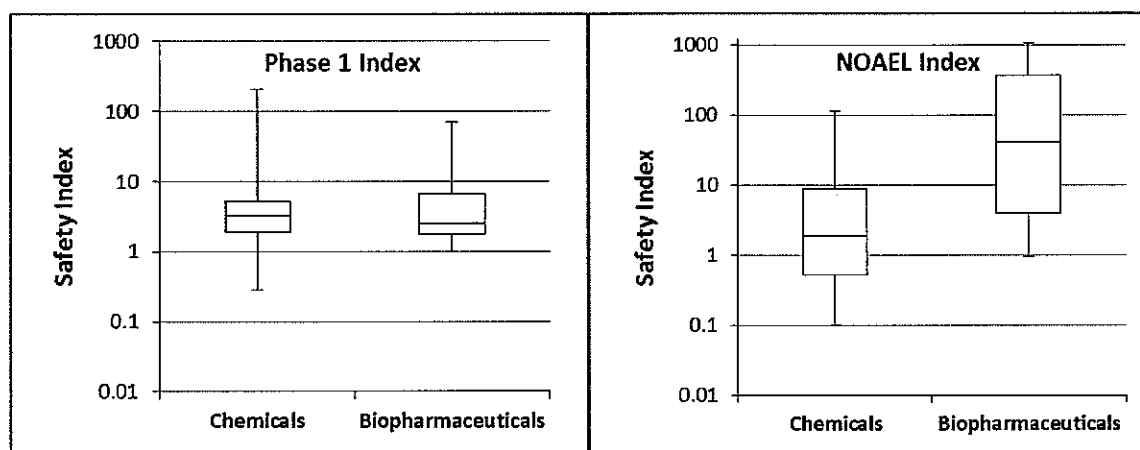


**Figure 4. Phase 1 Index and NOAEL Index classified by ATC codes.**

The ATC codes and the number of the Phase I Index and NOAEL Index were as follows: A, alimentary tract and metabolism (n=11 and n=9); B, blood and blood-forming organs (n=7 and n=7); J, antiinfectives for systemic use (n=12 and n=11); L, antineoplastic and immunomodulating agents (n=9 and n=9); and N, nervous system (n=8 and n=6).

### 3.4. Classification by molecular features (biopharmaceuticals versus chemicals)

Comparison of the Phase I Index and NOAEL Index between chemicals and biopharmaceuticals is shown in Figure 5. Results showed that the median of the NOAEL Index of biopharmaceuticals was larger than that of chemicals, with no notable differences in the Phase 1 Index. The median of the Phase I Index and NOAEL Index for both types of drugs were as follows: chemicals, 3.3 and 1.9 and biopharmaceuticals, 2.5 and 41.3. The Phase 1 Index and NOAEL Index was calculated for monoclonal antibodies, which accounted for half (6 out of 12 drugs) of the biopharmaceuticals examined. The median of the Phase 1 Index for monoclonal antibodies was 2.5, while that of the NOAEL Index was 194.4. Regarding the route of administration, the NOAEL Index on subcutaneous administration was larger than that on oral or intravenous administration. The median values of the Phase I Index for each route of administration were as follows: oral (3.8), subcutaneous (2.3) and intravenous administration (2.8). In contrast, median values of the NOAEL Index were as follows: oral (1.6), subcutaneous (104.5) and intravenous administration (1.0).



**Figure 5. Comparison of safety indices between chemicals (Phase 1 Index, n=48 and NOAEL Index, n=42) and biopharmaceuticals (Phase 1 Index, n=12 and NOAEL Index, n=10).**



### 3.5. Classification by administration route and “orphan drug” designation

Comparison of the Phase I Index and NOAEL Index among administration routes (PO, SC and IV) are shown in Figure 6, and that between orphan and non-orphan drugs in Figure 7. No notable differences in the Phase I Index were observed among administration routes, while the NOAEL Index in SC administration was larger than those in other administration routes. Regarding “orphan drug” designation, there were no remarkable differences in both safety indices.

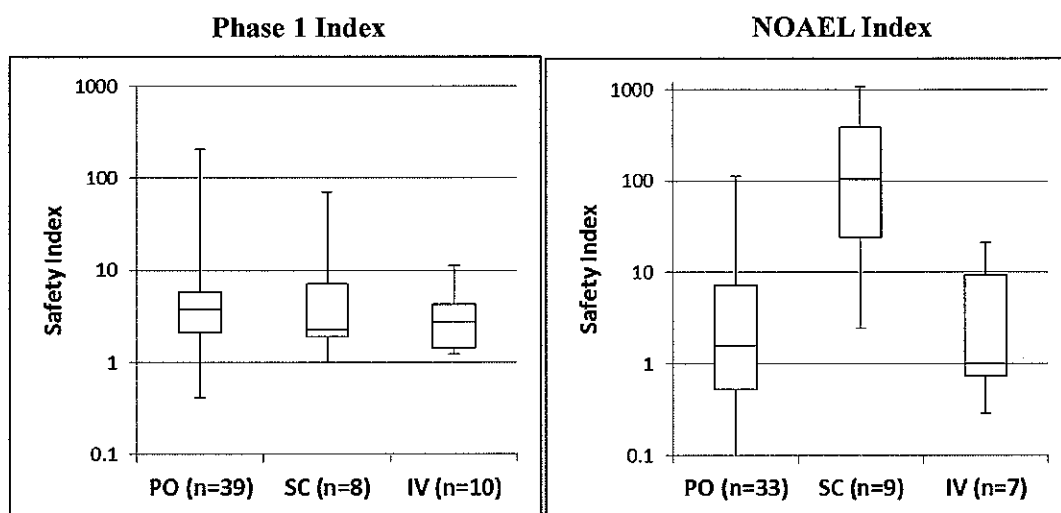


Figure 6. Comparison of safety indices among administration routs (PO, SC and IV).

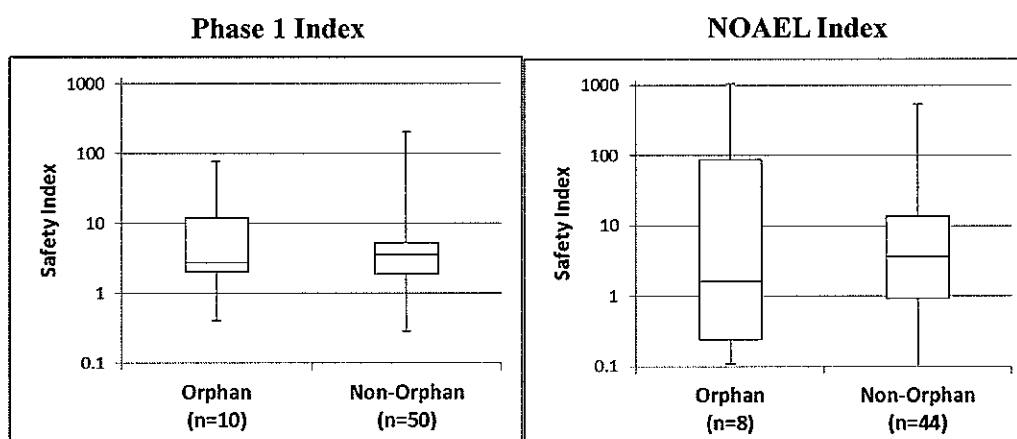


Figure 7. Comparison of safety indices between orphan and non-orphan drugs.

### 3.6. Drugs with both a Phase 1 Index and NOAEL Index of less than 3

Table 3 shows a list of drugs with both a Phase 1 Index and NOAEL Index of less than 3. Generally, lower safety indices indicate a greater likelihood of adverse events, as the drugs are sensitive to increases in exposure. Looking at the list, drugs used to treat infectious diseases or disorders of the nervous system and orphan drugs have been observed to be the majority of “the smaller index group”.

**Table 3. List of drugs with a Phase 1 Index and NOAEL Index below 3**

Drug	Indication	Phase 1 Index	NOAEL Index	ATC Code <sup>1)</sup>	Orphan
Daptomycin	MRSA infection	2.3	0.3	J	–
Tigecycline	Multiple drug resistant infection	1.4	0.5	J	–
Maraviroc	HIV-1 infection	2.3	0.8	J	+
Sitafloxacin	Newquinolone antimicrobial	1.0	0.5	J	–
Telaprevir	Chronic hepatitis C	1.1	0.1	J	–
Tebipenem pivoxil	Carbapenem antibiotic	1.7	0.8	J	–
Rotigotine	Parkinson's disease, Idiopathic restless legs syndrome	0.3	0.3	N	–
Pregabalin	Neuropathic pain	1.7	1.6	N	–
Blonanserin	Schizophrenia	0.9	1.6	N	–
Memantine	Alzheimer's disease	2.4	ND (<0.5) <sup>2)</sup>	N	–
Ambrisentan	Pulmonary arterial hypertension	0.4	ND (<1) <sup>2)</sup>	C	+
Eltrombopag Olamine	Chronic idiopathic thrombocytopenic purpura	1.9	2.4	B	+
Dabigatran etexilate	Prevention of ischemic stroke and systemic embolism	2.2	1.1	B	–
Pirfenidone	Idiopathic pulmonary fibrosis	2.7	0.3	L	+
Omalizumab	Bronchial Asthma	1.4	2.5	R	–

<sup>1)</sup> B, blood and blood forming organs; C, cardiovascular system; J, antiinfectives for systemic use; L, antineoplastic and immunomodulating agents; N, nervous system; R, Respiratory system

<sup>2)</sup> Could not be determined

## 4. Discussion

### 4.1. Relationship between the Phase I Index and NOAEL Index

The Phase I Index and NOAEL Index both exhibit a large degree of variation. Classification by ATC code showed that these indices were affected by the therapeutic area and the median of the safety indices were smaller in drugs used to treat infectious diseases and disorders of the nervous system. The median of the NOAEL Index of the biopharmaceuticals was larger than that of chemicals, with no notable differences in the Phase I Index.

Investigation of the relationship between the NOAEL Index and Phase I Index revealed that there was no significant positive correlation (Figure 3). This may be relevant to the fact that no maximum tolerable doses were defined in most of the drugs studied. The NOAEL Index may be an index for scientific facts obtained from toxicology studies, while the Phase I Index has a strategic aspect on the foundation of integrated assessment of clinical and preclinical safety information.

#### 4.2. Consideration on the Phase 1 Index

The inter-quartile range of the Phase 1 Index was 1.9 to 5.4, which indicates that safety and tolerability are confirmed exceeding the therapeutic exposure. This finding may be relevant to the recommended use of supra-therapeutic dose in the context of the thorough QT/QTc study design. Generally, a suprathreshold dose is a dose that produces maximum exposure in a so called “worst case scenario,” which includes but is not limited to plasma concentration increase by the concomitant use of drugs with metabolic inhibition potential, and administration to poor metabolizers and special population (e.g. elderly patients, patients with renal/hepatic impairment). For example, when *in vitro* metabolism data of a test drug suggest the predominant contribution of CYP3A4 to total body clearance of humans, the possible impact of drug-drug interaction (DDI) in clinical development is often determined by clinical DDI studies with strong inhibitors such as ketoconazole, followed by studies with moderate or weak inhibitors when required (5-6). Consideration is therefore required when deciding if the Phase 1 Index is sufficient in terms of “coverage of suprathreshold dose.”

#### 4.3. Consideration on the NOAEL Index

In contrast, the inter-quartile range of the NOAEL Index was 0.8 to 13.8, and the NOAEL Indices of 20 drugs were less than 1. This finding suggests that the safety and tolerability of the drugs were clinically investigated by exceeding the drug exposure of the NOAEL Index based on the assessment of clinical findings observed in Phase 1 and the nature of pre-clinical toxicity. Although the NOAEL Index calculated from most sensitive animal species may have a conservative aspect, it does not mean that a NOAEL Index lower than 1 is generally acceptable to proceed with clinical development. Here, no qualitative analysis of toxicity was taken into consideration. As such, appropriate interpretation of the NOAEL Index requires consideration of the following qualitative aspects: toxicological findings and their severity, seriousness and reversibility, and species uniqueness of observed toxicities.

For example, the median of the Phase 1 Index of aprepitant is 3.6, while that of the NOAEL Index could not be determined. A 14-week repeated toxicology study in rats indicated that NOAEL was less than 5 mg/kg/day, where the toxicological finding at 5 mg/kg/day was vacuolar degeneration of the thyroid follicular cell. Since this finding was thought to be a change secondary to the hepatic enzyme induction in rats, the applicant explained in the NDA dossier that translatability of the histopathological change into humans was low.

Due to serious toxicological findings such as convulsion, an exposure cap in Phase 1 studies is sometimes set below NOAEL to ensure safety, with the maximum possible clinical exposure not being limited by NOAEL. The interpretation of the NOAEL Index from the standpoint of translation into humans is therefore important for appropriately exploring safety and tolerability in Phase 1 studies and discussing the transition to the next clinical phase.

#### 4.4. Comparison of the safety indices between chemicals and biopharmaceuticals

The comparison of the safety indices between chemicals and biopharmaceuticals are shown in Figure 5. The NOAEL Index of biopharmaceuticals is larger than that of chemicals, while there appears to be no notable difference in the Phase 1 Index. This difference was more notable for monoclonal antibodies. This property might be due to the poorer quantitative translatability of biopharmaceuticals. In toxicology studies for biopharmaceuticals, relevant animal species that express the desired epitope and demonstrate a tissue cross-reactivity profile similar to that of human tissues have been used in accordance with the ICH S6 (R1) guideline (7), optimizing the ability to evaluate toxicity arising from the binding to the epitope and any unintentional tissue cross-reactivity. In addition, when a Phase 1 study is planned, especially a first-in-human study, the relevance and limitations on the quantitative translatability of toxicological data into humans need to be taken into consideration (8-10). To ensure an ascending dose level in a Phase 1 study, PD markers such as target binding or occupancy are often monitored, in addition to evaluation based on safety index. This approach is important to not only understanding whether or not drug exposure is sufficient to exert pharmacological effects, but also avoiding on-target toxicity, by integrating preclinical pharmacological and toxicological findings. The NOAEL Index in subcutaneous administration was larger than that of oral and intravenous administration, possibly due to the subcutaneous dosing routes of biologics with a higher NOAEL Index.

In 2006, very serious adverse reactions occurred in the first-in-man clinical trial of TGN412 in London (11). TGN1412 is an agonistic anti-CD28 monoclonal antibody that was being developed as a medicine to treat leukaemia and autoimmune diseases such as rheumatoid arthritis. An initial dose, which was set 1/500 of NOAEL in cynomolgus monkey, was given to healthy volunteers and all volunteers developed a cytokine release syndrome



with multi-organ failure and required intensive treatment and supportive measures. This is a case of the poorer quantitative translatability of biopharmaceuticals.

#### 4.5. Features of drugs with a Phase 1 Index and NOAEL Index of less than 3

Drugs with a Phase 1 Index and NOAEL Index of less than 3 are listed in Table 3. The majority of this list consists of drugs used to treat infectious disease and defects of the nervous system as well as orphan drugs and is consistent with the outcome of stratified analysis by ATC code. In Japan, orphan drugs are indicated for the treatment of serious diseases, including difficult-to-treat diseases, for which there are a limited number of patients (< 50,000). Benefit-risk balance in this category may result in relatively low Phase I and NOAEL Indices.

Nervous system disorders have been acknowledged to have a high degree of unmet medical needs (12-17), and CNS (Central Nervous System) drug development is believed to be more challenging and have a higher risk than other indications. Reasons for this include a lack of knowledge of fundamental biology and pathophysiological underpinnings of many CNS disorders, and high use of subjective diagnosis and primary endpoints. Further, low tolerability is sometimes observed, which leads to a lower Phase 1 Index due to the nature of the target molecule.

Here, the drugs for infectious diseases categorized in “the smaller index group” including HIV-1 infection (orphan designation), multi-drug resistant infection and chronic hepatitis C, which are considered to have a high degree of unmet medical needs. Of note, the NOAEL Index was smaller than that of the Phase 1 Index. Dabigatran etexilate has been used as an oral anticoagulant to satisfy unmet medical needs. While warfarin has been widely used as an anti-coagulant, it has a narrow safety margin and is difficult to handle due to its

interaction with food and drugs and frequent laboratory monitoring. As mentioned above, it was suggested that a common feature of “the smaller safety index category” is for diseases with a low standard of care and a high degree of unmet medical needs.

The Phase 1 Index and NOAEL Index of 6 drugs (DPP4 inhibitors) indicated for type 2 diabetes was calculated and the median of the indices were 7.6 and 8.8, respectively, which indicates that the median of these safety indices were larger than that for all drug examined (Table 2). This finding may be due to a higher standard of patient care, more manageable conditions, and a more competitive market.

#### 4.6. Importance of accurately predicting a target therapeutic dose

When calculating safety indices, it is also of importance to predict a target therapeutic dose as accurately as possible. The application of pharmacokinetic/pharmacodynamics (PK/PD) modeling and simulation would support it (18-19), although the present study did not address this point. Recently PK/PD modeling and simulation has been applied not only to the late phase development, but also to the preclinical and early phase clinical drug development. Integrating preclinical and clinical data, its application in the early development helps us to predict a target therapeutic dose range.

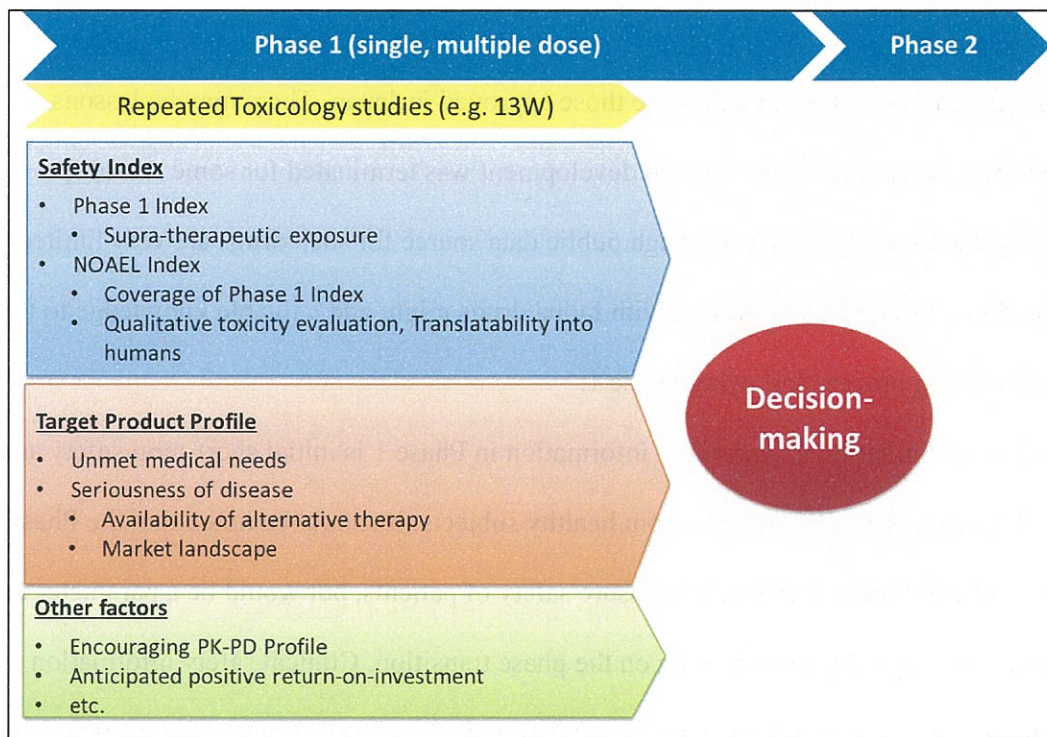
#### 4.7. Factors affecting decision-making process following Phase 1

In a decision-making process regarding further drug development based upon the Phase 1 results, safety indices play a key scientific element. Firstly, we need to appropriately interpret the safety indices by considering qualitative aspects of toxicological findings (e.g. severity, seriousness, reversibility, and translatability of the observed toxicities). Secondly, it is important to evaluate the potential benefit-risk balance in light of the target product profile of a test drug, where its clinical positioning is clarified and the acceptable benefit and risk balance is elucidated for the decision-making. For example, when sufficient Phase 1 Index (safety/tolerability at supra-therapeutic exposure) is not obtained due to the lack of tolerability/safety and/or low NOAEL Index, it may be considered difficult to further advance the development. In that case, however, we need to evaluate the benefit-risk balance in light of the target product profile. If unmet medical needs like seriousness of the targeted disease condition and availability of alternative effective therapeutic options outweigh the possible safety concerns, a test drug could move on to Phase 2. From a scientific perspective, PD data in Phase 1, for instance, biomarker measurements and PET (positron emission tomography) target occupancy studies to show the proof of pharmacology in humans, would support the decision making. Encouraging clinical PD findings would affect the decision in a positive way, and PK/PD modeling and simulation would support the quantitative decision making, integrating pre-clinical PK/PD data.

Besides scientific evaluation, it needs to be noted that the likelihood of the return-on-investment of a test drug generally affects the decision making. Factors affecting the return-on-investment include but are not limited to drug development cost, marketability of a test drug and the success probability of clinical development. If there are some safety issues, the clinical development strategy may be more complicated and the risk of failure as

well as the development cost would be higher. From a financial perspective, marketability enough to recover the possible investment may be one of the important factors for the decision-making. As I mentioned earlier, orphan drugs are a component in “the smaller index category” (see Table 3). When a test drug qualifies as an orphan drug, the government provides various development incentives for the sponsor (e.g. subsidies, guidance and consultation, longer market exclusivity period). It is an important option in clinical development strategy to utilize the orphan drug/medical device designation system to satisfy the unmet medical needs, by providing therapeutic options for the treatment of serious diseases.

As mentioned above, there are multiple factors affecting the decision-making following Phase 1 (Figure 8). The safety indices are a key determinant from a safety standpoint, and in terms of efficacy, positive PD data encourage a transition of a test drug to Phase 2. Financially, the return-on-investment is another important factor. Multi-disciplinary discussion should be a critical success factor for the appropriate decision-making.



**Figure 8. Decision-making process following Phase 1.**

#### 4.8. Limitation

Drugs analyzed in this study were those approved in Japan. There may be lessons learned from analyzing drugs of which development was terminated for some reasons, especially due to safety issues, although public data source for such drugs are very limited. If the situation allows, further research with failed drugs might add valuable knowledge to the decision-making process following Phase 1.

Another limitation is that safety information in Phase 1 is initial short-term safety and tolerability data generally obtained from healthy subjects. It should be noted that the Phase 1 Index is not a definitive parameter to ensure safety of patients, but would be a parameter to support the strategic decision-making on the phase transition. Clinical safety information needs to be accumulated in large patient population during the clinical development and post-marketing.

## 5. Conclusion

In the present study, the Phase 1 Index and NOAEL Index of drugs recently approved in Japan were calculated and characterized based on drug attributes such as therapeutic area (ATC code), molecular features (chemicals versus biopharmaceuticals), route of administration and indication. Our results indicated that the safety and tolerability of the drugs examined here were ensured in Phase 1 at an exposure exceeding the therapeutic exposure by 3.2 fold (the median of Phase 1 Index). The Phase 1 Index and NOAEL Index were both affected by the therapeutic area, which might be due to the difference in unmet medical needs for certain diseases. Further, qualitative aspects of toxicological findings need to be considered to interpret the safety indices. In conclusion, this study provides a qualitative measure for interpreting the Phase 1 Index versus the NOAEL Index and might help inform the multi-disciplinary decision-making process following Phase 1.

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## Appendix

Appendix 1. List of individual data in a descending order for Phase 1 Index

INN	Phase 1 Index	NOAEL Index	Orphan drug designation	ATC code <sup>1)</sup>	Dosing route	Molecular feature <sup>2)</sup>
Linagliptin	204.7	17.0	-	A	po	c
Fingolimod	75.6	0.1	+	L	po	c
Romiplostim	70.5	1067.3	+	B	sc	b
Alogliptin	36.1	89.8	-	A	po	c
Adalimumab	18.3	58.8	-	L	sc	b
Rilpivirine	13.7	ND	+	J	po	c
Tolvaptan	11.9	16.7	-	C	po	c
Mirabegron	11.6	0.8	-	G	po	c
Palonocetron	11.3	13.7	-	A	iv	c
Indacaterol	11.0	9.5	-	R	po	c
Teneligliptin	8.8	11.5	-	A	po	c
Ustekinumab	8.5	540.1	-	L	sc	b
Etravirine	7.1	0.1	+	J	po	c
Sitagliptin	6.5	1.2	-	A	po	c
Abatacept	6.1	4.7	-	L	iv	b
Anagliptin	5.2	6.1	-	A	po	c
Aliskiren	5.1	0.2	-	C	po	c
Febuxostat	5.0	3.4	-	M	po	c
Nalfurafine	4.9	0.3	-	V	po	c
Bazedoxifene	4.7	14.2	-	G	po	c
Iguratimod	4.2	9.8	-	L	po	c
Vildagliptin	4.1	1.2	-	A	po	c
Laninamivir octanoate	4.1	2.1	-	J	inhalation	c

Ramelteon	3.9	113.6	-	N	po	c
Edoxaban	3.8	6.4	-	B	po	c
Apixaban	3.8	3.6	-	B	po	c
Aprepitant	3.6	ND	-	A	po	c
Thrombomodulin alfa	3.6	0.9	-	B	iv	b
Minodronic acid	3.3	0.3	-	M	po	c
Caspofungin	3.2	1.0	-	J	iv	c
Duloxetine	3.1	0.3	-	N	po	c
Rivaroxaban	3.0	7.2	-	B	po	c
Raltegravir	2.8	5.1	+	J	po	c
Pirfenidone	2.7	0.3	+	L	po	c
Certolizumab pegol	2.6	3.7	-	L	sc	b
Golimumab	2.5	382.6	-	L	sc	b
Memantine	2.4	ND	-	N	po	c
Daptomycin	2.3	0.3	-	J	iv	c
Maraviroc	2.3	0.8	+	J	po	c
Rivastigmine	2.3	4.2	-	N	patch	c
Dabigatran etexilate	2.2	1.1	-	B	po	c
Teriparatide	2.0	No data	-	H	sc	b
Azilsartan	2.0	5.2	-	C	po	c
Exenatide	1.9	104.5	-	A	sc	c
Eltrombopag	1.9	2.4	+	B	po	c
Canakinumab	1.9	330.1	+	L	sc	b
Tebipenem pivoxil	1.7	0.8	-	J	po	c
Pregabalin	1.7	1.6	-	N	po	c
Galantamine	1.6	No data	-	N	po	c
Peramivir	1.4	20.9	-	J	iv	c

Tigecycline	1.4	0.5	-	J	iv	c
Omalizumab	1.4	2.5	-	R	sc	b
Rasburicase	1.2	No data	-	V	iv	b
Telaprevir	1.1	0.1	-	J	po	c
Sitafloxacin	1.0	0.5	-	J	po	c
Liraglutide	1.0	23.9	-	A	sc	b
Lubiprostone	1.0	No data	-	A	po	c
Blonanserin	0.9	1.6	-	N	po	c
Ambrisentan	0.4	ND	+	C	po	c
Rotigotine	0.3	0.3	-	N	patch	c

<sup>1)</sup> A, alimentary tract and metabolism; B, blood and blood-forming organs; C, cardiovascular system; G, genito urinary system and sex hormones; H, systemic hormonal preparations, excl. sex hormones and insulins; J, antiinfectives for systemic use; L, antineoplastic and immunomodulating agents; M, musculo-skeletal system; N, nervous system; R, respiratory system; and V, various

<sup>2)</sup> c, chemicals; b, biopharmaceuticals.

Appendix 2. List of individual data in descending order for NOAEL Index

INN	Phase 1 Index	NOAEL Index	Orphan drug designation	ATC code <sup>1)</sup>	Dosing route	Molecular feature <sup>2)</sup>
Teriparatide	2.0	No data	-	H	sc	b
Galantamine	1.6	No data	-	N	po	c
Rasburicase	1.2	No data	-	V	iv	b
Lubiprostone	1.0	No data	-	A	po	c
Rilpivirine	13.7	ND	+	J	po	c
Aprepitant	3.6	ND	-	A	po	c
Memantine	2.4	ND	-	N	po	c
Ambrisentan	0.4	ND	+	C	po	c
Romiplostim	70.5	1067.3	+	B	sc	b
Ustekinumab	8.5	540.1	-	L	sc	b
Golimumab	2.5	382.6	-	L	sc	b
Canakinumab	1.9	330.1	+	L	sc	b
Ramelteon	3.9	113.6	-	N	po	c
Exenatide	1.9	104.5	-	A	sc	c
Alogliptin	36.1	89.8	-	A	po	c
Adalimumab	18.3	58.8	-	L	sc	b
Liraglutide	1.0	23.9	-	A	sc	b
Peramivir	1.4	20.9	-	J	iv	c
Linagliptin	204.7	17.0	-	A	po	c
Tolvaptan	11.9	16.7	-	C	po	c
Bazedoxifene	4.7	14.2	-	G	po	c
Palonocetron	11.3	13.7	-	A	iv	c
Teneligliptin	8.8	11.5	-	A	po	c
Iguratimod	4.2	9.8	-	L	po	c

Indacaterol	11.0	9.5	-	R	po	c
Rivaroxaban	3.0	7.2	-	B	po	c
Edoxaban	3.8	6.4	-	B	po	c
Anagliptin	5.2	6.1	-	A	po	c
Azilsartan	2.0	5.2	-	C	po	c
Raltegravir	2.8	5.1	+	J	po	c
Abatacept	6.1	4.7	-	L	iv	b
Rivastigmine	2.3	4.2	-	N	patch	c
Certolizumab pegol	2.6	3.7	-	L	sc	b
Apixaban	3.8	3.6	-	B	po	c
Febuxostat	5.0	3.4	-	M	po	c
Omalizumab	1.4	2.5	-	R	sc	b
Eltrombopag	1.9	2.4	+	B	po	c
Laninamivir octanoate	4.1	2.1	-	J	inhalation	c
Pregabalin	1.7	1.6	-	N	po	c
Blonanserin	0.9	1.6	-	N	po	c
Vildagliptin	4.1	1.2	-	A	po	c
Sitagliptin	6.5	1.2	-	A	po	c
Dabigatran etexilate	2.2	1.1	-	B	po	c
Caspofungin	3.2	1.0	-	J	iv	c
Thrombomodulin alfa	3.6	0.9	-	B	iv	b
Tebipenem pivoxil	1.7	0.8	-	J	po	c
Maraviroc	2.3	0.8	+	J	po	c
Mirabegron	11.6	0.8	-	G	po	c
Tigecycline	1.4	0.5	-	J	iv	c
Sitafloxacin	1.0	0.5	-	J	po	c



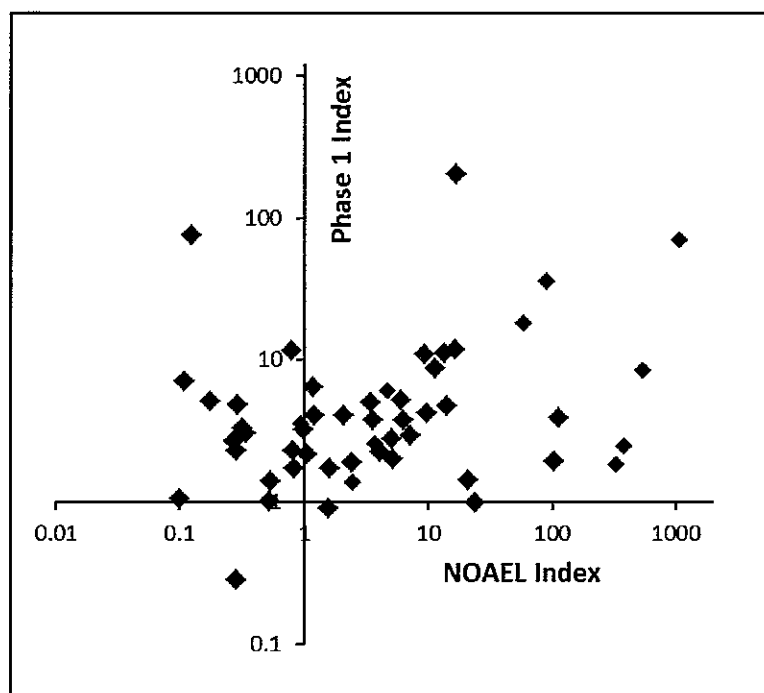
Duloxetine	3.1	0.3	-	N	po	c
Minodronic acid	3.3	0.3	-	M	po	c
Nalfurafine	4.9	0.3	-	V	po	c
Daptomycin	2.3	0.3	-	J	iv	c
Rotigotine	0.3	0.3	-	N	patch	c
Pirfenidone	2.7	0.3	+	L	po	c
Aliskiren	5.1	0.2	-	C	po	c
Fingolimod	75.6	0.1	+	L	po	c
Etravirine	7.1	0.1	+	J	po	c
Telaprevir	1.1	0.1	-	J	po	c

<sup>1)</sup> A, alimentary tract and metabolism; B, blood and blood-forming organs; C, cardiovascular system; G, genito urinary system and sex hormones; H, systemic hormonal preparations, excl. sex hormones and insulins; J, antiinfectives for systemic use; L, antineoplastic and immunomodulating agents; M, musculo-skeletal system; N, nervous system; R, respiratory system; and V, various

<sup>2)</sup> c, chemicals; b, biopharmaceuticals.



Appendix 4. Plot of Phase 1 Index versus NOAEL Index of the 52 drugs, in which biopharmaceuticals are indicated in red.



Appendix 5. Plot of Phase 1 Index versus NOAEL Index of the 52 drugs, in which drugs with a Phase 1 Index and NOAEL Index below 3 are indicated in red, and drugs (DPP4 inhibitors) for type 2 diabetes in blue.

