

Single dose of ab123 for treatment of alzheimer's disease



INTRODUCTION

Design a single dose study of AB123 based on preclinical data. AB123 is belonging to a neurological class of molecule called beta-C kinin which enhance production of brain derived neurotropic factor. In Alzheimer's disease its production is diminish. AB123 clinical indication is amelioration of cognitive dysfunction associate with Alzheimer disease. Study conduct in mouse, rat, dog and monkey AB123 enhance LPT in rat and transgenic mouse model of AD rat and monkey with entrohinal cortex damage showed improvement in learning and memory performance compare to control animal.

Preclinical study gives all nonclinical pharmacokinetics, toxicokinetic and metabolism. Where non clinical pharmacokinetic testing done in rat, dogs and monkey by IV and oral administration, show good bioavailability approximately 100% in rats, 55% in dogs and 70% in monkey half life was 6 hour in rats and 10 hour in monkey. AB123 major metabolic transformation is hydroxylation in inactive metabolite then glucoronidation. Substance get from glucoronidation is known as glucoronide their water solubility is higher so it's easily eliminate through urine. Ab123 don't have any inhibitory effect on cytochrome P450.

Safety pharmacology gives an idea that AB123 don't have any cardiovascular, respiratory and nervous adverse effect. No cardiovascular effect on dogs at dose 300mcg/kg and no respiratory effect in male rats at dose 750mcg/kg. No CNS effect on rats at dose 750mcg/kg.

Toxicological studies show mild emesis, reversible increase in transaminase, reversible increase in serum creatinine and proteinuria thus the NOAEL level for rats is 750mcg/kg and NOAEL for dog is 300mcg/kg.

To design a maximum recommended starting dose (MRSD) for first in human for new drug in healthy volunteer, there is a standard process by which MRSD is selected.

PROCESS OF SELECTING MRSD

According to FDA guideline

(Reference: first joint annual meeting 2005 AGAH and club phase 1, Bruno reigher medicine science, clinical pharmacology)

DETERMINE NO OBSERVE ADVERSE EFFECT LEVEL (NOAEL)

NOAEL is a basic part of non clinical risk assessment and it's a higher dose level dose not produces a significant increase in adverse effect when compare with control group. The mostly use definition of NOAEL is

“ Highest experimental point that is without adverse effect”

(Ref: dorato MA, Engelhard)

NOAEL and NOEL is different.

“ NOEL is not observe effect level refer to any effect not just adverse effect.”

(Ref: US department of health and human service food and drug administration centre of drug evaluation and research.)

<https://assignbuster.com/single-dose-of-ab123-for-treatment-of-alzheimers-disease/>

There are three types of non clinical toxicological studies are use to decide NOAEL.

- Over toxicity (clinical sign, macro micro lesion)
- Surrogate marker of toxicity (serum liver enzyme level)
- Exaggerated pharmacodynamic effect

Preclinical AB123 study determines NOAEL in rat is 750mcg/kg/day whereas NOAEL in dog is 300mcg/kg/day.

HUMAN EQUIVALENT DOSE CALCULATION

Human equivalent dose can be calculated by,

- body surface area dose conversion
- mg/kg conversion
- Other exception body surface area scaling between specie.

BSA conversion

Before starting a new clinical studies suitable method of allometric dose translation of drug should be main concern. According to Shannon Reagan-shaw, minakshi nihal

“ The animal dose should not be extrapolated to human equivalent dose by simple conversion based on body weight, for more appropriate method of animal studies to human studies; suggested method is body surface area (BSA) normalization method.”

(REF: dose translation from animal to human studies revisited; Shannon Reagan-shaw, minakshi nihal, nihal ahmad).

<https://assignbuster.com/single-dose-of-ab123-for-treatment-of-alzheimers-disease/>

Body surface area coordinate across several specie with limitation of biology like blood volume, metabolism, plasma protein, caloric spending, oxygen usage and renal function.

Reference Freireich et al (1966) and Schein et al (1970)

“ Investigator reported that for antineoplastic drug dose lethal to 10% rodent and MTD in non rodent both correlate with human MTD, when dose normalized to same administration schedule and express as mg/m²”

According to this analysis body surface area increase clinical study safety by resulting in low initial dose estimate.

Mg/kg conversion

Sometime scaling based on body weight is appropriate in species i: e mg/kg conversion but it has to be notice that mg/kg scaling give twelve, six and two fold higher HED then mg/m²

NOAEL occur similar mg/kg dose over test specie

Toxicology study gives two NOAEL in different specie then either

- Drugs administer orally and limited by local toxicity in that case scaling by mg/kg is appropriate.
- The drug related toxicity in human in depends upon specie exposure with dose on mg/kg basis.

In some anti sense drug, the Cmax correlate across non clinical specie with mg/kg dose in such case mg/kg scaling is justified.(reference ngeary et al. 1977)

Other exceptions to mg/m² scaling

- Use alternative route like topical, subcutaneous etc in this case dose is limiting by local toxicity.
- Protein administer intravascular such therapeutic are normalized to mg/kg.

SELECTION OF APPROPRIATE SPECIE

Once the human equivalent dose is get from NOAEL, then next step is to pick appropriate animal for HED for following process in MRSD. There are some factor which influence selection of appropriate specie

Differences in therapeutic index in specie e. g absorption, distribution, metabolism and excretion.

Some animal are more predictive to human toxicity.

“ Selection of most appropriate specie for certain biological product e. g human protein consideration of various factors unique to this product factor such as animal specie relevant receptor or epitop may affect specie selection”

(Reference ICH guidance for industry)

It is obvious that before determine initial dose in human the ADME of therapeutic is not known like

<https://assignbuster.com/single-dose-of-ab123-for-treatment-of-alzheimers-disease/>

“ non clinical assessment of phosphorathioate anti sense drug, monkey consider appropriate specie because monkey experience same dose limiting toxicity where as rodent don't for this class of drug the MRSD would usually be based on the HED, for the NOAEL in monkey regardless of whether it was lower than in rodent until unique dose limiting toxicity is observed”.

(Reference: statistics and experimental design for toxicologist and pharmacologist fourth edition by Shayne C Gad)

APPLICATION OF SAFETY FACTOR

Once HED is determine in appropriate specie then safety factor should apply to provide a safety margin in human when receive an initial clinical dose. This safety factor is use for instability in assuming animal toxicity study in human resulting

- Unsureness sometime human are more sensitive to certain product compare to animals.
- Some toxicity are difficult to detect in animal like headache, myalgia etc.
- Receptor density difference.
- Uncertain toxicity
- Animal species difference toward ADME of the noval drug

These differences can be minimizing by lowering HED.

AN INCREASE SAFTEY FACTOR

Sometime in calculating MRSD divide HED factor that is greater than 10 these conditions include,

- Steep dose response curve
- Saviour toxicity
- Toxicity without warning sign
- Irreversible toxicity
- Animal model with limited utility
- Improper dose response data
- Novel therapeutic target
- Variable bioavailability
- Non-monitric toxicity
- Unexplained mortality

(Reference: statistics and experimental design for toxicologist and pharmacologist fourth edition, ventana clinical research advancing science, service and success)

DECREASE SAFETY FACTOR

Safety factor decrease in well characterized drug class which is

- Administer by same route
- Same duration of action
- Similar metabolic profile
- Similar bioavailability
- Similar toxicity profile

(Reference ventana clinical research Beatrice setnik PhD)

<https://assignbuster.com/single-dose-of-ab123-for-treatment-of-alzheimers-disease/>

Decrease in safety factor should be done in therapeutic whose toxicity easily monitor, predictable and reversible.

FACTOR OF PHARMACOLOGICALLY ACTIVE DRUG (PAD)

There is no estimation for PAD define in guidance but should be use in determining the initial dose. PAD is usually lower then MRSD.

ADDITIONAL FACTS

Expert scientific group on phase one clinical trial UK

- If different method gives different MRSD, then lower value should be used.
- Minimum anticipated biological level recommended as a useful approach to calculate safe starting dose.

(Reference; advance science, service and success).

CALCULATE STARTING DOSE OF AB123

As preclinical toxicology study provides NOAEL dose in rat is 750mcg/kg/day and NOAEL in dog is 300mcg/kg/day.

HED based on NOAEL in dog

NOAEL in dog is 300mcg/kg/day—0. 3mg/kg/day

Mg/kg conversion factor dog to man is 20

Therefore HED for man SA 1. 8m²

$$20 \times 0.3 \times 1.8 = 10.8 \text{ mg/m}^2$$

For mg/kg factor for dog to man is 0.54, if man weight 70 kg then HED is

$$0.54 \times 0.3 \times 70 = 11.34 \text{ mg/kg}$$

Hence HED based on surface area recommended because it's lower of two.

Apply safety factor 10 for MRSD = 0.8 mg

HED based on NOAEL in rat

NOAEL for rat is 750 mcg/kg/day—0.75 mg/kg/day

Conversion factor for man to rat is 6

Therefore HED for man surface area 1.8 m² is

$$6 \times 0.75 \times 1.8 = 8.1 \text{ mg/m}^2$$

For mg/kg factor for rat to man is 0.16, if man weight 70 kg then HED is

$$0.16 \times 0.75 \times 70 = 8.4 \text{ mg/kg}$$

Hence HED for body surface area recommended and it's lower of 2.

Apply safety factor 10 give MRSD = 1 mg

Thus MRSD factor from dog is 0.8 mg and from rat is 1 mg. Thus the initial starting dose recommended is 0.8 mg.

STOPPING RULES

The easy method to evaluate a toxicity or adverse effect is to design stopping rules stopping rules is of two types

- Bayesian approach- evaluate proportion of patient with side effect
- Hypothesis testing approach- using sequential probability ratio test (sprt) to consider normal acceptable side effect rate has exceeded.

(Reference- PUbH 7470: Statistics for translational and clinical research)

Investigator may stop trial if differences in outcome between the intervention and control group are so unimpressive that any prospect of positive result with plan sample size is unlikely

- As toxicological studies indicate loss of weight with high doses, emesis in non rodent.
- In high doses serum transaminase (ALT & AST) increase majority of rats. ALT found in liver and AST found in heart and muscle so of there is any damage in liver it may cause increase in serum transaminase. So liver impairment use an indication as a stopping rule.
- Serum urea and creatinine increase in majority of animal with high doses serum and creatinine indicate either body is dehydrated or there is acute or chronic renal failure. So first in human study, increase in serum and creatinine level use as a stopping point.
- Abnormal proteinuria is appearing in mostly animal with high doses. First in human trail. Proteinuria is a significant risk factor for renal disease and cardiovascular morbidity.
- Organ weight changes appear in liver (increase) and thymus (decrease).

- Mild lymphoid depletion seen in few animal with high doses, it s occur due to increase loss of lymphocyte in bone marrow.

Toxicological studies indicate that all these changes are reversible after recovery period.