Confirmation of extrapolation based on PK/PD data and modeling

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Reflection Paper – *Validation/Confirmation*

- As well as potentially answering questions related to efficacy in and of themselves, **the data observed in the target population** as part of the extrapolation plan **should be used to validate the extrapolation concept** […]
- specifically to **validate the modelling approaches and assumptions** used for extrapolation, and to confirm the PK and PD predictions, the predicted **degree of differences** (or understanding) in disease progression, and in clinical response.

Case study HIV – Background

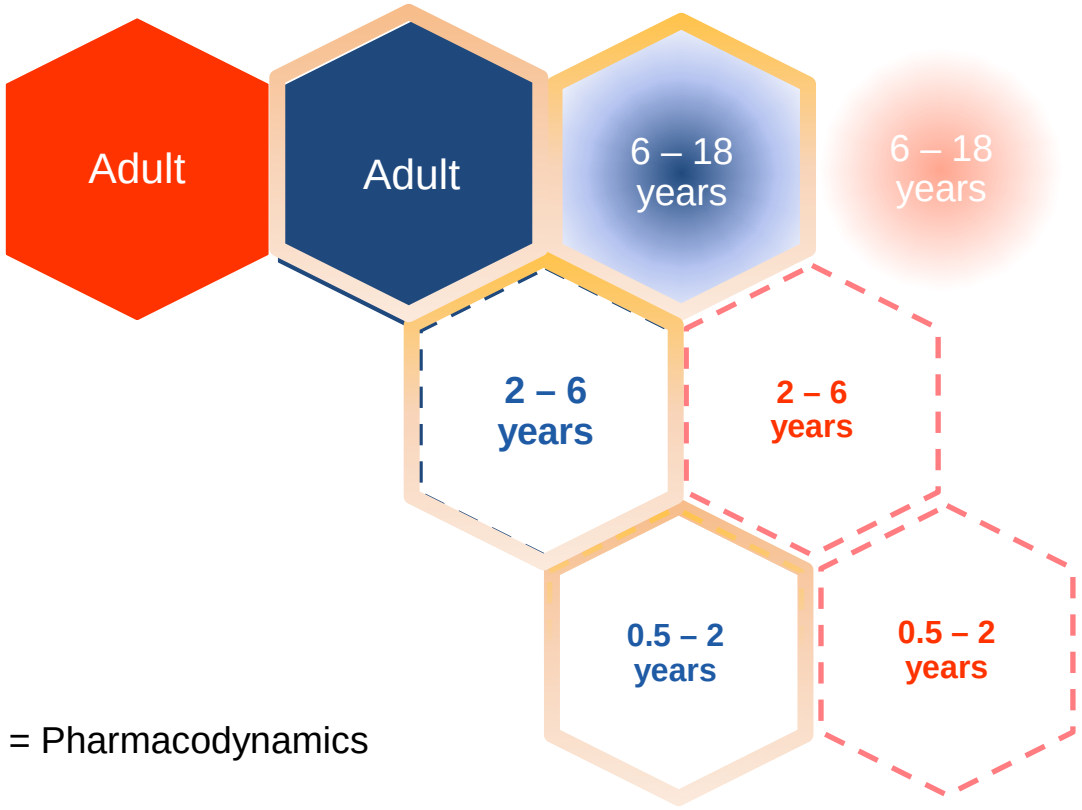
- Drug X is approved for adults and children >12 years for the treatment of HIV-1 virus infection
- For extrapolation to children in this therapeutic area, the draft guideline states:
  - *“it is assumed that the PK/PD relation for a direct acting antiviral is roughly similar regardless of the age of the patient”*
- Pharmacokinetics can then be used to bridge efficacy from adults to children

* Draft Guideline on the clinical development of medicinal 4 products for the treatment of HIV infection, EMA 2013

The pediatric development program

- A pediatric clinical study of pharmacokinetics (PK), safety, tolerability and antiviral activity is ongoing
- Age-defined cohorts from <18 years down to 4 weeks of age are studied sequentially
- At this stage, data are available from children 12 – 18 and 6 – 12 years of age
- The objective is determine a posology that will result in an exposure in children that is comparable to adult patients

PKPD backbone for Case 1 (Tx of HIV – 1)



= Pharmacodynamics

= Pharmacokinetics

= model

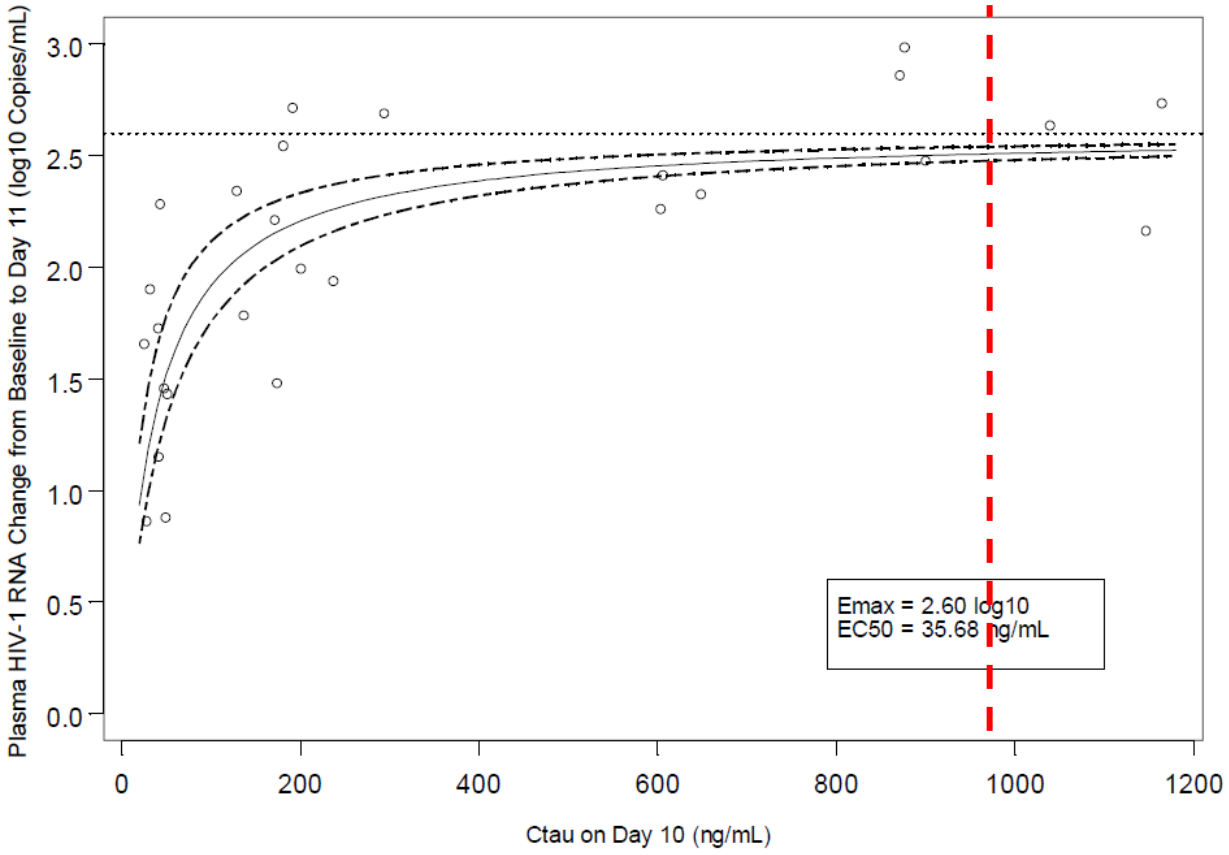
Degree of uncertainty

= not available

(some of the) Assumptions

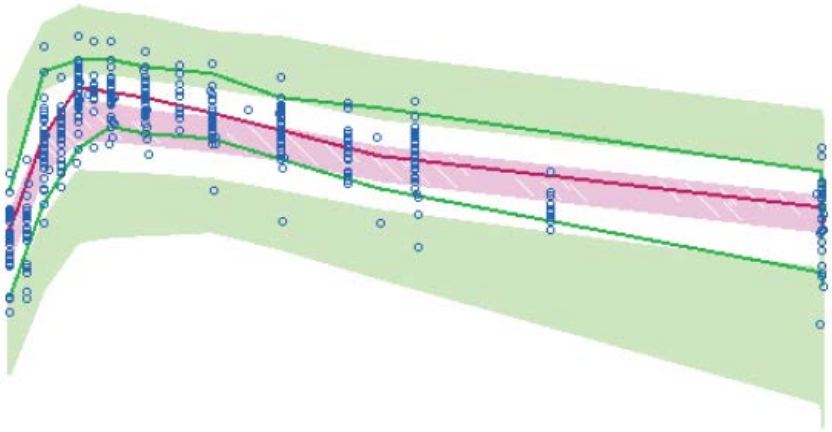
- Observed PK (e.g. AUC, Cmin, Cmax) can be used as a surrogate marker for antiviral activity
- Observed PK can be approximated by a model built on principles of clinical pharmacokinetics (absorption, distribution, metabolism/elimination)
- The individual PK will depend on body size and organ maturation (in children < 1 year of age)
- The variability in PK is similar between adults and children

Observed PK (e.g. AUC, Cmin, Cmax) can be used as a surrogate marker for antiviral activity



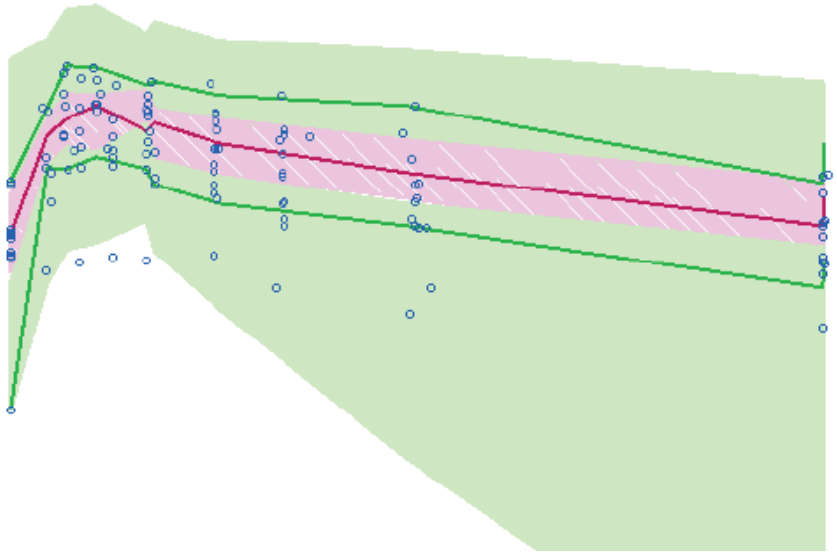
Observed PK can be approximated by a model

Bad fit?



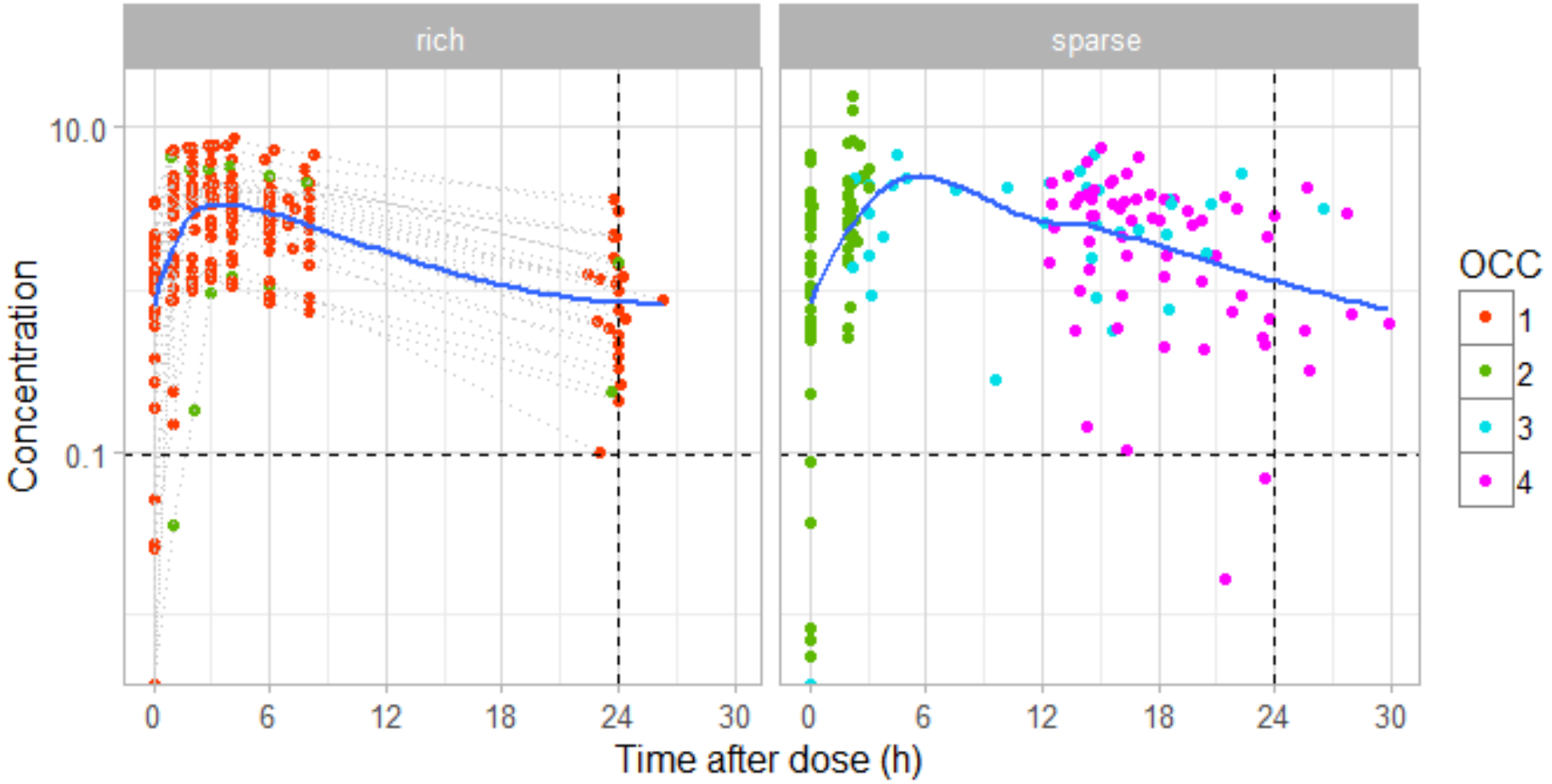
Adult patients: more data, less uncertainty, visible bias

Good fit?

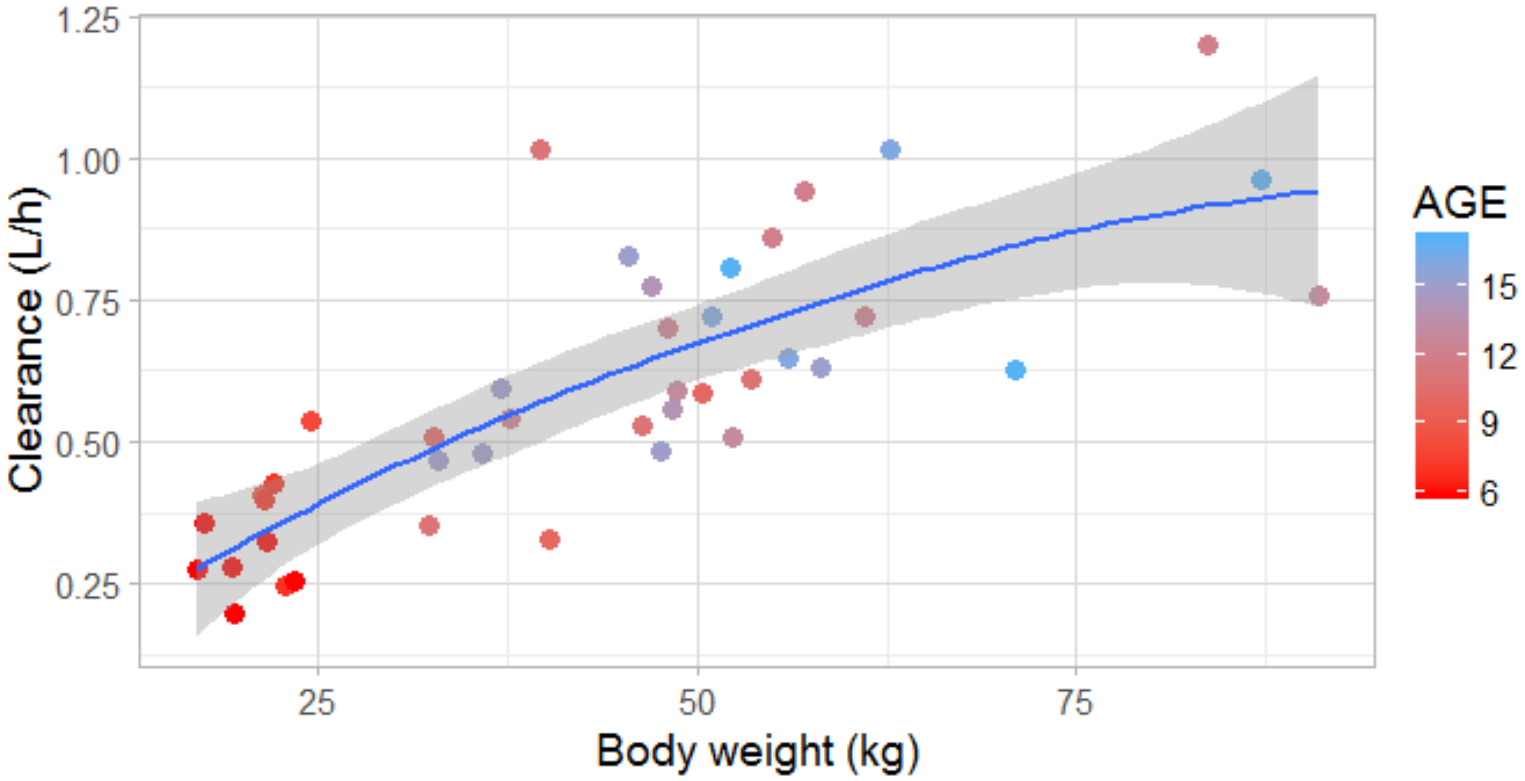


Children, 6 months to 1 year of age: less data, more uncertainty, bias not seen

The variability in PK is similar between adults and children



The individual PK will depend on body size (and organ maturation)



Reflection paper: *Optimising decision making when patients are scarce*

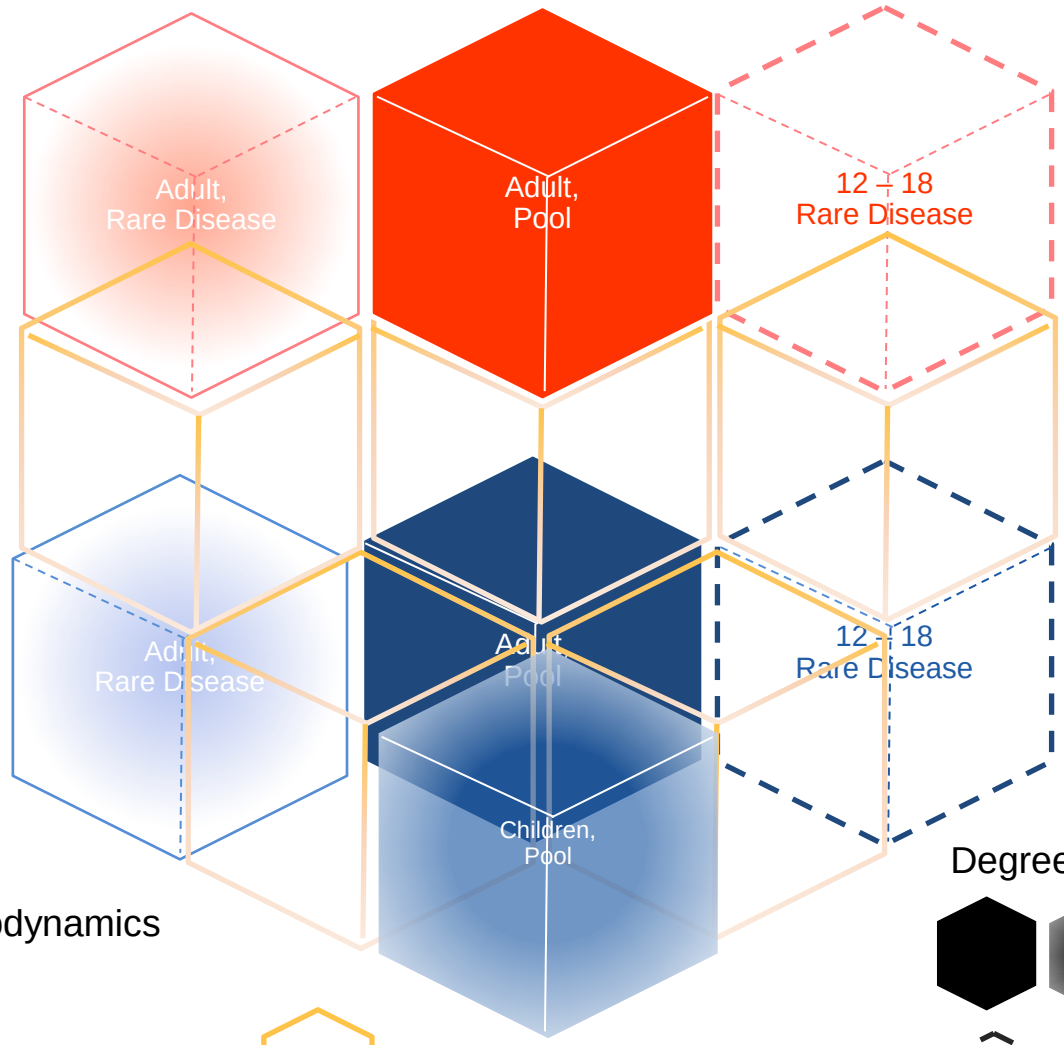
- […] less conventional and/or less commonly seen methodological approaches may be acceptable *if they help to improve the interpretability* of the study results.
- In small populations, it is even more important to ensure that all the *available scientific knowledge is summarised in advance*,
- In this situation the extrapolation principles and tools may be applied for a rational interpretation of the limited evidence in the target population in the context of *data from other sources*.
- By *systematic synthesis of evidence* from the source population(s) and explicit quantification of the differences between populations, the robustness of data generated in the target population can be better quantified, and conclusions drawn for the target population.

Case 2: Rare Disease

- Chronic inflammatory disease
- Onset typically > 12 years of age
- The same characteristical clinical signs and symptoms are seen in adults and adolescents
- A monoclonal antibody has been approved in the EU (and the US) for treatment of the rare disease in adult patients
- The MAH is now seeking approval for extending the indication to children 12 – 18 years of age

Rare Disease cont'd

- "*EMA's Paediatric Committee (PDCO) agreed that clinical trials in subjects with [the rare disease] below the age of 18 years would not be feasible due to the rarity of this disease in this population, but that extrapolation was appropriate based on the similarity of [the rare] disease in adults and adolescents*"
- How can PKPD (modeling and simulation) be utilized to support extrapolation in the *complete absence* of data in the Target population?



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When the mind is in a state of uncertainty,
the smallest impulse directs it to either side.