Toxicity and Dose Escalation / Progression Rules in Integrated Protocols

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Medicines and Healthcare Products Regulatory Agency

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Following the triggering of Article 50, the MHRA will continue to play a full, active role in European regulatory procedures.

We will continue to contribute in both the centralised and decentralised regulatory procedures, including new rapporteur and RMS appointments and to maintain the programme for implementing the clinical trial regulation.

We will be actively engaged in European and national scientific advice services.

We will continue to provide the full service that companies in the UK have come to expect from us. We also continue to participate fully in EU inspection related duties.

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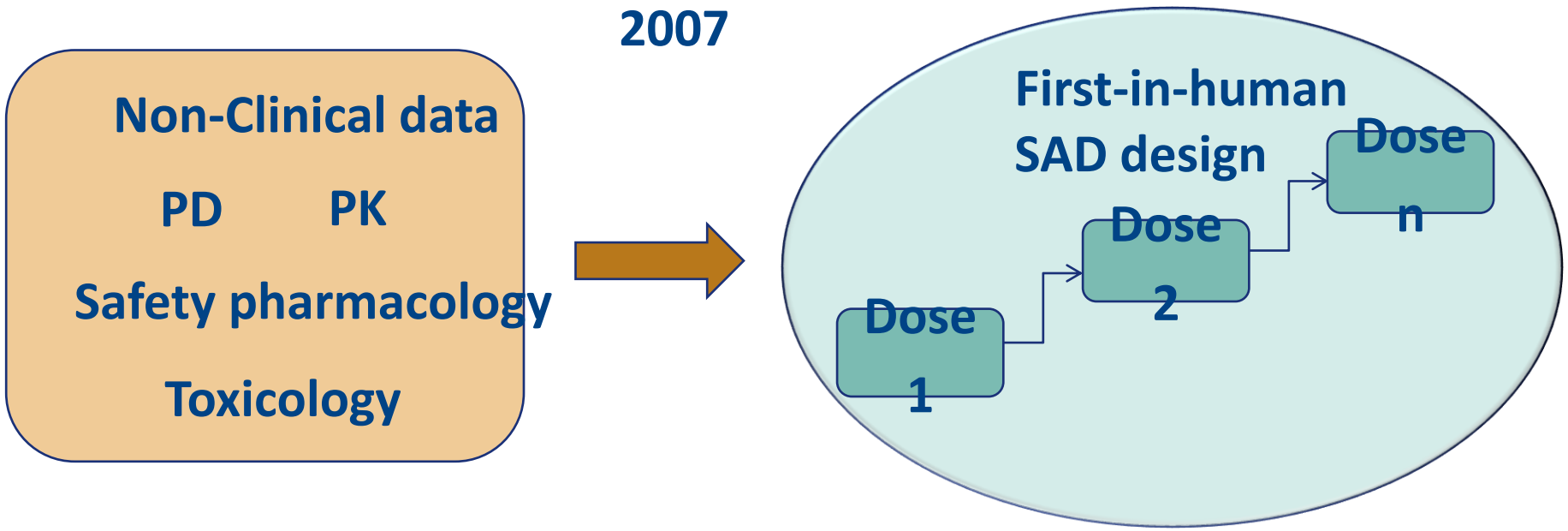
The EMA co-ordinated two reviews, one nonclinical and on clinical into the incident.

The EU nonclinical experts had access to the IB and the primary reports.

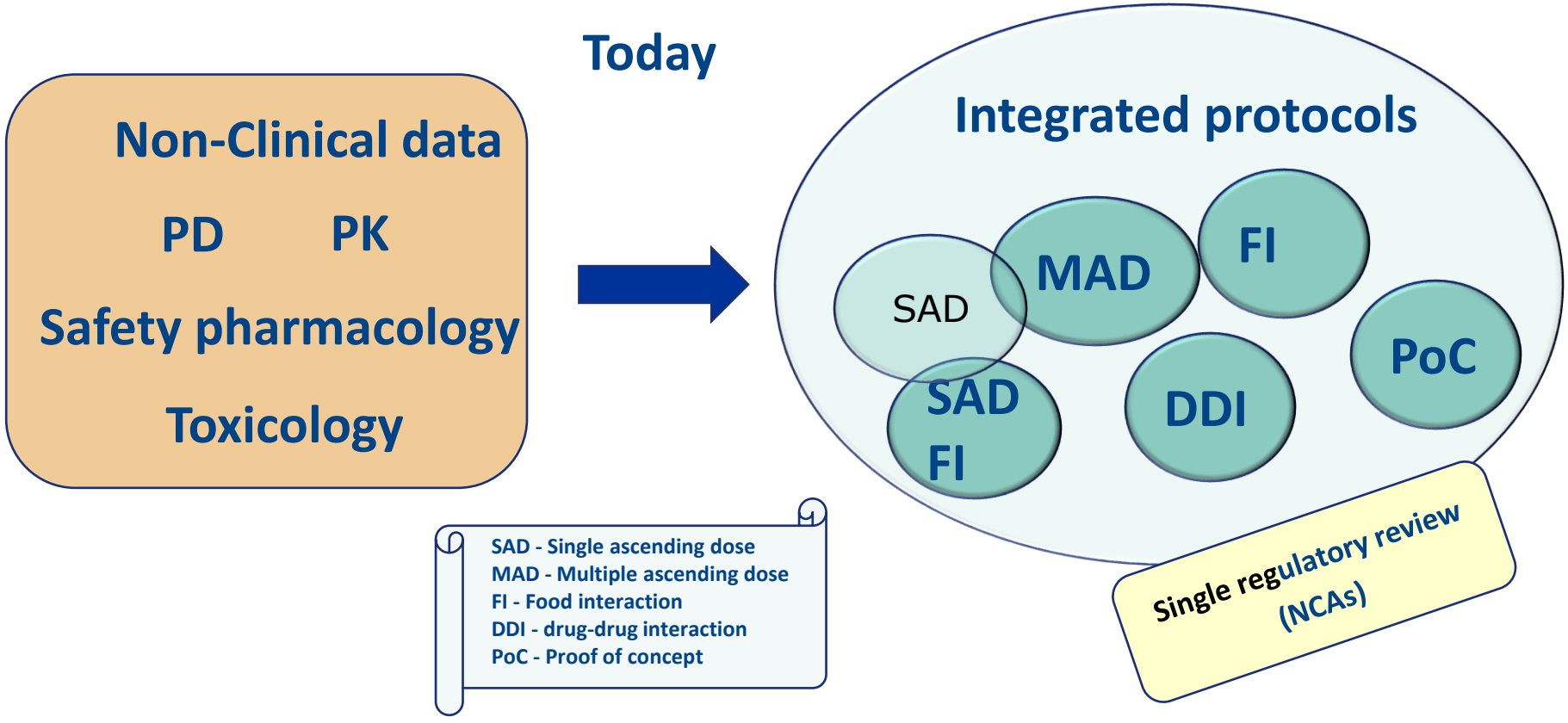
The IB was initially on the ANSM, the French medicines agency, website but has now been removed. Primary reports have not been released for public examination.

Following the review, it was decided to revise the 2007 Risk Mitigation guideline.

- **Evolution of practices for FIH clinical trials**



Increasing trend to perform FIH dosing within integrated protocols



Guideline revision - aims

- Update in line with current practice CT designs
- Promote a more effective early drug development
- Support better use of totality of available data before and during clinical trials
- Safeguard of study participants

Table of contents

2007

2016/2017

The revision of the guideline has not called for an increase in the amount of nonclinical data required to support FIH trials.

HOWEVER, THE GUIDELINE HAS AGAIN EMPHASISED THE CRITICAL VALUE OF PHARMACOLOGY AND THE MODE OF ACTION OF AN IMP.

When planning FIH/early CTs, sponsors and investigators should identify the potential factors of risk and apply appropriate risk mitigation strategies.

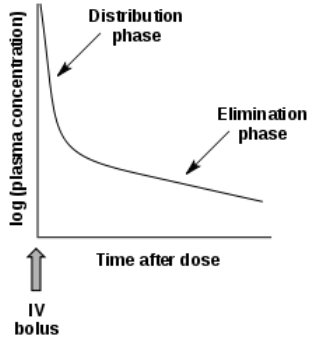
- Primary PD address mode of action related to therapeutic use; knowledge on interaction of IMP with intended target / related targets
  - Target interactions preferably linked to functional response
    - Receptor binding / occupancy, enzyme inhibition, duration & (ir)reversibility, dose-response relationships, physiological target turn-over
- Selectivity, specificity, secondary PD incl. downstream/physiologically integrated endpoints
- Dose/concentration-response curve of PD effects established
- State-of-the-art PK/PD modelling recommended
- Proof of concept; support to safety assessment

Pharmacokinetics

- PK & TK as *per* ICH guidelines S3, S6(R1), S9, M3(R2) available in all species used for pivotal non-clinical safety studies
- Support interpretation of non-clinical data

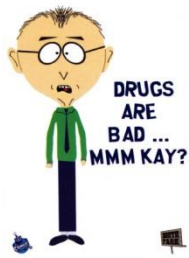
Safety pharmacology

- Standard core battery before first administration in humans, as *per* ICH S7A, S7B, S6(R1), S9, M3(R2)
- Additional studies case-by-case basis



Toxicology, as *per* ICH M3(R2), S6 or S9

- Studies in relevant species, include Toxicokinetics
- Toxicity can be due to exaggerated PD – BUT don't ignore when establishing starting dose / dose escalation range !
- PD can support mechanistic explanations of toxicity findings; help interpretation of human relevance of findings
- Target organs - warrant particular monitoring ?
- Serious toxicity - more cautious approach for dose selection
- Mortalities and/or serious toxicity followed up carefully in toxicity studies incl. *e.g*. histopathological examination of deceased animals



Useful Information from non- clinical safety studies

- Target organ of toxicity
- Dose /exposure – toxicity relationship
- Reversibility?
- NOAEL - No Observed Adverse Effect Level (?)
- Systemic exposure (TK) data
- Adequate to characterise potential adverse effects that might occur under conditions of clinical trial to be supported

Careful dosing selection of an IMP is a vital element to safeguard the subjects participating in FIH and early CTs.

Special attention should be given to the estimation of the exposure anticipated to be reached at the initial dose to be used in humans and to subsequent dose escalations to a predefined maximum expected exposure.

It should be noted that the expected exposure in humans at a dose to be given, in comparison to the exposure at which certain effects were observed in animals or earlier in the study in humans, is considered more relevant than the relative dose levels between animals and humans.

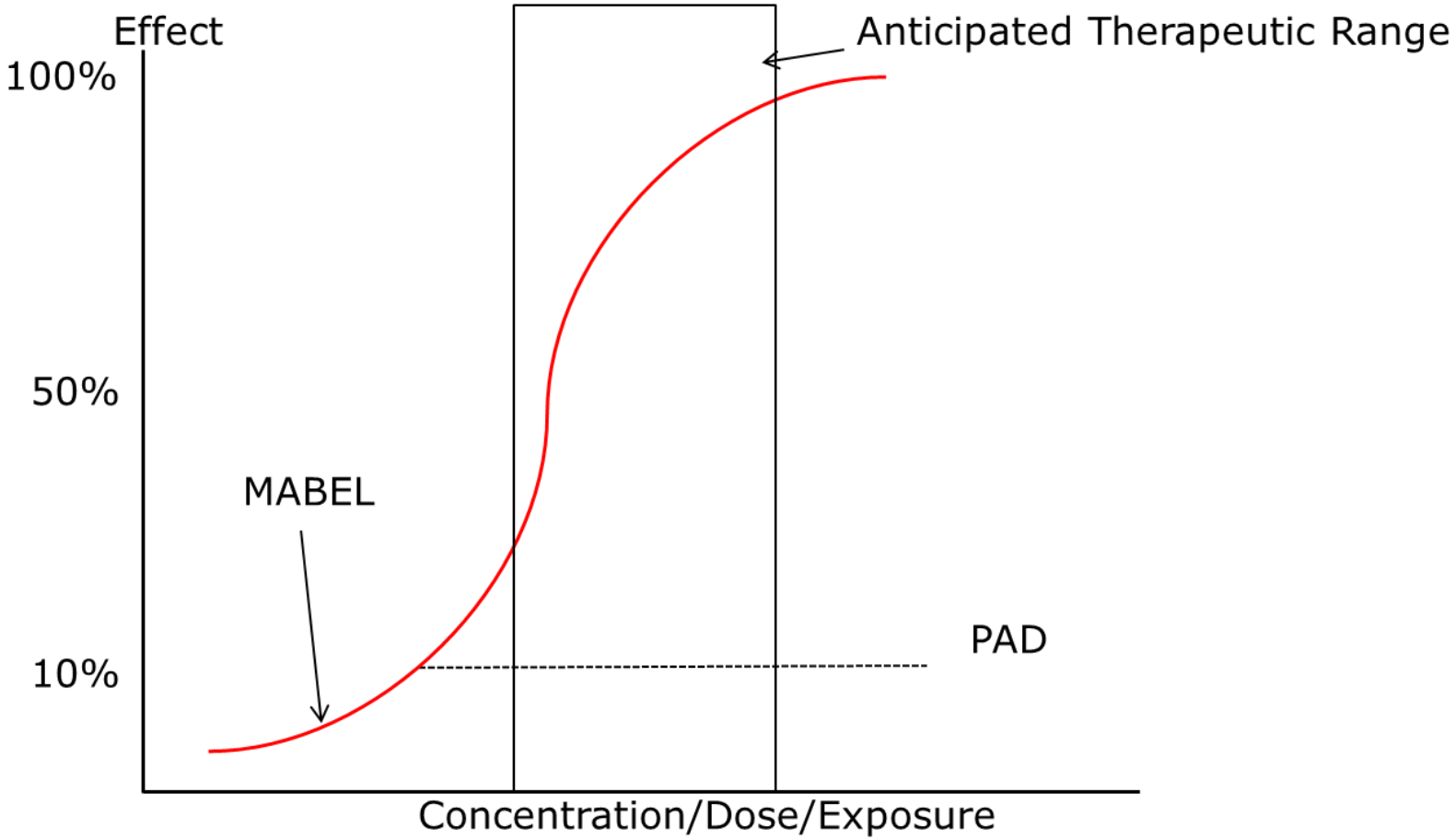
The planned dosing selection should also take into account a reasonably rapid attainment of the trial objectives without exposing excessive numbers of subjects.

The starting dose and a maximum exposure, as well as dose escalation steps during the CT, should be justified and outlined in the protocol.

Decision-making criteria for adapting the planned dose escalation steps based on emerging clinical data should also be described in detail.

Starting Dose Estimation

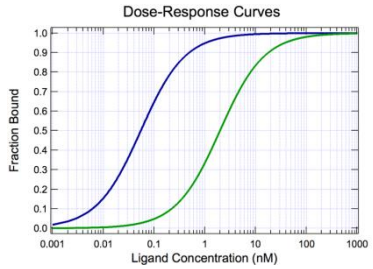
- Exposures at NOAEL in most relevant species used to estimate equivalent exposure for humans
  - State-of-art modelling (*e.g.* PK/PD and PBPK); allometric factors.
- Exposure at PD effects in relevant PD studies
  - MABEL (Minimal anticipated biological effect level); PAD (pharmacologically active dose); ATD (anticipated therapeutic dose) range in humans
  - Species differences into account
- Safety Factors
  - The novelty of the active substance, pharmacodynamic characteristics, the relevance of the animal models, uncertainties related to the estimation of the MABEL, PAD and the expected exposure in humans.


Effect
100%
50%
10%
Anticipated Therapeutic Range
MABEL
PAD
Concentration/Dose/Exposure

The starting dose for healthy volunteers should be a dose expected to result in an exposure lower than the PAD, unless a robust justification can be made for a higher dose.

Depending on the level of uncertainty regarding the human relevance of findings observed in nonclinical studies and the knowledge of the intended target, the starting dose should either be related to the MABEL, PAD or NOAEL.

A justification for the starting dose should be included in the protocol and may be included in the IB.



Similar considerations also apply for the identification of a safe starting dose in patients.

The goal of selecting the starting dose for FIH/early CTs in patients, *i.e*. where there are no previous data in healthy volunteers, is to identify a dose that is expected to have a minimal pharmacological effect and is safe to use.

The starting dose should also take into account the nature of disease under investigation and its severity in the patient population included in the CT.
In some instances, a starting dose that is substantially lower than the human expected therapeutic dose **may not be appropriate**.

Dosing Escalation

Criteria for dose increases during a CT should be outlined in the protocol.

The maximum fold increase in dose/exposure from one cohort to the next, as well as a maximum number of cohorts to be evaluated, should be stated.

The dose increment between two dose levels should be guided by the dose/exposure-toxicity or the dose/exposure-effect relationship defined in the non-clinical studies and adapted following review of emerging clinical data from previous cohorts.

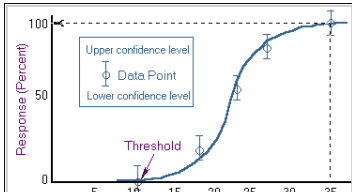


FIGURE 1: Typical Sigmoid Dose-Response Relationship

Dosing Escalation

The size of the dose increments should take into account the steepness of the dose/exposure-toxicity or dose/exposure-effect curves and uncertainties in the estimation of these relationships.

Furthermore, if there is evidence of non-linear PK potentially resulting in a supra-proportional increases in exposure, smaller dose increments, particularly in the later parts of SAD/MAD, should be considered.

If emerging clinical data reveal substantial differences from non-clinical or modelling and simulation data, adjustment of the planned dose levels may be warranted.

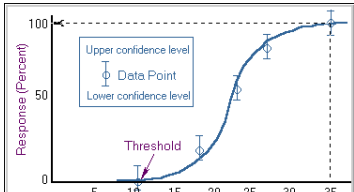


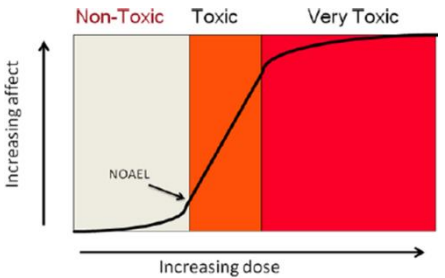
FIGURE 1: Typical Sigmoid Dose-Response Relationship

Maximum Exposure and Dose

An expected maximum exposure level, which should not be exceeded in the study without approval of a substantial amendment, should be pre-defined in the protocol for each study part.

This is usually based on the NOAEL in the most relevant nonclinical species.

The maximum exposure should be justified based on all available data, including PD, PK, findings in toxicity studies and exposure at the expected therapeutic dose range.

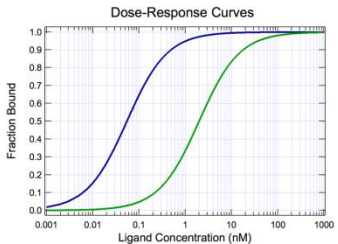


Maximum Exposure and Dose

In general, the maximum exposure of healthy volunteers should be within the estimated human pharmacodynamic dose range.

However, exposure levels exceeding the pharmacodynamic dose range can, if scientifically justified and considered acceptable from a safety perspective, be carefully explored, taking into consideration uncertainties/risk factors.

For trials or trial parts that include patients, the maximum tolerated dose (MTD), if applicable, should be **clearly defined and not be exceeded once it has been determined**.



For integrated protocols, criteria to move from one part to another should be predefined in the protocol.

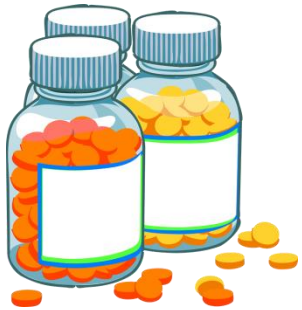
When definite doses cannot be predefined in all study parts, dose selection criteria should be included in the protocol.

These criteria should integrate CLINICAL data from previous study parts.

Moving from Single to Multiple Dosing

The selection of an appropriate dosing interval and duration of dosing for all multiple dosing cohorts and study parts should take into account the specific PK and PD characteristics of the IMP, the available non-clinical safety data, and all data from subjects in previous single dose cohorts.

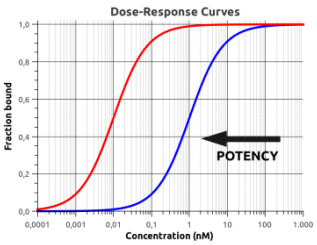
Particular attention should be paid to linear *versus* non-linear PK in the expected concentration range, the PK half-life *versus* duration of action, and the potential for accumulation.



Multiple dosing parts can explore different dosing regimens and schedules, such as a move from once daily dosing to twice daily dosing.

A maximum duration of dosing should be stated in the protocol for every cohort. The expected exposure after multiple dosing should have been covered during preceding SAD parts/trials.

If, however, emerging clinical data following multiple dosing suggests tolerance to adverse effects seen in a SAD part of a study, higher exposures in a MAD part can be considered, provided this option is pre-specified and below the set maximum exposure, or by a substantial amendment to the protocol .




AND THAT'S MY LAST SLIDE. ANY COMMENTS?
Dilbert.com DilbertCartoonist@gmail.com
YOU STOLE AN HOUR OF MY LIFE. SOMETHING INSIDE ME DIED. I WILL NEVER HAVE ANOTHER GOOD DAY.
zzzz
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I WENT IN WITH LOW EX-PECTA-TIONS.
AVOIDS THE DELUSION THEY WANT TO LISTEN TO YOU!

Any Questions ?

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