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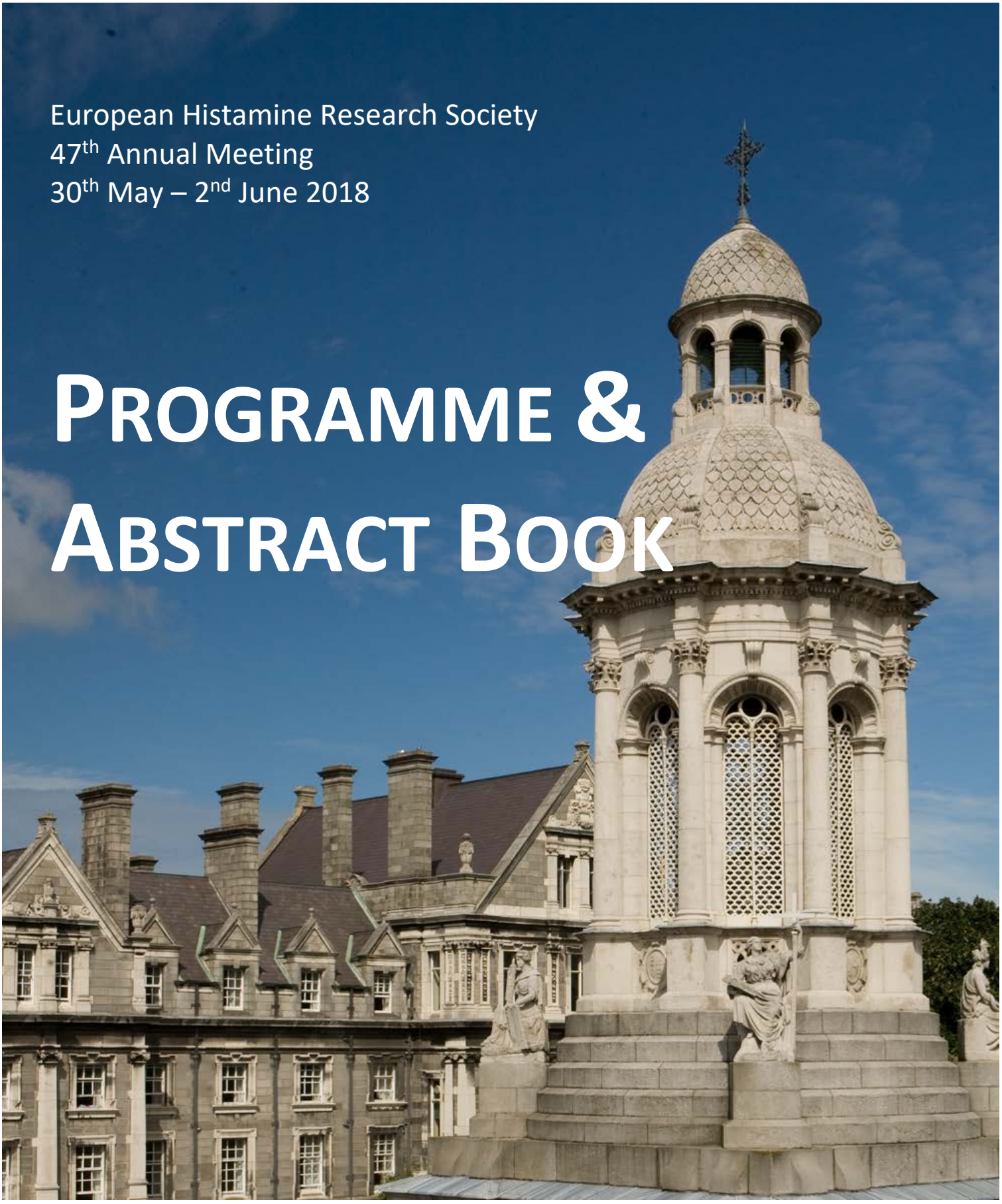
Programme & Abstract Book



Invited Lectures

L4

Cardiovascular Safety of the Histamine H3 Inverse Agonist Pitolisant: From Nonclinical to Clinical Aspects

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Pitolisant (Wakix®), a histamine H3 receptor inverse agonist was approved by EMA for the treatment of narcolepsy with or without cataplexy. We explored its cardiovascular preclinical and clinical safety profile taking into account both ICHS7B and E14 guidelines, respectively and the new initiative driven by FDA and industry (CiPA) to better detect life threatening drug-induced cardiac arrhythmias.

ICHS7B assays included *in vitro* hERG channels, *in vivo* dog studies with follow-up investigations in other proarrhythmia models.

CiPA initiative included *in vitro* studies on ion channels, stem cell-derived human ventricular myocytes, and *in silico* modelling to simulate human ventricular electrophysiology. These revealed Pitolisant to have modest calcium channel blocking and late INa reducing activities at high concentrations, which resulted in Pitolisant reducing dofetilide-induced early after-depolarizations (EADs). Studies in human cardiomyocytes with dofetilide or E-4031 given alone and in combination with Pitolisant confirmed these properties. *In silico* modelling supported that the ion channel effects measured are consistent with results from both cardiomyocytes and rabbit Purkinje fibres and categorized Pitolisant as a drug with low torsadogenic potential. Both sets of data excluded Pitolisant from having clinically relevant QT-liability/pro-arrhythmic potential and suggest that a single hERG assessment may be too reductive in early drug development.

Furthermore, results from the two sets of nonclinical studies correlated well with those from two clinical QT studies. Indeed, the single/multiple ascending dose (SAD/MAD) as well as the thorough QT (TQT) studies excluded a clinically relevant effect of Pitolisant on QTcF interval and the resulting risk of proarrhythmia. These studies with Pitolisant add value to the growing body of evidence supporting replacement of a TQT study with a suitable cost effective alternative (SAD/MAD) which takes into account drug concentrations.

Invited Lectures

L5

H3 Receptor Inverse Agonists: Wake Promotion Without Drug Abuse Risk Shown with Pitolisant

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Pitolisant (Wakix®), a histamine H3 receptor inverse agonist was approved in March 2016 by EMA for the treatment of narcolepsy with or without cataplexy. As first in class, it was of importance to explore its drug abuse potential preclinically in in vivo models and clinically.

The increase in dopamine release in the nucleus accumbens, the locomotor sensitization and the conditioned hyperlocomotion, common features of drug of abuse, were evidenced for Modafinil, a drug used in narcolepsy, whereas Pitolisant was without any effect on these indices. In rodents, it was also without any effect on locomotion and even reduced the cocaine-induced hyperlocomotion. Finally, Pitolisant was devoid of any significant effects in the three standard drug abuse tests (i.e. conditioned place preference in rats, self-administration in monkeys and cocaine discrimination in mice) and in physical dependence tests.

In clinics, a good compliance of patients to the prescribed drug treatment regimen, no drug abuse-related adverse events and no withdrawal symptoms were recorded In addition, a double-blind crossover trial in drug addicts showed that Pitolisant did not induce “drug liking” more than placebo.

Hence, in contrast with typical amphetamine-like psychostimulants and with modafinil (whose drug abuse potential is still controversial), no potential drug abuse liability for Pitolisant was evidenced in various rodent and primate models (Uguen M. et al. Brit. J. Pharmacol. 2013). These results together with those obtained in various rodent models with a prototypic histamine H3 receptor antagonist (Hudzik T.J. et al. Psychopharmacol. 2013) and confirmed clinically for Pitolisant are in favour of the lack of drug abuse potential and dependence, giving marked advantage for this new therapeutic class.