

Orphan Medicines Office/ COMP

Non-clinical animal models used in support of the orphan drug designations in infectious diseases

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Introduction

The aim of this project of the EMA/COMP Non-clinical Models Working Group is to review non-clinical models used to support orphan drug designations (ODDs) in rare infectious diseases. We would like to put these models in the context of the available literature data and assess animal models, as well as rare infectious diseases that are difficult to study in a non-clinical setting. This analysis may lead to a more efficient utilisation of animal models in establishing the pharmacodynamic feasibility of potential therapies for rare infectious diseases in the context of orphan designation, thereby helping and streamlining in critical development decision making regarding use in the clinical setting.

Results

- 26 rare and designated infectious diseases were identified comprising 60 ODD applications.
- Of these ODDs, 24 contained non-clinical data only, making it 40% of applications for rare infectious diseases, for which products were not evaluated in human yet.
- The most prevalent animal species used to test designated products was mouse, followed by non-human primate and rabbit.
- Significant benefit was not required in 38% of the designated conditions. Interestingly, these are mainly viral conditions.
- Non-rare infections that accompany rare diseases (e.g., infections in cystic fibrosis) were not assessed, since the clinical aspects addressed in such applications were considered pertinent to underlying rare disease.

Conclusions

- Non-clinical research in the field of rare infectious diseases is often challenging due to the bio-hazard and human-specific nature of the pathogens.
- Many acceptable and established non-clinical models of infectious diseases exist, which may be used to support the feasibility or medical plausibility of new medicinal products being used in a specific rare infection.
- In the ODD setting it was noted that in 62% of the conditions designated by the COMP there were authorised medicines and therefore the additional criteria of significant benefit had to be established which could be challenging in the setting of non-clinical *in vivo* models.

1. Avian Influenza 2 mouse mouse, squirrel, prairie dog, non-human primate, rabbit mouse encephalitis 7. Mon-TB mycobacteria mouse, squirrel, prairie dog, non-human primate mouse encephalitis 1. Wariola 1 mouse mouse, squirrel, prairie dog, non-human primate mouse encephalitis 7. Meningococcus 1 mouse, squirrel, prairie dog, non-human primate mouse survival, seroconversion rates survival, seroconversion rates survival, seroconversion rates survival, seroconversion rates survival, respiratory rate, weight loss, development of secondary lesions and primate rabbit mouse, squirrel, prairie dog, non-human primate, mouse squirrel, prairie dog, non-human primate, mouse seroconservation rates survival, respiratory rate, weight loss, development of secondary lesions survival, dermal lesion formation, weight, virus-specific artibody titers, cytokine production, viral load viral load, poxvirus lesions, mortality virus-specific artibody titers, cytokine production, viral load viral load, poxvirus lesions, mortality virus-specific artibody titers, cytokine production, viral load viral load, poxvirus lesions, mortality virus-specific artibody titers, cytokine production, viral load viral load, poxvirus lesions, mortality virus-specific artibody titers production, viral load viral load, poxvirus lesions, mortality virus-specific artibody titers survival, passate colony forming unit the lungs survival, lung / spleen colony forming unit survival passame endotoxin levels presence of intracellular mycobacteria in the lungs survival, lung / spleen colony forming unit survival passame endotoxin levels presence of intracellular mycobacteria in the lungs survival, lung / spleen colony forming unit survival passate celerance, mouse survival, fungal burden in infected cell cultures, inhibition of microsporidia growth in vitro survival, parasite burden, infarct score, mouse survival parasite cultane, number and size of cysts, histology of		No	Medical condition	No of	Non-clinical models	Clinically relevant endpoints in models	
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 Leishmania 5 mouse, dog, hamster IgG titres, T cell proliferation, cytokine production, parasite clearance, number of amastigotes in liver cells, lesions Malaria (Plasmodium) primate reoccurrence of parasitemia, percentage of cure Trypanosoma 1 mouse, non-human parasite clearance 		23.	Echinococcus	1	mouse, rat	survival, parasitic burden, number and size	
 Malaria (Plasmodium) Trypanosoma Malaria (Plasmodium) mouse, rat, non-human parasite clearance, effective dose, mortality, reoccurrence of parasitemia, percentage of cure mouse, non-human parasite clearance, effective dose, mortality, reoccurrence of parasitemia, percentage of cure 		24.	Leishmania	5	mouse, dog, hamster	IgG titres, T cell proliferation, cytokine production, parasite clearance, number of	
		25.		7		parasite clearance, effective dose, mortality, reoccurrence of parasitemia, percentage of	
		26.	Trypanosoma	1	·	parasite clearance	