Pediatric multiple sclerosis
Escalation and emerging treatments

ABSTRACT
Over the last 20 years, there have been significant advances in multiple sclerosis (MS) therapeutics, with regulatory approval for 13 therapies in adults by the European Medicines Agency (EMA) and Food and Drug Administration. However, there is only limited approval for interferon-β and glatiramer acetate use in children 12 years and older by the EMA. Availability of disease-modifying therapies to children and adolescents with MS is variable by region, and is extremely limited in some regions of the world. Up to 30% of children experience breakthrough disease requiring therapies beyond traditional first-line agents. Recent legislation in both the United States and Europe has mandated clinical studies for all new therapeutics applicable to children. Several clinical trials in children are underway that will provide important information regarding the efficacy and safety of newer drugs. This review summarizes the current knowledge of breakthrough disease, escalation, and induction treatment approaches in children with MS, especially pertaining to disease course and disability outcomes in this group of patients. In addition, ongoing clinical trials and approaches and challenges in conducting clinical trials in the pediatric population are discussed. Neurology® 2016;87 (Suppl 2):S103–S109

GLOSSARY
AOMS = adult-onset multiple sclerosis; ARR = annualized relapse rate; CI = confidence interval; EDSS = Expanded Disability Status Scale; EMA = European Medicines Agency; FDA = Food and Drug Administration; GA = glatiramer acetate; IFN = interferon; IPMSSG = International Pediatric MS Study Group; JCV = JC virus; MS = multiple sclerosis; NEDA = no evident disease activity; NMO = neuromyelitis optica; PIP = Pediatric Investigation Plan; PML = progressive multifocal leukoencephalopathy; POMS = pediatric-onset multiple sclerosis; PREA = Pediatric Research Equity Act.

Over the last 20 years, there have been significant advances in multiple sclerosis (MS) therapeutics, with regulatory approval for 13 therapies in adults by the European Medicines Agency (EMA) and Food and Drug Administration (FDA).1 There is limited approval for interferon (IFN)–β and glatiramer acetate (GA) use in children ≥12 years of age by the EMA. Safety data for IFN–β–1a SC TIW (Rebif) for children >2 years of age is included in the European label. Availability of disease-modifying therapies to children and adolescents with MS is variable by region, and is extremely limited in some regions of the world. Several clinical trials in children are underway that will bring important information regarding the efficacy and safety of newer drugs (table 1). This review summarizes the current knowledge of breakthrough disease, escalation, and induction treatment approaches in children with MS, especially pertaining to disease course and disability outcomes in this group of patients.

CONCEPTUAL APPROACHES TO TREATING CHILDREN WITH MS
The ultimate goal of therapy in MS is to prevent relapses and to halt disability accrual. The concept of zero disease activity has been termed NEDA, measured by absence of clinical and MRI disease,2,3 and is increasingly being viewed as the overall goal for treatment. However, the impact of low subclinical disease activity (e.g., rare new lesions on MRI) on long-term MS outcome is unclear. Despite advances in MS therapeutics, no one MS therapy has 100% efficacy on NEDA, and NEDA is achieved in approximately 50% of adult patients with MS followed for 2 years in any therapeutic trial.4 Longitudinal data have shown that only 7% of adult patients with...
<table>
<thead>
<tr>
<th>Study drug</th>
<th>Comparator</th>
<th>Design</th>
<th>Phase</th>
<th>Estimated enrollment</th>
<th>Start date</th>
<th>Stop date</th>
<th>Sponsor and NCT no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon beta-1a (Avonex)</td>
<td>Placebo</td>
<td>Randomized controlled, double-blind, double dummy design</td>
<td>3</td>
<td>190</td>
<td>July 2013</td>
<td>September 2017</td>
<td>Novartis NCT01892722</td>
</tr>
<tr>
<td>Fingolimod (Gilenya)</td>
<td>Placebo</td>
<td>Open-label, randomized</td>
<td>3</td>
<td>185</td>
<td>July 2014</td>
<td>July 2016</td>
<td>Biogen Idec NCT02201108</td>
</tr>
<tr>
<td>Dimethyl fumarate (Tecfidera)</td>
<td>Placebo</td>
<td>Open-label, randomized</td>
<td>2</td>
<td>3</td>
<td>January 2015</td>
<td>July 2015</td>
<td>Sanofi NCT02283853</td>
</tr>
<tr>
<td>Teriflunomide (Aubagio)</td>
<td>Placebo</td>
<td>Open-label, randomized</td>
<td>3</td>
<td>142</td>
<td>August 2014</td>
<td>September 2020</td>
<td>Biogen Idec NCT02428218</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>Placebo</td>
<td>Randomized, double-blind</td>
<td>1</td>
<td>2</td>
<td>November 2016</td>
<td>November 2018</td>
<td>Immune Response Pharma Inc. NCT0200718</td>
</tr>
</tbody>
</table>

**Table 1: Current interventional clinical trials in pediatric multiple sclerosis (MS) (listed on clinicaltrials.gov, search term pediatric MS, June 2015)**

**Secondary outcome measures**
- PK, MRI outcomes, cognitive battery
- MR imaging outcomes, cognitive battery
- PK measures
- New MRI Gd lesions
- WBC measurements
- Immune measures, EDSS score

**Abbreviations:** ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale; PD = pharmacodynamics; PK = pharmacokinetics; Gd = gadolinium-enhancing lesions; WBC = white blood cells.

**Short- and Long-term Consequences of Pediatric MS**

As summarized in "Pediatric multiple sclerosis: Clinical features and outcome" (p. S74), pediatric MS appears to be overall a more inflammatory disease than adult MS, with more frequent relapses and MRI lesion accrual. Paradoxically, long-term disability accrual measured by the Expanded Disability Status Scale is slower in pediatric-onset MS (POMS) than adult-onset MS (AOMS); however, patients with POMS will be more disabled than patients with AOMS at a younger age. Between 30% and 50% of children with MS experience significant cognitive issues (see "Pediatric multiple sclerosis: Cognition and mood," p. S82), and adults with POMS may have more difficulty with processing speed than patients with AOMS. Given that children experience MS during a critical point in their overall brain, cognitive, social, and educational development, outcomes tailored to pediatric MS have only just started, and there are limited longitudinal datasets available to answer this question. Although difficult to achieve on a population or cohort level, NEDA is the ultimate goal for individual treatment in pediatric MS. However, given the current treatment options and available treatment data in pediatric MS, this may be challenging to achieve in all patients.

**Individualized therapy.** The identification of patients with high and low risk for disease activity and disability accrual falls into the overall concept of personalized or individualized medicine, which should also be considered in pediatric MS, particularly as more therapies become available. Validated outcome predictors are limited in adults and nonexistent in children with MS.

**Induction vs escalation therapy.** Another relevant concept when considering approaches to treating pediatric MS is the idea of stepwise escalation in therapy vs initiation with potent agents, which, if followed by de-escalation, can be termed induction therapy. There is presently insufficient evidence in adult and pediatric MS to favor one approach over another, and consideration of the overall disease course, safety, and efficacy of various drugs currently guides therapeutic decisions. The terminology of first- and second-line treatments is disappearing in the academic literature and is being supplanted with the concepts of escalation/induction and individualized therapy; however, the terms first/second-line treatments are still often used by payers and regulatory agencies.

**References**
Inadequate Treatment Response to Initial Therapy

The current knowledge on treatment with IFN and GA in children, which have been the most commonly used therapies in pediatric MS over the last 10 years, is summarized in "Pediatric multiple sclerosis: Conventional first-line treatment and general management" (p. S97). IFNs and GA are reported to decrease the relapse rate in adult patients with MS by approximately 30%. In absence of placebo-controlled double-blind treatment studies, several retrospective or open-label studies in children treated with IFN or GA have demonstrated similar or greater reductions in relapse rates. However, as in adult patients with MS, many children experience breakthrough disease.

Definitions for inadequate treatment response vary and have to take into account age (higher relapse rates in pediatric than adult patients with MS), disease duration (relapse rate declines over time), and disease activity prior to treatment initiation. A recent International Pediatric MS Study Group (IPMSSG) consensus statement proposes the following definition of inadequate treatment response in pediatric MS: if the patient has been fully compliant on treatment for at least 6 months and demonstrates (1) no reduction in relapse rate or new T2 or contrast-enhancing lesions (as compared to pretreatment); or (2) 2 or more confirmed relapses (clinical or MRI) within a 12-month period. This definition might be conservative with regards to relapse activity, and another review has suggested that an annual relapse rate >0.6 in the first 2 years of disease or >0.35 in years 2–5, or ≥3 new lesions in the first year and ≥2 lesions in years 2 and 3, would indicate inadequate treatment response.11

None of these definitions has formally been applied to pediatric MS cohorts, and the percentage of children with inadequate treatment response is therefore unknown. A retrospective analysis of 258 treated pediatric patients with MS revealed that 28% were considered by their health care practitioners to have refractory disease on their first therapy (mainly IFN and GA), and were therefore switched to a second therapy after a mean of 1.3 years. Medication changes included lateral switches between IFN and GA therapies, as well as use of natalizumab, daclizumab, and cyclophosphamide, among others.

Adherence. Medication switches on account of poor tolerance or noncompliance were reported in 16% of patients after mean treatment duration of 1.1 years.12 Self-reported rate of nonadherence (defined as not taking the prescribed medication >20% over the past month) was as high as 37%–47% in recent surveys of pediatric patients with MS. A Russian study found that in adolescents with MS, adherence was better in therapies with fewer weekly injections.13 In the absence of reliable biological adherence markers, discrimination between inadequate treatment responses secondary to refractory disease or secondary to nonadherence remains a major challenge. Use of clinic-administered therapies or oral therapies could potentially increase adherence, particularly in the adolescent population, and should be a focus for further study.

Current Knowledge on Second-Line Treatments in Pediatric MS

None of the currently available immunomodulatory or immunosuppressive treatments in use for adult patients with highly active relapsing-remitting MS has completed randomized controlled trials in the pediatric population. However, the increasing number of published reports of second-line agent use in children and adolescents with MS confirms the need for additional therapies in this age group.

Natalizumab. Natalizumab, a humanized monoclonal antibody targeting the α4 subunit of α4β1 integrin, was first introduced in 2004. In its pivotal randomized controlled phase III trial, it demonstrated a 68% reduction of the annualized relapse rate (ARR) (p < 0.001), a 42% reduction of 12 weeks sustained progression of disability (p < 0.001), and an 83% reduction of new T2 lesions on MRI compared to placebo (p < 0.001).14 However, 3 months after its initial approval, natalizumab was temporarily withdrawn from the market, following the occurrence of 3 cases of progressive multifocal leukoencephalopathy (PML).15–19 Natalizumab was reintroduced for the second time into the US market and the European Union in 2006, with the stipulation of a Global Risk Management Plan, mandated in the United States (TOUCH: TYSABRI Outreach: Unified Commitment to Health) and voluntarily in the rest of the world (TYGRIS: TYSABRI Global Observation Program in Safety). Three risk factors for PML associated with natalizumab use have been identified: (1) positive serostatus for anti-JC virus (JCV) antibodies; (2) prior use of immunosuppressants; (3) duration of natalizumab therapy.20 The overall PML incidence, as of June 3, 2015, in natalizumab-treated patients was 3.96 cases/1,000 patients (95% confidence interval [CI] 3.64–4.30 per 1,000 patients), with the highest risk in JCV-positive patients who have received prior immunosuppression and treatment duration of >24 months (11.2/1,000; 95% CI 8.4–15.2/1,000).21
Neutralizing antibodies were found in 2 out of 16 patients with MS overall were JCV antibody positive, which was considerably higher than reported in other studies. A German/Austrian cohort including 20 pediatric patients treated with natalizumab led to profound reduction of the ARR (3.7 vs 0.4; \( p < 0.004 \)) and median EDSS score (2 vs 1; \( p < 0.024 \)). The frequency of anti-JCV antibodies was 39% and 38%, which is lower compared to the reported prevalence in adults of 57%. Side effects were mild to moderate in both series and comprised infections and hypersensitivity. Neutralizing antibodies were found in 2 out of 16 patients. In both cases, natalizumab was withdrawn due to a severe relapse or anaphylaxis. Interestingly, a German study found that 50% of their pediatric patients with MS overall were JCV antibody-positive, which was considerably higher than reported in other studies. Discontinuation of natalizumab is often associated with return of clinical and MRI activity. In 6 out of 8 pediatric patients who discontinued natalizumab, ≥1 relapse occurred within the following 6 months.

Mitoxantrone. Mitoxantrone is approved for adult patients with rapidly evolving relapsing-remitting and secondary progressive MS according to the MIMS trial. However, mitoxantrone is associated with increased risk of cardiomyopathy in up to 12% of patients, therapy-related acute leukemia (up to 2.8%), liver toxicity, and amenorrhea, and therefore is rarely used. One report documents mitoxantrone use in 4 pediatric patients with MS with 3.8–18 years of follow-up. Laboratory abnormalities including anemia, leukopenia, and elevation of liver enzymes returned to normal levels after cessation of therapy. One patient developed transient asymptomatic left ventricular dysfunction during treatment. Leukemia was not reported in this case series; however, cardiomyopathy and leukemia may occur many years after treatment cessation.

Cyclophosphamide. Cyclophosphamide may be effective in reducing clinical and MRI activity. Cyclophosphamide therapy is associated with significant safety concerns, including an increased risk of bladder cancer as well as the risk of secondary leukemia and infertility. A retrospective multicenter study reported treatment of 17 pediatric patients with severe relapses or ongoing relapse activity despite conventional therapy. Before the onset of cyclophosphamide therapy, the 14 patients had a mean of 3.8 relapses per year, which decreased to 1.1 during the first year of cyclophosphamide therapy. Seven patients remained relapse-free. The EDSS remained stable or decreased in 10 out of 12 patients. After cessation of therapy, 50% of patients with a follow-up of more than 1 year experienced relapses and required further second-line therapies. Short-term side effects included nausea and vomiting in 15/17 patients, alopecia in 10/17 patients, and menstrual irregularities in 5 patients, as well as anemia and thrombocytopenia. Lymphopenia was achieved in all children, according to therapy goals. Long-term side effects included the development of bladder cancer in one patient, amenorrhea in 3 girls, and sterility in one patient. Secondary leukemia was not reported in these cases.

Rituximab. Rituximab is an anti-CD20 chimeric monoclonal antibody that has been shown to suppress clinical and MRI activity in MS and neuromyelitis optica (NMO). A retrospective review documents rituximab use in 144 children and adolescents with pediatric autoimmune and inflammatory disorders of CNS: NMDA receptor encephalitis (n = 39), opsoclonus myoclonus ataxia syndrome (n = 32), NMO (n = 20), MS (n = 4), neuropsychiatric systemic lupus erythematosus (18), and other neuroinflammatory disorders (n = 35). A definite, probable, or possible benefit was reported in 125 of 144 (87%) patients. Rituximab improved neurologic outcomes with a 7.6% risk of transient adverse infectious events. A separate retrospective study reported rituximab therapy in 11 pediatric patients, including 8 patients with NMO and 3 patients with MS. Two out of the 3 children with MS remained relapse-free on follow-up while 1 patient continued to experience relapses. The treatment was well-tolerated and no serious infections occurred. Another report of 14 Swedish pediatric MS patients (mean age 16.5 years) found rituximab treatment to be safe and well-tolerated. None of the patients experienced new relapses after a median treatment duration of 23.6 months. A related agent is ocrelizumab, a fully humanized monoclonal antibody to CD20, which completed phase III trials in adult relapsing-remitting MS in 2015.
**Fingolimod.** Fingolimod has had some limited use in children. A retrospective review from Brazil documented 17 children between the ages of 14 and 17 treated with fingolimod. Mean pretreatment ARR was 2.8, EDSS was 2.05 ± 0.98. Patients were followed for a mean of 8.6 months (range 1–18 months). Only one patient had a relapse 14 months after starting treatment. Of the 12 patients with an MRI 3–6 months after the start of treatment, 1 patient had a new lesion. No major adverse events were noted in this study.37

Several drugs are currently in clinical trials for pediatric MS (table 1). Ongoing trials include those for 3 oral therapies, which are approved for adult MS by the EMA and FDA: fingolimod, dimethyl fumarate, and teriflunomide. Mechanism of action and adverse events observed in adult MS are provided in table 2.

### CONCEPTS AROUND EMERGING CLINICAL TRIALS OF NOVEL AGENTS IN PEDIATRIC MS

All the pediatric MS treatment studies published to date are observational studies. However, federal mandates from the US Congress introduced in 2003 and amended in 2007 and similar mandates from the European Union in 2008 require pediatric studies to be performed for all new therapies. In the United States, the Pediatric Research Equity Act (PREA) passed in 2003 required a pediatric assessment for certain applications unless waived or deferred. The PREA was amended in 2007 to apply to any new active ingredient, indication, dosage form, regimen, or route. Waivers are granted if drug will not be used substantially in children, or if ineffective or unsafe in children, or if formulation cannot be made. An accompanying piece of legislation termed the Best Pharmaceuticals for Children Act was passed in 2002 and amended in 2007, and allowed the voluntary submission of a written request if studies are needed in the pediatric population, allowing the sponsor 6 months of additional marketing exclusivity. Similarly, the EMA and its pediatric committee, the PDCO, advises on Pediatric Investigation Plans (PIPs). As of July 2008, the condition for registering a new drug is an agreed-upon PIP. Similar to the written request, compliance with the PIP is rewarded by 6 months of additional market exclusivity.

Given these mandates, the need for randomized clinical trials in pediatric MS was recognized. The IPMSSG published 2 consensus statements around this topic. The first, published in 2012,10 summarized consensus from 50 IPMSSG members and concluded the following:

- Exposure of pediatric patients with MS to new therapeutic agents should occur in the context of carefully designed clinical trials.
- Placebo-controlled trials in pediatric MS should be of brief duration and should have rigorous monitoring to ensure a rescue strategy for children in the placebo arm who experience rapid accrual of physical, cognitive, or MRI burden of disease.
- Development and growth parameters should be included in all studies, as well as long-term impact on fertility.
- Contraceptive use and close pregnancy monitoring should be considered for female patients of child-bearing potential.

The second article is a summary statement from a meeting held in January 2012 with representatives from the FDA, EMA, Health Canada, academic neurologists, and representatives from pharmaceutical companies. The major additional conclusions were as follows:

- Randomized controlled trials are necessary from a regulatory standpoint for drug approval, and will provide robust data to guide clinical care.
- Patient study populations should include <10-year-old participants.
- Relapse is a clinically meaningful outcome measure for trials meeting regulatory requirements.
- Inclusion of an internationally applicable neuropsychological battery for pediatric MS that is sensitive to cognitive deficits in pediatric MS and suited for detecting reliable change is needed.

### Table 2: Dosing and potential adverse events for oral agents currently in clinical trials in pediatric multiple sclerosis (MS)

<table>
<thead>
<tr>
<th>Name</th>
<th>Route/adult dosing schedule</th>
<th>Mechanism of action</th>
<th>Adverse events observed in adult MS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fingolimod</strong></td>
<td>Oral/once daily</td>
<td>Sphingosine-1-phosphate receptor modulator, which prevents lymphocyte from lymph nodes</td>
<td>Bradycardia at first dose, varicella infections, herpetic infections, macular edema, lymphopenia, PML (rare)</td>
</tr>
<tr>
<td><strong>Dimethyl fumarate</strong></td>
<td>Oral/twice daily</td>
<td>Nrf2 antioxidant pathway modulator</td>
<td>Flushing after dosing, GI upset, lymphopenia, PML (rare)</td>
</tr>
<tr>
<td><strong>Teriflunomide</strong></td>
<td>Oral/once daily</td>
<td>Reversible inhibition of dihydroorotate dehydrogenase, a mitochondrial enzyme involved in pyrimidine synthesis for DNA replication, affecting T- and B-cell proliferation</td>
<td>Hair loss, liver test abnormalities</td>
</tr>
</tbody>
</table>

Abbreviations: GI = gastrointestinal; PML = progressive multifocal leukoencephalopathy.
• A prospective registry is needed to obtain data on safety and clinical outcome in patients exposed to MS therapies during childhood to evaluate long-term impact.

Various aspects of clinical trial design were discussed, including the use of placebo vs active comparator and ARR vs time to relapse designs, as well as estimated sample sizes needed for these various designs. Since then, several clinical trials in pediatric MS have been launched, and their design and specifics are summarized in table 1.

**VIEW TO FUTURE APPROACHES TO THERAPY WITH CURRENTLY AVAILABLE AND EMERGING KNOWLEDGE OF THERAPEUTICS IN PEDIATRIC MS**

Apart from those listed in table 1, additional therapies are in or have completed late-stage trials in adult MS. Many of these newer agents will require pediatric studies. Some considerations for moving forward with such studies are listed in table 3.

The emergence of newer classes of drugs that are being developed for MS, including remyelinating therapies,38 neuroprotective therapies,39 and symptomatic treatments,38 presents new opportunities and challenges when considering use in pediatric MS. Some of these classes will apply to children, and consideration of outcome measure for pediatric studies is critical for effective evaluation of these therapies.

The most important factor to keep in mind when considering long-term treatment is how therapies impact pediatric patients and their families over the short and long term. A major need is a means to evaluate the long-term outcomes of therapies on the physical, developmental, cognitive, and psychosocial outcomes in patients with childhood-onset MS into adulthood, potentially through the implementation of long-term outcome registries. International collaboration among physicians, patients and their families, regulators, and the pharmaceutical industry is required in all of the aspects discussed above.

**AUTHOR CONTRIBUTIONS**

All authors contributed to the drafting, revising, and review of this article.

**STUDY FUNDING**

This supplement is made possible by funding from the MS Cure Fund, Danish MS Society, German MS Society, Italian MS Association, MS International Federation, MS Research Foundation (Netherlands), National MS Society (USA) and Swiss MS Society.

**DISCLOSURE**

T. Chitnis has received personal compensation for advisory board/consulting for Biogen-Idec, Merck-Serono, and Novartis, and has received research support from Merck-Serono and Novartis Pharmaceuticals. She serves on pediatric clinical trial advisory boards for Genzyme-Sanofi and Novartis. A. Ghezzi has received honoraria for speaking from Biogen-Idec, Merck-Serono, Novartis, Genzyme, Teva, and Allergan, and for consultation from Merck-Serono, Teva, Novartis, and Biogen-Idec, and received support for participation in the National and International Congresses from Schering, Biogen-Idec, Merck-Serono, Novartis, Genzyme, and Teva. B. Bajis-Kornek has received honoraria for speaking from Genzyme, Biogen-Idec, Teva, Merck-Serono, Novartis, Bayer, and Merck-Serono and for consultation from Genzyme, Merck-Serono, and Bayer. A. Boyko has received personal compensation for advisory board/consulting and participated in clinical trials sponsored by for Biogen-Idec, Merck-Serono, TEVA, Genzyme-Sanofi, and Novartis. G. Giovannoni has participated in the following: AbbVie: steering committee member on the Daclizumab trials; Biogen-Idec: steering committee member on the BG12 and Daclizumab trials; has received consultancy fees for advisory board meetings, honoraria for speaking at Physicians summit, GSK consultancy fees in relation to their phase 3 MS trial program, and consultancy fees for advisory board meetings from Merck-Serono; was a steering committee member for Novartis on fingolimod and siponimod trials; received consultancy fees for advisory board meetings; and was a steering committee member for Teva. D. Pohl has received compensation for consulting or conference presentations from Bayer, Biogen-Idec, Merck-Serono, and Teva. Go to Neurology.org for full disclosures.

Received August 19, 2015. Accepted in final form February 18, 2016.

**REFERENCES**


Table 3 Considerations for future clinical trials in pediatric multiple sclerosis (MS)

| 1. There are a limited number of children worldwide with MS; therefore it is recommended that only one phase III trial be initiated for each agent, and to avoid the situation of multiple studies, possibly to satisfy different regulators, for one drug. Wherever possible, all international trials should be harmonized. |
| 2. Pharmacokinetic and pharmacodynamics studies should precede and inform dosing for phase III/III trials. |
| 3. There is a need for increased awareness and training of clinicians treating children with MS in clinical trial methodology and understanding the risks and benefits that clinical trials offer. |
| 4. Further discussions with patients and their families regarding their goals for treatment and clinical trials and to develop patient-centered outcomes are needed. |
| 5. Continued discussion and information about the state of the field for regulators and the pharmaceutical industry is required. |
| 6. There is a need to explore strategies to facilitate and expedite clinical trials in pediatric MS. |
| 7. Methodology to evaluate long-term safety and efficacy outcomes in pediatric patients with MS, particularly those participating in clinical trials, is needed. |


