Clinical Pharmacology & Therapeutics

CLINICAL PHARMACOLOGY & THERAPEUTICS (ISSN 0009-2936; EISSN 1532-6535) is published monthly on behalf of the American Society for Clinical Pharmacology and Therapeutics by Wiley Subscription Services, Inc., a Wiley Company, 111 River St., Hoboken, NJ 07030-5774 USA. Periodical Postage Paid at Hoboken, NJ and additional offices.

COPYRIGHT AND PHOTOCOPYING (in any format)
Clinical Pharmacology & Therapeutics © 2020 the American Society for Clinical Pharmacology and Therapeutics. All rights reserved. No part of this publication may be reproduced, stored or transmitted in any form or by any means without the prior permission in writing from the copyright holder. Authorization to copy items for internal and personal use is granted by the copyright holder for libraries and other users registered with their local Reproduction Rights Organization (RRO), e.g. Copyright Clearance Center (CCC), 222 Rosewood Drive, Danvers, MA 01923, USA (www.copyright.com), provided the appropriate fee is paid directly to the RRO. This consent does not extend to other kinds of copying such as copying for general distribution, for advertising or promotional purposes, for republication, for creating new collective works or for resale. Permissions for such reuse can be obtained using the RightsLink “Request Permissions” link on Wiley Online Library. Special requests should be addressed to: permissions@wiley.com.

DELIVERY TERMS AND LEGAL TITLE
Where the subscription price includes print issues and delivery is to the recipient’s address, delivery terms are Delivered at Place (DAP); the recipient is responsible for paying any import duty or taxes. Title to all issues transfers Free of Board (FOB) our shipping point, freight prepaid. We will endeavor to fulfill claims for missing or damaged copies within six months of publication, within our reasonable discretion and subject to availability.

BACK ISSUES
Single issues from current and recent volumes are available at the current single issue price from cs-journals@wiley.com. Earlier issues may be obtained from Periodicals Service Company, 351 Fairview Avenue – Ste 300, Hudson, NY 12545, USA. Tel: +1 518 822-9300, Fax: +1 518 822-9305, Email: psc@periodicals.com.

SCOPE
Clinical Pharmacology & Therapeutics is the authoritative cross-disciplinary journal in experimental and clinical medicine devoted to publishing advances in the nature, action, efficacy, and evaluation of therapeutics. Original articles and letters reflect the highest level of research in pharmacology and therapeutics. Commentaries and Point-Counterpoint provide a forum for perspectives on contemporary scientific, political, economic, and social issues. State of the Art summarizes the latest advances in the science of drug discovery, development, regulation, and utilization. CPT highlights issues transforming the practice of clinical pharmacology, including ethics, education, and public policy. Bench-to-bedside translation in therapeutics is presented in the context of clinical applications of basic pharmacology, discovery, and translational medicine and drug development.


EDITORIAL
Manuscripts must be submitted online at: http://cpt mssubmit.net. A detailed guide to Authors is available at the above website address. For online submission problems, consult the help section at submission site or contact the Editorial Office: Tel +1 703 836 6981. Email: cpt@ascopt.org

PUBLISHER
All business correspondence and inquiries should be addressed to Clinical Pharmacology & Therapeutics, Wiley, 111 River Street, Hoboken, NJ 07030-5774. Tel: +201 748 6000 Publishing Manager: Brian Coughlin (bcoughli@wiley.com) Production Editor: Farhath Jabeen S (cpt@wiley.com) Advertising and Supplements: Kurt Polesky (kpolesky@wiley.com) Commercial Reprints: Dave Surdel (dsurdel@wiley.com)

SOCIETY
All members of ASCEPT receive Clinical Pharmacology & Therapeutics as part of their membership. For information about membership and the Society, address correspondence to: American Society for Clinical Pharmacology and Therapeutics, 528 North Washington Street, Alexandria, VA 22314, USA, Tel: 11 703 836 6981. Fax: +1 703 836 5223. Email: info@ascopt.org

Postmaster: Send all address changes to CLINICAL PHARMACOLOGY & THERAPEUTICS, John Wiley & Sons Inc., C/O The Sheridan Press, PO Box 465, Hanover, PA 17331, USA.

JOURNAL CUSTOMER SERVICES
For ordering information, claims and any enquiry concerning your journal subscription please go to: https://hub.wiley.com/community/support/onlinelibrary or contact your nearest office.

Americas: Email: cs-journals@wiley.com; Tel: +1 781 388 8598 or +1 800 835 6770 (toll free in the USA & Canada).

Europe, Middle East and Africa: Email: cs-journals@wiley.com; Tel: +44 (0) 1865 778315.

Asia Pacific: Email: cs-journals@wiley.com; Tel: +65 6511 8000.

Japan: For Japanese speaking support, Email: cs-japan@wiley.com.

Visit our Online Customer Help at https://hub.wiley.com/community/support/onlinelibrary

INFORMATION FOR SUBSCRIBERS
Clinical Pharmacology & Therapeutics is published in 12 issues per year. Institutional subscription prices for 2020 are:
Print & Online: US$18585 (US), US$18585 (Rest of World), €1389 (Europe), £1162 (UK). Prices are exclusive of tax. Asia-Pacific GST, Canadian GST/HST and European VAT will be applied at the appropriate rates. For more information on current tax rates, please go to https:// onlinelibrary.wiley.com/library-info/products/pricelists/payment. The price includes online access to the current and all online backfiles to January 1st 2016, where available. For other pricing options, including access information and terms and conditions, please visit https://onlinelibrary. wiley.com/library-info/products/pricelists.

Wiley’s Corporate Citizenship initiative seeks to address the environmental, social, economic, and ethical challenges faced in our business and which are important to our diverse stakeholder groups. Since launching the initiative, we have focused on sharing our content with those in need, enhancing community philanthropy, reducing our carbon impact, creating global guidelines and best practices for paper use, establishing a vendor code of ethics, and engaging our colleagues and other stakeholders in our efforts. Follow our progress at www.wiley.com/go/citizenship.

Wiley is a founding member of the UN-backed HINARI, AGORA, and OARE initiatives. They are now collectively known as Research4Life, making online scientific content available free or at nominal cost to researchers in developing countries. Please visit Wiley’s Content Access – Corporate Citizenship site: http://www.wiley.com/ WileyCDA/Section/id-390082.html. View this journal online at wileyonlinelibrary.com/journal/cpt

Clinical Pharmacology & Therapeutics accepts articles for Open Access publication. Please visit https://authorresources.wiley.com/author-resources/ Journal-Authors/open-access/onlinemanuscriptreview for further information about OnlineOpen.

Disclaimer: The Publisher, the American Society for Clinical Pharmacology and Therapeutics, and Editors cannot be held responsible for errors or any consequences arising from the use of information contained in this journal; the views and opinions expressed do not necessarily reflect those of the Publisher, the American Society for Clinical Pharmacology and Therapeutics, and Editors, neither does the publication of advertisements constitute any endorsement by the Publisher, the American Society for Clinical Pharmacology and Therapeutics, and Editors of the products advertised.

Printed in the USA by The Sheridan Group.
Regulatory science and decision-making need to accommodate the local social, medical, and economic environment. At the same time, regulatory science shares a common remit across the globe as a patient-centric discipline contributing to society and human welfare. There are strong arguments that the impact of clinical pharmacology can be enhanced through the advancement and harmonization of regulatory science innovation and policies across global regulatory authorities. A series of CPT articles addresses the question if international regulators are talking to each other across borders and demonstrate why collaborative innovative regulatory science is a key enabler of bringing life-changing medicines to patients.

### CONTENTS

#### IN THIS ISSUE

- Benefit-Risk Analysis for RCC Drugs
- LRRK2 Could Inform Parkinson's Trial Design
- Insulin and Pancreatitis Progression Risk
- Whole Exome Sequencing can Provide PGx Profile
- Reconsidering Solubility

#### EDITORIAL

481 Are Regulators Talking to Each Other Across Borders?
Piet H. van der Graaf

#### NEWS & VIEWS

- 484 HIGHLIGHTS
- 486 ASCPT NEWS

#### PERSPECTIVES

#### COMMENTARY

492 Regulators’ Advice Can Make a Difference: European Medicines Agency Approval of Zynteglo for Beta Thalassemia
Martina Schuessler-Lenz, Harald Enzmann and Spiros Vamvakas

#### REVIEWS

#### STATE OF THE ART

495 Using a Benefit–Risk Analysis Approach to Capture Regulatory Decision Making: Renal Cell Carcinoma
G. K. Raju, Karthik Gurumurthi, Reuben Domike, Harpreet Singh, Chana Weinstock, Paul Kluetz, Richard Pazdur and Janet Woodcock

- 507 Are the European Medicines Agency, US Food and Drug Administration, and Other International Regulators Talking to Each Other?
Tania Teixeira, Sandra L. Kweder and Agnes Saint-Raymond

This journal is a member of, and subscribes to the principles of, the Committee on Publication Ethics (COPE) www.publicationethics.org.
514  Evaluation of Therapeutics for Severely Debilitating or Life-Threatening Diseases or Conditions: Defining Scope to Enable Global Guidance Development
Maggie Liu, F. Owen Fields, Judith S. Prescott, Akintunde Bello, Nancy Bower, Salima Darakjy, James Hartke, Vivek Kadambi, Daniel Lapadula, Aubrey Stoch and Mazin Derzi

521  Improving the Safety of Medicines in the European Union: From Signals to Action
Joanne Potts, Georgy Genov, Andrej Segec, June Raine, Sabine Straus and Peter Arlett

RESEARCH ARTICLES

530  International Coherence of Pediatric Drug Labeling for Drug Safety: Comparison of Approved Labels in Korea and the United States
Yun-Kyoung Song, Nayoung Han, Gilbert J. Burckart and Jung Mi Oh

541  European Medicines Agency’s Priority Medicines Scheme at 2 Years: An Evaluation of Clinical Studies Supporting Eligible Drugs
Emilie Neez, Thomas J. Hwang, Samali Anova Sahoo and Huseyin Naci

553  Development of a Disease Progression Model for Leucine-Rich Repeat Kinase 2 in Parkinson’s Disease to Inform Clinical Trial Designs
Malidi Ahamadi, Daniela J. Conrado, Sreeraj Macha, Vikram Sinha, Julie Stone, Jackson Burton, Timothy Nicholas, Jill Gallagher, David Dexter, Massimo Bani, Babak Borojerdi, Hans Smit, Jonas Weidemann, Chao Chen, Minhua Yang, Romeo Maciucu, Rachael Lawson, David Burn, Kenneth Marek, Charles Venuto, Bob Stafford, Mussie Akalu, Diane Stephenson and Klaus Romero on behalf of the Critical Path for Parkinson’s (CPP) Consortium

563  Prospective CYP2C19-Guided Voriconazole Prophylaxis in Patients With Neutropenic Acute Myeloid Leukemia Reduces the Incidence of Subtherapeutic Antifungal Plasma Concentrations
J. Kevin Hicks, Rod E. Quilitz, Rami S. Komrokji, Timothy E. Kubi, Jeffrey E. Lancet, Yanina Pasikova, Dahui Qin, Wonhee So, Gisela Caceres, Kenny Kelly, Yasmina S. Salchert, Kevin Shahbazian, Farnoosh Abbos-Aghababazadeh, Brooke L. Fridley, Ana P. Velez, Howard L. McLeod and John N. Greene

571  Evaluation of CYP2C19 Genotype-Guided Voriconazole Prophylaxis After Allogeneic Hematopoietic Cell Transplant

580  Use of Insulin and the Risk of Progression of Pancreatitis: A Population-Based Cohort Study
Jaelim Cho, Robert Scragg and Maxim S. Petrov

588  Changing Body Weight–Based Dosing to a Flat Dose for Avelumab in Metastatic Merkel Cell and Advanced Urothelial Carcinoma
Ana M. Novakovic, Justin J. Wilkins, Haiqing Dai, Janet R. Wade, Berend Neuteboom, Satjit Brar, Carlo L. Bello, Pascal Girard and Akash Khandelwal
597  Model-Informed Dose Selection for Xentuzumab, a Dual Insulin-Like Growth Factor-I/II—Neutralizing Antibody
      Zinnia P. Parra-Guillen, Ulrike Schmid, Alvaro Janda, Matthias Freiwald and Iñaki F. Troconiz

607  Ischemic Stroke and Systemic Embolism in Warfarin Users With Atrial Fibrillation or Heart Valve Replacement Exposed to Dicloxacillin or Flucloxacillin
      Maja Hellfritzsch, Lars Christian Lund, Zandra Ennis, Tore Stage, Per Damkier, Mette Bliddal, Peter Bjødstrup Jensen, Daniel Henriksen, Martin Thomsen Ernst, Morten Olesen, Anne Broe, Kasper Bruun Kristensen, Jesper Hallas and Anton Pottegård

617  Repurposing of Diagnostic Whole Exome Sequencing Data of 1,583 Individuals for Clinical Pharmacogenetics

628  Variability and Heritability of Thiamine Pharmacokinetics With Focus on OCT1 Effects on Membrane Transport and Pharmacokinetics in Humans
      Ole Jensen, Johannes Matthaei, Felix Blome, Matthias Schwab, Mladen V. Tzvetkov and Jürgen Brockmöller

639  Exposure–Response Analyses for Upadacitinib Efficacy and Safety in the Crohn’s Disease CELEST Study and Bridging to the Extended-Release Formulation
      Mohamed-Eslam F. Mohamed, Ben Klünder, Ana P. Lacerda and Ahmed A. Othman

650  Evaluating the Role of Solubility in Oral Absorption of Poorly Water-Soluble Drugs Using Physiologically-Based Pharmacokinetic Modeling
      Christina Fink, Dajun Sun, Knut Wagner, Melanie Schneider, Holger Bauer, Hugues Dolgos, Karsten Mäder and Sheila-Annie Peters

662  Dual Roles for the TSPYL Family in Mediating Serotonin Transport and the Metabolism of Selective Serotonin Reuptake Inhibitors in Patients with Major Depressive Disorder
      Sisi Qin, Andy R. Eugene, Duan Liu, Lingxin Zhang, Drew Neavin, Joanna M. Biernacka, Jia Yu, Richard M. Weinshilboum and Liewei Wang