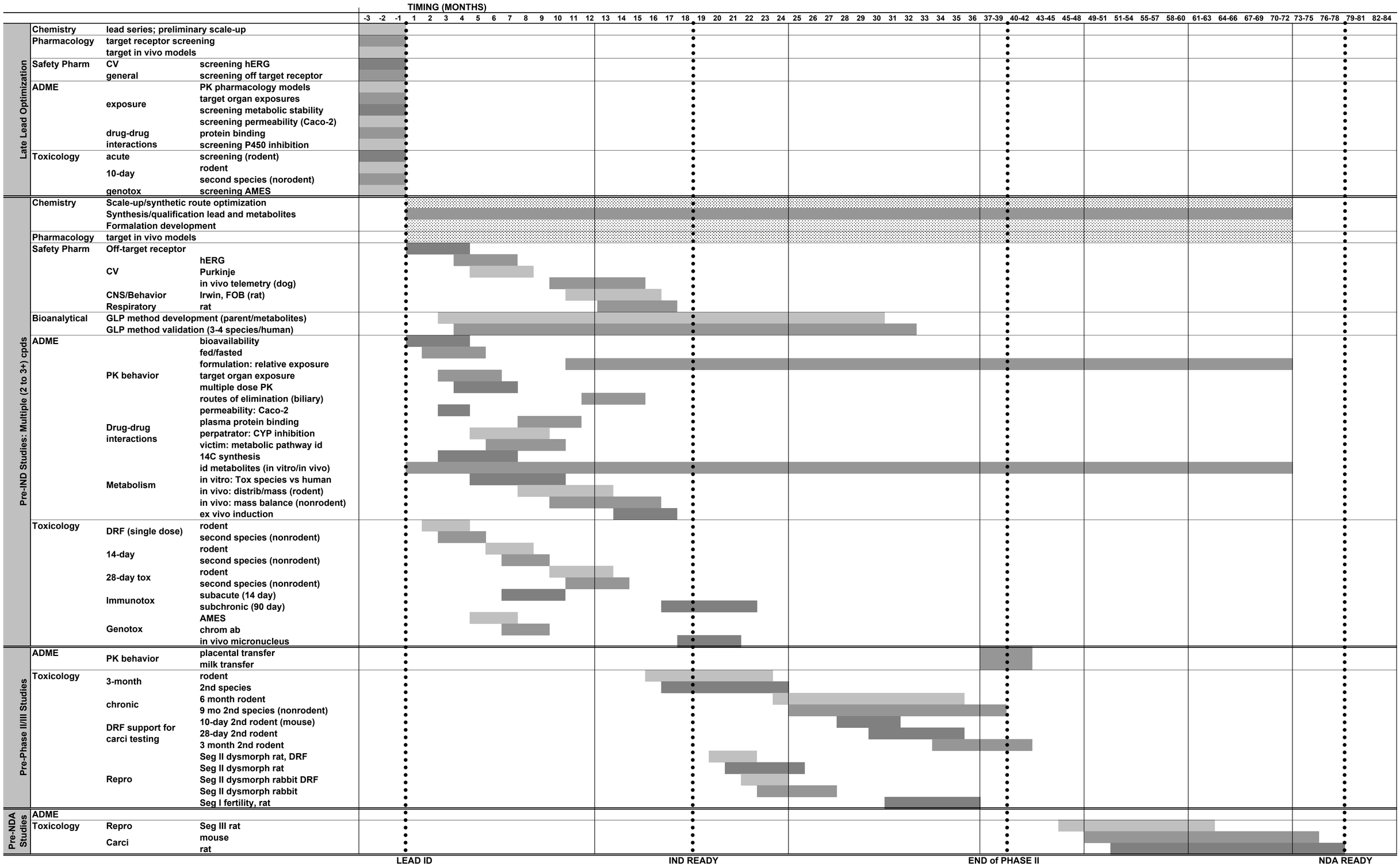
TIMING (MONTHS)
-3 -2 -1 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37-39 40-42 43-45 45-48 49-51 51-54 55-57 58-60 61-63 64-66 67-69 70-72 73-75 76-78 79-81 82-84
Late Lead Optimization
Chemistry
lead series; preliminary scale-up
Pharmacology
target receptor screening
target in vivo models
Safety Pharm
CV
screening hERG
general
screening off target receptor
ADME
PK pharmacology models
exposure
target organ exposures
screening metabolic stability
screening permeability (Caco-2)
drug-drug interactions
protein binding
screening P450 inhibition
Toxicology
acute
screening (rodent)
10-day
rodent
second species (norodent)
genotox
screening AMES
Pre-IND Studies: Multiple (2 to 3+) cpds
Chemistry
Scale-up/synthetic route optimization
Synthesis/qualification lead and metabolites
Formalation development
Pharmacology
target in vivo models
Safety Pharm
Off-target receptor
CV
hERG
Purkinje
in vivo telemetry (dog)
CNS/Behavior
Irwin, FOB (rat)
Respiratory
rat
Bioanalytical
GLP method development (parent/metabolites)
GLP method validation (3-4 species/human)
ADME
bioavailability
fed/fasted
formulation: relative exposure
PK behavior
target organ exposure
multiple dose PK
routes of elimination (biliary)
permeability: Caco-2
Drug-drug interactions
plasma protein binding
perpatrator: CYP inhibition
victim: metabolic pathway id
14C synthesis
Metabolism
id metabolites (in vitro/in vivo)
in vitro: Tox species vs human
in vivo: distrib/mass (rodent)
in vivo: mass balance (nonrodent)
ex vivo induction
Toxicology
DRF (single dose)
rodent
second species (nonrodent)
14-day
rodent
second species (nonrodent)
28-day tox
rodent
second species (nonrodent)
Immunotox
subacute (14 day)
subchronic (90 day)
Genotox
AMES
chrom ab
in vivo micronucleus
Pre-Phase II/III Studies
ADME
PK behavior
placental transfer
milk transfer
Toxicology
3-month
rodent
2nd species
chronic
6 month rodent
9 mo 2nd species (nonrodent)
DRF support for carci testing
10-day 2nd rodent (mouse)
28-day 2nd rodent
3 month 2nd rodent
Repro
Seg II dysmorph rat, DRF
Seg II dysmorph rat
Seg II dysmorph rabbit DRF
Seg II dysmorph rabbit
Seg I fertility, rat
Pre-NDA Studies
ADME
Toxicology
Repro
Seg III rat
Carci
mouse
rat
LEAD ID
IND READY
END of PHASE II
NDA READY