

Evaluation of Drug-Drug Interaction in Nested Patient Studies

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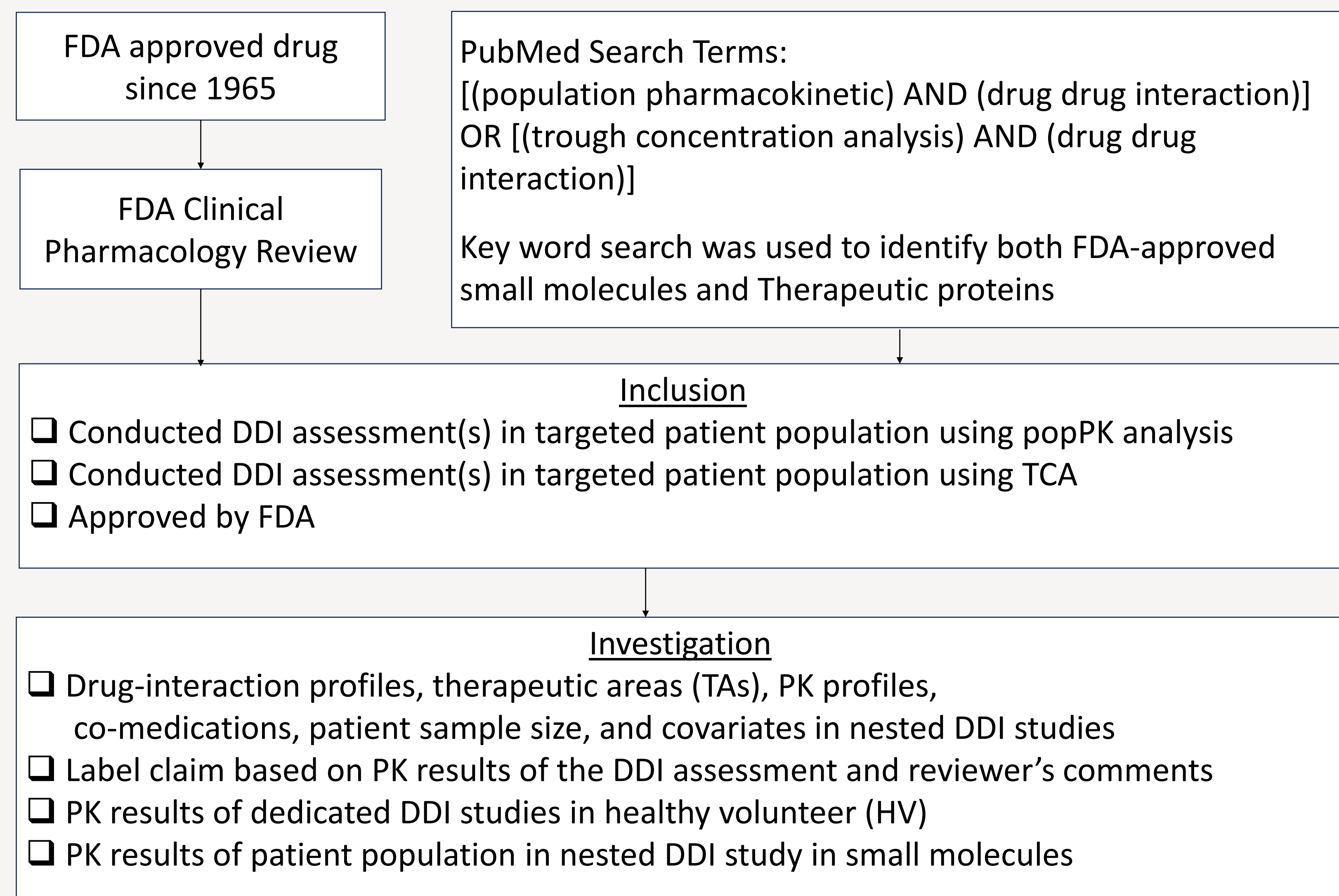
Introduction

- Usage of population-based approach gained acceptance by the US Food and Drug Administration (FDA) in assessing drug-drug interactions (DDIs)
- Population-based approach can detect clinical effects in target patient populations and confirm DDI assessments from dedicated studies in healthy volunteers
- FDA Clinical DDI guidelines value the use of prospective nested studies to evaluate DDI in patient populations alongside population pharmacokinetic (popPK), which can yield informative and sometimes conclusive analyses

Objectives

- To evaluate the utilization of population pharmacokinetic analysis or trough concentration analysis in nested drug-drug interaction studies from FDA drug approvals

Methods



Conclusion

- popPK analysis is commonly used to support DDI assessment in targeted patient populations
- In small molecules, popPK analyses are frequently utilized to confirm the known DDI risk in CYP-mediated DDI assessments
- Therapeutic protein submissions use popPK approach to confirm the absence of DDI liability complying with FDA guidelines
- Co-medication DDI assessment with popPK analysis alone may support label claims in submissions
- Reasons for failure in label claims included inappropriate assumption of PK parameters for simulation, inadequate popPK-based evaluation, and insufficient data and sampling

Results

Therapeutic proteins (TPs)

28 TPs were evaluated

- All 28 TPs utilized popPK analysis to assess DDI potentials in patient population
- All TP DDI assessments were accepted by FDA reviewers

Figure 1. TA categorization of evaluated TPs

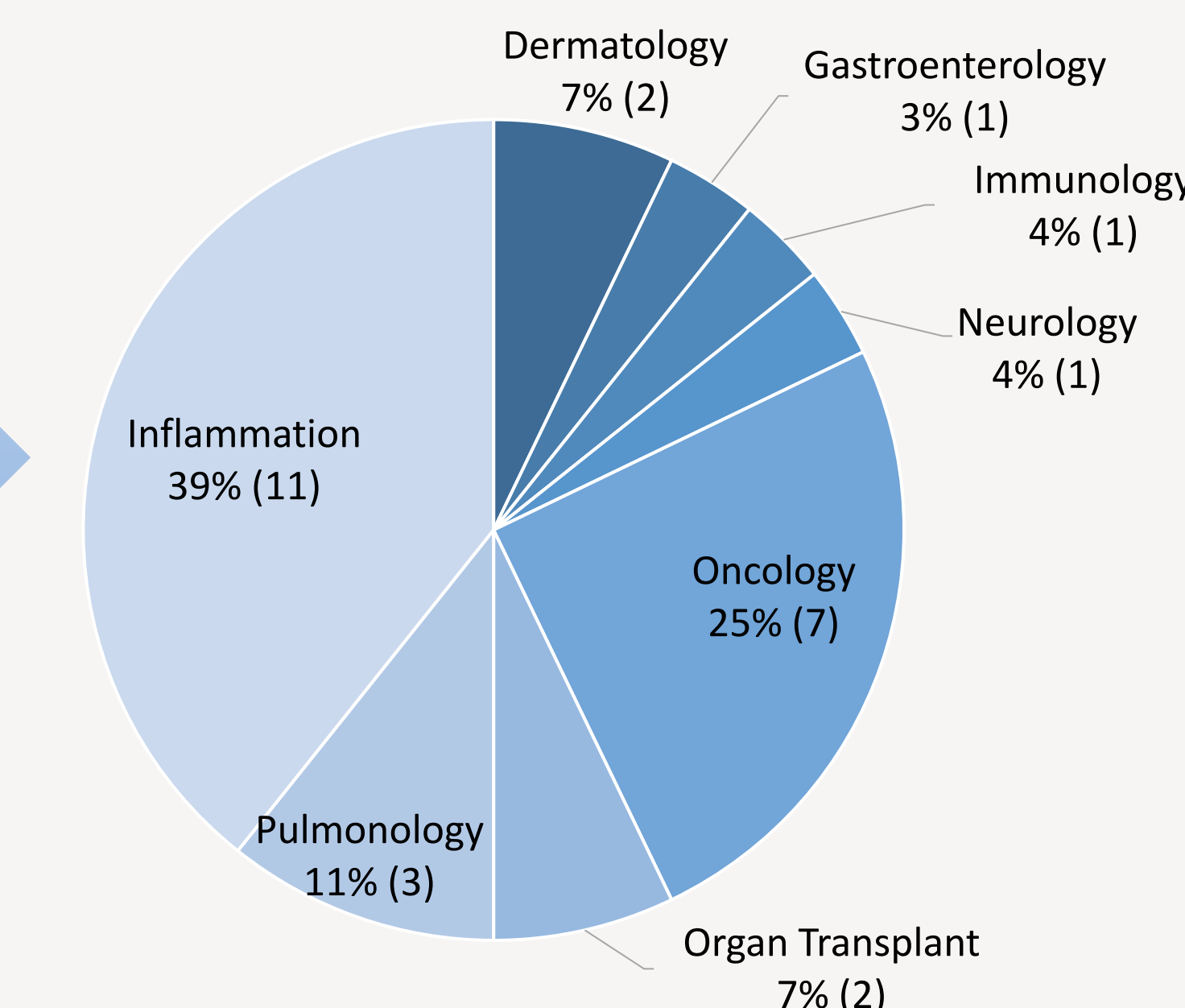


Figure 2. Summary of patient sample size reported in TPs using popPK analysis

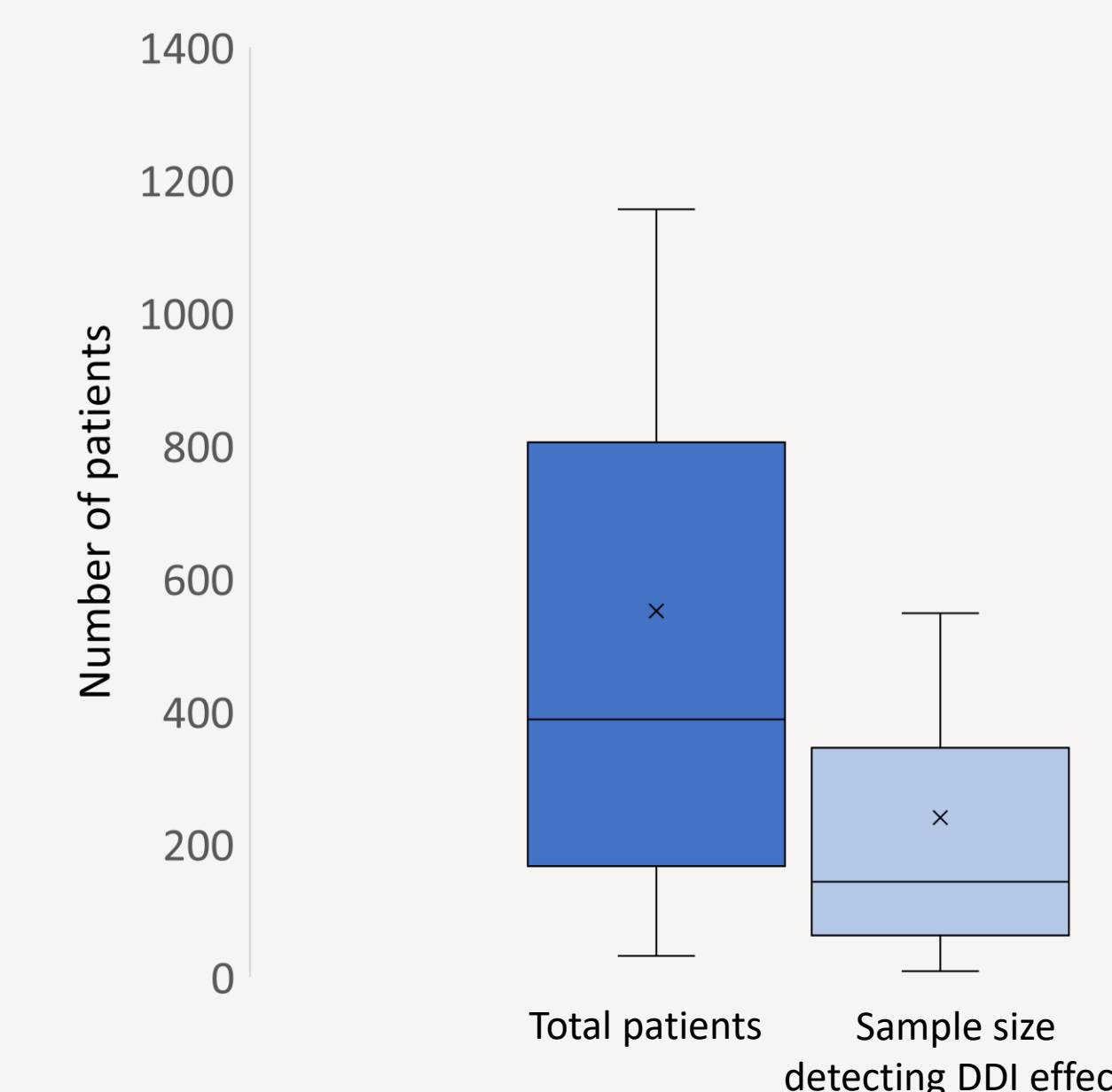


Table 1. Summary of patient sample size parameters in TPs

Parameters	Total patients	Sample size detecting DDI effect
Median	447	218
Q1, Q3	235, 719	95, 393
Min, Max	60, 1093	45, 548

Max, maximum; Min, minimum; Q1, first quartile; Q3, third quartile

Small molecules

35 small molecules were evaluated*

- 4 applied TCA in nested patient studies
- All 4 DDI assessments were accepted by FDA reviewers
- 31 drugs applied popPK analysis to assess DDIs in patient population
- 30 out of 36 DDI assessments with popPK analysis to support label claims were accepted by FDA reviewers

Figure 3. TA categorization of evaluated small molecules

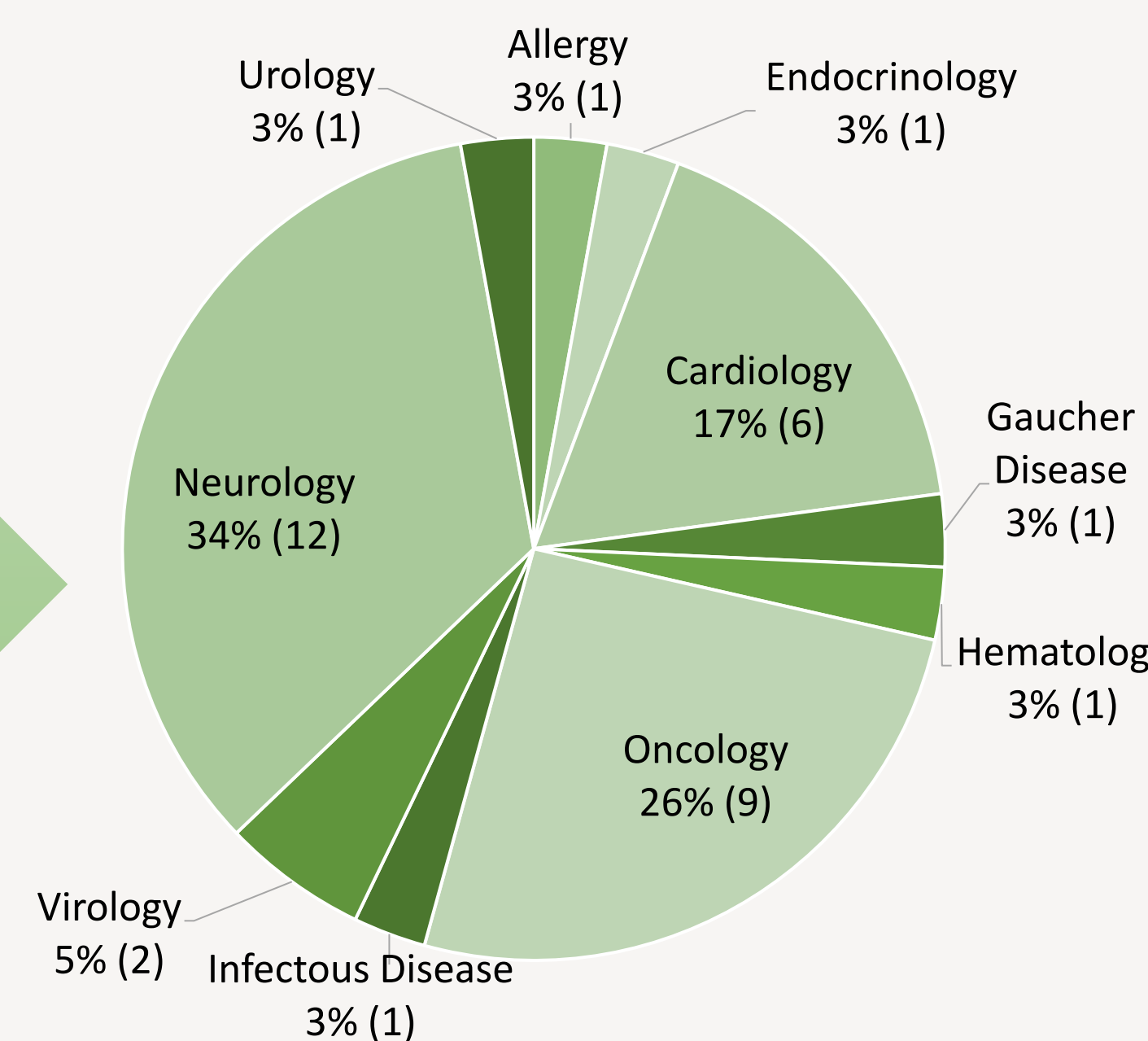


Figure 4. Summary of patient sample size reported in small molecules using popPK analysis

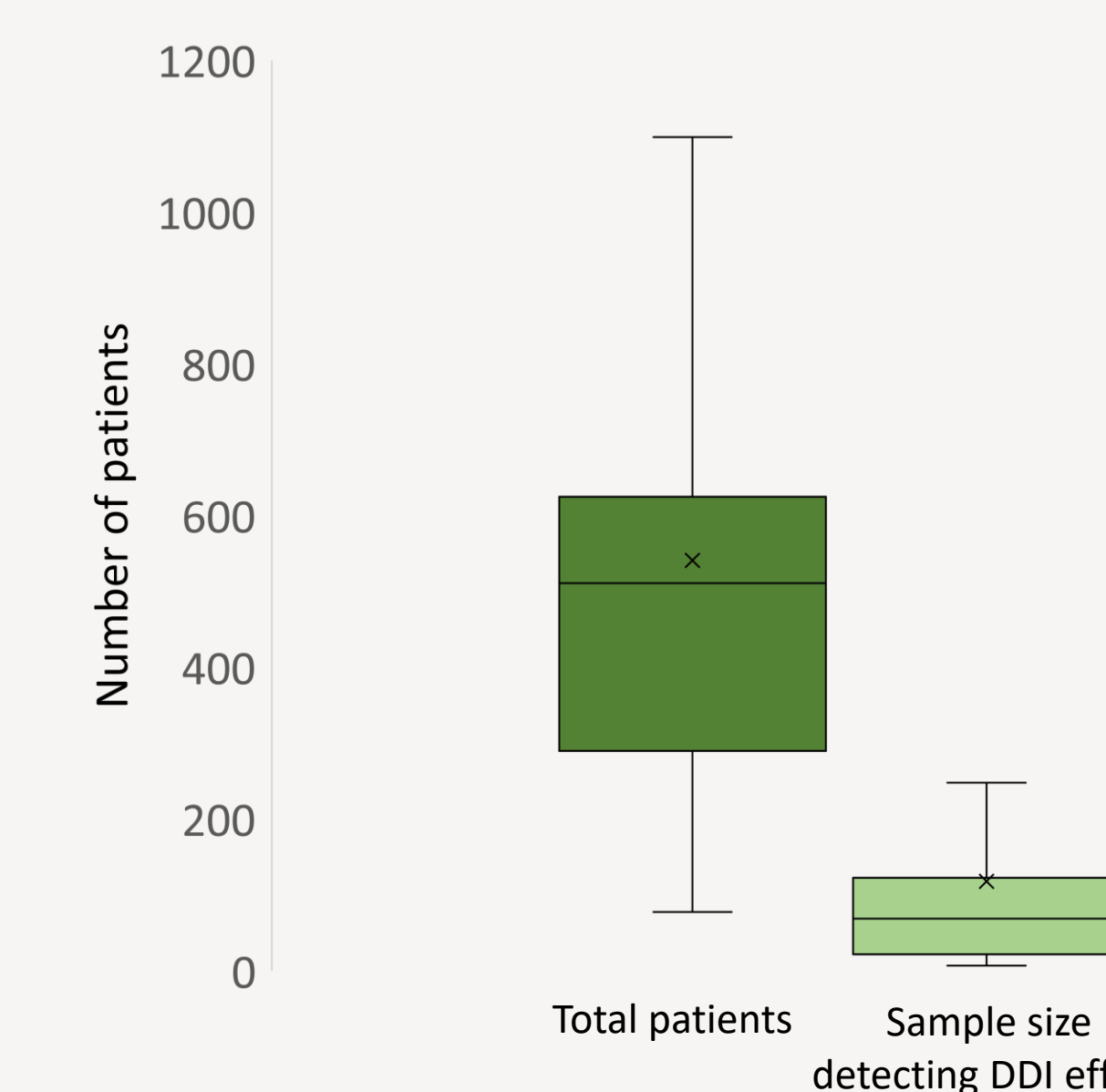


Table 2. Summary of patient sample size parameters in small molecules

Parameters	Total patients	Sample size detecting DDI effect
Median	511	69
Q1, Q3	290, 625	22, 117
Min, Max	32, 1937	9, 1139

Max, maximum; Min, minimum; Q1, first quartile; Q3, third quartile

Figure 5. Summary of the types of DDI assessments of evaluated small molecules using popPK analysis to support label claims (N= 36)

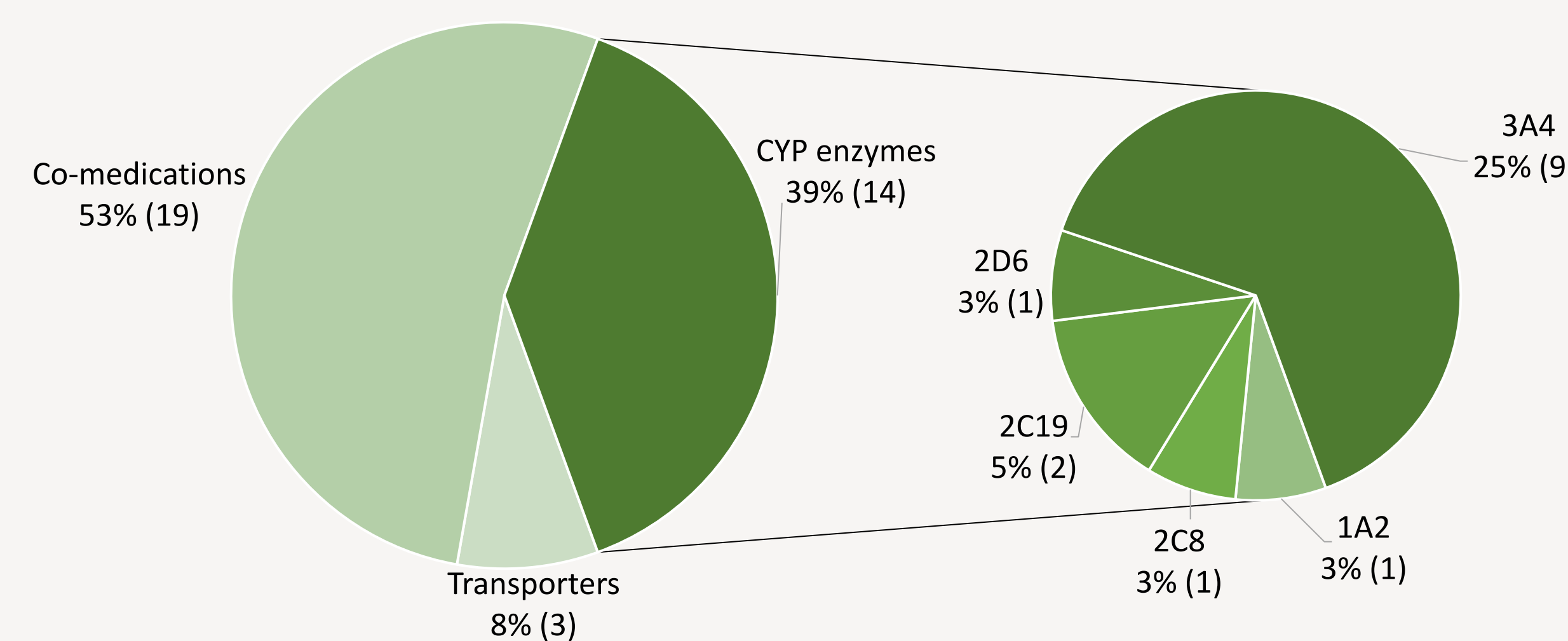
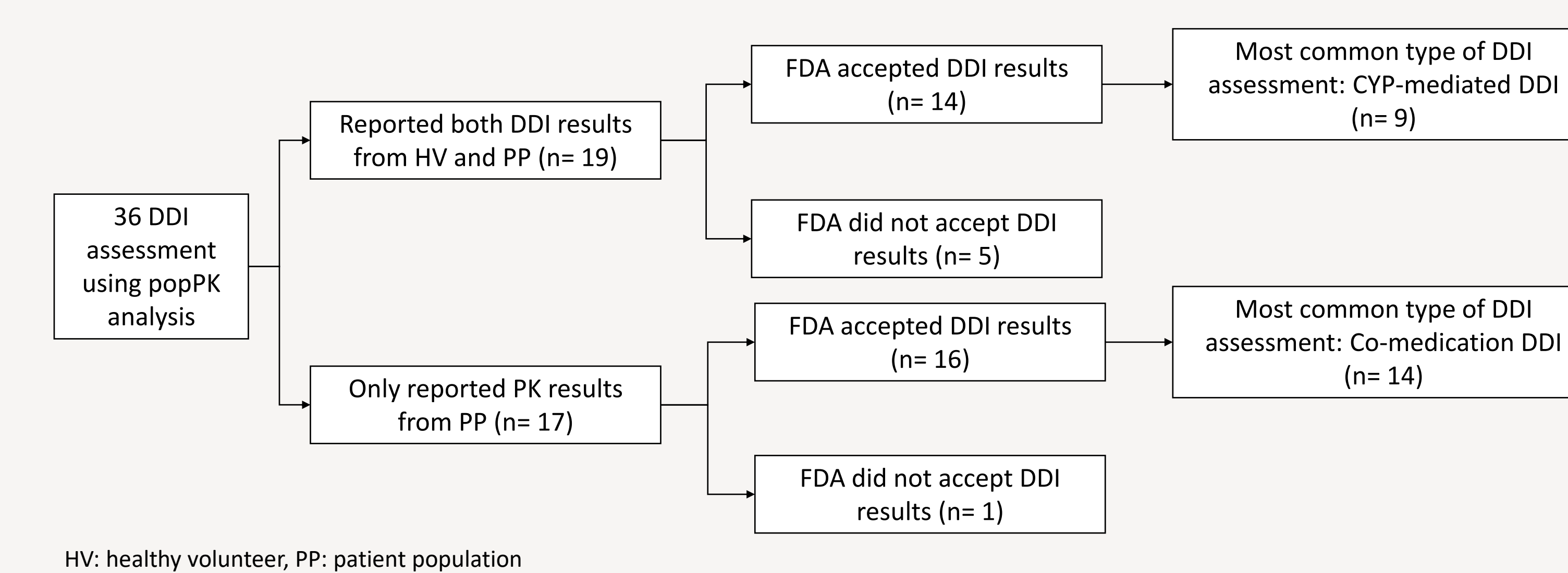


Figure 6. Summary of label instructions for small molecules using popPK analysis to evaluate DDIs



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